National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Problems of Drug Dependence 1997: Proceedings of the 59th Annual Scientific Meeting

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IN MEMORIAM

SYDNEY ARCHER
January 23, 1917 - August 22, 1997

Dr. Sydney Archer, a Research Professor and former Dean of Science at Rensselaer Polylechnic Institute, died from a stroke on August 22, 1996 in Albany, New York. Syd, as he was known to his numerous colleagues and friends, was a Charter Fellow and former member of the Board of Directors of the Committee (now College) on Problems of Drug Dependence. He was an active participant in CPDD meetings for more man four decades.

Syd was born in Brooklyn on January 23, 1917. He received his B.S. in Chemistry from the University of Wisconsin in 1937. After completing his Ph.D. in Organic Chemistry at Pennsylvania State University in 1940, he was a postdoctoral fellow at Northwestern University and the University of Chicago. In 1943, Syd started his career at Sterling-Winthrop Research Institute as a Research Chemist. He became Director of the Chemistry Division in 1964, and from 1968 to 1973. Syd was Vice President and Associate Director of Research at Sterling-Winthrop. Syd synthesized hundreds of opioids during his tenure at Sterling-Winthrop, including pentazocine and

cyclazocine. He was the first to demonstrate that the substitution of a N-cyclopropylmethyl group for the N-methyl group in the benzomorphan series resulted in compounds displaying antagonist properties. Syd was instrumental in introducing partial agonists into the opioid field, compounds with both agonist and antagonist properties. In 1968, he was the recipient of the Medicinal Chemistry Award from the American Chemical Society.

While at working at Sterling-Winthrop, Syd was also an Adjunct Professor at Rensselaer Polytechnic Institute, teaching medicinal chemistry in the evenings. His lectures on medicinal chemistry were also well known by his many colleagues, particularly. those that saved on NIDA Study Sections with him. Syd's enthusiasm for chemistry and its applications was boundless and contagious.

Upon retiring from Sterling-Winthrop in 1973. Syd launched a second career, as a Research Professor of Medicinal Chemistry at Rensselaer Polytechnic lnstitute in Troy, New York. He was Dean of the School of Science from 1980 to 1985. Syd played a central role in the creation of the New York State Capital District Center for Drug Abuse Research and Treatment. Holding more man 100 patents. Syd was named Inventor of the Year by the Eastern New York Patent Law Association in 1978. For the past two decades, most of his research in the drug abuse field focused on novel approaches for designing new drugs to treat heroin, cocaine, and alcohol abuse. Also, Syd synthesized a number of fluorescent opioids. He made key contributions in identifying opioid receptors on immune cells, and on microglia, the brain's macrophages, that can become infected with HIV-1. Syd was continuing to synthesize new compounds up to the time of his death.

Syd will be remembered for his inspiration, boundless enthusiasm, and optimistic outlook. He always focused on the future and had an endless supply of new ideas and energy. Also, Syd will be remembered for knowing the best restaurants in the world and for his strong appreciation of classical music. Syd was an extremely supportive colleague, and I was privileged to collaborate with him for a number of years. Syd is survived by his wife. Therese, and his three children, David, Eve, and Daniel.

Prepared by: J. M. Bidlack

Department of Pharmacology and Physiology, University of Rochester, Rochester, NY

DRUG ABUSE AND ADDICTION: RESEARCH PROGRESS AND FUTURE PROSPECTS

A. I. Leshner

National Institute on Drug Abuse, National Institutes of Health, Rockville, MD

I am extremely happy to be here again this year--to have the opportunity to meet face-to-face with so many of the talented scientists who are moving the drug abuse and addiction research field forward and to hear about the great science that you have been doing over the past year. I want to offer my congratulations to the College on Problems of Drug Dependence (CPDD) as a whole and to Marty Adler for superb leadership efforts in bringing together this impressive showcase of the state of the science of drug abuse and addiction.

Since I took on the directorship of the National Institute on Drug Abuse (NIDA), three CPDD meetings ago, I have tried to come up with a different theme each year to bring to the annual meeting. The first year I came, my theme was 'I've got a secret'. This year I've brought a different theme -- 'the science is going great and people know it.'

What I would like to do this morning is to bring you up to date on some of NIDA's activities in a variety of areas and to share with you my perspective on the state of our science and my assessment of the progress we have made together in bringing public perception and scientific reality about drug abuse and addiction closer to being on the same track.

First of all I want to talk about some of the things that have been happening in NIDA, as well as some of the things that have been happening in the field, or, generally, because I think they have enormous relevance to everything that we are doing. And I want to make sure that everyone is aware of the policy and process issues that may affect your lives as grantees of the National Institutes of Health (NIH). Let me just take a few minutes to talk about those issues.

REVIEW ISSUES

As many of you know, there has been a lot of activity surrounding the topic of grant review during the past year, both at NIDA and within the NIH Division of Research Grants (DRG) as a whole. For example, as part of reinvention activities and the ongoing effort to maintain high standards for peer review at the NIH, a subcommittee of the NlH Committee on Improving Peer Review was formed and tasked with examining the process by which scientific review groups rate grant applications and making recommendations to improve that process. What has resulted after two years of deliberations has been a change in the criteria for the rating of grant applications to NIH. Basically, there is an attempt to move away from a focus on the fine details of a proposal and to look at a broader set of issues, such as the overall impact that the research proposed will have on the field and the approach the investigator intends to take. Another criterion relates to innovation and creativity and the issue of whether or not novel approaches will be used in conducting the research. And, of course, the qualifications of the investigator also weigh heavily in the review process. Obviously, not all criteria will be applied equally to every proposal. But since all criteria will be looked at by the study section for each proposal, I encourage all of you to become familiar with them. You can get a description of these new criteria either on the NIDA homepage, the NIH homepage, or the CPDD homepage. In addition, this information is being sent out with every grant application. Use of the new criteria began in May and will be effective for the September round of Council.

The second item that I want to mention relates to the process that has been going on this year of integrating the review of neuroscience research grants into the rest of the NIH system. As most of you know, the integration of NIDA, NIMH and NIAAA into the NIH grant review system has necessitated reexamination of the overall NIH review in certain areas of scientific investigation, A major objective is to integrate the review of grant applications from these institutes into the DRG peer review structure. These integration efforts will help to ensure quality peer review that identifies the most meritorious science for each institute to consider for funding. Basic and clinical neuroscience research has been the initial focus, with behavioral science to be considered next. What is happening in the neuroscience area essentially, is that all of the proposals from the seven NIH institutes that fund neuroscience

research are being reshuffled into the newly created study sections. At this point, the neuroscience activities are conceptually complete. I encourage you to look at the desctiptor of those activities on the NIH and the NIDA homepages.

POLICY ITEMS

There have also been a number of policy areas of importance to the field that we have devoted a significant amount of time addressing this year. One example here relates to the administration of drugs to human subjects. The National Advisory Council on Drug Abuse, recognizing the importance of designing, reviewing, and conducting such research within the fundamental ethical principles governing all biomedical and behavioral research with human subjects has been working over the past year to develop a set of recommended guidelines. The Council's guidelines are not intended to supplant the functions of either the IRB or OPRR but, instead are advisory to applicants, IRBs, IRGs and others. They are not codified and do not constitute Federal regulation. Rather, the guidelines ate intended to encourage a sensitive, ethical approach which is also consistent with the best current practices and experience in the field of drug abuse research They are meant to inform the IRB who obtalns local authority for looking at the studies about the conditions under which, under normal circumstances, drugs of abuse might be administered to human subjects. The Council recommends consideration of a number of general issues including risk/benefit, informed consent, subject selection, and confidentiality as well as a number of specific issues including informed consent medical and psychological screening and services, administration of drugs to individuals who have never used drugs, involvement of individuals currently addicted to drugs, drug doses and routes of administration, prior and current drug treatment status, pregnancy, age of research participants. study personnel training and experience, HIV risk reduction counseling and testing, safety of research participants outside of the research site, referral to treatment, incomplete disclosure, and payment for participation in research.

NIDA BUDGET

In terms of our budget, prospects for next year look optimistic. The President's FY 98 funding request for NIH is $13.078 billion, including $521.9 million for NIDA--a $32.8 million increase over FY 97. This represents a 6.7% overall increase for NIDA. against an NIH increase of 2.6%. The purpose of NIDA's increase is two-fold. About half of these funds are to be directed to anti-addiction medication development The other half is to be dedicated to advances in prevention and treatment research. These categories cover essentially everything that NIDA is involved hi. As I have said before, we are no longer in that era that occurred during the late 1980's--where an increase of 14% would be considered meager. In these times of cutbacks and tight budgetary constraints even a 2.6% increase for the National Institutes of Health is a major statement by the President of his enthusiasm for the work that NM does. And both Dr. Varmus and Secretary Shalala have been touting the work NIDA supports as something that they believe in. So I am hopeful that we will be able to hold on to this increase, and, as NIH's budget may rise in the process, we will keep our special status as well. This is the direct result of a lot of work by many different people. And although it may take some time, I think it is clear to all of you that, ultimately, the advocacy efforts of your society really do pay off.

I am hopeful that fiscal year 1998 will turn out well as some rather unusual budgetary events ocurred in fiscal year 1997. In total we have received about $11 million added to our budget over the course of the past year. From General McCafrey, Director of the Office of National Drug Control Policy (ONDCP), we received $4.8 million for anti-cocaine medication development and another $4.2 million as part of the Resident's methamphetamine initiative. Since the total of that initiative is $10 million. the fact that $4.2 million of it came to NIDA. is a statement that the administration understands that science is a meaningful way to get a handle on the drug problem in this country. I think that those on the board with whom we met yesterday and the Deputy Director of the ONDCP, would agree that we are experiencing a very special set of circumstances at this particular point in history, where the administration actually understands the power of science. I would also add that Dr. Harold Varmus, the Director of NIH, has also, at his discretion, added $2 million to our funding for anti-cocaine medication development.

STATE OF THE SCIENCE

In many ways, science in the area of drug abuse and addiction has had a phenomenal year! And what I would actually like to do for a few moments is tout the enormous progress the field has been making--thanks largely to your efforts -and to share with you what I see as a very positive future ahead. In my view, the science that all of you have been doing and reporting has made this a spectacular year! It is unbelievable to me. having been the NIDA Director now for three and a half years, how rapidly and how continuously we seem to be accelerating the rate of advances in this field. I am very proud and pleased to say we probably know more about drug abuse and addiction than we know about any other thing that affects the brain directly or indirectly. And although all of us in this room by now are used to this great rate of advances, I have been having a wonderful time bragging to a variety of different sectors who are not, as yet, so well informed about our current level of understanding about drug abuse and addiction and the phenomenal progress that is being made. Even though much of this information is news to these audiences, it is becoming increasingly evident that we are finally beginning to make some headway in closing the gap between scientific reality and public perception about drug abuse and addiction.

SHAPING NIDA'S RESEARCH AGENDA

It has been a wonderful year in terms of recognition of the power of science, and you are the vehicle for its practice The question is how will the money we receive to support drug abuse research best be spent? NIDA continues to use a variety of mechanisms to further shape our research agenda and to set our course for the future needs of the field. In addition to the many areas of emphasis already included in our research portfolio. NIDA is also moving ahead on our three new initiatives for FY 1997-1998 -- *the Treatment Initiative, the Methamphetamine Initriative and the Child and Adolescent Initiative.*

Treatment Initiative

Having shown that addiction is a treatable disease. NIDA-supported research has made extensive progress in developing treatments, both pharmacologic and behavioral, But there is still a great deal more we need to do in this area. Thus, NIDA is mounting a major treatment initiative which will take therapies (both behavioral and pharmacologic) that are shown to he effective in small scale studies and evaluate them in large, multi-phased, multi-site trials. An equally important part of this initiative will be to close the gap between what we know through scientific research about the treatment of drug addiction and the public's perception of drug addiction treatment. This we hope to accomplish by broadening the dissemination of our research findings.

As part of its Treatment Initiative. NIDA will conduct and disseminate research to improve the efficacy, outcomes, effectiveness, and accessibility of existing treatments. We will implement the next step of our Behavioral Therapies Development Program by applying a mum-phased controlled evaluation process to the theory-based behavioral therapies that were developed in Phase I. Once the therapies are tested in the larger clinical trials, they will be replicated in real life treatment settings. In addition, NIDA will conduct research to integrate new treatment medications into existing treatments as well as develop new. comprehensive treatment approaches which involve not only pharmacotherapies, but behavioral and psychosocial strategies as well. And we will build upon our current translational research on treatment in the managed care arena.

The development of effective medications for the treatment of addiction remains a lop priority for NIDA, especially the development of an anti-cocaine medication and will comprise an important part of our *Treatment Initiative. In* the area of medications development NIDA will conduct and support research to identify new and novel molecular targets to he tested for anticocaine medication development. To find an anti-cocaine medication, NIDA will screen and test a large number of the available compounds that exist in the compound libraries of pharmaceutical companies. NIDA's Medications Development Program will also establish a network of sites capable of delivering high quality clinical data for multi-phase trials to a variety of targeted populations. And to fully reap health benefits from the knowledge gained through fundamental clinical trial treatment investigations, NIDA will continue its efforts to transfer its knowledge and technology to the private sector, where firms like biotechnology and pharmaceutical companies can produce products that treat or prevent addiction.

Methamphetamine Research Initiative

NIDA's Community Epidemiology Work Croup (CEWG) and other monitoring mechanisms have indicated that there have heen significant increases in methamphetamine use in specific areas of the country. In fact, half of you in this room--those of you who have come from the West Coast, undoubtedly understand why methamphetamine use is such a big issue. Those on the East Coast may not be as aware of it, but in San Diego, methamphetamine has just passed crack and cocaine as the drug of choice. at least for people who are entering the criminal justice system. Thus, NIDA has, over the past year, become involved in a variety of activities to help ensure that methamphetamine use does not become a national epidemic. Knowing that research provides the foundation needed for long-term solutions to the methamphetamine abuse problem, NIDA is launching a *Methamphetamine Research Initiative* to complement existing national efforts. As part of this initiative, NIDA will conduct research that will elucidate the neurobiological mechanisms of methampbetamine's actions in the brain and identify molecular targets for possible medication development. NIDA supported research will also focus on understanding the consequences and long-term damage of methamphetamine use to the brain, especially the dopamine system, as well as the drug's effects on other organ systems. And NIDA will support research to develop methamphetamine prevention programs that are specifically geared toward the unique charactecristics of the methamphetamine user, as well as treatment approaches that are specifically tailored for poly-drug addiction to mehamphetamine and other substances.

Child and Adolescent Initiative

The problem of drug abuse among youth is another topic that has received unprecedented attention in recent years. This is a critical area where translational research is desperately needed. As data from the 1996 Monitoring the Future Study and other research-based monitoring tools show drug use among youth continues at unacceptable levels. For this reason. we have launched a *Child and Adolescent Initiative* the goal of which is to use the basic science of development to identify the determinants of drug taking behaviors among children and adolescents and apply these findings to the development of new and improved prevention and treatment approaches. As part of this initiative, NIDA will support research that identities the pathways leading to drug addiction in children and adolescents. This research will focus on the risk and protective factors in increasing or decreasing the probability that a child will become susceptible to addiction. NIDA-supported research will also develop and test prevention programs that are age appropriate and based on the findings from the study of attitude formation and change. In addition, NIDA will build its research portfolio to focus on the basic behavioral processes involved in decision-making at various stages of child and adolescent development. And NIDA will conduct cognitive research to measure the impact that peer pressure has on a child's susceptibility to drug-taking behaviors. The research will also attempt to determine the interplay between peer pressure and risk and protective factors.

INFORMATION DISSEMINATION

As I stated earlier, we have been making extraordinary advances in the science of drug abuse and addiction. The science the field has been producing--much of which will be reported over the course of this meeting--is, in fact, something in which we can and should take a great deal of pride. But as I mentioned at last year's meeting, it is vital that we go beyond doing the science and get the word out about our findings. During the past year we at NIDA have been engaged in numerous efforts to disseminate the findings of much of your research by sponsoring satellite symposia at the annual meetings of many professional groups. For example. in August NIDA co-sponsored the *Conference On Drug Abuse (CODA)* with the American Psychological Association, Science Directorate, as a satellite conference to APA's annual convention. The goal of CODA was to highlight the best in drug abuse and addiction research and included numerous drug abuse symposia, paper and poster sessions. NIDA also sponsored a number of satellite symposia held in conjunction with the *Society for Neuroscience* annual meeting. And as I hope all of you are well aware, we at NIDA have worked with CPDD on the dedicated HIV/AIDS track that is running through this meeting covering a multitude of areas relating to AIDS and drug abuse--two epidemics that during the last decade and a half have become increasingly interlocked.

ADVANCES IN CHANGING PUBLIC PERCEPTION

Although the science is going well, advancing the science is only part of what we need to accomplish. The ultimate worth of our efforts lies in the extent to which our research is useful to those it is intended to help and that the findings we generate are actually implemented in practice. In addition to generating superb science, NIDA, as well as many other factions of the drug abuse and addiction field, have continued to work very hard over the past year to increase public awareness about the nature of drug abuse and addiction and to advance our goal of bridging what I have calling the "great disconnect" between public perception and scientific reality.

For example. NIDA has organized several more *"Town Meetings"* entitled *"Understanding Drug Abuse and Addiction: Myths Vs. Reality"* in which NIDA researchers discussed ways that state policy makers, organizations. schools and communities can utilize the latest scientific research to assess state and local drug problems and develop programs to meet these needs, Thus far, we have held these meetings in Miami and Tampa, Florida; Anchorage Alaska; Columbus, Ohio; St. Louis, Missouri; Dallas, Texas and Chicago Illinois. In the coming year, we plan to continue these meetings in several more locations across the country.

We have also been working hard to continue building a constituency for NIDA. As part of this effort, in November we hosted our *Third Annual Constituent Conference* where we presented NIDA's 'Report Card highlighting specific actions taken by the Institute in response to constituent group recommendations and discussed strategies to prepare the field for implementing promising prevention and treatment approaches as they become available.

The first year we held this meeting representatives from 20 groups came: the second year 30 groups were represented; and this year the number of organizations that participated grew to 40. What we are seeing is the beginning of a coalescence around the science of drug abuse and addiction, and hopefully. they will be joining with groups like CPDD in being our support system and also our information diffusion system. We have been going to their meetings and writing columns for their newsletters. These groups represent the science, the practice, and the advocacy in lay communities. These meetings have been valuable vehicles for obtaining advice about all kinds of information we need, and, then, we tell the participants what we have done about their ideas and suggestions. Some of you have been to these meetings, and they are very interesting. From my perspective, they are very useful because they certainly keep one grounded in what the issues are and their concern to people who have to the the problems on the front line

NIDA also sponsored a *National Conference on Prevention Research* last fall which provided a forum for presenting the most successful prevention strategies and programs developed through research to prevent and reduce drug abuse among youth. Much of the research presented and discussed at this conference was then compiled by NIDA into the first research-based guide ever developed for preventing young people from using drugs. The guide, entitled, *"Preventing Drug Abuse Among Children and Adolescents: A Research-Bared Guide"* contains state of the art science-based principles on the content, structure, and delivery of effective drug abuse prevention interventions as well as examples of successful prevention interventions. Here again is an attempt to take the science and make it useful. The principles contained in this guide, derived from ten years of prevention research, are intended to serve as advice, literally. to communities developing their own prevention programs or evaluating them. In recent years, there has been an attempt to move drug prevention away from the question of whether a particular method works to much more important questions, including why does it work and what are the elements that are critical to a particular situation? Thus far we have distributed 100,000 copies and have been astounded at how hungry the field is for this kind of information.

We have also engaged in efforts to better inform health care professionals with the facts about drug abuse and addiction by co-sponsoring a day-long symposium with the journal *Hospital Practice* (a publication of McGraw-Hill Companies, Inc.) entitled *"New Understandings of Drug Addiction"*. The purpose of this meeting was to bring primary care physicians current information on the biology of drug addiction and its implications for treatment. Proceedings from the symposium were published in a *Hospital Practice Special Report* which is going out to over 120,000 primary care physicians. This report contains very good descriptors for a primer of what we have learned about drug abuse and addiction, neuroscience, behavioral science, clinical issues, and a few service issues are included in it as well.

As I am sure many of you know, the May 5, 1997 issue of *TIME* magazine. featured an extensive piece on the. biological basis of addiction, highlighting the work of many of NIDA's grantees. This piece was not only well done but, in my view, is symbolic of a very slow but hopefully increasing understanding that there is more to drug abuse and addiction than just failure to quell a moral weakness. I think the science that you all do is what is fueling this very slow but gradual process, and I think the evidence points to this rising tide of understanding about what is happening.

Another event we participated in, that I personally was very pleased about, was the NIH Office of Science Education sponsored Mini-Med School held on Capitol Hill. in May. This activity was intended to provide Congressional staff with information about the basics of medicine and medical research in order to help them make more. informed policy decisions. The lecture I gave on drug abuse and addiction was broadcast on C-SPAN enabling us to reach an enormous viewing audience.

We have had some other kinds of public events, and, again, I know some of you have been involved in those activities. Next March, Bill Moyers is going to do a five-part special on addiction and recovery for public television that NIDA has played a part in and I know be has interviewed a number of you as well. The producers of the special have asked us to co-produce a number of their handouts that will go out to teachers and to their general viewing audience as part of this effort. We also just gave out our first series of PRISM Awards in Hollywood to television personalities, shows, and movies that do an accurate job of depicting drug abuse and addiction.

There is no doubt that, relative to many other areas, the science of drug abuse and addiction is doing well in many respects. In addition to the enormous scientific progress that all of you have been making individually, overall, people are beginning to recognize that our collective efforts are paying off. Not only are individual scientists gaining recognition in the lines of work that they want to do, but I think we are also beginning to see a very gradual change in understanding the way in which science can be brought to bear on the issue of drug abuse and addiction. The fact that we have been singled out by members of the administration, the Congress, and many other groups as sources for accurate, up-to-date Information to help get a handle on these issues is an important testimony to science. Furthermore, it is testimony to the hunger and the need for the kind of work that all of us are doing. There also seems to be a gradual change in public opinion about the nature of drug abuse and addiction and public understanding of the facts is the only chance we as a country have to get a handle on the problem. Although things ate going well we cannot rest on our laurels too long. In order to continue and even accelerate the progress we are making in ensuring that *science will replace ideology as the foundation for drug abuse and addicton prevention,treatment and policy strategies* it is essential that we keep the momentum going!--both in advancing the science and in getting the word out about the findings our science is generating.

INTRODUCTION OF THE NATHAN B. EDDY MEMORIAL AWARD RECIPIENT

W. L. Dewey

Research and Graduate Studies, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

Ladies and Gentlemen,

It is indeed a pleasure and an honor for me to present Dr. Martin Adler the Nathan B. Eddy award winner for 1997. Marty was nominated for this award for many reasons: his many scientific contributions, his leadership role in our discipline, his excellence as a teacher and role mode, his endless and tireless work for the field and for his phenomenal continuance of the work of Dr. Eddy to oversee the activity of CPDD.

Dr. Adler is a world leader in the area of understanding the effects of opioids and opiates on thermoregulation. The effects of opiates on thermoregulation like the effects of these drugs on some other systems are species specific, dose dependent and often affected by many other biological variables. Dr. Alder has elucidated how and why each of these variables affect opiate pharmacology.

Just as the opiates can cause an increase in body temperatute under certain conditions and a decrease at other conditions they also cause seizures at some and have antiseizure activity under other conditions. Dr. Adler has done a great deal to expand our knowledge in this area as well. In addition, he has been instrumental in our understanding of the complex effects of opiates on the eye.

It is obvious that Dr. Adler has chosen some of the more complex systems to study effects of the opiates. He has done more than anyone else to elucidate the mechanisms by which these interesting drugs alter these biological systems. He has identified the endogenous ligands and the specific opiate receptor types involved in each of these interesting pharmacological phenomena. His studies included both acute and chronic administration of the opioids. Information generaled by his laboratory following chronic administration has been important in our attempt to understand the mechanisms of the development of tolerance and physical dependence to opiates.

In recent years be has expanded the breadth of his interests to include interesting investigations into the effects of the opiates on the immune system. He had the wisdom to choose excellent collaborators who have sound knowledge of this system. Dr. Adler contributes much to this group as one of the worlds leaders in the pharmacology of opiates.

Even though I believe the contributions of the work described above are enormous, they do not tell the whole story of the contributions of this man to science. He is a stimulating lecturer who makes difficult concepts understandable to his audience. Dr. Adler has educated an impressive number of graduate students and postdoctoral fellows who have gone on to be contributing independent investigators in their own right. He has contributed to the field of pharmacology and more significantly to drug abuse research in other ways. He has been an excellent field editor of the most prestigious journal in the field of pharmacology as well as a tireless reviewer of papers for many other journals. Dr. Adler has served the more broad field of pharmacology by contributing expertly to his department and to his professional society.

But it is in the specific field of substance abuse that Marty's service contributions are beyond comparison. He has contributed extensively to the National Institute on Drug Abuse. He has served on study sections and review groups for an extended period of time. He has chaired NIDA study sections at least twice in his career. He has served on the editorial board of the NIDA monograph series and on the search committee for the Director of the Institute, His contributions as executive secretary of the College on Problems of Drug Dependence can not be overstated. When he took on this responsibility it was a time of major transition in the organization. He set-up the offices in Philadelphia simultaneously with the most impressive growth in participation of scientists and scope of activity of the organization. He has kept this organization together as officers come and go and as the committee of twenty some people become a membership organization of hundreds. The glue that kept it all together has been Marty

Adler. The fact that he is one of the worlds leading researchers in his area has allowed him to be an executive officer who contributes far beyond what normally is expected. This certainly is reminiscent of the important contributions of Dr. Eddy to this field.

Dr. Marty Adler has contributed to biomedical research in every conceivable way. In each, he has contributed with distinction and has been an example for all of the rest of us. It is a pleasure to have worked with Marty Adler in so many ways and it is a privilege to be in the same field with such an outstanding scientist. It is now my pleasure to ask Marty to come forward and accept this award and present the 1997 Nathan B. Eddy Award Lecturer.

Respectfully submitted.

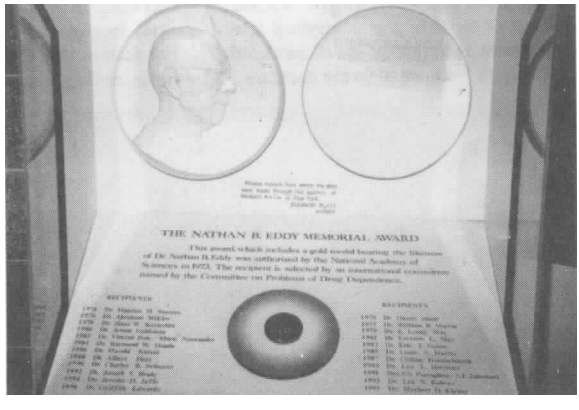
NATHAN B. EDDY AWARD LECTURE

M. W. Adler

Department of Pharmacology, Temple University, Philadelphia, PA

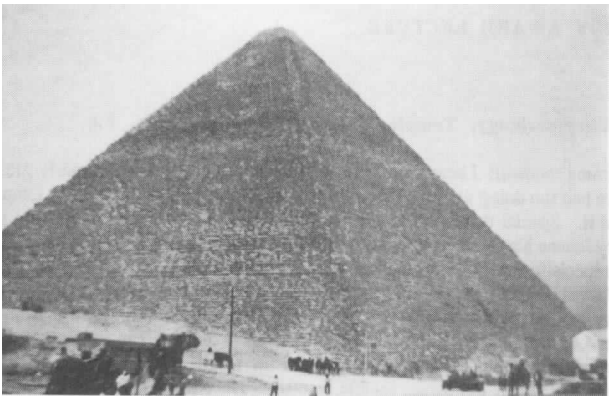
This is an overwhelming moment! I beard someone say recently that it was particularly great to receive an award for something you've had fun doing all your life. I want to thank CPDD, the Awards Committee, and Dr. Billy Martin, who chaired it. Special thanks go to my nominators - Drs. William Dewey who spearheaded the effort Robert Balster. Mary Jeanne Kreek, Joseph Brady, Thomas Crowley, and Louis Harris. I also want to thank Dr. Steven Holtzman, especially for the phone call informing me that I was to be the recipient of the 1997 Eddy Memorial Award. It was probably the most pleasant shock I have ever had. Let me also thank Ellen Geller, with whom I work every day but who never let me know that I had been nominated. It was an Oscar-deserving performance. A lot of what I have accomplished over the years at Temple can he credited to her. But I wouldn't even he here if it wasn't for my wife Toby who arranged for me to get into graduate school while I was in Korea. She and an ex-professor of mine, Dr. James Ingalls, contacted Dr. Michael Clay at Columbia and I was accepted with a teaching assistantship----all without my knowledge. Toby told me about it on one of my monthly phone calls that I was able to get through from Korea. All I had to do was accept. It took me a month to get over the surprise, but on the next call. I had her accept for me.

I only met Dr. Eddy a couple of times since I didn't attend a CPDD meeting until the early '70s. This award was named to honor him, and a look at the scientists who have won the award is like looking at the Who's Who of the drug abuse research field.



Each of the people on this list is undoubtedly deserving of the honor, but it's almost a shame that we have only one such award each year because our field includes so many distinguished and deserving scientists.

I thought long and bard about what I should talk about in this lecture and I asked several friends and colleagues for their suggestions. As one would expect when asking a group of scientists for an opinion not necessarily based on any facts, there was little overall consensus as to the best approach. The closest I could come to finding some common threads in the suggestions was that the talk should he personal. it should include some science (but not too much since the purpose was not to intentionally put the audience to sleep), and, if possible, there should he a take-home message.



The key to the longevity and stability of the pyramid is the broad base. I'm going to start with the take-home message: at many institutions, we are training our students too narrowly and without a broad base, a situation which will impede many of them to or 20 years after they complete their training. What I'm going to try to do in this talk is to Integrate that message into a somewhat cursory look at some of my research over the years to illustrate why one needs to have a rather broad base.

My graduate training began at Columbia University, where I received the Master's degree and did a thesis on stress. Most of the coursework consisted of the first year of medical school courses, supplemented with some special courses and laboratories in experimental physiology and in biochemistry. For reasons that I won't go into, I felt that Columbia was not the place where I wanted to do my doctorate, so I went to see Dr. Alfred Gilman at Einstein.

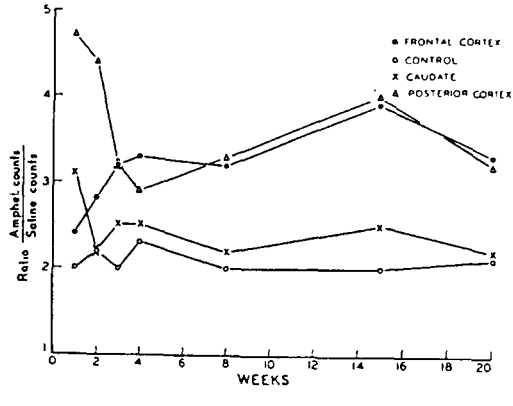
The nervous system was the research emphasis at Einstein because of an NIH interdisciplinary training program. While taking most of the second year medical school courses - microbiology, pathology, and pharmacology - I started my research with Dr. Murray Jarvik. Fortunately or unfortunately, Dr. Gilman accepted nothing less than outstanding performance and his students were expected to be in the upper 10% of the medical school class. That would have been difficult anywhere. but at Einstein it was trial by torture. In addition to the coursework, graduate

students were expected to take part in the Microbiology Journal Club. We were also offered the opportunity to assist in setting up organs and tissues for the daily Pathology conference. That was great since we were paid a small stipend, enough so that we could have bought a Big Mac every couple of days if McDonald's had been in existence at that time. Believe it or not, there really was life before McDonald's. In Pharmacology, graduate students set up all demonstrations and all laboratories. Before we graduated, we also took all or parts of several other courses including Physical Diagnosis, Radioisotopes, Statistics, Experimental Neurology, and Experimental Psychiatry. In other words, we took a lot of coursework. But we also did a lot of research and 12-hour days and a minimum of 6 days a week were the norm.

In terms of research, Dr. Jarvik was interested in learning and memory and was using monkeys in his work. He used a visual discrimination and delayed response test and was interested in the effects of centrally acting drugs. Circuitry was never my strong point, but we had to learn to build our own circuits for the specific tests we were using. We decided that we should try to automate some of the apparatus, so we (mostly Dr. Jarvik) got some old Western Telegraph units and designed and built an apparatus that let us do the counting of the responses automatically and tell us if the responses were correct, incorrect, premature, random, etc. It turns out that we had built one of the early, although very crude, versions of a computer readout device.

Things were working quite well until I met Josephine. I'll bet that most of you never knew that I had a Josephine in my life. Josephine was one of the rhesus monkeys we used in our studies and she decided to show me that she was smarter than I was. Murray and I would set up the test apparatus and have the one who did not set it up try to solve the problem. One day, 1 gave up after 2 hours. Murray then put Josephine into the chamber and within 5 minutes, she bad solved the problem. One of the drugs I was testing was amphetamine. Unfortunately, Josephine died, although the dose was not particularly high. Well, Josephine's intelligence and her death made me decide that I wanted to find out why she had died. I was particularly intrigued by the fact that she had had a prefrontal lobectomy a year earlier. The only clue in the literature was a small series of studies carried out in the late 1940s and early 1950s reporting that amphetamine could cause convulsions in monkeys with cortical damage. Josephine showed an initial excitation followed by depression and death, but no seizures.

I decided that I would study the effects of several centrally acting drugs after cortical ablations in rats. I devised an apparatus for doing that and for making electrolytic lesions in the caudate nucleus. Cortical ablations were in 2 areas, the frontal cortex (including area 10) and the posterior cortex (including area 17). Luckily, I had taken a course in histology and was able to work with a technician to determine the extent of the brain damage, and I had taken pathology so I was able to determine glial infiltration, etc. To make a long story very short, bilateral ablations of the frontal or posterior cortex resulted in an increased responsiveness to amphetamine, and there was no change after caudate lesions. Further. it took several weeks for the increased sensitivity to become manifest after the cortical ablations. These results led to me paper of which 1 think I am most proud (Adler, M.W., Changes in sensitivity to amphetamine in rats with chronic brain lesions, J. Pharmacol. *134*:214:221, 1961.)



Submission of this paper also led to a protracted struggle to get the work published, because the editor of JPET initially refused to accept the term "denervation supersensitivity" as a possible explanation. To the best of my knowledge, this was the first paper to use that term for the brain. Until that time, Cannon and Rosenblueth's 1949 definition of "denervation supersensitivity" was applied only to the peripheral nervous system. The support of Dr. Gilman and my 2 mentors (Drs. Murray Jarvik and Seth Sharpless) finally led me to tell the editor that I would withdraw the paper rather than use some new term that he wanted me to devise. He relented.

With the end of my doctoral work in sight, I had to decide whether to go for a postdoctoral position or take a faculty position somewhere. I was the first to receive a Ph.D. in any discipline from the Albert Einstein College of Medicine. The year was 1960. Since we had one and eight-ninths children and some debt when I received the degree, I decided to go for a faculty position. Times were certainly different. With the statement from Dr. Gilman that "my students do not look for a job, jobs look for my students" ringing in my ears, I waited. In less than 2 weeks, the phones started ringing and the mail started coming in. I guess that I had at least a dozen offers in a month, ranging from faculty positions in physiology, biochemistry, and pharmacology in outstanding medical schools to a couple from industry. I was flattered and overwhelmed. I quickly decided to go into academia A friend (Dr. David Brodie from Merck) had Dr. Roger Sevy, the chair of Pharmacology at Temple University School of Medicine, contact me. I went to see him and immediately decided that was the place for me. The final offer that I accepted was for the huge salary of $7200/year. which still allowed me to begin to pay off my debts. Happily, that went up quite rapidly. The choice of Temple was undoubtedly one of the best choices I've ever made and I've never been sorry that I made that choice. Because I've now been at Temple for over 36 years, it's a good thing that I feel that way.

As soon as I arrived at Temple, I applied for an NIH grant and got one for 3 years. It had to do with brain lesions and seizures and we used flurothyl (hexaflurodiethyl ether) as our principal agent to induce seizures. We found that there was a marked increase in the duration of the seizures and a decease in the threshold after frontal and posterior cortical ablations. In other words, the denervation supersensitivity that we had seen with amphetamine extended to convulsant agents as well. We also carried out numerous studies with flurothyl itself in normal tats since it had so many advantages over pentylenetetrazol, the standard chemical convulsant, and it led to several studies in collaboration with Dr. Everett Maynert and his group at the Johns Hopkins School of Medicine. Repeated seizures produced a marked decrease in the seizure threshold. Interestingly enough, however, we found no changes in whole-brain levels of serotonin, norepinephrine, or dopamine. We also continued to study the effects of lesions in various areas of the brain of rats, especially the limbic system and lateral geniculate nucleus, and their relationship to seizures and sensory input, and we studied the relationship of the time course of brain damage to the ability of anticonvulsants to antagonize seizures.

I guess that the next phase of my research life began when I lost my grant in 1967. While trying to decide what to put in my next application, I went to a FASEB meeting. I was on a bus going somewhere at the meeting and I sat next to someone that I had met only casually. We started talking about research and funding and I told him my situation. He suggested that I start studying morphine. I told him that I wasn't interested in morphine but was interested in seizure mechanisms and lesions and he said, "Perfect ---morphine causes seizures." I was glad that I followed the advice of that scientist since I've been a druggie ever since. That person was Dr. Joseph Cochin.

It turned out that Joe was chairing the study section, although I didn't know it at the time and he didn't tell me. Subsequently, our group and the group at Boston University became friends. not only because of Joe but because of Dr. Conan Kornetsky whom I had met through Murray Jarvik. The story I just told you about Dr. Cochin was an example of his abiding interest in helping young scientists. When Joe died in 1986. Conan Kornetsky, with my strong support, proposed to CPDD that an award be given yearly, in Joe's honor, to a young scientist. Dr. Lisa Gold. winner of this year's Cochin Award is a perfect example of the type of bright young scientist that Joe always went out of his way to help.

For the next 3 or 4 years, I continued to study seizures, brain lesions, and morphine, but began more and more to look al the withdrawal syndrome and possible sites of morphine dependence in the brain. In 1971, I received a telephone call telling me that a new institute, the National Institute on Drug Abuse, was being formed. First, my grant from NIMH on brain lesions and morphine was switched to a new NIDA number (DA00049). Second, I was informed that NIDA was given a sizable amount of start-up funds and I was invited to submit a new grant application for some of those funds. Talk about being in the right place at the right time! I spoke to several of my colleagues at Temple and we decided to apply. Although this was prior to the actual discovery of the opioid receptors. their existence had been postulated by Drs. William Martin, Akira Takemori, Phillip Portoghese, and Avram Goldstein (all Eddy Award winners). Our group also believed that opioid receptors must be the explanation for the actions of opioid drugs and we titled the grant "Narcotic Receptors in Addicted and Non-Addicted States." Our work was to be based on graded dose-response data to determine drug-receptor affinity. My fellow Temple faculty members on that application were Drs. Ronald Tallarida (Professor of Pharmacology), Concetta Harakal (currently Professor Emeritus), Marcus Reidenberg (currently Professor of Pharmacology and Medicine at Cornell). Philip Gildenberg (currently a neurosurgeon in Texas), and Mr. Michael Loughnane (currently using his considerable skills in bioengineering in his own company). We've continued with that grant and it is now starting its 24th year. Long live NIDA! Of the original group, Ron Tallarida and I are still part of it. In 1974, Ellen Geller joined us and in 1976, Alan Cowan. Both are still active and important parts of our group.

After we submitted the grant application, we received a site visit, the norm at the time. One of my site visitors was Dr. William R. Martin. 1 didn't know Bill personally at the time, but his wise counsel at the site visit and in subsequent years did much to help me in this field. Bill was an extraordinary scientist and an extraordinary human being. He was a true gentleman in every sense of the word and I feel honored to join him as an Eddy Award winner.

Being awarded that grant changed my research completely. I got out of the brain lesion field and into one of opiates, antagonists, and effects on a variety of systems. In particular, we began to work on 4 systems or

endpoints: analgesia, the pupil, body temperature, and seizures. The only area in which I had any real background at that time was seizures and one of our first papers on this grant demonstrated that there was a lowered seizure threshold during the withdrawal syndrome.

Shortly after starting the grant, 1 went on a 6-month research leave to the Mario Negri Institute for Pharmacologic Research in Milan. Professor Silvio Garattini was and still is the Director of that prestigious institution. I waked with Professor Luigi Valzelli on behavioral effects of opioids and with Dr. Rosario Samanin on analgesia and the role of the raphe nuclei. Several papers resulted from that work. A study with raphe lesions in rats was particularly important to my thinking since we were able to determine that it was the location of the lesion rather than the drop in serotonin that was responsible for the decreased effect of morphine on antinociception. Thus, it was the "hard-wiring" that was the determinant of the change.

Our group at Temple continued to study morphine and naloxone on antinociception and that led to another paper of which I'm particularly proud (Tallarida, R.J., Harakal, C., Maslow, J., Geller, E.B. and Adler, M.W., The relationship between pharmacokinetics and pharmacodynamic action as applied to *in vivo* pA: application to the analgesic effect of morphine. J. Pharmacol. Exp. Ther. *206*:38-45, 1978.) In this paper, using the rat tail-compression method for assessing antinociception,we (mostly Ron Tallarida) developed a time-dependent method for determining pA_2 values *in vivo*. The pA_2 method that we developed has proven to be useful in determining pA_2 for a variety of agonist-antagonist combinations.

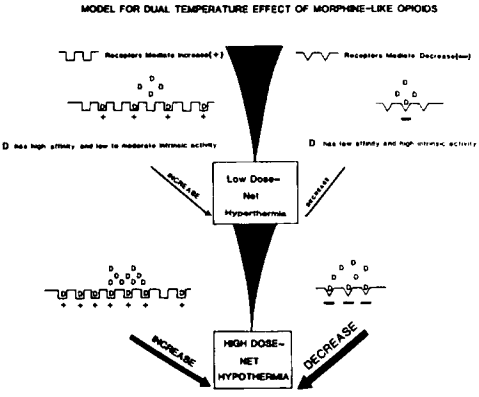
Our studies with morphine and seizures produced quite a surprise. All of the literature and texts at that tune said that morphine caused seizures. We found the opposite. After doing multiple replications of our findings and after arguing with the reviewers (later, Bill Martin told me that he was one of them), the paper showing that morphine had anticonvulsant effects in the rat and that the effect was independent of the effect on respiration was finally published in 1976. Much of this work was carried out by Chen-Ho (Geraline) Lin, who was a post-doc in my lab at the time. Our findings of the anticonvulsant properties of morphine led us to a large series of studies and finally culminated in a paper in Science in 1979 that classitied 20 opioids into 4 classes based on their effects on seizure thresholds, stereospecificity, dose-response relationships, naloxone sensitivity, and tolerance and cross-tolerance. We concluded in the paper that multiple opioid receptors were involved. Of course, by this time the opioid receptor had been shown to exist and the endogenous ligands for those receptors identified. Three of the five scientists that contributed the most to those findings - Drs. Avram Goldstein, Eric Simon, and Hans Kosterlitz - are former winners of the Eddy Award.

Dr. Frank Tortella who was a postdoctoral fellow in my laboratory at the time, extended our findings on seizures by showing that the route of administration of the opioid was a critical variable in whether the final effect was excitatory or inhibitory. He also demonstrated anticonvulsant actions of opioid peptides.

Along with our studies on analgesia and seizures, we began a series of investigations on the effects of opioids on the pupil. As all of you know, morphine causes miosis in humans and that is one of the cardinal signs of opioid overdosage. In most species, such as mice, rats, cats, horses, and primates, however, morphine causes mydriasis. In rats, we found that there was a dose-related mydriasis and a dose-related fluctuation in the size of the pupil. These effects were both antagonized by naloxone. Although the effects of opioids on the pupil are dramatic, we later concluded that the endogenous opioid system is not a prime component of pupillary stability or diameter. However, we were also able to demonstrate that, contrary to what everyone believed at the time, some tolerance does develop to the pupillary effects of morphine.

Along with our studies of opioids on analgesia, brain excitability, and pupillary size, we also studied the effects of opioids on body temperature and thermoregulation. One of our earliest studies in this field was part of a thesis project by one of my students, Frank Baldino. After identifying warm-sensitive and cold-sensitive neurons in the rat preoptic anterior hypothalamus, he was able to show that iontophoretically applied morphine excited warm-sensitive neurons and inhibited cold-sensitive cells. A collaborator in these studies was Dr. Alexander Beckman at the University of Pennsylvania.

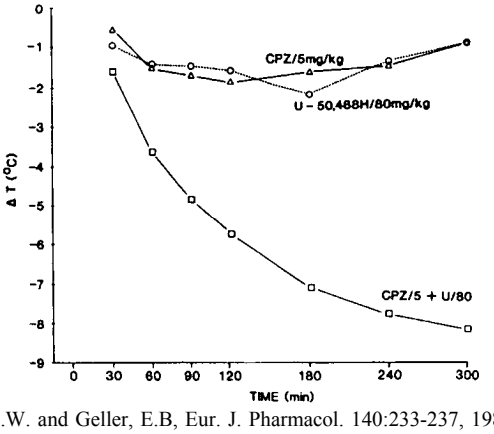
In studying the effects of a large group of opioids on body temperature, we found that they could be put into 5 groups and we postulated in 1980 that all of the effects could be explained by a 2-receptor model. In a JPET paper in 1983, we expanded on that idea and we presented a diagram of how the 2-receptor system might work, using morphine as our example.



(*From* Geller, E.B., Hawk, C., Keinath, S.H., Tallarida, R.J. and Adler, M.W., JPET, 225:391-398, 1983.)

In our conclusions to that paper, we stated that "until highly selective and, perhaps. truly specific opiate receptor agonists and antagonists are available, it may be useful to think of thermoregulatory actions of opioids in rats after s.c administration as being mediated by two receptors," Time has proven us correct. We now know that hyperthermic responses in the rat (and most likely most or all species) are mediated via the μ opioid receptor and hypothermic responses via the κ receptors. Furthermore, the hyperthermic effects are mediated almost solely in the brain while the hypothermic responses are a combination of central and peripheral effects. Interestingly, the δ receptor does not seem to be involved in temperature regulation at normal ambient temperatures. In the past two years, all of our ideas with the μ and κ receptors and their role in thermoregulation have been confirmed with the use of antisense oligodeoxynucleotides. Similarly, we have used antisense oligos to confirm much of our analgesia work.

In the course of our studies on thermoregulation, we decided to see what would happen if we combined a κ opioid agonist with a neuroleptic such as CPZ which causes a moderate degree of hypothermia. To say that we were surprised by the findings would be an understatement.



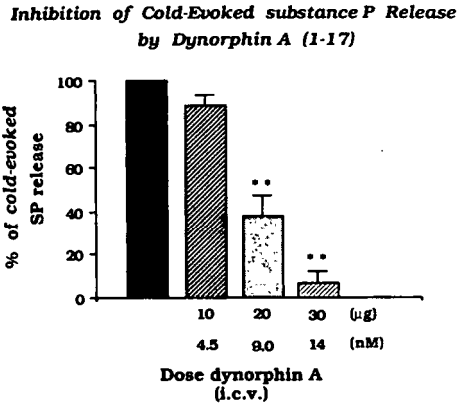
(*From* Adler, M.W. and Geller, E.B, Eur. J. Pharmacol. 140:233-237, 1987.)

That graph was published in 1987 and Ellen Geller and I were granted a patent based on these results. Unfortunately, there is still no clinically useful κ agonist on the market. When there is, a combination such as this could prove extremely useful in such diverse applications as cardiac surgery, treatment of the near-drowning syndrome, protection of the brain and spinal cord after stroke, and as an adjunct in cancer chemotherapy.

That the endogenous opioid system is the key system in thermoregulation is of great importance since thermoregulation allows not only for survival but is necessary for the functioning of virtually all enzymatic processes in the body. Although we knew the importance of the opioid system, we didn't how how it worked. Two postdoctoral fellows in my laboratory, Drs. Thomas Lynch and Cynthia Handler, along with several others in the group, supplied the key. We were able to build our own whole-body, gradient-layer calorimeters to measure oxygen consumption, heat exchange, and body temperature in freely moving rats. One of our first papers using the calorimeters was published in 1992.

ln that and a subsequent group of papers, we were able to demonstrate that the μ and κ opioid systems produce their opposite effects by means of oxygen consumption and heat-loss/heat-gain mechanisms and thus regulate body temperature. I'll get back to this in a little while.

A little less than ten years ago, we slowly began to move into two entirely new fields. The first was the interaction of various neuropeptides with the opioid system in terms of seizures, analgesia. and thermoreguladon. I had begun to question the idea that all of the effects of the opioids could be explained on the basis of the site of action of the drugs, the neuronal connections involved, and the neurotransmitter systems. It seemed to me that it was just too simple an explanation for such a wonderfully tuned system as the brain with all its checks and balances. redundant pathways, and feedback loops. I started to think about what I had been taught many years ago when I took courses in anatomy, neuroanatomy, and physiology. We were taught that in some systems there were two levels of control, one for the large effects and one to tine tune those effects. Why shouldn't there also be several levels of control for the chemical transmission of information and the activation of neurons? When the neuropeptides came on the scene, there was the additional level of control that I felt was needed. Our first report was presented in 1988 at a FASEB meeting and was followed by a full publication in 1990. One of my graduate students, Paul Tiseo, measured the release of substance P (SP) and somatostatin in the spinal cord of rats after noxious cold or heat. We had perfected the use of the cold-water tail-flick method in rats in 1985 to determine antinociceptive actions of κ agonists. Heat caused an increase in somatostatin, while cold produced an increase in SP. Because our group had previously shown that cold-induced pain was blocked by the κ agonists dynorphin A_{1-17} and U50,488H, then release of SP should be blocked when the agonist was administered to a rat and the rat was exposed to cold-induced nociception. And it was!



(*From* Tiseo, P.J., Adler, M.W. and Liu-Chen, L.-Y.J. Pharmacol. Exp. Ther. 252:539-545, 1990.)

This dose-related effect of dynorphin could be blocked by naloxone and the same picture could be seen with U50,488H. When Dr. Li Xin joined our group as a postdoctoral fellow in 1992, he introduced the technique of *in vivo* microdialysis in freely moving rats to our group. Using that technique, we were able to replicate in the PAG what we had found in the spinal cord. Actually, 1992 was a very good year, since I received a MERIT Award from NIDA that year. That has given me the freedom to explore new avenues and I think we've been quite successful.

We have since gone on to study several neuropeptides, including SP, CCK, neurotensin, TRH, and somatostatin in terms of opioid-induced analgesia, thermoregulation, and anticonvulsant activity. We believe that the actions of the opioids on the nervous system are the result of the interaction of the endogenous opioid peptide system of ligands and receptors with various neuropeptides and neurotransmitters. Our hypothesis is as follows:

> "When a perturbation occurs in the thermoregulatory (*i.e., POAH*) or the nociceptive (*i.e., PAG*) systems of the brain, a cascade of chemical events takes place that involves a number of neuropeptides and cytokines acting via the endogenous opioid system to produce an action. That action subsequently involves systems receiving afferents from the PAG and the POAH and the final effects are then executed through the more traditional neurotransmitter systems. The specific neuropeptides or cytokines involved are dependent on the particular effect being produced and the particular brain nuclei involved."

I believe that the specific cascade differs for different events and different areas of the brain. Indeed, we have begun to accumulate data to support that hypothesis and I would like to show you two cartoons based on data we've found in our laboratory.

The second of the two fields that we began to move into about ten years ago was that of drugs of abuse and the immune system. Awareness of the AIDS epidemic was rising and it was rapidly noted that a large proportion of the reported cases were associated with two types of risk behaviors: homosexual contacts and drug abuse. For several decades, most texts in pharmacology and medicine contained statements to the effect that drug users had a much higher incidence of several diseases. This was attributed to the dual causes of living in unsanitary conditions and poor nutrition. The more I thought about this, the more I began to wonder if the drugs themselves might not have an effect on the immune system. I began a study of the effects of cocaine on the immune system of male and female mice with Dr. Francis Havas of our Department of Microbiology and Immunology. In 1987, we published our findings that neither low nor high doses of cocaine altered antibody production, resistance to infection with *Streptococcus pneumoniae,* or resistance to tumors in BALB/c mice

At about this time, NIDA invited a few of us to get together to discuss the possibility of studying drugs and the immune system. I don't remember all who were there, but they included Drs. Herman Friedman from the University of South Florida, Arthur Falek and Bob Donahoe from Emory University, and Joseph Wybran. Joe was a physician from Belgium who had shown and published a remarkable paper (Wybran, J., Appelboom, T., Famaey, J.-P. and Govaerts, A., Suggestive evidence for receptors for morphine and methionine-enkephalin on normaI human blood T lymphocytes, J. Immunol. *123*:1068-1070, 1979.) In it, he concludes that "these observations suggest that normal human blood T lymphocytes bear surface receptor-like structures for morphine. Such findings may provide a link between the central nervous system and the immune system." I'm sorry to say that just a few short years later, this brilliant scientist and humanitarian was assassinated in the parking lot behind his hospital. An award honoring his memory is given yearly by the Brain/Immune group that meets as a satellite meeting to the CPDD.

NIDA's interest in the field stemmed from the association between drugs of abuse and AIDS. Congress became interested in supporting research in this area and NIDA agreed to be the lead institute. Dr. Marvin Snyder of NIDA, a former CPDD Morrison Award winner, was instrumental in this effort. The progress that has been made by NIDA grantees in understanding the interrelationships between drugs of abuse and immunoregulation in just a few years is nothing short of phenomenal.

My studies with Dr. Havas made me realize that I knew very little about immunology. The little that I did know came from the course in Microbiology that I had taken when I was a graduate student, and knowledge about immunology at that time was extremely rudimentary. I approached Dr. Toby Eisenstein, a member of the Department of Microbiology/lmmunology at Temple, who is a microbiologist and immunologist and expert in the field of host/parasite resistance and began to proselytize her about studying opioids and the immune system. My brainwashing worked. The first fruits of our collaboration were presented at a meeting of the New York Academy of Sciences in 1990. That study with the *in vivo* administration of morphine showed that the secondary immune response to tetanus toxoid was markedly suppressed. Ellen Geller and I decided to sit in on a graduate course in immunology at Temple and, although we certainly did not become immunologists, at least we learned some of the terminology.

At about the same time that we were beginning to find some *in vivo* effects of morphine. Dr. Eisenstein and I felt that we should begin to look at the mechanisms involved while continuing to explore what happens in the whole animal and in ex vivo measurements. We enticed two mote scientists from Temple to join our small group, Dr. Thomas Rogers, a molecular immunologist specializing in studies with T cells and Dr. Lee-Yuan Liu-Chen, a molecular and biochemical pharmacologist. Based on our pilot results, the four of us submitted a grant application to NIDA on October 1, 1989. Following a site visit, the grant was approved and funded. The hypothesis was simple:

> "Opioids alter selective components of the immune system, resulting in the compromising of immune competence, and the various types and subtypes of opioid receptors play a differential role in these effects."

Next came some fascinating results that we published in 1991 in PNAS under the sponsorship of Dr. Hans Kosterlitz. Dr. Dennis Taub, a graduate student at the time who is currently doing research at the National Institute on Aging, played a lead role in those studies. Using selective opioid agonists and antagonists *in vitro,* we reported that μ and κ opioid receptors are involved in regulation of lymphoid cell production of antibodies. The effects were blocked by the selective antagonists.

Our work in this field has expanded dramatically. Among our findings, we reported that the strain of mouse used can markedly affect the response of the immune system to opioids. We also found that morphine-induced macrophage suppression can be restored by the cytokiies IL-1, IL-6, and IFN-γ, but not some other cytokines, and that opioids inhibit cytokine production by macrophages. The primary effects of opioid immunosuppression seem to be on the macrophage and the T cell. We have also recently reported on two cDNA sequences in the R1.1 thymoma cell line. Two kappa-opioid sequences have been identified, one that is like the one in the nervous system and one that is a truncated form. Whether that represents an active site is not known at this time, but Drs. Rogers and Liu-Chen are working on it. Finally, a paper that has just appeared in the J. of Infectious Diseases demonstrates that morphine can produce sepsis in mice. The mechanisms and the full consequences of that finding will be explored in depth by Dr. Eisenstein.

Well, although I have a full plate of research and I feel quite satiated and satisfied, I've always felt that one should leave room for dessert. When that dessert is something that you hadn't anticipated would be so wonderful. the enjoyment is all the greater. I think that I've found the dessert. My two lines of research, opioids and endogenous neuropeptide systems, and opioids and immunocompetence are blending into an exciting new field--the interactions of cytokines and neuropeptides.

We have found and reported that the fever praduced in rats by IL-1ß and TNF-α can be blocked by CTAP. the selective μ receptor antagonist. Furthermore, the fever can be explained by the release of ß-endorphin. Thus, the role of the endogenous opioid system in thermoregulation now seems to encompass cytokine-induced fever. I showed you some of these ideas in the cartoon about the thermoregulatory system. Just as when a peripheral peptide found in the brain was then called a neuropeptide, so too might we be witnessing a new era in brain research with the findings that glib are brain macrophages, that they produce cytokines in the brain, they interact with endogenous opioid systems, and that cytokine receptors may exist on neurons.

Well, I think that I've gone on far too long. Maybe I should have done what a friend recently did. She had prepared a 45-minute presentation but was informed at the last minute that she had only 20 minutes allocated. She said, "don't worry, since I'm from New York, I won't cut anything out. I'll just talk faster." I think I should have listened to her. But I would like to reiterate the message I started with: at many institutions, we are c training our students too narrowly and without a broad base, a situation which will impede many of them 10 or 20 years after they complete their training.

I want to thank Temple University for providing me with a home and for not bothering me too much, I also thank all my students and colleagues at Temple over the years and some of them are shown on the next slide.

TEMPLE COLLABORATORS

- Alan Cowan, Ph.D
- Jon K DeRiel, Ph.D
- Toby K Eisenstein, Ph D
- Ellen B. Geller, M.A.
- Philip Gildenberg, M.D., Ph.D
- Jeffrey I Greenstein, M.D
- Concetta Harakal, Ph D.
- H. Frances Havas, Ph.D.
- Earl E. Henderson, Ph.D.
- Augustin Legido, M.D
- Lee-Yuan Liu-Chen, Ph.D.
- Michael H Loughname, M.S.
- Oleszak, Emilia A., Ph.D
- Charles A. Papacostas, Ph.D.
- Marcus M. Reidenberg, M D.
- Thomas J. Rogers, Ph.D.
- Mikhail Rojavin, Ph.D.
- Benjamin F. Rusy, M D.
- Gerald H Sterling, Ph.D.
- Ronald J. Tallarida, Ph.D.
- Li Xin, Ph D

COLLABORATORS - ELSEWHERE

Alexander L. Beckman, Ph D.
Joseph Cochin, Ph.D.
Silvio Garattini, M.D.
Amos D. Korczyn, M D
Wjochecj Kostowski, Ph.D
Everett W. Maynert, Ph.D
Eugenia Monferini, Ph.D.
Frank Porreca, Ph.D.
Carl E Rosow, M.D., Ph.D.
Rosario Samanin, Ph.D.
Eric J Simon, Ph D.
Toni L. Stanton, Ph.D
Dennis D Taub, Ph.D.
Frank C. Tortella, Ph.D.
Luigi Valzelli, M.D.
Shu-Fen Zhao, M.D.

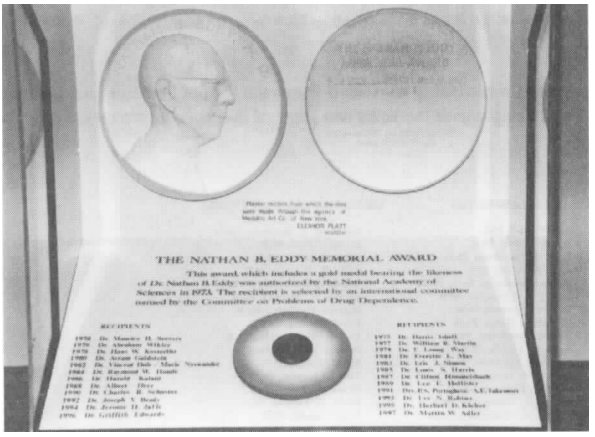
PREDOCTORAL AND POSTDOCTORAL TRAINEES

Jill U. Adams, Ph.D
Candido Alicea, Ph.D.
Frank Baldino, Ph.D.
Stanley M. Belkowski, Ph D.
Jeffrey Bell, Ph D
Elizabeth F. Berman, Ph.D.
Jeanine Bussiere, Ph D
Chiara Cerletti, Ph D.
Xiao-Hong Chen, M.D
Suchandra Ghosh, Ph.D.
Paul M Gochin, Ph.D.
Liming Guan, Ph D
Cynthia Handler, Ph.D.
Mark S. Kramer, M.D., Ph.D
Chen-ho Lin, Ph D
Thomas J Lynch, Ph D.
Rodney B. Murray, Ph.D.
Frank Porreca, Ph.D.
Natalie S Pressman, M.D.
Dennis D. Taub, Ph.D.
Paul J. Tisea, Ph.D.
Frank C. Tortella, Ph.D.
Alexander Zwil, M.D

I thank the many people at NIDA who have provided the money these many years with which to feed my research habit. I particularly want to thank Dr. Alan Leshner, the Director of NIDA, for all of his efforts in persuading Congress and the public that those of us doing drug abuse research are doing (as Dr. Joseph Brady says) "good deeds" and are helping to illuminate the mechanisms involved in drug abuse.

Last, but certainly not least, I want to thank my family, especially my wife Toby, for all the backing and support they have given me over all these years. I'm pleased that my daughter Eve, my son Charles and his wife Laura and their children, Ilyssa and Jennifer, are also in the audience now.

It feels wonderful to have my name added to the illustrious scientists who have received the Nathan B. Eddy Memorial Award. I am truly honored and I accept the award with a great sense of humility.



Thank you all!

SYMPOSIUM IV

OPIOIDS AND NEUROPEPTIDES IN IMMUNE FUNCTION AND HOST DEFENSE AGAINST RETROVIRUSES

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Opioids and neuropeptides are well established to be immunomodulalory. In the case of the alkaloid opioids, the experimental evidence shows immunosuppression. Naturally occurring opioid peptides and other neuropeptides can be immunosuppressive or immunopotentiating. Important questions which remain to be addrersed are the mechanisms of the immunosuppression and the significance of the decrease in host immune responses for resistance to infection. Other questions of importance are, can we find opioids that can be used for analgesia that do not depress immune function, and can immunopotentiating opioids be used therapeutically to enhance immune responses and resistance to infection? This symposium addresses these questions, with particular attention to immunomodulation of HIV expression by opioids and other neuropeptides.

OPIOID-INDUCED IMMUNOMODULATION: EVIDENCE FOR THE ROLE OF NITRIC OXIDE

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In recent years, the role of nitric oxide in Immune processes has become apparent as demonstrated by studies showing that it is involved in the control of bacterial and parasitic growth, the development of autoimmune disease, and the regulation of cells within the immune system. Despite extensive knowledge of the biochemistry of nitric oxide, little is known about the *in vivo* regulation of inducible nitric oxide synthase (iNOS), the enzyme responsible for nitric oxide production by cells of the immune system. The present study tested the hypothesis that Lipopolysaccharide (LPS) induced expression of iNOS by splenocytes is modulated by opioid receptors in the central nervous system. To determine parameters of iNOS expression, rats received injections of LPS, and using RT-PCR and western blotting, it was found that the maximal iNOS mRNA and protein expression occurs at 100 µg/kg, with peak expression at 8 hours.

To evaluate the effect of opioids on iNOS expression, N-methylmorphine, the quaternary form of morphine, was administered ICV to rats, at doses of 0, .04, .4. or 40 µg in combination with a systemic Injection of LPS (100 µg/kg). The results show that iNOS mRNA and protein expression are increased in a dose-dependent manner by the central administration of N-methylmorphine. Serum nitrite levels were also significantly increased, providing further evidence that activation of central opioid receptors enhances iNOS expression. In contrast, the ICV administration of the opioid antagonist N-methylnaltrexone to rats at doses of 0, .01, .1, 1.0, or 10 µg produced a dose-dependent reduction in iNOS mRNA and protein expression. These results suggest that endogenous opioids may play a role in the regulation of iNOS expression. This research extends our knowledge of the *in vivo* regulation of nitric oxide production, and may have important implications for the treatment of septic shock.

OPIOIDS WITH DIFFERENTIAL IMMUNOMODULATORY EFFECTS *IN VIVO* AND *IN VITRO*

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Central nervous system mediated, morphine-induced immunosuppression has teen hypothesized to be due to activation of the hypothalamic-pituitary-adrenal (HPA) axis or the sympathetic nervous system or both (Weber and Pert; Science 245:188-190, 1989). Morphine microinjection into the PAG resulted in suppression of splenic NK cell activity, splenic and thymic T-lymphocyte proliferation, and inhibition of splenic macropbage phagocytosis and nitric oxide and TNF production. Peritoneal macrophage phagocytosis was also inbibited. Plasma ACTH and corticosterone concentrations was determined before and after injection of morphine in jugular catheterized Fischer 344N male rats. A temporal increase in ACTH was observed which peaked at 40 minutes (9-fold) following PAG morphine injection and was accompanied by a subsequent 2-fold sustained increase in corticosterone. The glucocorticoid antagonist, RU486, was ineffective in blocking either the suppression of NK cell activity or T cell proliferation. Consequently, we examined the role of the sympathetic nervous system on the observed immunosuppression. Catecholamine levels were measured kinetically and continuously in splenic microdialysates from freely moving Fischer 344N rats, both before and after bilateral administration of morphine or saline into the PAG. Our results indicate that morphine induces a substantial increase in norepinephrine (NE), serotonin (5-HT), and metabolite levels. The elevated levels of NE, and 5-HT reach a maximum between 15 to 30 minutes after injection of morphine, and then gradually decline. Both NE and 5-HT levels return to a basal level approximately 150 minutes after morphine injection. We have also compared the immunosuppressive effects of morphine with buprenorphine, a potent analgesic and partial agonist at the opioid receptor, that does not induce immunosuppression. Preliminary data indicates that buprenorphine fails to alter the levels of bioamines and does not decrease lymphocyte proliferation or NK cell activity. In conclusion morphine injection into the PAG leads to an increase in catecholamine levels within the spleen, and is correlated with changes in splenic lymphocyte function. ACTH and corticosterone increases following PAG morphine are correlated with changes in immune function, but are apparently not associated. These findings, along with the failure of buprenorphine to alter splenic catecholamines, suggest that the sympathetic nervous system, but not the HPA axis, plays a major role in immunosuppression observed following PAG morphine.

We have also identified a potent non-peptidic delta opioid receptor-selective analgesic which does not suppress immune function. PAG or ICV administration of SNC80 did not suppress splenic NK activity. No functional changes were seen with thymic or splenic T-cell proliferation in response to interleukin-2 (IL-2), R73 (antibody to CD3/TCR). or IL-2 + R73. Cell surface staining followed by flow cytometric analysis showed no change in the following cell populations: CD3+. CD4+, CD8+, or NKP.R1+. Similarly, no difference was found in cell surface antigen density from any tissue compartment studied. These results suggest that ligands with this opioid receptor subtype selectivity could be useful in the treatment of pain in certain clinical situations where suppression of immune function is undesirable. Examples include burn victims, AIDS patients, and cancer patients being treated for intractable pain and opting for adoptive immunotherapy.

Although the central nervous system mediated indirect effect of opioids has been shown to suppress immune function the direct effect of certain novel opioid derivatives on cells of the immune system, has been shown to induce immunopotentiation *in vivo* (Sanchez S.R., Rice K.C., *et al.,* NIDA Res Monogr, 1996). Studies with naltrindole (NTI), selective for the δ_2 opioid receptor, and benzylidenenaltrexone (BNTX, selective for theδ_1 opioid receptor, have been shown to act as antagonists in cIassical neuronal opioid receptor systems. We have identified a class of novel NTI-derived non-peptidic opioid receptor ligands with direct immunopotentiating effects on mitogen stimulated lymphocytes. *In vitro,* the NTI analogues SoRI 9331 and 9340 consistently produced a dose dependent (10^{-7} to 10^{-6} M) potentiation of lymphocyte proliferation following mitogen stimulation. BNTX related compounds, SoRI 9334 and 9336, produced no significant effect on T-cell proliferation. Future studies will address structure/activity relationships of these and other compounds and investigate the cellular mechanisms of

immunopotentiation. This series of novel non-peptidic opioid ligands could serve as immunotherapeutic agents with potential use in the treatment of infectious diseases including AIDS and cancer, and as adjuvants for poorly immunogenic vaccines.

In conclusion, our studies provide examples of opioids which suppress, enhance or have no effect on the immune system, depending on the anatomical site of administration (central vs peripheral), receptor selectivity of the opioid agonist (mu, delta, kappa). Further understanding of the neuroanatomical site of action, peripheral pathways connecting the brain and the immune system, and structure and function of opioid receptors on immune cells should eventually lead to realizing the immunotherapeutic potential of opioids.

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EFFECT OF MORPHINE ON REACTIVITY TO HIV PEPTIDES

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Previous work by our laboralory has shown that various HIV structural and regulatory peptides manifest immunomodulatory activities. We demonstrated that a recombinant, HIV fusion protein, env-gag, consisting of domains from gp41 and p24 could induce: 1) proliferation of $CD3^+$ and $CD3^-$ lymphocytes from normal donors, 2) *de novo* polyclonal B cell activation, and 3) suppression of pokeweed stimulated immunoglobulin synthesis. Further, env-gag selectively suppressed natural killer (NK) cell activities of mononuclear cells from HIV infected patients in comparison to normal controls. Since we earlier reported that NK cell activities were suppressed in a cohort of intravenous drug users, we undertook a series of experiments to determine if various recreational drugs may serve as cofactors in susceptibility and progression of HIV infections. Initial studies with ethanol demonstrated that it could selectively suppress env-gag induced proliferation and NK activities of lymphocytes from HIV infected patients. Suppression of NK activities could be reversed *in vitro* with interferon alpha ± interleukin 2, suggesting that these cytokines could be useful in the treatment of AIDS patients. Other experiments within our laboratory demonstrated that env-gag, together with an excitatory amino acid agonist, could induce encephalopathy in a rodent model. Now we report that morphine can also potentate some of these biological activities of HIV peptides. We have shown that morphine can suppress env-gag induced lymphocyte proliferation. Also, we observed that morphine can induce spontaneous apoptosis of lymphocytes from healthy donors. Thus we conclude that some of the immunomodulatory effects of morphine may be due to induction of apoptosis of immunocompetent cells. It has recently been recognized that receptors for certain chemoattractive cytokines or chemokines may also serve as entry co-receptors for HIV. Further, the natural ligands of these receptors, the chemokines, can compete with HIV for binding, and thus have a protective effect on the host. Preliminary data from our laboratory demonstrate that morphine can enhance expression of chemokine receptors and suppress production of the chemokines. Both of these activities are associated with increased susceptibility to infection with HIV and progression of disease. In summary, our data support our hypothesis that morphine is a co-factor in susceptibility to AIDS.

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SUBSTANCE P UPREGULATES HIV EXPRESSION IN HUMAN MACROPHAGES

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Substance P (SP) is an undecapeptide which regular a number of important immunologic and inflammatory functions, and is a neurotransmitter in the conduction of nociceptive stimuli. Substance P stimulates human peripheral blood monocytes to produce inflammamry cytokines, including IL-l, IL-6, IL-10, IL-12, and TNF-α. TNF-α upregulates HIV expression in T cells and monocytes *in vitro.* We have recently demonstrated that substance Penhances TNF and IL-10 production by monocyte macrophages isolated from both adult human peripheral blood and placental cord blood. We have further demonstrated that substance P modulates HIV replication in human peripheral blood monocytederived macrophages. Recently, using nested RT-PCR analysis, we have identified the presence of mRNA for the neurokinin l receptor (the receptor for substance P), and for the beta and gamma transcripts of the substance P gene in human peripheral blood isolated monocytes and macrophages. These transcripts were confirmed by DNA sequencing. The addition of HIV BAL to monocyte/macrophages upregulates the expression of SP protein and mRNA in monocytederived macrophages. Thus, SP may be an important determinant in HIV infection. and may affect HIV-AIDS disease. in the CNS.

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SYNERGISM OF MET-ENKEPHALIN AND AZT IN RETARDING A MURINE RETROVIRUS INFECTION

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Combination of antiviral chemotherapy using azidothymidine (AZT) and methionine enkephalin (Met-ENK), as an immunostimulatory compound, has previously been shown by us to decrease morbidity and mortality due to murine retrovirus infection, Friend leukemia virus (FLV), in BALB/c mice. *In vitro* Met-ENK (50-100 μg/ml) and AZT (1 μg/ml) were used in a combined protocol for treatment of established FLV infection. In a model using FLV, AZT was able to reduce viral titers in susceptible *Mus dunni* cells while Met-ENK was not, thus, confirming that the neuropeptide does not have direct anti-viral activity. However, Met-ENK treated spleen cells added to AZT reduced FLV replication in culture. These studies further demonstrated that Met-ENK effects were mediated via opioid receptors on lymphocytes, as activity could be inhibited by the opioid receptor antagonist naloxone. Additionally, results indicate thast, at least in part, Met-ENK effects were due to the induction of interferon gamma (IFN-γ), which inhibited FLV replication. Furthermore, the antiviral activity induced by Met-ENK was neutralized by anti-IFNγ antibody, but not irrelevant antiserum. Thus, cytokines, most specifically IFN-γ are important in the ability to inhibit retrovirus infection *in vitro.* The dam suggest that this combination may provide benefit in human retrovirus infections.

ACKNOWLEDGMENTS: Supported by PHS grants DA 10161 and DA 07245.

SYMPOSIUM V

THE EFFECTS OF PRENATAL COCAINE EXPOSURE ON CNS DEVELOPMENT

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The dramatic increase in the availability of cocaine in the United States over the last two decades has been associated with a large number of women who have used cocaine while they were pregnant. Early anecdotal reports indicated that infants exposed to cocaine while *in utero* exhibited manifestations of abnormal central nervous system (CNS) development. Predictions followed of an epidemic of these 'crack babies' who would overwhelm existing social support systems. This symposium reviewed both animal and human studies that, in response to this use of cocaine by women during their reproductive years, have examined the effects of cocaine on the developing mammalian CNS.

Is cocaine a teratogen? (RH Finnell, Texas A&M University, College Station TX) A teratogen is any type of environmental agent that compromises the normal development of the embryo or fetus. In general, birth defects are rare events, and only 2-3% of these defects are thought to result from exposure to a teratogen. However. these outcomes should be preventable, emphasizing the importance of identifying teratogens. Six principles have been established in the identification of a teratogen (Wilson, 1977). 1. The susceptibility of the organism depends on the genotype of the conceptus and the manner of interactions with the environment. This principle can be supported by both variations in susceptibility and phenotype. Cocaine can result in multiple birth defects in animal models (e.g. Finnell *et al.,* 1990; Webster and Brown-Woodman, 1990), including CNS, cardiovascular, and genitourinary malformations. 2. The susceptibility to a teratogen changes with the developmental stage of exposure. The most sensitive time of susceptibility for major structural defects is thought to be during the period of organogenesis. immediately after implantation and in the first third of a pregnancy. Studies examining different periods of exposure to cocaine demonstrate conflicting results (Fantel and MacPhail, 1982), but there is sufficient evidence to support this principle of teratology. 3. Agents must act in specific ways to initiate abnormal development. Postulated mechanisms for cocaine's effects on the embryo/fetus include uterine artery vasoconstriction, hypoxia, and the generation of reactive oxygen species. Studies of embryo explants support these mechanisms (Fantel *et al.,* 1992). 4. The final manifestations of abnormal development include death, malformation, growth retardation, or a functional disorder. Several studies have demonstrated that cocaine administered to a pregnant animal can lead to these outcomes. 5. Access to the adverse environmental agent and its influences depend on the nature of the compound. Cocaine does cross the mammalian placenta and fetal CNS cocaine levels can be higher than those in the maternal CNS. 6. Does a dose-response relationship exist between the teratogen and abnormal outcomes? Although not as well established, there does appear to be an increase in malformations with higher doses of cocaine (e.g. El-Bizri *et al.,* 1991). Prenatal cocaine exposure does not result in a characteristic postnatal syndrome, as has been established with ethanol and the fetal alcohol syndrome. The existing animal studies do strongly suggest, however, that cocaine is a teratogen.

The effects of cocaine in molecules that regulate CNS development. (SA Mackler, University of Pennsylvania and Philadelphia VAMC, Philadelphia PA) Studies of maternal cocaine treatment and CNS development must address several experimental factors. Comparisons among many published studies are made difficult by these complex issues, which include the amount and timing of cocaine administration to the pregnant animal, where and what types of changes should be examined for in the CNS. and whether or not effects in the postnatal period result from abnormal fostering by the drug-treated mother. Exposure of the embryo or fetus to cocaine may affect molecules that both: 1) contribute to the phenotype of a differentiated neuron; and 2) are necessary for normal development throughout the CNS (these two categories are not mutually exclusive). Examples of specific molecules found in differentiated neurons include those present in dopammergic and related CNS pathways, where the effects of cocaine are critical in the mature adult. In the forebrain and midbrain of the neonatal rat, levels of mRNAs (deBartolomeis *et al.,* 1994) and biogenic amines (El-Bizri *et al.,* 1991) along with monoaminergic receptor sensitivities (Henderson *et al.,* 1991) and binding to dopamine uptake sites (Stadlin *et al.,* 1994) were largely unaffected by

maternal cocaine treatment. Some proteins in these dopaminergic pathways exhibited transient alterations in function which did not persist into adult ages.

Molecules that regulate CNS development have also been examined. Examination of the midgestation mouse, after maternal cocaine treatment during initial neural tube development, revealed few changes in mRNA levels encoding multiple proteins involved in CNS and vascular development (Mackler *et al.,* 1996). These data suggest that, even if cocaine leads to uterine vasoconstriction and hypoxia, these are specific and limited changes in gene expression. mRNAs for subunits of the $GABA_A$ receptor were increased at gestational day 10.5 (Mackler *et al.,* 1996), and GABA can exert a trophic influence early in CNS development. A detailed study of sonic hedgehog (shh) mRNA expression has recently been conducted (Mackler and Koebbe, unpublished data). shh plays a critical role in the induction of neuronal phenotypes along the ventral CNS, including dopaminergic cells in the midbrain. Cocaine treatment for 3 days preceding the appearance of shh mRNA did not alter its spatial and temporal pattern of expression. In addition, the appearance of shh in the eye and limb buds also did not change after maternal cocaine. treatment. Fetuses and neonates without obvious structural defects after maternal cocaine treatment do not appear, in the majority of experiments, to exhibit permanent biochemical and physiological alterations.

A comparison of the developmental effects of cocaine and methaphetamine. (CV Vorhees, University of Cincinnati, Cincinnati OH) Animal studies describing offspring behavior after exposure to cocaine have been reviewed (Spear 1995, Vorhees 1996); the present discussion is restricted to the effects of the stimulants cocaine. m&amphetamine (MA), or 3.4-methylenedioxymethamphetamine (MDMA) on spatial learning. Critical factors in these experiments include the dose, dose rate, and stage of development at exposure, along with controls for litter effects, drug-induced diet reductions, and maternal rearing. In addition, for assessments of spatial learning using Morris mazes. the ratio of the search area to target size is important: tbe higher this ratio, the greater the spatial demands and more valid the results. In one study, an impairment was observed on the first trial of learning in cocaine-exposed offspring (s.c. 10 mg/kg on E3-17; tune of conception=E0), but no specifications for the task were provided (Smith *et al.,* 1989). Another study found no impairment in cocaine-exposed offspring (p.o. 60 mg/kg on E13-20; Riley and Foss, 1991). but the spatial configuration ratio was 67:1, near the lower limit for assessing spatial learning. Reduced learning also occurred in the first 8 trials of acquisition (s.c. cocaine 40 mg/kg on E7-21) using surrogate dams (Heyser *et al.,* 1995). Analyses of swim path types in this study revealed no other differences, suggesting that the cocaine deficit was not a true spatial deficit. Others have investigated the effects of prenatal cocaine on working memory. Radial arm maze deficits occurred in cocaine offspring (s.c. 30 mg/kg on E7-19; Levin and Seidler, 1993). Abnormal Morris maze working memory without radial arm memory deficits has also been seen (s.c. cocaine 15 mg/kg b.i.d. on E7-19; spatial configuration ratio 256:1; Cutler *et al.,* 19%). These data on prenatal exposure suggest that cocaine may have some effect on working memory, but either a modest or no effect on spatial learning/refetence memory. In contrast reuptake inhibitor-releaser stimulants (MA and MDMA) have pronounced effects on spatial learning/reference memory. For prenatal MA (s.c. 15 or 20 mg/kg b.i.d. on E7-12 or 13-18; Acuff-Smith *et al.,* 1995). reference memory was affected without acquisition deficits. By contrast, neonatal exposure to MA (b.i.d. doses of s.c. 15-30 mg/kg MA) resulted in large spatial learning deficits in the Morris maze (spatial ratio 317:1) after postnatal days (P)11-20 treatment, but not after P1-10 treatment (Vorhees *et al.,* 1994; 1997). This effect has been found in three different strains of rats and ranges from a 20-50% deficit in performance depending on the dose and strain. Similar spatial acquisition deficits occurred in rats after P11-20 treatment with MDMA (b.i.d. 20 mg/kg), along with deficits in sequential learning in a multiple-T swimming maze (b.i.d. 5,10 and 20 mg/kg). Overall, the data suggest that there are striking differences between cocaine and other stimulants in their effects on spatial learning and memory. These effects are dependent on the stage of brain development at which exposure occurs.

Does prenatal cocaine use adversely affect human infants? (H. Hurt, Albert Einstein Medical Center, Philadelphia PA). The long-term outcomes of children exposed to cocaine while *in utero* are not clear. These outcomes are extremely difficult to measure, and many confounding variables that are present in groups of women who used cocaine. during their pregnancies have complicated most studies. These variables include poor prenatal care, the use of other drugs, the presence of sexually-transmitted diseases and other ilhtesses, and chaotic lifestyles. The children of cocaine-using mothers may be raised in unenriching home environments and have minimal interactions with their caregivers. Many previous studies, which have been limited by these multiple confounders, also have had inherent

problems in their design, including the absence of proper control groups, small numbers of subjects, examiners that have not been blinded 10 the childrens' exposure status. the use of nonstandard instruments, and inadequate adjustments for confounding variables. Cocaine does adversely affect human pregnancy, including fetal loss, abruptio placentae, preterm labor, preterm delivery, and meconium-stained amniotic fluid. What about immediate effects on these babies when they are born? Most investigators have concentrated on studies of central nervous system function. There are findings from many studies that demonstrate neurobehavioral abnormalities in the immediate postnatal period (e.g. Eisen *et al.,* 1991). It is in the long-term period, up to ages when these children will enter school. that results are now being described. Differences in recognition memory and information processing between cocaine-exposed and control infants at 13 months have been reported (Jacobson *et al.,* 19%), and infant motor performance is abnormal at four and seven months. These changes in infant motor performance are no longer detectable at 15 months of age (Fetters and Tronick, 19%). Deficits in cognitive function, using the Bayley Scales of Infant Development, the Stanford-Binet, and the McCarthy Scales of Childrens' Abilities in children 2 to 3 years of age, have not been identified (Griffith *et al.,* 1994). Less age-appropriate play and representational play have been reported in toddlers exposed to multiple drugs, but no differences in play were observed after comparing videotapes of 83 cocaine-exposed to 93 control children. In the latter study the examiners were blinded 10 the drug exposure status of each child. The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) was performed in an inner-city cohort of 71 cocaine-exposed and 78 control children. No differences in IQ were noted al the age of four years. This cohort was subdivided into three groups by reports of the frequency of maternal cocaine use: no exposure; light exposure (<3 times per week); and heavy exposure (>3 times per week). No differences in IQ scores were observed and the results from this study do not support a dose-response relationship between cocaine exposure during pregnancy and long-term cognitive function. All of these studied children lived in an inner-city environment in families with a low socioeconomic status (Hurt *et al.,* 1996). and these factors may have contributed to the low IQ scores observed in all three groups. Another study of older children after cocaine exposure while *in utero* (Richardson *et al.,* 1996) did find a decreased ability to sustain attention at six years of age when compared to a non-cocaine-exposed group. In summary, the data so far do not conclusively demonstrate a long-term detrimental effect that is solely attributable to cocaine exposure *in utero.* Concern for adverse outcomes on cognitive performance, based on animal studies and anecdotal reports, should remain high and careful observation of these children will need to occur during the early school years. It is critical to define if identifiable problems are present so that appropriate interventions can be designed. Children may be able to recover from subtle structural or chemical alterations that occur in response to cocaine exposure during development; however, the environment in which they are raised may not allow them to achieve age-appropriate levels of cognitive function.

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SYMPOSIUM VI

DRUGS OF ABUSE, IMPULSIVITY AND RISK-TAKING

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Summary

Impulsivity and drug abuse are closely related. Drug abuse is believed to result from impulsive tendencies, and it is sometimes also thought to cause impulsive behavior. Impulsive behavior may be defined as the tendency to act without thought to future consequences. Thus. for example, some young people may experiment with drugs without regard to the risk of future addiction and its attendant health risks. Further. it is believed that certain drugs. such as alcohol, acutely increase lhe likelihood of engaging in risky behaviors, such as driving, without regard to the consequences. Researchers have developed operational definitions and laboratory models of impulsive behavior which frame the concept of impulsivity in terms of control by immediate versus delayed consequences, and in terms of certain versus uncertain consequences. In this symposium, researchers will present their models of impulsive behavior, and discuss lhe relationship of impulsivity to drug abuse. In addition, the possible physiological and neurochemical mechanisms which underlie impulsive behavior with be discussed. Behavioral models of impulsive behavior, using both humans and non-humans as subjects, will enable researchers to systematically explore the behavioral and neural processes involved in impulsivity. Dr. Ainslie will present a quantitative model of impulsive decision making which provides a framework for systematic study of impulsive behavior. Drs. Schuster, Johanson and Greenwald will present results from experiments in which they have tested patients with antisocial personality disorder on a Iaboratory-based procedure designed to measure impulsivity. Dr. Pihl will present results regarding physiological and biochemical mechanisms which may underlie aggressive and impulsive behavior. Drs. Richards. Sieden and de Wit will present data on the effects of abused drugs on models of impulsive behavior and risk taking in humans and rats. As discussant Dr. Heyman will attempt to integrate lhe various approaches to impulsive behavior discussed in the symposium.

A Picoeconomic Approach to Addiction

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Substance abusers usually suffer from a failure to integrate their decisions over time, sometimes to the point of actual dissociation. Conventional utilitarian analyses of substance abuse cannot lake this integration problem into account because they assume that people discount the value of delayed goals in proportional, exponential curves. However, there have been several experiments showing that people's spontaneous valuations of one-lime events decline in a hyperbolic curve as a function of delay. This finding is consistent with a large hody of animal research. Hyperbolic discount curves suggest an innate tendency for people's preferences at one time to differ from those of later times. Integration among successive motivational states will then require strategic bargaining much like that among agents engaged in limited warfare. Substances of abuse seem to be both exacerbators of intertemporal conflict and tools in intertemporal bargaining.

MEASURES OF IMPULSIVITY TRAIT AND STATE CHARACTERISTICS

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Studies are presented which support three points. The first point is that "impulsivity", variously measured, is related to drug abuse and the form of comorbid psychopathology. An assessment of 300 drug dependent women revealed live clusters of which one, impulsivity, did not distinguish the drug abused but did differentially correlate with a diagnosis of ASPD. The second point is that impttlsivity is a concept with many possible and frequently used but not often non related measures. In a second study, ninety eight, young adult males completed an extensive battery of putative paper and pencil and behavioral tests of impulsivity. For the paper and pencil tests four factors were determined and none of them were strongly correlated with the behavioral measures. The final point is that specific frontal cortical and serotonergic functioning is linked to impulsivity. Here the results of studies are presented which show that a relative dysfunction in working memory predicts impulsive/aggressive behavior and that a tryptophan depletion manipulation increases behavioral impulsivity in individuals at risk for alcoholism and with histories of aggressive behavior.

EFFECTS OF ABUSED DRUGS ON A LABORATORY MODEL OF IMPULSIVITY AND RISK TAKING IN HUMANS AND NON-HUMANS

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These studies illustrate the use of a laboratory model of impulsive behavior in humans and laboratory animals. The model is based on the concept that impulsive individuals discount the value of future consequences (rewards and punishers) more than non-impulsive individuals. In the procedure. reinforcer magnitude is adjusted as a function of the subjects' choice responses. We present results of several studies in healthy young adults, psychiatric outpatients and rats. In all studies, discounting was well characterized by a hyperbolic discount function. In healthy young adults, discounting of reward value was moderately correlated with paper pencil tests of impulsivity, but alcohol had no effect on this behavior. In psychiatric outpatients, individuals with a history of impulsive symptoms discounted the value of delayed and uncertain rewards more than other patients without a history of impulsivity. In rats, amphetamine decreased discounting whereas haloperidol increased discounting. Scrotonin lesions affected probability discounting (made the rats more risk prone) without affecting delay discounting. Taken together, these results indicate that discounting by delay and probability represent a similar behavioral process in humans and rats, and that the procedure is a valid and sensitive measure of impulsivity. Parallel studies with humans and non-humans may provide a powerful approach to studying the behavioral and biological processes which underlie impulsive decision making.

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EFFECTS OF ANTISOCIAL PERSONALITY DISORDER (APD) ON RISK-TAKING BEHAVIOR

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Antisocial drug abusers engage in high levels of risk-taking, including adverse socioeconomic activities (e.g., criminality) and behavior (e.g., using dirty needles, unsafe sex) that increases the likelihood of HIV transmission. This study validates a new laboratory model of economic risk-taking (Quick Decision Task, Greenwald *et al.,* in preparation) in methadone-stabilized clients (50-80 mg/day) diagnosed with APD and non-APD matched Controls. On two consecutive days, testing occurs before and after methadone dosing. On discrete trials in a mock traffic tight situation, participants (11 APDs and 6 Controls to date; target n= 18/group) begin keyboard responding during the green light and, during the yellow light (3-7 s), decide whether to complete different fixed ratios (FR 15 - FR 50; response cost) or stop responding before the red light appears. Probability of risk-taking (trying to complete the FR, independent of outcome) to earn the reinforcer ($0.25 per trial) is assessed under varying punishment conditions (12.5%, 37.5% or 100% of money loss). i.e., money is subtracted for unsuccessful risk-taking depending on the condition. Initial results show significant linear increases in risk-taking with lower response cost and less certain punishment, and trends toward increased risk-taking for APDs (group effect), particularly with more certain Punishment (group x punishment interaction). At present, no systematic effects of time since methadone administration (possibly related to early withdrawal signs) on risk-taking have emerged. APDs also report levels of gambling behavior that are substantially greater than Controls. If these interim findings persist with the full sample, they suggest that APDs engage in greater overall economic risk-taking and are relatively less sensitive (i.e., their behavior is not suppressed) to possible monetary loss than their non-APD counterparts. The present methods represent a promising new approach to study determinants of and treatment interventions for pathological risk-taking.

ACKNOWLEDGMENT: Supported by NIDA grant DA 05569.

SYMPOSIUM VII

RECENT PROGRESS IN TRANSPORTER RESEARCH

R. Blakely, S. Jones, J. Justice, M. Kuhar, and N. Volkow

Introduction

This symposium reviews developments in neurotransmitter transporter research from molecular, cellular. system and human level. At the molecular level, Kuhar discusses development of DAT inhibitors leading to potential new medications for the treatment of cocaine abuse. Also at the molecular level, Justice describes studies on substrates which help to characterize the kinetics and mechanism of the catecholamine transporters. At the cellular level, the regulation of neurotransmitter transporters affects the temporal and spatial charactecristics of neurotransmission, by controlling the extent uptake removes transmitters following release. Blakely discusses this regulation from a genetic point of view. At the system level, the consequences of the absence of transporters are examined by Jones in DAT knockout mice. In humans. the relationship between the extent of DAT transporter occupancy and subjective feelings are examined.

TRANSPORTERS AND MEDICATIONS DEVELOPMENT

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Because the dopamine transporter (DAT) is thought to be a key "receptor" site for cocaine and other psychostimulants, it is a key target for medications strategia. There are many kinds of medication needs. Substitute agonists are accepted and proven in the addiction field. However, no such medication exists for cocaine abusers and much research is directed towards this need. Key features of substitute-agonist medications include high potency and selectivity for the transporter, a slow entry into the brain and a reasonably long duration of action. Also, it is necessary that a high occupancy of DAT by medications is achieved under treatment conditions. Our group has been examining a series of phenyltropane compounds that include several compounds with useful features. RTI-113 is potent and selective for the DAT. enters the brain more slowly than cocaine and is long acting. In studies in primates, it generalizes 100% to cocaine. Also, in primates, it causes an efflux of dopamine as measured by microdialysis. In rats, pretreatment results in a dose-responsive reduction in cocaine self-administration; these doses result in a high (>50%) occupancy of DATs. Thus, many phenyltropane compounds may be useful medications for cocaine abusers.

CHARACTERIZATION OF SUBSTRATE TRANSPORT AT CATECHOLAMINE TRANSPORTERS

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One of the goals of NIDA is the development of medications useful in the treatment of drug abuse. A primary target of this research effort is the dopamine transporter because it is the site at which cocaine appears to act to produce its reinforcing effects. Thus, considerable work has been done to study inhibition of transport and structural requirements of inhibitors. To better uderstand the mechanism of the dopamine (DAT) and the norepinephrine (NET) transporters, we have been examining these transporters from the point of view of substrates rather than inhibitors. Using voltammetric methods combined with transporters expressed in cell lines, the kinetics of catecholamine transporters can be characterized with respect to uptake and efflux under a variety of conditions, using a range of substrates. Rotating disk electrode voltammetry provides rapid mixing and a complete time course of the

concentration of substrates added to a medium containing cells expressing hNET or hDAT. The decreasing concentration of electroactive substrates such as DA and NE can be followed as they are taken up from the medium into the cells until steady state is reached, and their efflux observed when a second substrate is then added to the medium. When two electrodes are used, it is possible to simultaneously observe the uptake of an electroactive substrate such as tyramine and the induced efflux of dopamine.

The effects on the rate of transport of ring substituents at the para position of phenylethylamine were examined for the series H, F, OH, CH3, OCH3, NH2, Cl, Br, and NO2 The rate was found to vary inversely with size of the substituent. Regression coefficients above .95 were found for several measures of size used in structure activity studies. Other structure activity parameters, such as bydrophobicity or Hammet's sigma did not correlate significantly with rate of transport. Evidently, as the size of the substituent increases, the substrate is less able to be transported, either because it binds less effectively, or because the transport step is retarded. Preliminary work suggests that binding is affected in a manner similar to the rate of transport, suggesting that it is the primary factor affecting the observed substituent effect.

REGULATION OF COCAINE AND ANTIDEPRESSANT-SENSITIVE NOREPINEPHRINE AND SEROTONIN TRANSPORTERS

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The biogenic amine transporters constitute powerful modulators of DA, NE, and 5HT action by efficient clearance of transmitter away from synaptic spaces. These transporters share structural similarity and ate encoded by separate genes on different chromosomes. The powerful consequences of exogenous agents that alter transporter function, including addictive agents and antidepressants, raise the question of whether nature has figured out how to regulate transport systems using endogenous mechanisms. I will describe our recent studies to evaluate kinase-mediated acute regulatory influences impinging on biogenic amine transporter function, focusing on studies of the cloned norepinephrine and serotonin transporters. These studies will be placed in the light of recent findings suggesting genetic mechanisms contributing to altered transporter function and behavior in humans.

PROBING THE PHYSIOLOGY OF DOPAMINE IN GENETICALLY ALTERED MICE LACKING THE DOPAMINE TRANSPORTER

S. Jones, R. Gainetdinov, and M. C. Caron

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Targeted inactivation of the dopamine transporter gene in mice produces a phenotype in which the animals display marked spontaneous hyperlocomotion and no further increase in locomotion after psychostimulant administration (Giros *et al,* 1996). The dopamine transporter plays an important role in calibrating the duration and intensity of dopamine neurotransmission in the CNS. In mice lacking the transporter, basal extracellular concentrations of DA in the striatum are 5-times higher than in normal mice, clearance of extracellular DA is 300-times slower and is governed solely by diffusion. Electrically stimulated dopamine release was induced by 75% in homozygotes and 50% in heterozygotes when compared to wild type values, a finding consistent with HPLC measurements which showed greater than a 90% decrease in striatal dopamine in homozygotes and 40% in heterozygotes. Our findings demonstrate that the marked increase in spontaneous locomotor activity in mice without transporters, despite low levels of dopamine and receptors, is probably due to the prolonged time that DA spends in the synapse after release. These alterations in DA dynamics are accompanied by dramatic adaptive changes in the synthesis, storage, release and degradation of intracellular DA. In addition. DA autoreceptor function was completely disrupted in mice lacking the transporter. These changes uncovered previously unappreciated points of DA homeostatic regulation. Thus, the dopamine transporter not only controls the duration of extracellular dopamine signals but plays a critical role in regulating presynaptic dopamine function.

RELATIONSHIP BETWEEN COCAINE-INDUCED SUBJECTIVE EFFECTS AND DOPAMINE TRANSPORTER OCCUPANCY

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The reinforcing effects of cocaine are generally accompaniecd by self-reports of euphoria or "high". Although the mechanism(s) underlying this effect has not been investigated in humans, studies with laboratory animals have provided compelling evidence that inhibition of dopamine transporters (DAT) is involved in the reinforcing effects of cocaine. However, the relationship between self-reports of "high" and acute DAT blockade has never been established. Methods: Occupation of DAT by different doses of cocaine was measured with PET using [11C]cocaine as a DAT ligand in 18 active cocaine abusers. The ratio of the distribution volume of [11C]cocaine in striatum to that in cerebellum, which corresponds to Bmax/Kd +1, was our measure of DAT availability. In parallel subjective effects ("high", "rush", "restlessness and "cocaine craving") were measured to assess the relationship between DAT occupancy and cocaine's behavioral effects. Results: intravenous cocaine reduced the binding of [11C]cocaine in the striatum but not in cerebellum. Bmax/Kd measures were significantly induced by all doses of cocaine and the estimated DAT occupancies corresponded to: 73 % for 0.6 mg/kg; 60% for 0.3 mg/kg; 48 % for 0.1 mg/kg iv and 40 % for 0.05 mg/kg. For subjects tested twice with the same cocaine dose the test-retest reproducibility of DAT occupancy measures were within 10 %. DAT occupancies were significantly correlated with cocaine plasma concentration ($r = 0.81$, $p < 0.0001$). Cocaine also produced dose- dependent increases in self-reported ratings of "high" which were significantly correlated with the levels of DAT blockade ($r = 0.55$ $p < 0.001$). Discussion: These results provide the first documentation in humans that DAT occupancy is associated with cocaine induced subjective effects. They also suggest that DAT occupancies equal to or greater than 60% are required to produce significant effects on ratings of "high".

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SYMPOSIUM VIII

DRUG ABUSE AND THE GENOME

G. Uhl, L. Yu, E. Simon, M. J. Kreek, and T. R. Kosten

NIDA, Indiana University, NYU Medical Center, Rockefeller University, and Yale University

Dr. Uhl indicated how the genes relatted to several abused substances have now been identified: the dopamine transporter for psychostimulant reward, and the opiate receptor for opiate reward. Analyses of site-directed mutants and chimeras have yielded evidence for participation of different features of these receptor proteins for intrinsic activity, affinity, G-protein recognition and phosphorylation.

The DAT gene accounts for the pharmacologically-defined dopamine transporter. Extensive DAT structure/function studies first identified sites at which mutations could selectively influence dopamine transport or cocaine analog recognition, providing substantial support for development of cocaine antagonists. Availability of DAT and VMAT2 cDNAs revealed that amphetamine reward in murine models depends on actions at synaptic vesicles as well as at DAT, while cocaine reward does not depend on intact vesicular transporter function. They also document how cocaine reward in murine models is sensitive to even modest, 30-50% differences in the levels of expression of DAT.

Studies in transgenic mice, with interruption of the μ receptor gene document the absolute dependence on intact μ receptor function for full morphine analgesia and reward Indeed, much of the analgesia that delta and kappa agonists provide also appears to be μ dependent Active post-translational receptor regulation of the mu receptor contrasts with little transcriptional regulation even after prolonged opiate agonist treatment.

Neuropeptide neurotransmitter genes are often subject to extensively regulated expression. Some of this regulation can be. mimicked through use of relatively short heavily-regulated promoter elements. Transcription factor genes can also be regulated in response to synaptic activities and drugs. Transcription factor regulation can display striking adaptive changes with chronic drug regimens, but drug receptor genes, including those for opiates and psychostimulants, are often minimally regulated by drug administration.

We believe that identification of each of the genes regulated by abused substances, characterization of the patterns of regulation, and mimicking this regulation in model systems provides one of the most powerful currently-available tools to identify potential candidate molecular underpinnings for addiction.

Dr. Yu summarized how drugs of abuse affect brain neurotransmitter systems, thereby exerting their CNS effect. Molecular cloning and cellular studies in the recent years have begun to unravel how drugs of abuse may influence neurotransmitter signal transduction. This presentation provided a general overview of neurotransmitter signal transduction, with emphasis on second messenger pathways and in channel functions, using opioid receptors and dopamine receptors as prototype examples.

The major second messenger pathway that opioid and dopamine receptors affect is the adenylyl cyclase/cAMP pathway. After binding of opioids or dopamine. these receptors activate specific classes of G proteins, thus affecting the intracellular cAMP level by either increasing (D1-type dopamine receptors) or decreasing (D2-type dopamine receptors and opioid receptors) the adenylyl cyclase activity.

These receptors also modulate neuronal excitability by regulating the activity of specific ion channels. For example, by expressing the cloned mu opioid receptor in cells, it can be shown that opioids can inhibit certain calcium channel activities. This suggests that one way for opioids to inhibit synaptic activity is by decreasing presynaptic calcium channels. Furthermore, activation of the expressed mu opioid receptor results in opening of a class of G protein-activated potassium channels (GIRK channels), causing a hyperpolarization of the cell. This could be another cellular mechanism of neuronal inhibition.

One emerging paradigm of neurotransmitter signal transducdon is that protein kinases may play a major role in regulating neurotransmitter receptor activity. For instance, when protein kinase C or calcium/calmodulin-dependent protein kinase is activated, mu opioid receptor coupling to the GIRK channels is reduced, resulting in rapid desensitization. This desensitization resembles the clinical phenomenon of opioid tolerance, i.e., upon repeated opioid usage, the responsiveness of the subject is reduced. Further studies areneeded to determine whether such protein kinase-mediated processes contribute to the onset of opioid tolerance, and may provide clues for more effective ways of clinical intervention.

Dr. Simon dealt with several aspects of his recent studies on opioid receptors. In line with a broad interpretation of the Symposium title, they all relate to opioid receptor genes (or cDNA). The first portion summarized studies by Dr. Matthew Andria on the promoter region of the human receptor gene. Dr. Andria has cloned the genomic DNA that encodes the human receptor. He has sequenced the 5' terminal portion and has concentrated his studies on the DNA upstream of the start codon for protein synthesis. He has made constructs in which this sequence or portions thereof, were used to promote the expression of a luciferacc indicator gene, when the plasmid wastransfectwd into differentiated SK-SY5Y cells. He has demonstrated that two short segments of approximately 50 bp have promoter activity. He has also shown that promoter activity is greatly decreased when the DNA is methylated enzymatically *in vitro*. Finally, he has shown significant differences in level of methylation between cell lines that express receptors and lines that do not. The results have led him to the hypothesis that methylation is a very important regulator for expression or non-expression in nervous tissues, while it appears to be one of several regulators of non-expression of the gene in non-neuronal tissues.

The second part of the lecture summarized his work on the bovine receptor including its purification to homogeneity and its reconstitution and recoupling with G proteins in liposomes. Recent work by Ms. Irma Onoprishvill, Dr. Sven Villem, and Dr. Andria on the cloning of the bovine receptor and its expression in HEK 293 cells was presented.

The final portion of the talk dealt with a site-directed mutagenesis study by Dr. George Ehrlich carried out on the recombinant receptor. Two extracellular loop and six transmembrane cystcine residues were replaced by serine (or alanine). It was found that the replacement of the transmembrane cysteines had little or no effect on opioid agonist or antagonist binding. However, as expected from analogy with other G protein-coupled receptors, the extracellular cysteine residues, which form a disulfide bridge, are essential for ligand binding. Their replacement resulted in complete absence of binding. The presence of the mutant receptor in the cell membrane was demonstrated by immunocytochemistry carried out on the cells by Dr. Boris Veksler.

Dr. Kreek gave the final presentation on molecular and clinical studies of effects of drugs on dynorphin, kappa receptor and related gene expression and activity. The amino acid sequence of the kappa receptor is closely related to the other two opioid receptors (mu and delta) with most differences in the N terminal (ligand binding end of receptor protein) and the C terminal (G protein signal transduction end of the receptor protein). The kappa receptor binds dynorphin with high aftinity, and dynorphin appears to act as a neurotransmitter between the caudate-nucleus accumbens (NA) and the substantial nigra-ventral tegmental area (VTA). In this pathway, it acts as a feedback loop for the dopamine system. This feedback activity is supported by direct application of dynorphin into the VTA where it reduces dopamine release in the nucleus accumbens.

In animals given 14 days of a binge pattern of cocaine administration, both basal and cocaine stimulated release of dopamine in the NA and caudate were reduced compared to baseline dopamine levels, and dynorphin may contribute to this reduction through the above feedback loop. In a test of this hypothesis using molecular biology techniques, preprodynorphin messenger RNA levels were measured in the caudate and NA. These mRNA levels were elevated consistent with greater synthesis and release of dynorphin. This dynorphin could then reduce dopamine release through the above feedback inhibition pathway to the VTA and substantial nigra. This rise in preprodynorphin was blocked by administration of a D1 receptor antagonist during the 14 day cocaine hinge cycle. but was not blocked by a D2 dopamine antagonist.

These molecular biological findings led to clinical studies of dynorphin effects on dopaminergic systems. Using prolactin blood levels as a marker of dopaminergic activity, dynorphin was found to increase prolactin in a dose dependent manner. This increase was only partially blocked by naloxone (30 mg IV) or nalmefene suggesting that this dynotphine effect was not entirely mediated by kappa opioid receptors. Nevertheless, dynorphin and other kappa ligands may be potential treatment agents for not only opioid but also stimulant dependence, because of its efficacy in reducing dopaminergic activity in the brain's reward pathway between the VTA and NA.

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SYMPOSIUM IX

COMMUNITY-BASED OUTREACH AS AN HIV RISK REDUCTION STRATEGY FOR OUT-OF-TREATMENT INJECTION DRUG USERS (IDUS)

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Introduction: This presentation reviews the literature on the impact of two widely used outreach models on HIV risk and protective behaviors. The typical outreach intervention offered in NIDA's NADR and Cooperative Agreement programs hid indigenous community workers to meet drug users in the streets and injection settings. provide risk reduction information and referrals to services, and distribute condoms and bleach; usually, outreach also included making arrangements for IDUs to receive HIV antibody testing and pre- and post-test counseling. which included demonstration and rehearsal of risk reduction skills. Behavioral and ecologic data were collected at baseline and six months post-intervention. Methods: We reviewed 36 published studies that evaluated the effectiveness of the outreach-based intervention in facilitating changes in risk behaviors of IDUS, using single and multiple samples of IDUS. Results: Outreach interventions have helped IDUs reduce their risk-taking behavior, particularly drug and needle using practices, and to a lesser extent sex risk behaviors. The following summary of published data illustrates the magnitude of changes. Termination of drug injection: Nine of 10 studies reported significant numbers of IDUs who stopped injecting at follow-up (between 24 and 31% of IDUs reported stopping; the median at follow-up was 26%). Reduced frequency of injection: Sixteen of 17 studies reportced significant decreases in injection frequency (range: 11 to 62 fewer injection events per month; median was 28 fewer injection/month.). Reduced multiperson reuse of syringes/needles: Sixteen of 20 studies reported significant decreases in multiperson reuse of injection equipment (range: 14 to 43% fewer IDUs reused syringes; median was 19%). Reduced multiperson reuse of drug preparation paraphernalia: Eight of studies reported significant decreases in multiperson paraphernalia reuse (range: 16 to 34% fewer reports of equipment reuse in last month; median was 27% fewer reports). Reduced HIV incidence accompanying reductions in risk behaviors: a single study reported on both behavioral and serological outcomes and found significant reductions in injection risk as well as HIV incidence. Conclusions: Outreach-based intervention has been a successful risk reduction strategy. Outreach has provided access to the means for behavior change, and a significant proportion of IDUs have changed their behaviors following exposure to outreach interventions.

DRUG TREATMENT AS AN HIV PREVENTION STRATEGY

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Drug abuse treatment can be a powerful tool for preventing infection with HIV. Treatment can directly prevent HIV infection by causing patients to decrease their risky needle use and sexual behavior; treatment can indirectly prevent HIV by assisting patients toward rehabilitation and serving as a platform for other HIV prevention services. Recently published research on the utility of drug treatment as an HIV prevention strategy has focused primarily on methadone maintenance treatment (MMT). Recent studies provide clear evidence that MMT reduces HIV risk behaviors, particularly needle use. The research provides less definitive evidence that MMT reduces needle sharing and unsafe sexual behavior. Studies of HIV seroconversion can be more conclusive than studies of self-reported HIV risk behaviors about the prevention of HIV infection. Several studies of HIV seroconversion published in the early 1990s indicate that MMT protects against acquiring HIV infection. Thus the literature is clear that MMT has a significant effect in preventing HIV infection. Future studies need to take into account self-selection processes, such as treatment dropout of high-risk drug users, and they need to investigate other treatment modalities for heroin or stimulant abuse to determine their effects on HIV risk and HIV infection.

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SYMPOSIUM X

GENETIC AND ENVIRONMENTAL INFLUENCES ON DSM-III DRUG USE AND DIAGNOSES OF ABUSE/DEPENDENCE

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Information was obtained on drug use (five times or more) and DSM-III diagnoses of abuse and/ or dependence or dependence alone for male and female twins, recruited from addiction treatment centers. Univariate structural equation analysis was used to estimate heritable and environmental influences from liability correlations of monozygotic (MZ) and dizygotic (DZ) twins. Given a normally distributed liability, individuals with scores above a certain threshold will have used drugs five times or more, or have received a diagnosis. Threshold estimates were obtained from population prevalences of the Epidemiological Catchment Area (ECA) study (which also used DSM-III diagnoses), and stratified for characteristics of the twin sample. The models included a second threshold, for treatment status, to account for the clinical nature of the twin sample. Under models, including heritable (h^2), Common environmental (e^2), and specific environmental (e^2) influences. estimates were:

DRUG ABUSE: TOWARD A REFINED PHENOTYPE

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Substance abuse shows heterogeneous clinical expression and multiple etiologies, including genetic and environmental influences. Efforts to estimate genetic and environmental profiles of individuals have received relatively little attention in genetic research, although the benefits of doing so have been recognized. Without the ability to separate relative genetic and environmental influence in individuals efforts to identify specific genes must contend with unwanted environmental "noise." Refining phenotypes to reduce heterogeneity has been a valuable strategy for developing better understandings of etiology including identification of genes contributing to a variety of diseases such as breast cancer and Alzheimer's. Recently, we reported symptoms that distinguished relative genetic and environmental loading in alcohol dependent individuals. Using data from a treatment-based twin study, symptoms with significantly higher monozygotic (MZ) than dizygotic (DZ) concordance rates were assigned to a "genetic" scale, while symptoms that did not were assigned to environmental scale(s). Genetic and environmental scales were subsequently evaluated among alcohol dependent Caucasian men in the Epidemiologic Catchment Area Study. Factor analyses identified a single dimension for the genetic scale items. Two factors were found among the environmental scale items generating two scales: general environmental and dyssocial environmental. Use of these tree scales in a hierarchical cluster analysis empirically identified three "naturally occurring" subtypes of alcohol dependence: mild, severe and dyssocial. Only the severe subtype showed evidence of substantial genetic influence. Most recently, preliminary analyses of the National Longitudinal Alcohol Epidemiologic Survey replicated the empirical identification of the mild, severe and dyssocial subtypes and again indicated that only the severe subtypes shows substantial genetic influence as measured by the genetic symptom scale developed in the twin sample. Attempts to identify specific genes influencing alcohol dependence may benefit from focusing on the more homogeuous and seemingly genetically influenced severe subtype. Furthermore this approach to refining phenotypes for molecular genetic analyses may be applicable to substance abuse disorders in general.

SYMPOSIUM XI

ETHICAL LABORATORY RESEARCH WITH HUMANS: THE DEVIL IS IN THE DETAILS

M. W. Fischman and C.-E. Johanson

College of Physicians and Surgeons of Columbia University and Wayne State University School of Medicine

Experimental studies with humans conducted in a laboratory setting are an important component of our field's research portfolio aimed at understanding, treating and preventing drug abuse. This symposium discussed a number of issues that investigators should consider in conducting scientific studies of drug-related phenomena within a laboratory setting with humans.

THE NUTS AND BOLTS OF SETTING UP A NEW LABORATORY

C.-E. Johanson

Wayne State University School of Medicine

In addition to the usual ethical concerns, special issues emerge in human laboratory-based research that are usually not considered by ethical review committees. Although these issues may be Seen as practical rather than ethical problems, satisfactory solutions have ethical overtones. A few examples are given below.

Medical Issues: While medical backup is usually required. level of coverage can vary considerably. Obtaining medical backup is often difticult and *quid pro quo* issues, such as courtesy aurhorship, can raise ethical questions. Solutions for handling medical/psychiatric problems in potential candidates and making arrangements for treatment are not always clear and can involve violating volunteers' expectations.

Drug Issues: Obtaining controlled substances is very complicated and differs by state and institution with many of the "regulations" a matter of tradition. not law. Requirements for storage, inventory, access, and drug administration are often vague with little consensus or firm guidelines.

Confidentiality Issues: Standard procedures for storage of information with identifiers (e.g., consent forms) are available but leakages occur despite investigators' best efforts. These limits to confidentiality are often the result of conflict among different regulations. For instance, social security numbers are required to pay subjects and this identifier paired with the source of the payment are readily accessible within an institution.

Treatment Issues: If non-treatment studies involve administration of abused drugs to substance abuser participants, a decision must be made as to whether to recruiT those wanting treatment. Problems can arise if treatment is included as there will be tensions between those conducting the research and those providing treatment. Given that most studies are not long-ten-n, provision for referrals or continued treatment must be considered. This can be problematic if the research involves medications that are not yet marketed.

Representativeness: The Federal Government mandates that consideration be given to the sex and ethnicity of participants in research studies so as to insure representativeness. Although guidelines for determining what is representative are vague, there is an implied threat that if the sample is not representative, sanctions will follow. But what is representative varies by study as well as by city, and for studies that do not involve treatment and use a very small sample, it is hard to fathom what is appropriate.

ETHICAL CONSIDERATIONS IN ADMINISTERING DRUGS TO HUMANS

M. W. Fischman

College of Physicians and Surgeons of Columbia University

Although excellent animal models are available to address many issues in drug abuse research, findings should be confirmed in humans and, in addition, questions exist that can only be answered in humans. Federal regulations mandate multiple levels of review including the local institutional review board (IRB), appropriate Federal funding

agencies (e.g., NIDA, NIAAA), the NIH Office for the protection of Research Risks (OPRR), and the Food and Drug Administration (FDA). The informed consent process serves as the main protection for volunteers and it is the investigator's obligation to assure the integrity of the process with particular attention to addressing risks.

Other concerns related to the administration of drugs of abuse are frequently raised. These include: 1) exposure may cause or exacerbate drug abuse/dependence; 2) individuals who abuse/ate dependent on drugs may not consider the risks involved because of their desire to get drugs; and 3) exposure is often non-therapeutic and therefore without benefit to the individual. However, exposure to drugs in a therapeutic context (e.g., opiates) does not generally lead to abuse, and exposure for research purposes is unlikely to promote increased (or decreased) use after study cessation. There is no basis to the assertion that drug abusers are so driven to obtain drug that they are incapable of weighing the risks of participation. In fact, excepting when intoxicated by drug, these individuals can be quite capable of participating in a consent process. As with all research with human participants, the investigator must assess an individual's capacity to provide consent prior to enrolling anyone in a protocol and refuse participation where capacity is diminished regardless of the reason. In many cases the study of drugs of abuse occurs within a non-therapeutic context. Therefore, other benefits to the individual must exist. These can include: 1) contact with health care professionals; 2) HIV/AIDS risk reduction education; 3) food, lodging and isolation from the risky lifestyle of the drug abuser if the research is residential; and 4) referral to treatment.

participant selection criteria cannot be stated in the absence of experimental context. They are related to drug under study, route and doses used, setting in which drug is administered, and question being asked. For example, study drugs could be low dose oral caffeine or moderate dose i.v. cocaine administered in settings varying from inpatient hospital to outpatient laboratory. Oral caffeine studies dictate a different (and broader) population than intravenous cocaine, and inpatient vs outpatient settings dictate different study designs. Thus, participant criteria vary along a continuum (e.g., non user to drug dependent individual, never in drug treatment to repeated unsuccessful treatment attempts, etc.), and the specific study must determine the precise criteria to be used. Clearly, participant safety is of primary importance and the investigator has the responsibility for implementing protocols that minimize risks and maximize benefits. In summary, drug abuse research is necessary and important, and as with other biomedical research, careful implementation of research protocols and concern for the well being of participants assures that it can be carried out ethically.

SCIENTIFIC AND ETHICAL CONSIDERATIONS RELATED TO GENETIC STUDIES

R. Pickens

Division of Intramural Research, NIDA

Genetic knowledge has the potential for both improving and harming the individual and society. Benefits are related to improvements in treatment (environmental modification, gene therapy) and prevention (early intervention, avoidance). Harm is related to loss of privacy, discrimination in employment and insurance, damage to family relationships, and anxiety due to inaccurate risk assessment (related to probability of gene expression, environmental influences). As a result ethical, legal and social implications of genetics research are a major concern for the Human Genome project. A number of practical issues are also involved in laboratory genetic research Genotype studies attempt to relate genotype (genetic constitution) to phenotype (result of gene/environment interaction). One of the most frequently used laboratory strategies is the at-risk family study, in which offspring with a positive family history for a substance use disorder are compared to offspring with a negative family history for the disorder. Although not actually a genetic study, recent data suggest familial alcoholism increases risk for both alcohol dependence (OR=2.7) and drug dependence (OR=4.0). The sensitivity of family history as a method far predicting alcohol and drug dependence is relatively low; however, with relative risk of family history on alcohol dependence being similar to risk of drinking alcohol before age 18 (OR=2.6) and being mate (OR=2.4).

POPULATION-BASED HUMAN LABORATORY RESEARCH

S. Kellam

The Johns Hopkins University School of Public Health and Hygiene

The population laboratory is built within the social and political structure of the population itself. Such laboratories can be developed within defined residential geographic areas. elementary school catchment areas, and so forth. The ethical issues in building and maintaining such a laboratory are not unlike those faced in other areas of human research although problems of confidentiality and representativeness of participants in the studies become paramount. Two processes are initially important in developing a partnership between the scientists and leaders of the community social and political structure: an analysis of the institutions and power structure within the population and an analysis of the values, priorities and language interpretation of the constituencies and their leaders. The goal is to define the scientific problem to the right people in a way that is understandable and acceptable. Implementing the research also involves negotiation with specific leaders of all community organizations whose constituencies lie within the population itself rather than within an agency "downtown". ln order to achieve partnership with community and institutional leaders along with teachers and parents, the process of engagement and working through trust issues is paramount as is a deliberate negotiation around mutual self-interests of all who are participating.

Our prevention research in Woodlawn, on the south side of Chicago. and Baltimore has used several models for this process over the past 30 years. The research has focused on directing interventions at early antecedents along developmental trajectories leading to problem outcomes such as drug abuse. Such designs always require randomization to the intervention and control conditions, preferably at the level of individual children, teachers, classrooms, and even schools. The model in use in the latest generation of trials in Baltimore involved follow-up at age 19-21 of the 2311 first-grade children who were the total first grade population in 1985-87 of 19 schools in Baltimore and who participated in two prevention intervention trials. The community base required for the intensive assessment at follow-up was an extension of the prior base involving the Johns Hopkins School of Public Health Prevention Research Center and the Baltimore City Public Schools. But because the participants were now making the transition to adulthood, the Morgan State University, a traditional African American community university, became an important newally. We were able to establish mutual interests around recruiting and developing top undergraduates as our research assistants and interviewers through a minority supplement funded by NIH. This minority training program provided us with needed additional resources while at the same time provided an opportunity to develop a program of advanced training in order to help minority undergraduates develop strengths for application to graduate education in public health. Morgan, joining together with the Baltimore City Public Schools Board of School Commissioners and the Johns Hopkins School of Public Health allowed for a strong community base in addition to a useful undergraduate training program. A community board comprised of leaders within these institutions and overlapping with other community organizations provides the authority for the research to move ahead with continual negotiations, understanding, and acceptance.

DISCUSSANT

E. M. Sellers

Addiction Research Foundation

The principles of bioethics include autonomy (the morality of mutual respect) and beneficience (the morality of achieving good and avoiding harm). In other words "do not do to often that which they would not have done unto them, and do for them that which one has contracted to do" and "do to others their good." The principle of autonomy requires, as a condition of mutual respect, that individuals be protected against both deception and coercion. The principle of beneficience requires that there be a net benefit to others. Therefore, one should consider the good from the research and the harm from *not* doing the research.

In many cases. human research is congruent with moral authority. However. what is actually done or required may not be derived from moral authority. Successful "population laboratory" research must incorporate the principles of bioethics since it derives from the social and political structure of the studied population and requires a partnership which embraces the values and priorities defined in terms of the population good and harm. Population laboratory

research, therefore, has an advantage that direct and indirect good and harm must be clear and have the approval of the constituency with whom the research is done. In contrast, at the institutional level, individual attitudes and beliefs can be particularly powerful in shaping the application and interpretation of the bioethical principles of autonomy and beneticience. Such variation probably accounts for why institutional decisions on similar issues can be different. To offset idiosyncratic views, researchers must deliberately and systematically anticipate issues and educate review committees since, in a secular pluratistic society, consensus needs to be developed among informed and representative individuals on these committees. As researchers in this field, we can contribute to the evolution of bioethical considerations by sharing our innovations and involving trainees in bioethical issues. We need to persuade colleagues and trainees lhat a body of knowledge exists mnceming bioethical issues and that bioethics not only informs the quality of research but also enhances its success.

SYMPOSIUM XIII

NOVEL APPLICATIONS OF HUMAN DRUG DISCRIMINATION FOR UNDER-STANDING THE EFFECTS OF ABUSED DRUGS

C. R. Rush, J. B. Kamien, K. L. Preston, B. J. Smith, K. A. Perkins, and C. E. Johanson

University of Mississippi Medical Center, Jackson, MS; Addiction Research Foundation, Toronto, Ontario, Canada: National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD; University of Vermont School of Medicine, Burlington, VT; University of Pittsburgh, Pittsburgh, PA; and Wayne State University, Detroit, MI

Between 1985 and 1995, there has been a striking, positively-accelerating increase in the use of drug discrimination procedures to examine the effects of commonly abused drugs in humans, with approximately 100 publications to date. Human drug discrimination researchers ate now beginning to apply these procedures in novel ways to understand the behavioral and pharmacological effects of commonly abused drugs. For example, it has long been thought that the discriminative-stimulus and subjective-effects of drugs covary (Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster *et al.,* 1981). Recent studies have demonstrated that the discriminative-stimulus and subject-rated effects of drugs overlap, but clearly they are not isomorphic (e.g., Perkins *et al.,* 1994; Rush *et al.,* 1995). In fact, human drug discrimination procedures may be more sensitive than the more commonly used subject-rated drug-effect questionnaires, especially to the effects of low doses of drug (Perkins *et al.,* 1994). Finally, antagonism studies using drug discrimination procedures have begun to explore receptor mechanisms underlying the discriminative stimulus effects of drugs in humans (e.g., Smith *et al.,* 1996).

The papers presented in this symposium reviewed recent empirical data from studies that used human drug discrimination procedures. The goats were to highlight: 1) the utility of human drug discrimination, 2) novel applications of these procedures, and 3) that the use of human drug discrimination procedures in conjunction with other measures (e.g., subject-rated drug-effect questionnaires) will further our understanding of the behavioral and pharmacological underpinnings of drug abuse. Below are abstracts prepared by each of the participants.

USING HUMAN DRUG DISCRIMINATION PROCEDURES TO STUDY THE PHARMACOLOGY AND ABUSE OF OPIOIDS

K. L. Preston and G. E. Bigelow

As part of a program to study the pharmacology and receptor activity of mixed agonist-antogonist opioids in humans, our laboratory developed a method for testing drug discrimination in human subjects analogous to the methods widely used in animal laboratory research. In a series of studies testing marketed opioid analgesics, methodological aspects of the drug discrimination procedure were systematically varied and evaluated. Eight studies have evaluated the effects of varying tbe training drugs, the dose of the training drugs, the number of training drugs, the available response alternatives, and the type of pharmacological pretreatrnents. Subjects were experienced opioid abusers, and dependent variables were measures of discrimination and subjective effects. Discrimination measures differentiated among the agonist/antagonists, though training condition clearly altered discrimination responding. Three-choice procedures and two-choice procedures with an "other" response alternative appeared to be more sensitive for differentiating among drugs with different but overlapping pharmacological profiles than simple drug/placebo two-choice procedures. There was general concordance between discriminative and subjective measures. The results show drug discrimination to be a useful tool for evaluating the pharmacology of opioids in humans.

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STUDYING ETHANOL PHARMACOLOGY USING HUMAN DRUG DISCRIMINATION PROCEDURES

J. B. Kamien

Drug discrimination procedures have not been used to study the human behavioral pharmacology of ethanol. Establishing ethanol discrimination by humans begins to fill this research gap. In the present study, fourteen healthy male and female volunteers (20-38 years) were trained to discriminate drinks containing 0.32 g/kg ethanol (e.g., Drink A) from placebo drinks (e.g., Drink B) to which very small amounts of ethanol were added to mask possible olfactory and gustatory stimuli. During the first four daily sessions, subjects were informed of the drink label at the time of administration. During the next 4 to 12 sessions, subjects received Drinks A and B in randomized block fashion, were not informed of drink labels and earned money for correctly identifying which drink they had received. Seven of fourteen subjects met the criterion for discrimination (accurate drink code identification on 4 consecutive or 5 of 6 consecutive sessions). Subsequently, the dose-response function for ethanol was determined by administering drinks containing 0.1, 0.17, 0.32 and 0.56 g/kg. Ethanol produced dose-related increases in ethanol-appropriate responding and on several measures of subjective effects characteristic of ethanol. Over-ah, this research established ethanol discrimination by humans, providing a baseline for studying ethanol's mechanism(s) of action related to alcohol abuse. Further, ethanol discrimination by humans promises to provide a robust model in which to evaluate possible medications for the treatment of alcoholism and alcohol abuse.

USING HUMAN DRUG DISCRIMINATION AND THE NOVEL-RESPONSE PROCEDURE TO INVESTIGATE FUNCTIONAL VERSUS COMPETITIVE ANTAGONISM

B. J. Smith and W. K. Bickel

The novel-response procedure provides a response altemative appropriate for stimulus effects unlike either training condition (i.e., placebo or drug). Previous studies demonstrated that drugs occasioning full substitution for placebo or triazolam under a two-response procedure were distinguishable under the novel-response procedure. Drug combination data assessing the effects of triazolam alone (0, 0.10, 0.32 and 0.56 mg/70 kg; triazolam-placebo), and each dose in combination with 560 mg/70 kg caffeine (i.e., triaxolam-caffeine) under both a two-response and novel-response procedure have been gathered in 12 participants. Participants were trained to discriminate 0.32 mg/70 kg triazolam from placebo, and then were tested under the two-response and novel-response procedures. Under the two-response procedure, the triazolam-placebo dose effect curve was indistinguishable from triazolam-caffeine combinations, with full substitution for triazolam occurring in both cases. Under the novel-response procedure, triazolam-placebo combinations occasioned similar effects. In contrast, 0.10 mg/70 kg triazolam-caffeine occasioned 55% novel-appropriate responding and no triazolam-appropriate responding; at 0.32 mg/70 kg triazolam-caffeine 45% novel-and 55% triazolam-appropriate responding were occasioned; and at 0.56 mg/70 kg triazolam caffeine, 75% triazolam- and 2590 novel-appropriate responding occurred. That is, when triazolam-caffeine combinations were. administered, triazolam-appropriate responding increased, while novel-appropriate responding decreased, as a function of triazolam dose. These results indicate that the novel-response procedure is useful for distinguishing relative effects of drug combinations in situations where the two-response procedure appears insensitive.

NICOTINE DISCRIMINATION AND SELF-ADMINISTRATION

K. A. Perkins

Relative to the animal research on nicotine discrimination and the human research on discrimination of other drugs. there has been very little research on human nicotine discrimination. This is largely due to methodological difficulties in administering rapid,fixed doses of nicotine atone to human participants. We have conducted a series of nicotine discrimination studies employing a nasal spray nicotine dosing procedure that administers in fairly rapid

fashion fixed doses of nicotine in isolation. In these studies, we have found mat: 1) smokers and nonsmokers can discriminate nicotine from placebo nasal spray; 2) nonsmokers show greater sensitivity in discrimination at higher nicotine doses, suggesting tolerance; 3) discrimination responding of women is less sensitive than that of men across dose; 4) discrimination behavior depends partly on initial training dose and does not reflect an inherent characteristic of the drug; 5) mecamylamine, a central and peripheral nicotine antagonist, attenuates nicotine appropriate responding but trimethaphan, a peripheral only antagonist, does not; and 6) behavioral discrimination of nicotine appears to be more sensitive across doses than traditional subjective effects measures, demonstrating a clear advantage to the use of drug discrimination procedures in humans, Results of this research are very similar to findings in animal studies of nicotine discrimination, showing strong cross-species generalization. Across studies. nicotine-appropriate responding is consistently associated with the subjective response of "head rush" hut only inconsistently with ottriaxolamher responses. We have only recently begun to compare nicotine discrimination with self-administration; findings so far do not show a direct relationship, although subjective responses to nicotine may predict magnitude of self-administration. Future research will examine common environmental manipulations (e.g. physical activity, other acute drug intake) that may alter nicotine discrimination and possibly influence nicotine self-administration.

STUDYING THE RELATIONSHIP BETWEEN THE DISCRIMINATIVE-STIMULUS AND SUBJECT-RATED EFFECTS OF ABUSED DRUGS IN HUMANS

C. R. Rush and S. H. Kollins

The discriminative-stimulus and subject-rated effects of commonly abused drugs are generally thought to covary. In a traditional human drug-discrimination experiment, volunteers are trained to discriminate between drug and placebo. Following acquisition of the discrimination, other drugs are tested. Drugs that increase drug-appropriate responding generally produce subject-rated drug effects similar to those observed with the training drug. For example, in a recent experiment we examined the discriminative-stimulus and subject-rated effects of methylphenidate, bupropion and triazolam in *d*-amphetamine-trained humans. Metbylphenidate occasioned dose-dependent increases in drug-appropriate responding, and produced subject-rated effects that were indistinguishable from those observed with d-amphetamine. Bupropion. a dopamine uptake blocker, occasioned intermediate levels of drug-appropriate responding, and produced subject-rated drug effects that were both similar and dissimilar to those observed with d-amphetamine. Triazolam, by contrast, occasioned low levels of drug-appropriate responding, and produced subject-rated drug effects that were different from those observed with *d*-amphetamine. These results suggest a high degree of concordance between the discriminative-stimulus and subject-rated rated effects of drugs.

In another experiment we examined the influence of training dose on the discriminative-stimulus and subject-rated effects of d-amphetamine. Four subjects were trained to discriminate between 10 mg *d*amphetamine and placebo (i.e., low-dose group), while 4 other subjects were trained to discriminate between 20 mg d-amphetamine and placebo (i.e., high-dose group). Following acquisition of the discrimination, a range of doses of *d*-amphetamine (1.25-20 mg) was tested in each group. *d*-Amphetamine increased drug-appropriate responding as a function of dose and produced clear dose-related stimulant-like subject-rated drug effects (e.g., "Like Drug") in the low-dose group, The dose-response functions for discrimination performance and subject-ratings were virtually identical, further supporting the notion that the discriminative-stimulus and subject-rated effects of drugs covary. In the high-dose group, *d*-Amphetamine also generally increased drug-appropriate responding and subject-rated drug effects as a function of dose. However, the dose-response functions for discrimination performance and subject-ratings were somewhat dissimilar. These findings suggest that the discriminative-stimulus and subject-rated effects of abused drugs are not isomorphoric, and that discrimination performance in humans is not based solely on "subjective" drug effects. Continuing to use the human drug discrimination paradigm in novel ways will allow us to more clearly determine the conditions under which the discriminative-stimulus and subject-rated effects of drugs covary or dissociate.

References: Available upon request.

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SYMPOSIUM XIV

PTSD AND SUBSTANCE ABUSE: EPIDEMIOLOGY, GENETICS AND NEUROBIOLOGY

R. K. Price[1], N. Breslau[2], H. D. Chilcoat[2], E. Triffleman[3], W.R. True[4], and T. R. Kosten[1]

[1]Washington University School of Medicine; [2]Henry Ford Health Science Center; [3]Yale University School of Medicine; [4]St. Louis University School of Public Health and St. Louis VA Medical Center; and [5]Yale University School of Medicine and VA Connecticut Healthcare System

A NOSOLOGIC AND ETIOLOGIC OVERVIEW

Dr. price began with an introduction to the symposium. The literature on post-traumatic stress disorder **(PTSD)** and PTS symptoms has shown their associations with a number of factors including substance abuse. However. causality involving **PTSD** and substance abuse is far from established. In 1980, the symptomatology of **PTSD** in **DSM-III** was delineated in four groups: exposure, reexperience of event, avoidance and numbing, and increased arousal. The duration, onset, and clinical significance and impairment were added in **DSM-III-R** and **DSM-IV.** Some observed associations, such association with suicide risk and depression, may he a result of symptom overlap, but they could also be causal. Associations with substance abuse and childhood behavior problems. on the other hand, may be etiological, but there may be underlying forces, such as shared genetic susceptibility. Finally, even if tbe causal relationship between **PTSD** and substance abuse is evidenced, it is critical to understand the neurobiological mechanism for effective treatment of comorbid **PTSD** and substance abuse.

CHARACTERIZING TRAUMA EXPOSURE AND PTSD AMONG TREATMENT-SEEKING SUBSTANCE ABUSERS

Dr. Triffleman presented results from an on-going, longitudinal study of Axis **I** and **II** disorders among treatment-entering substance abusers. At baseline, 370 patients were enrolled in the study through two outpatient addiction clinics and another addiction treatment inpatient unit. The two clinics were primarily cocaine treatment sites. The subjects were administered the **ASI,** the **SPSE,** a 14-item checklist of stressful events, and the **SCID PTSD** module. The mean age was 32.6 years old and 56% were female. The sample included 56% white, 35% African-American and 9% Hispanic. A majority met at least one lifetime substance dependence disorder: 74% cocaine, 59% alcohol, 52% opioids, 37% marijuana, 14.9% sedatives, and 10% stimulants. The mean first age of regular substance use was 15 years of age. The level of traumatic exposure was high: 95% bad been exposed to at least one form of trauma The mean total types of exposures was 4.3. The lifetime diagnosis of **PTSD** was met in 19.9% of the sample and 6.7% had current **PTSD.** The mean age of onset was 17.3 years old. Of those with lifetime **PTSD,** 76% were female. While both genders experienced exposure to multiple traumatic events, female patients endorsed more traumatic events, and exposures tended to occur at an earlier age. The prevalence of lifetime **PTSD** was also significantly different by gender. In the multivariate analysis, witnessing family violence, childhood sexual abuse which occured prior to the onset of regular substance use, and gender were independent significant predictors of the lifetime **PTSD.** The presence of criminal victimization, exposure to physical illness, rape and gender, but not lifetime **PTSD,** were significant predictors of the current drug severity. Although the study was limited by a retrospective design and tbe convenience sample, results are consistent with those from general community samples.

TESTING CAUSAL PATHWAYS BETWEEN PTSD AND DRUG USE DISORDERS

Dr. Chilcoat's presentation set out to test three hypotheses about the causal pathways between **PTSD** and drug use disorders: self medication of **PTSD;** drug abuse as a risk factor for exposure (high-risk); and drug abuse as a risk factor for **PTSD** following exposure (susceptibility). Data were collected as part of a longitudinal study of young adults, randomly selected from a list of 400,000 health maintenance organization members in southeast Michigan. Of the 1,200 members randomly selected at baseline in 1989 when they were 21-30 year old, 1,007 (84%) participated. At the follow-ups in 1992 and 1994, 979 (97%) and 971 (97%) respondents, respectively, completed interviews. The demographic characteristics of the study respondents were generally representative of the geographic areas from which the sample was drawn: 63% were female, 81% white, and 45% married. Psychiatric disorders were measured by the NIMH DIS-IIIR. Drug abuse or dependence **(A/D)** was determined according to DSM-IIIR criteria for stimulants, sedatives or tranquilizers, marijuana, cocaine, heroin or other opiates, PCP. hallucinogens and prescribed medication. In the **PTSD** section, each respondent could have up to three distinct episodes at each of the three follow-up intervals. The earliest traumatic event and onset of **PTSD** were used for this analysis. The qualifying stressors were limited to those defined by **DSM-IIIR.** To account for temporal sequencing of traumatic events, **PTSD** and drug **A/D.** Cox proportional hazardl models were used with time dependent covariates. Results from the Cox regression models for the drug **A/D** outcome provided support for the self medication model: adjusted for race, sex and education, individuals with **PTSD** had a 4.5 fold increase in the risk of onset of drug **A/D** compared to those who were not exposed to a traumatic event. On the other hand, exposure to a traumatic event without **PTSD** was not associated with increased risk of drug **A/D.** Further analyses showed that early conduct problems and depression prior to **PTSD** also signaled increased risks for drug **A/D. PTSD** without prior depression signaled a four-fold increase in the risk of drug **A/D,** with an even greater risk when **PTSD** followed the onset of depression, suggesting independent contributions of **PTSD** and depression to the risk of drug **A/D.** Strongest evidence for self-medication was found for prescribed drugs. No evidence was found to support the high-risk hypothesis. The evidence for the susceptibility model was weak: drug **A/D** signaled a small and insignificant increase in risk of **PTSD** following exposure. Overall, evidence supports the self-medication model. However, the results are consistent with the possibility that there is a shared vulnerability for **PTSD** and drug **A/D.**

PTSD AND DRUG ABUSE: TIME SEQUENCE AND EARLY PREDICTORS

Dr. Price presented a first set of results from her on-going follow-up study of Vietnam War soldiers. Half of the veteran respondents were drawn randomly from the Army list of "drug-positives" based on urine testing at the time of departure. Another half, the "general" sample, was randomly drawn from the population. A total of 942 veterans were surveyed in 1972; of them, 571 were re-interviewed in 1974, along with 284 civilian comparison respondents who were chosen from the Selective Service lists and matched to the general sample. The follow-up study respondents are all males who are reaching mid to late 40's. Among the drug-positive sample, 30% are African Americans. After two decades of hiatus, 90.5% of the 1,092 eligible and surviving members were contacted. The presentation utilized data from the first 276 cases available for data analysis. This subsample is under-represented by **D+** veterans. The time sequence of hard drug use, traumatic events, and, **PTSD** syndrome were examined. along with causal relations among "early" predictors and subsequent hard drug use and **PTSD** syndrome. Three time periods for the event variables were constructed from two questions about the most traumatic events: **T1,** from early childhood to the service induction date; **T2** from the induction to September 1971 (departure); and **T3,** from October 1971 to present. The measures of **PTSD** and drug use were constructed separately for each time period. The sum of **PTSD** syndrome criteria were used for path analysis, and the threshold of meeting all four criteria was set to create dichotomous variables which approximate **DSM-IV** criteria without duration requirement. The number of hard drugs used within a period was used for path analysis, The results showed that the **PTSD** syndrome level is high when it is compounded by drug use. The current estimates of an approximation of the lifetime **PTSD** syndrome without the duration requirement are 41.7% among **D+** veterans. and 20.9% among **D-** veterans. When multiple traumas are assessed for different time periods, **PTSD** is found to be relatively common in this age group; however, war-time trauma was most intensely experienced and most likely to lead to PTSD. The results regarding the relationship between drug use and exposure were equivocal. Overall,

PTSD appears more likely to affect subsequent hard drug use than the opposite; however. the evidence was Inconclusive. A small set of predictors included in this analysis failed to predict **PTSD** well. The current results are limited by the small sample size available, retrospective assessment of **PTSD,** and different durations represented by the three time periods.

COMMON RISK FACTORS FOR POST-TRAUMATIC STRESS DISORDER AND DRUG ABUSE/DEPENDENCE: BIVARIATE TWIN ANALYSES

Dr. True, using a behavior genetic paradigm, investigated the issues regarding shared genetic and environmental risk factors for the co-occurrence of **PTSD** and illicit drug abuse. The data for the current analyses was derived from the Vietnam Era Twin Registry. The Registry compiled records of approximately 4000 identical and fraternal male twins in which both siblings served in the military during the Vietnam Era (1964-1975) from over 7,300 twins ascertained from the computer tape of 5.5 million veterans. Twins were matched based on the last name, social security number and the date of birth; zygosity was determined from similarity questions and blood group typing. The diagnostic data were obtained from telephone interviews conducted in 1992-93 using the **DIS-IIIR.** The prevalence of **PTSD** was 9.6% among this analysis sample. The prevalence rates for drug abuse/dependence (D/A) was 7.2% for marijuana, 4.3% for stimulant and 10.1% for any illicit drug. The rates are approximately three times as high among those with **PTSD** compared to those without . Using **MX** and **PRELIS2,** univariate and bivariate analyses examined the degree to which the observed associates between **PTSD** and illicit drug abuse are due to shared and unique genetic influences, and experiences shared and not shared by twins. The analyses were based on 1.842 **MZ** pairs and 1.474 **DZ** pairs. The tetrachoric correlation of **PTSD** among **MZ** pairs was .38 compared to .14 among **DZ** pairs, suggesting a dominance genetic effect. The **MZ/DZ** correlation ratios were smaller for stimulants and marijuana. The univariate estimates under the best fitting models showed somewhat ambiguous results: for **PTSD,** additive genetic variance was 17.4% (C.I. 0-45%), nonaddictive genetic variance was 20.2% (C.I. 0-49%) and the unique environmental error variance was 62.3% (C.I. 51-73%). About a third of the variance was explained by the additive genetic component for any illicit drug **A/D,** and marijuana **A/D,** while 53.5% (C.I. 41-66%) of the variance was explained by the additive component for stimulants. The bivariate analyses showed significant additive genetic effects common to **PTSD** and drug **A/D** with non-significant shared environment effects. The bivariate models showed that common additive genetic effects explained 42.1% of the variance in risk for any illicit drug **A/D,** 42.0% of the variance in risk for marijuana **A/D,** and 54.9% for stimulant **A/D.** However, the low prevalence rates for marijuana and stimulant **A/D** may be a reason for ambiguous results of the shared environmental effect.

NEUROBIOLOGY OF PTSD AND DRUG ABUSE

Dr. Kosten provided an overview of the current knowledge on the neurobiology of **PTSD** relevant for substance abuse. Psychophysiological findings in **PTSD** support increased sympathetic nervous system reactivity including excessive sweating, tachycardia shortness of breath and anxiety. Biochemical correlates of **PTSD** such as 24 hour urinary cateholamines, have also supported increased sympathetic activity. Low levels of 24 hours urinary cortisol. however, have been found in veterans with **PTSD,** which may be a result of chronic noradrenergic activation and decreases the release of corticotropin releasing hormone **(CRH)** and **ACTH.** Beta endorphinm (coreleased with **ACTH)** levels are also low and may lead to relapse to opioid abuse in former abusers. This delayed pattern of drug abuse in humans with **PTSD** has a parallel in drug self-administration by animals after inescapable shock exposure **(IS),** which is a model of **PTSD.** After an **IS** exposure, animals self-administer drugs such as alcohol in a delayed pattern that is distinct from use during acute stress. Finally, drug withdrawal states often exacerbate **PTSD** symptoms by activation of central noradrenergic systems, and treatment of withdrawal may provide simultaneous reduction in stress related symptoms. Thus, increased adrenergic activity might well lead to substance abuse for acute self-medication, although chronic use of these substances worsen the underlying **PTSD.** In the future, the animal models of **PTSD** may help clinicians to select the most promising medications with the least abuse potential for clinical testing of efficacy in **PTSD.**

DISCUSSANT

Dr. Breslau highlighted the findings common to the studies presented earlier, and discussed them in the light of the genetic and neurobiological findings presented by Drs. True and Kosten. Despite the differences of sample. similarities were found between Dr. Triffleman's study from a treatment-seeking sample and Drs. Chilcoat and Breslau's findings from a general population study. These included: a high prevalence of trauma but a much smaller prevalence of **PTSD;** a higher prevalence of **PTSD** in women; a small ratio of the current to lifetime **PTSD;** and no evidence of association between exposure, per se, and psychiatric problems. Neither Dr. Chilcoat nor Dr. Price's study found evidence supporting the role of drug abuse in increased risk for exposure to trauma. There appears to be weak evidence of drug abuse increasing the vulnerability of **PTSD.** The evidence is stronger for the self-medication hypothesis given the findings of **PTSD** increasing the risk of drug abuse. However, Dr. True's paper suggests a strong genetic contribution to the co-occurrence of **PTSD** and drug use disorders, Dr. Kosten's summary also leads to the possibility that distinct abnormality in patients with **PTSD** might represent pre-existing vulnerabilities. These findings together suggest the importance of identifying pre-existing vulnerabilities that may be common to substance abuse and **PTSD.**

Authors and Titles of Presentations:

R. K. Price. A nosologic and etiologic overview. E. Triffleman, J. Poling, B. Rounsaville. Characterizing trauma exposure and PTSD among treatment-seeking substance abusers. H.D. Chilcoat, N. Breslau. Testing causal pathways between PTSD and drug use disorders. R. K. Price, B.D. Li. E.L. Spitznagel. PTSD and drug abuse: Time sequence and early predictors. W. R. True, S. A. Eisen, H. Xian, J. Scherrer, M. Lyons, A.C. Heath. Common risk factors for post-traumatic stress disorder and drug abuse/dependence: Bivariate twin analyses. T. R. Kosten. Neurobiology of PTSD and drug abuse. N. Breslau. Discussant.

SYMPOSIUM XV

SUMMARY - CPDD SYMPOSIUM ON HIV IN THE BRAIN

B. J. Hoffer[1], H. E. Gendelman[2], S. J. O'Brien[3], N. Sacktor[4], and C.* A. *Wiley[5]

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Dr. Ned Sacktor provided a comprehensive review of HIV dementia HIV dementia affects 15-20% adults and children with AIDS. HIV dementia is rare during the asymptomatic phase. It is an indicator of AIDS in only 3% of cases. Risk factors for the development of dementia include lower CD4 count, anemia, low weight, and constitutional symptoms. Progression of HIV dementia is variable with 30% cases having a slow course. Rapid progression is associated with lower CD4 count and evidence of CNS immune activation. The protective effect of combinations of antiretroviral medications and protease inhibitors is uncertain. In one longitudinal cohort of homosexual men, the Multicenter AIDS Cohort Study (MACS). with the past 1 1/2 years, the incidence seems to be decreasing.

The most common presenting symptoms are problems with memory, gait difficulty, mental slowing, and depressive symptoms. Early symptoms affect behavior, cognition. and motor function. Late features include severe apathy, psychomotor retardation, poor insight, delirium, and increased tone and reflexes. Frequently associated conditions include myelopathy, peripheral nerve disease, and seizures. Cognitive decline, specifically in tests of psychomotor speed that is sustained in a subsequent follow-up visit, is an excellent indicator of an increased risk of developing dementia, AIDS, and death.

In intravenous drug users (IVDU), cognitive impairment may be HIV-related. due to the effect of chronic drug/alcohol use, or due to non-specific reasons such as fatigue, mood changes, insomnia medication side effects, or systemic disease. Dr. Sacktor compared neuropsychological testing in 2 longitudinal cohorts, a cohort of IVDU's, and a cohort of homosexual men. ln the IVDU cohort, HIV- and HIV+ IVDU's scored lower on neuropsychological tests compared to age and education matched norms in the homosexual cohort. At the baseline visit, there was no difference between HIV+ and HIV- IVDU's on any neuropsychological test after adjusting for education. In a long-term 4-year follow-up, there was no difference between AIDS-free HIV+ and HIV- IVDU's on any neuropsychological test after adjusting for education. However, HIV+ IVDU's who had progressed to AIDS had mild decline in cognitive performance compared to asymptomatic HIV+ IVDU's. This pattern in IMU's is similar to longitudinaI studies in homosexual men. Therefore, it is concluded that intravenous drug use is not a risk factor for progression of cognitive symptoms in HIV infection.

In terms of mechanisms, HIV virus does not infect neurons directly. Rather, HIV infects macrophages causing macmphage activation, expression of endothelial adhesion markers, blood-brain barrier damage, and with induced inhibitory control of macrophage activation, macrophages release a cascade of neurotoxins which stimulate, astrocyte proliferation causing neuronal death. Potential neurotoxins include cytokines, such as TNF-alpha, arachidonic aid and its metabolites, platelet activating factor, free O_2 radicals, nitric oxide (NO), glutamate, and quinolinic acid. Recently, Immunological nitric oxide synthase (iNOS). an important enzyme for the generation of NO in the CNS, was found to be increased in patients with severe dementia in postmortem cortical tissue. Furthermore, gp 41 induced iNOS in primary cultures of mixed rat neuronal and glial cells. and iNOS killed neurons through an NO-dependent mechanism. Thus, gp41 induced NO formation may contribute in part to the pathogenesis of HIV dementia. It is unlikely that any one of these neurotoxins acts alone: rather, it is probably a cascade of many of these neurotoxins that lead to the problems in HIV dementia

Recent controlled drug trials suggest that cognitive impairment associated with HIV dementia is in part reversible, suggesting that there may be reversible and irreversible components to the pathophysiology of HIV dementia. In the reversible component, there is limited CNS macrophage infection, macrophage activation with release of cytokines. platelet activating factor, and free O_2 radicals causing astrocytic reaction and neuronal dysfunction. In the

irreversible component, there is productive CNS macrophage infection with intense macrophage activation. With decreased CD4 inhibitory control, there is a release of more inflammatory mediators and NO, causing astrocytic reaction, blood-brain barrier disturbance, and neuronal death.

Dr. Clayton Wiley also presented a comprehensive review of HIV encephalitis. Infection with Human Immunodeficiency Virus (HIV) is followed by a chronic and abundant systemic replication of HIV. While macrophage tropic virus appears to be particularly important in transmission, during the decade of so-called "latent-phase" infection, cells within lymphoid structures produce the majority of virus. Late in infection severe immunosuppression accompanies depletion of the host CD4 t-cells. Where the virus resides al this stage of infection is unknown, however, patients surviving for extended periods of time with immunosuppression do have a large amount of virus within me brain. While there has been some controversy regarding the association between HIV encephalitis and the neurobehavioral symptomatology, clearly patients with a high central nervous system (CNS) viral load are more likely to exhibit neurocognitive abnormalities.

One reason for the controversy associating brain viral load and clinicaI symptomatology is that CNS viral load can only be assessed through post-mortem analysis. A systemic surrogate marker of brain viral load would substantially aid clinical studies. Because of the blood brain barrier (BBB), levels of virus in the blood would not be expected to be concordant with CSF viral loads. Unfortunately, even CSF which is within the BBB is frequently discordant with the brain parenchyma with respect to a wide variety of markers.

Dr. Wiley has found that elevated HIV RNA levels in post-mortem CSF samples is associated with high viraI load in brain tissue at autopsy. Analysis of longitudinal samples showed that this relationship was only true in Iater stages of life. If, as he has hypothesized, elevated HIV load in the brain is a substrate for HIV neurocognitive disorders then his findings would suggest that antemortem-CSF HIV-RNA would be a useful clinical surrogate marker for neurocognitive disorders only in the later stages of disease

The close correlation between CSF and brain tissue viral loads suggests that in the months preceding death, there may be significant utility to assaying viral copy number in CSF, not only to guide clinical therapy for neurocognitive disorders but also to help in assessment of efficacy of experimentalanti-viral therapies. The hypothesis is that elevated brain viral load precedes the development of these late stage neurocognitive abnormalities and neuropathology. Therefore, identifying patients with elevated CSF viral load offers a window of opportunity, during which treatment of CNS HIV infection might prevent the development of a fixed neurologic lesion. Having the CSF as a surrogate marker for brain viral load will expedite me development of effective CNS therapies.

Dr. Howard GendeIman's presentation focused on cellular and molecular mechanisms of HIV infection in me CNS. The neuropathogenesis of central nervous system (CNS) HIV infection revolves around mononuclear phagocytes, brain macrophage/microglial infection and immune activation in brain. Macrophages secrete neurotoxic factors that elicit neuronal injury and lead to neural ceII death associated with the significant cognitive and motor impairments seen during progressive neurologic disease Neurotoxic factor production requires virus entry and replication. the evolution and selection of neurovirulent and HIV strains and the production of viral and cellular immune factors injurious to human neurons. The Ievels of viral replication are not always associated with cognitive and molor impairments. This has led to the notion that viral replication induces autocrine/paracrine production of cellular viral factors leading to metabolic encephalopathy. Dr. Gendelman's lab has developed *in vitro, ex vivo,* and animal model systems to study the effects of HIV-1 replication in brain tissue. The isolation/propagation of primary microglials, astrocytes, and human endothelial cells combined with cellular immune assays that demonstrate the effects that viral replication has on the secretion of immune neurotoxic factors, has enabled his laboratory to establish laboratory models of AIDS-dementia complex. Recently, his development of bIood-brain barrier model, the isolation of neurovirulent, microglial tropic viraI strains and the improvement murine animal models for neurological impairments has further permitted the laboratory to develop novel potential therapeutic approaches. A key hypothesis is that viral infection allows passage of monocytes into the brain.

Dr. Stephen J. O'Brien discussed genetic factors in AIDS resistance. A portion of the epidemiologic heterogeneity that is characteristic of the HIV-AIDS epidemic is likely to be the consequence of variation of genes whose products play a role in HIV pathogenesis. To identify such genes, Dr. O'Brien's group assembled lymphoblastoid β-cell lines from nearly 10,000 patients enrolled in prospective AIDS cohort studies. Genomic DNA from these individuals were screened for departures in population genetic equilibrium among population subdivisions of the cohorts with different infection or disease outcomes. Human polymorphisms for both candidate genes (e.g., immune response, genes, cytokines, receptors, HLA, oncogenes) and anonymous polymorphic marker loci were screened for allelic, genotypic and paired haplotype disequilibrium in cohorts of different risk groups, Ascertainment of previously unknown loci linked to anonymous markers was enhanced by using a new method termed Mapping by Admixture Linkage Disequilibrium (MALD). Genetic associations wee detected for two loci, HLA and CCR5 in AIDS cohorts for both infection effects and disease progression effects in HIV-1-infected patients. HLA contains several loci that mediate immune recognition and clearing of HIV infected cells. CCR5 encodes a chemokine receptor molecule. that serves a second co-receptor required for HIV infection of macrophage and monocyte lineage cells. Identification of "restriction genes", which delimit HIV infection and spread, provide important opportunities for drug, peptide and gene therapy by targeting cellular functions required for HIV infection and disease pathogenesis.

SYMPOSIUM XVI

COMBINED COCAINE AND OPIOID ABUSE: FROM NEUROBIOLOGY TO THE CLINIC

J. K. Rowlett[1], S. S. Negus[2], T. S. Shippenberg[3], N. K. Mello[2], S. L. Walsh[4], and R. D. Spealman[1]

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INTRODUCTION

Many intravenous polydrug abusers inject cocaine in combination with heroin either by injecting the two drugs serially or by combining the drugs in solution and taking them simultaneously (commonly know as a "speedball"). The increasing use of speedballs has led to their widespread inclusion in recent epidemiological studies of drug abuse in the United States. It has heen reported that speedball abusers exhibit a more severe psychopathology compared to other cocaine abusers, are more likely to fail in drug abuse treatment and are al increased risk of contracting HIV infection. Despite the prevalence of speedball abuse, the interactions between cocaine and opioid drugs are not well understood at either the clinical or preclinical level. This symposium examined current research on the pharmacological interactions between cocaine and abused opioids in order to provide a synthesis of current knowledge and to suggest potential directions for future research.

Neurobiology of cocaine and opioid abuse

The rewarding effecls of cocaine have been attributed to an increase in the functional activity of mesolimbic dopamine (DA) neurons. Evidence that endogenous as well as exogenous opioid agonists modulate the activity of this DA system has also been presented. This talk reviewed neurochemical data regarding the effects of cocaine administered alone or in combination with opioids upon mesolimbic DA neurotransmission as well as the role endogenous opioid peptide systems play in regulating the activity of mesolimbic neurons. The influences of cocaine upon opioid peptide gene expression and the dynamics of endogenous opioid peptide systems also were reviewed along with the relevancy of these findings for the developmenl of therapeutic agents to treat speedball abuse.

Discriminative stimulus effects of cocaine/opioid combinations

Drug discrimination procedures have been used extensively to characterize the pharmacological mechanisms of action mediating the abuse-related effects of cocaine and *mu* opioids, as well as between those drugs. In most of these studies, subjects were trained to discriminate either cocaine or a mu agonisl from vehicle and the effects of cocaine alone, *mu* agonists alone, and cocaine/mu agonisl combinations were examined. An important goal of these studies has been to evaluate the hypothesis that cocaine and *mu* agonists potentiate each other's discriminative stimulus (DS) effects. The results have been variable across studies, and in many instances, across subjects within a study. In subjects trained to discriminate cocaine from vehicle, *mu* agonists sometimes produce high levels of cocaine-appropriate responding and/or enhance the DS effects of cocaine. Similarly, in subjects trained to discriminate mu agonists, cocaine sometimes generalizes to the training stimulus and enhances the DS effects of the *mu* agonist. In many subjects, however, cocaine and mu agonists do not cross generalize and either do not alter or attenuate the other's DS effects.

Another approach for examining the DS effects of speedballs is to train subjects to discriminate a mixture of cocaine and a mu agonist from vehicle. We recently trained rhesus monkeys to discriminate a 10:1 mixture of cocaine and heroin (0.4 mg/kg cocaine + 0.04 mg/kg heroin). Increasing doses of the 10:1 mixture produced a dose-dependent generalizalion to the training stimulus, and both cocaine and heroin alone generalized completely to the training stimulus. In addition, many cocaine-like drugs (CFT, amphetamine, bupropion) and heroin-like drugs (alfentanil, fentanyl, morphine) produced high levels of speedball-appropriate responding, The DS effects of the

cocaine/heroin mixture could be antagonized by combined treatment with the DA antagonist flupenthixol and the opioid antagonist quadazocine, but either antagonist atone was less effective. These findings suggest that the DS effects of the cocain/heroin mixture includes aspects of both cocaine and heroin and that the mixture did not produce DS effects that were qualitatively different from either cocaine or heroin alone.

Reinforcing effects of cocaine/opioid combinations

Because both cocaine and mu opioid agonists function as reinforcers, it is possible that the reinforcing effects of cocaine and opioid combinations are enhanced compared to either cocaine or mu agonists alone. To examine this possibility, rhesus monkeys were trained to respond under a progressive-ratio (PR) schedule of intravenous drug injection. Under this schedule, the response requirement for obtaining an injection of drug is increased until responding stops and a measure of reinforcing efficacy can be defined as the maximum response requirement a subject will complete to obtain an injection. Using this procedure, cocaine dose-effect curves for injections/session typically are monophasic, i.e., responding increases with dose until an asymptote or a peak is reached. Heroin dose-effect curves, by contrast, are biphasic functions, i.e., increase to a peak and then decrease. When cocaine was combined with heroin, low doses of cocaine and heroin that did not maintain behavior when tested alone did so when tested in combination. Furthermore, combination with heroin resulted in a leftward shift in the cocaine dose-effect curve, indicating that heroin increased the potency of cocaine as a reinforcer. However, maximum injections/session for cocaine combined with heroin were not different from cocaine alone. suggesting that the relative reinforcing efficacy of combinations of cocaine and heroin were not greater than that of cocaine alone. The enhanced potency of the reinforcing effects of cocaine by combination with heroin may be a contributing factor to the abuse of speedballs.

Medications development for the treatment of combined cocaine-opioid abuse

The combined abuse of pharmacologically dissimilar drugs complicates the search for effective treatment medications. We have found that buprenorphine, an opioid mixed agonist-antagonist, significantly reduced both cocaine and opioid self-administration by rhesus monkeys and human polydrug abusers. We recently studied the effects of buprenorphine on self-administration of cocaine/heroin combinations using a model of speedball abuse developed in our laboratory. In this procedure, drugs and food (1 gm banana pellets) were available in four daily sessions on a second-order FR4 (VR16:S) schedule of reinforcement. Each heroin/cocaine combination was available for 10 consecutive days, and monkeys were treated daily with either saline or buprenorphine.

Daily treatment with 0.237 mg/kg/day buprenorphine shifted the speedball dose-effect curves for heroin+0.001 mg/kg/inj cocaine downward and to the right. Buprenorphine also decreased self-administration maintained by speedball combinations of heroin+0.01 mg/kg/inj cocaine and heroin+0.1 mg/kg/inj cocaine. However, buprenorphine was less effective in decreasing self-administration maintained by heroin in combination with 0.1 mg/kg/inj of cocaine than with 0.01 mg/kg/inj of cocaine. Thus, buprenorphine's effectiveness in decreasing speedball self-administration decreased as the dose of cocaine increased. These findings suggest the usefulness of the speedball model for evaluation of the effectiveness of medications for the treatment of speedball polydrug abuse. Our findings in rhesus monkeys are concordant with clinical trials, which found that buprenorphine decreased both cocaine and heroin abuse in polydrug abusers.

Human laboratory studies on cocainel/opioid combinations

Recent studies by Foltin, Fischman and colleagues and by Walsh and colleagues have evaluated the acute subjective and physiological effects of cocaine in combination with opioid mu agonists. The subjective effects of various dose combinations of mu agonists and cocaine were greater than those produced by either drug alone on measures such as "drug liking" and "high". The qualitative profile of subjective effects produced by the opioid/cocaine combination was toughly equivalent to the sum of effects produced by the two drugs singly, rather than producing novel or unique subjective effects. The cardiovascular effects of cocaine, including tachycardia and pressor action, were enhanced when cocaine was administered in the presence of the mu agonist. Other studies have compared the effects of cocaine in opioid-dependent subjects during chronic maintenance on mu opioid agonists. In studies of methodone-maintained patients, the subjective response to cocaine (e.g., "magnitude of drug effect", "good effect")

was significantly greater compared to control subjects. Similarly, some studies in buprenorphine-maintained patients reported that the subjective response to cocaine was either enhanced or not appreciably altered compared to a control condition. Enhanced cardiovascular responses to cocaine were also observed under these chronic opioid dosing conditions. These and other fmdings suggest that administration of mu agonists generally enhances the effects of cocaine in humans, particularly the positive subjective responses to cocaine. This enhancement of subjective effects has been observed following pretreatment with opioids under both acute and chronic dosing procedures. Whether or not enhancement of physiological responses is observed appears to depend upon the specific opioid agonist chosen for testing as well as the range of test doses. The observed enhancement of subjective responses produced by speedball combinations may account for the high prevalence of speedball abuse as well as the persistent abuse of cocaine in patients enrolled in opioid maintenance therapy programs.

Summary and Future Directions

This symposium has provided a synthesis of recent research aimed at understanding the interactions between cocaine and abused opioids. Dr. Shippenberg described neurobiological evidence that both exogenous and endogencus opioids can modulate the actions of cocaine in the mesolimbic DA system. There is also evidence for a reciprocal influence of cocaine on the endogenous opioid peptide system. Understanding the interplay between these two systems continues to be a major challenge facing research in this area. The escalation of dual cocaine-opioid abuse has prompted renewed interest in the interactions between these drugs in relevant animal models of addiction. As discussed by Drs. Negus, Rowlett, and Mello, an important, though still elusive, goal of this research is to characterize the complex effects that combinations of cocaine and opioids can have in behavioral experiments. Growing evidence indicates that prominent individual differences exist in the DS effects of cocaine-opioid combinations, yet virtually nothing is known about their neurobiological correlates. Along similar lines, studies involving i.v. drug self-administration in monkeys suggest that low doses of cocaine and heroin, which fail to maintain self-administration when tested singly, do so if combined under a progressive-ratio schedule of drug injection. However, this appears not to be the case under other conditions, where self-administration of cocaine may be reduced by the addition of high doses of heroin. Human laboratory studies reviewed by Dr. Walsh have generally shown that opioids enhance the positive subjective effects of cocaine, although the findings do not fit easily within any simple model of drug interaction. Given the prevalence of cocaine use among untreated opioid abusers and methadone-maintained patients, there is a critical need to identify pharmacological mechanisms underlying speedball abuse in order to develop effective therapeutic strategies. By providing a state-of-the-field review of multidisciplinary research, this symposium has helped lay the groundwork for achieving this goal.

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WORKSHOPS

MAKING AUDIENCES AMAZED, NOT GLAZED: TECHNIQUES FOR IMPROVING PRESENTATIONS

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During the last CPDD meeting, we were impressed with the number of presentations that suffered greatly even though the content was good. Despite use of the traditional format - background, methods, results and conclusions - the hypothesis was not always stated and then justified in the conclusions. Screen colors or design often distracted from the data Material was often cluttered, overly abundant, and difficult to mad. Many times this appeared to be so blatant as to suggest a total disregard of the audience. This disregard was not restricted to any particular level of seniority or experience. It is clear that few of us cannot improve our style and method of communication. From the presenters standpoint, better communication may result in a tangible reward. For the audience, the results are more interesting and less tedious.

A workshop was conducted which focused on improving oral presentations. It was divided into two parts: 1) improving screen-presented material, and an introduction to PowerPoint; and 2) suggestions for improving oral communication, with a series of "do's" and "don'ts." Subjects which were covered are shown below:

- Screen--presented material
- An introduction to PowerPoint, an example of presentation software
- Colors/Contrast/Compatibility
- Text selection: type size. font, BOLD
- The amount of information per screen
- Limitations of the # of different templates per presentation
- Built-m screen distractions
- Limiting the number of graphics (and type) per screen
- Presenting a full page of text OR NOT!
- Complex tables
- Consistency of screens
- Distracting symbols/logos
- Thickness of lines on graphs

- Giving an Oral Presentation (Tricks of the Trade)
- The Art of Speaking Well
- Using a Microphone
- Timing is Everything
- Speaking to groups of different sixes
- Body Positions, and the (not so) subtle messages they give your audience
- Gesttures and Pauses
- Stating the question or hypothesis; conclusion should reiterate the question and then show or not show support for it
- Restating the question from the audience when the microphone is not used
- Putting it together to turn your audience On instead of Off

FOOD, SEX AND DRUG INCENTIVES: IMPLICATIONS OF A COMMON SUBSTRATE FOR DEVELOPMENT OF ANTI-CRAVING MEDICATIONS

Co-Chairs: F. Vocci[1] and A. R. Childress[2]
Panelists: B. Gosnell[3], A. Phillips[4], D. C. S. Roberts[5], and A. R. Childress
Discussant: F. Vocci

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NIDA MDD Workshop

SUMMARY

Cocaine and opiates activate brain systems responsible for the reinforcing properties of "naturaI" rewards such as food and sex. This overlap in brain substrates may help explain the subjective phenomenology of drug effects: e.g., both male and female users describe the euphorigenic tush produced by cocaine and opiates as similar to, but several times stronger than, sexual orgasm (cocaine can trigger ejaculation in males), and they liken the desire for cocaine to strong sexual anticipation. Cocaine users note the 'taste' of the drug in the back of their throat both during use of the drug and in anticipation of it ("I wanted it so much I could already taste it"). These kinds of parallels suggest that research on the incentive states associated with food and sex may inform our understanding of incentive-based drug craving, and may facilitate the search for agents which would ameliorate it. To this end, the symposium surveyed state-of-the art knowledge on substrates of drug, food, and sexual reinforcement, and on the incentive states ("craving") associated with each. For each of the three areas (food, sex, and drugs), a basic scientist initially reviewed putative brain substrates of reinforcement and offered animal models of incentive motivation, followed by a clinical researcher (Dr. Childress) describing the human findings. The discussant and Co-Chair, Dr. Vocci, summarized the panelists' findings and led an open discussion on their implications for the development of anti-craving medications

Dr. Gosnell (food) noted that though food intake is essential for the survival of all organisms, not all feeding is in direct response to caloric needs. Foods rich in sugar or fat are generally considered quite pleasurable, and excessive consumption of such foods is often associated with obesity and eating disorders. Several tines of evidence indicate that endogenous opioids play a role in mediating the rewarding aspects of foods, and that the processes mediating food reward may share some of the mechanisms mediating drug reward. Opioid agonists stimulate food intake, and antagonists generally cause a reduction in intake. These effects are more pronounced for palatable foods and fluids than for water or standard lab chow, and appear to be more effective in satiated animals than in hungry animals. It has; therefore, been proposed that opioids participate more in me mediation of palatability than in the regulation of energy balance. There is some overlap between the brain areas associated with opioid stimulation of food intake and those associated with drug reward. and the pattern of receptor selectivity of agonists that will stimulate ingestive behavior when injected into certain regions (mu, delta > kappa) is similar to that seen in several other reward-relevant paradigms. Finally, the intake of sweetened food or fluids has been shown to alter the analgesic effects of morphine and to predict the self-administration of morphine, alcohol and amphetamine. There is a high co-morbidity for eating disorders and substance abuse, and continued research on mechanisms mediating the rewarding aspects of food may offer new insights into the causes and treatments of both disorders.

Dr. Phillips (sex) reviewed data underscoring the importance of brain dopamine (DA) systems for sexual behavior in the male rat. In the study of sexual behavior, a distinction is usually made between motivation and performance. DA is implicated in both aspects, with central administration of dopamine agonists facilitating both performance (copulatory rate, ejaculation and penile reflexes) and motivation (copulatory initiation, conditioned anticipatory or preparatory responses). Conversely, disruption of the DA system either through lesions or chemical

blockade with antagonists generally often disrupts performance and blunts motivational indices. *In vivo* microdialysis studies show that DA levels in the nucleus accumbens increase dramatically during the anticipatory (as soon as the receptive female is placed behind a proximal screen) and consummatory phases of sexual behavior in the male rat, dropping shortly thereafter. Electrovoltammetry studies confirm a similarly dynamic fluctuation in DA signal, with increases occurring in response to cues for the female, prior to copulation. Taken together, these data suggest a prominent role for limbic dopamine systems, particularly nucleus accumbens, in sexual incentive motivation.

Dr. Roberts (drugs) reviewed two decades of evidence for involvement of brain dopamine systems in cocaine and heroin reinforcement, noting that though these drugs are both powerfully rewarding, they also demonstrate some interesting and potentially important differences. Following an initial prime, cocaine self-administering animals will respond vigorously for the 'next' dose of cocaine. In contrast, heroin-trained animals receiving the first heroin injection of the session are not "primed" to respond for the next dose -- though they will emit hundreds of lever presses for the *initial* dose of the session. This difference. which may entail more than the different pharmacokinetics of the two drugs, may explain one difficulty in attempting substitution approaches for stimulants such as cocaine. Another difficulty in finding effective treatment agents may arise from the animal models used. Self-administration paradigms with FR1 response requirements are relatively insensitive to changes in drug motivation; a paradigm such as the progressive ratio (PR) schedule is more useful in this regard. Another model which shows promise for measure of drug motivation is a discrete trials paradigm, in which animals given limited access to drug eventually develop a circadian schedule of drug administration (administering drug during the active phase of the light-dark cycle). Using this paradigm, pre-treatment with the GABA B agonist baclofen (at doses that did not disrupt normal food and water intake) was found to delay onset of cocaine administration by 4-6 hours. lf CABA B agonists reduce drug incentive motivation (potentially by modulating brain DA release), they may offer significant promise as "anti-craving" agents in humans.

Dr. Childress offered clinical data indicating potential overlap of positive incentive states, including (male) patients' descriptions of the striking similarity between cocaine pleasure and sexual pleasure, and between cocaine desire aud sexual desire. This overlap is supported by preclinical data suggesting the importance of limbic DA systems in both states. Using *in vivo* brain imaging, it is now possible to study the incentive states for drugs and other appetitive rewards directly. Dr. Childress' recent study using positron emission tomography (PET) found a pattern of limbic (amygdala and anterior cingulate) increases and basal ganglia decreases in relative regional cerebral blood flow (rCBF) of cocaine users during a video which induced craving. This pattern did not occur in cocaine-naive controls, and the two groups did not differ in the response of other compared brain regions. These findings indicate limbic activation is one component of are-induced cocaine craving, and amygdalar activation to cocaine cues has now been confirmed by two other imaging teams. Imaging is now ongoing to find whether limbic activation is similarly involved in cue-induced desire for other rewarding drugs (opiates) and for natural rewards such as sex. If significant overlap is demonstrated, agents found helpful in one arena might show significant benefit in the other. On the other hand, significant overlap in positive incentive substrates would present the challenge of ending agents which can effectively modulate drug incentive motivation, but without completely blunting the ability either to experience, or to anticipate, normal pleasures.

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WORKSHOP: FIGHTING BACK—COMMUNITY INTERVENTIONS TO REDUCE DRUG ABUSE

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PROGRAM DESCRIPTION

The Robert Wood Johnson Foundation (RWJF) Program, "Fighting Back— Community Initiatives to Reduce Demand for Illegal Drugs" was born in 1989 out of a concern that the national issue of drug and alcohol abuse was a serious epidemic in our nation's communities. The Foundation M realized that alcohol and drug abuse seriously affected its national health programs for the elderly, the homeless, and the school based health initiatives. At the inception of Fighting Back, a National Program Office at Vanderbilt University Medical Center was established to oversee the program and a National Advisory Committee of specialists in substance abuse was recruited to assist in choosing the grantees.

Using a rigorous grant review process, 14 communities of 100,000 to 250,000 persons were chosen to develop community-wide strategies to change the use and abuse patterns of illegal drugs and alcohol in their areas. The Fighting Back (FB) communities chosen were sometimes an entire city, such as Vallejo, CA; Santa Barbara CA; Little Rock, AR; Worcester, MA; New Haven, CT; and Columbia SC; and parts of larger communities, such as Oakland, CA; Northwest, NM; San Antonio, TX: Kansas City, MO; Milwaukee, WI; Charlotte, NC; Washington, DC; and Newark, NJ.

Each FB community was required to define the nature and extent of its alcohol and drug abuse problem before it developed strategies. Each community was to organize a Citizens Task Force to engage all persons in the community affected by the problem. City officials, the police, judges, and neighborhood groups were all involved from the start., A Consortium of Providers, those who provided services to persons with substance abuse problems, was also required.

Funds were provided for two years of planning and five years of implementation. Each FB community developed its own set of programs following a set of guidelines. These included a public awareness campaign to keep the public informed, a prevention program targeted at children, youth, and young adults, and a broad range of accessible options for treatment and relapse prevention.

At each juncture of the planning and implementation process, the FB communities were required to review the progress of each initiative and submit a complete proposal to the reviewers. If a FB site made substantial progress. funds for the implementation were provided. This meant that some sites had funds withheld until satisfactory progress could be. demonstrated. At the mid-course of the implementation period, all sites submitted a revised proposal which was reviewed with the NPO, the National Advisory Committee, and the Foundation staff. At each major review period, the RWJF Board reviewed the recommendations by the staff before the additional funds were allocated. This process of refinement and review contributed to improved approaches as all of the participants involved in the FB programs became more experienced.

In eight years of implementation, the FB communities have organized a broad array of initiatives to counter the plague of alcohol and illegal drug use and abuse. One of these important initiatives is "Insure the Children" in Little Rock, AR. "Insure the Children" provided insurance for treatment of substance abuse or addiction to every student in the Little Rock school system. Those children identified by principals, teachers, or parents as having a problem with illegal drugs or alcohol were given an array of options, including inpatient and outpatient treatment. Evaluation showed that those treated had improved behavior both in the classroom and at home.

Gallup, NM, the site of Northwest New Mexico Fighting Back, or "Drunk Town, USA", developed a comprehensive approach for treatment of the intoxicated Navajos. Previously, the Navajos were placed in a 'drunk tank" to recover. No care of any kind was provided. Gallup started a humane treatment program at the Na'Nizooshi Treatment Center which has become the model for treatment of the Navajo alcoholoc/drug addict. Readmissions to this facility and admissions for alcohol/drug related injuries and illnesses in the Indian Health Service Hospital nearby have fallen steadily.

In Charlotte, NC, the "Stop the Killing" campaign (a church based program to reduce the drive-by shootings and cocaine purchasing in District II in Charlotte) has had significant impact on the perceptions of the community residents about neighborhood safety. The involvement of the community in making a difference in their lives and the lives of others has drawn the community together and made the streets safer.

In some of the FB communities, the effect of community policing has been particularly noticeable. In LittlIe Rock, Kansas City, New Haven, and Columbia. police stationed in neighborhood precinct buildings work collaboratively with the neighborhood residents to watch for crack cocaine sales in abandoned buildings and on corners. In Little Rock, a Codes Enforcer is part of the team provided by the city government to hold absentee Iandlords accountable for their dilapidated property. Neighborhood organizations work with the community police and the Codes Enforcer to monitor the activities of liquor store owners and drug dealers.

In three of the FB communities, the programs have been funded by the passage of taxes to sustain them. In McKinley Country, NM, the citizens passed a liquor tax. Kansas City passed a sales tax to fund alcohol and illegal drug reduction initiatives. In Little Rock, citizens passed a sales tax for the "future of Little Rock" which assures funding for the FB programs. In addition, the combination of citizen feedback and the passage of sales tax contributed to a revision to the plan for the Neighborhood Alert Centers. The number of planned centers was increased from 8 to 15 as part of the tax initiative.

Further programs created and sponsored by FB include reductions of billboard advertising in minority communities, in Milwaukee and San Antonio, and in mentoring programs for youth in Santa Barbara, Oakland, VaIlejo, Columbia, and San Antonio. Drug court diversion efforts by the judges in Santa Barbara and Worcester moved youth offenders from jail to treatment while treatment in the criminal justice system was popular in Columbia and Vallejo. Over 300 innovative initiatives like these have been started in the Fighting Back communities.

PROGRAM EVALUATION

As part of the Fighting Back program, a set of outcome-oriented evaluation studies of the program was designed to measure changes over time in community wide measures of substance use, abuse, and harm. Four types of studies were Iaunched: 1) surveys of adults and youth to assess drug and alcohol use and attitudes; 2) assessment of social indicators of harm caused by substance abuse; 3) ethnographic studies of the communities' response; and 4) systematic tracking of the program implementation in each community. The evaluation compares each FB site with two or three sites within each state.

The survey will be conducted every two years, starting in 1995, with respondents aged 16 to 44. The questions derive from previously validated national surveys. A meta-analysis of school surveys supplements the FB survey.

The indicators include data from the Uniform Crime Reports, deaths related to substance use, deaths from single vehicle auto accidents, and trends in treatment. The indicator data will go back to 1980.

Ethnographic studies of the communities assess the social processes and development of the community coalitions. These extended case studies clarify the dynamics and context of the life cycle of each program interpreted in the light of changes in the larger community, the region, and the country. Tracking the many strategies employed by the FB communities permits analysis in terms of their relative attention to dimensions like substance supply, the individual, the environment, and the life cycle of the program.

To date, significant differences in outcome between FB and the comparison communities have not emerged.

Among the factors contributing to these interim findings are the confounding of the comparisons by CSAP and other funding of the comparison sites, and the complexity of the substance abuse system, so that long term efforts are requited to bring about changes in both physical and social environments. An additional comparison will be made between the progress of the eight communities that have been selected for an additional five years of refunding and the six communities for which funding was terminated after five years.

WORKSHOP DISCUSSION

Discussion at the workshop identified some critical limitations of the evaluation studies and some possible alternative approaches. The current evaluation strategy was developed after implementation of the Fighting Back initiatives began, and this has led to many of the difficulties. One major limitation is that "head to head" comparisons of the Fighting Back cities with comparison sites within the same state, conducted many years after program initiation, might not detect the actual impact of Fighting Back, if, as is likely, the comparison cities also implemented the successful initiatives developed by Fighting Back cities. Dissemination of effective strategies (or diffusion of effective strategies) to the control cities would ordinarily be considered a positive outcome of a community-wide experimental approach, but in the evaluation approach being utilized, dissemination or diffusion serves to "contaminate" the research and decrease the likelihood of demonstrating positive effects of the initiatives.

A second but related limitation is that considerable new resources were made available to both the control and Fighting Back cities during the period of Fighting Back implementation. The resources available to cities under Fighting Back were relatively small ($3 million), especially in comparison to the resources available through combinations of federal block grant funds and other special initiatives (e.g., HUD grants, empowerment zones. CSAP and CSAT projects. etc.). The cumulative effects of these resources may have dwarfed the impact of Fighting Back, making it more difficult to evaluate its impact. Some of these resources were modeled after Fighting Back (e.g., Community Partnership Grants) and only became available to control cities because of Fighting Back, hut the current evaluation strategy would not "credit" Fighting Back for having this effect.

A third limitation of the evaluation methodology is that it does not account for the considerable variability of Fighting Back interventions. Fighting Back supported many activities within each of the cities, and it supported a different set of activities in each of the cities. Assuming that some, but not all of the interventions were effective, the evaluation methodology would not be able to ascertain which components were effective, which were ineffective, and which were counterproductive.

Some alternative evaluation strategies and models were then discussed. One conceptual model would view Fighting Back as developing a platform supporting demand reduction, and evaluation of the impact of Fighting Back should then focus on whether the platform was constructed and whether it supported demand reduction. Data from the current evaluation activities could be used in correlation analyses to address these issues. Rather than comparing Fighting Back to control cities, the data collected through the evaluation could be used to identify which of the many and various community initiatives and activities undertaken in all of the cities studied were associated with reductions in substance abuse, which initiatives appear to have no relation to substance abuse indices, and which, if any, appear counterproductive.

In addition to helping to identify potentially useful community initiatives, this strategy could also help to answer the question of whether Fighting Back had any impact. If, for example, community policing is identlfied as highly correlated with reductions in substance abuse (regardless of whether community policing was initiated in a Fighting Back city or a control city), it might be possible to assess Fighting Back's impact by evaluating whether community policing was implemented earlier or more successfully in Fighting Back cities compared to control cities.

Another approach to evaluation could be to examine what has happened in the 300+ communities that originally submitted proposals to the Foundation and were not funded. Comparing their programs to combat substance abuse with what has taken place in the FB sites could be fruitful. These 300+ communities had carefully considered what they wanted to do to cope with their substance abuse problems, and it is important to know what happened after their self-survey, in terms of any implementation, without outside Foundation funding.

ORAL COMMUNICATIONS I

REINSTATEMENT AND SPONTANEOUS RECOVERY OF NICOTINE-SEEKING IN RATS

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Reinstatement and spontaneous recovery of previously extinguished nicotine-taking behavior were examined in rats, Male subjects were trained to self-administer nicotine (30 μg/kg per infusion, IV; one 60-mm session per day for three weeks). Extinction sessions were then given for 5-10 days during which saline was substituted for nicotine. Subsequently, in the first set of tests for relapse to nicotine-seeking, the reinstatement of lever presses that previously delivered nicotine was examined after priming injections of saline and nicotine (75, 150 and 300 μg/kg, SC; and 30 and 60 μg/kg. IV). In the second set of tests for relapse, rats were tested for nicotine-seeking after an additional 21-day drug-free period during which they were not exposed to the self-administration chambers (a test for the spontaneous recovery of drug-seeking), and after priming injections of nicotine (150 and 300 μg/kg, SC). Reinstatement of extinguished food-reinforced behavior after exposure to nicotine was also determined. Priming injections of nicotine reinstated nicotine-seeking regardless of the route of administration. In addition, previously-extinguished nicotine-seeking recovered spontaneously after a 21-day period during which rats were not exposed to the drug-taking environment. Nicotine also reinstated extinguished food-reinforced behavior in rats with a history of nicotine self-administration, but not in drug-naive rats. The present results extend previous work with opioid and stimulant drugs on reinstatement of drug-seeking by the self-administrated drug. It also appear that, as with other positive reinforcers. the mere passage of time is a sufficient condition for the spontaneous recovery of extinguished nicotine-seeking.

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RECEPTOR MEDIATION OF THE DISCRIMINATIVE AND REINFORCING EFFECTS OF NICOTINE

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Central nicotinic cholinergic receptors, specifically of the high-affinity $\alpha4\beta2$ subtype, are thought to mediate the primary psychoactive effects of nicotine. To examine the importance of the $\alpha4\beta2$ receptor in nicotine's subjective and reinforcing properties, the potent $\alpha4\beta2$ antagonist erysodine (a DHβE analog) was administered to rats trained to discriminate or self-administer nicotine. In rats trained to discriminate injections of nicotine in a two-lever procedure of food-maintained behavior, erysodine dose-dependently blocked the effects of the training dose. In addition, erysodine produced rightward shifts in the nicotine dose-response curve. Given alone erysodii had few nicotine-like effects and did not affect response rate. Eryscdine also appeared to reverse adverse effects associated with high doses of nicotine. Erysaline was also examined in rats trained to intravenously self-administer nicotine under a fixed ratio schedule. Noncontingent nicotine injections before test sessions resulted in dose-dependent decreases in drug intake that were. not due to generalized decreases in response rate. Like nicotine (and mecamylamine), acute pretreatment with erysodii produced decreases in nicotine intake that were not due to a general decrease in response rate. Chronic treatment with mecamylamine or etysodine produced decreased intake over time similar to that observed in rats undergoing nicotine extinction over a seven day period. Taken together, these results suggest a critical role for the $\alpha4\beta2$ receptor in both the discriminative stimulus effects of nicotine and its reinforcing properties.

EFFECTS OF PRICE INCREASES AND BRIEF ABSTINENCE ON CIGARETTE SMOKING: BEHAVIORAL ECONOMIC ANALYSIS

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We investigated in the behavioral economics laboratory the combined effects of two public policy initiatives designed to reduce cigarette smoking: tax increases and bans on public smoking. Human subjecls responded to earn money which could be spent on cigarette puffs or taken home at the end of each 3.5-hour session. The price of cigarette puffs was changed between sessions (1-60 cents/puff). Before half of the sessions, subjects abstained for approximately 6 hours (analogous to a workplace smoking ban). Subjects smoked ad-lib before the remaining sessions. Independenl of abstinence effects, price increases produced significant decreases in smoking. Demand for cigarettes shifted from inelastic (i.e., insensitivity to price changes) to elastic as prices increased. Pre-session abstinence increased demand intensity for cigarettes (i.e., total intake al low prices). However, demand was more elastic when subjects had abstained before the session. The latter result reflects a price x abstinence-condition interaction: cigarette consumption was less affected by abstinence as prices increased. These findings suggest that the beneficial effects of public and workplace smoking bans are likely to be eclipsed by the reductions in cigarette smoking that would be produced by significantly increasing the excise tax imposed on cigarette purchases.

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MECHANISMS OF ACUTE TOLERANCE TO NICOTINE IN MICE

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Desensitization to nicotine's effects is believed to play an important role in the development and maintenance of dependence to this drug. The objective of this study was to investigate the mechanisms of acute tolerance to nicotine's antinociceptive effect after intrathecal (i.t.) injection. Male ICR mice were pretreated i.t. with different doses of nicotinic agonists 10 min prior to a second i.t.injection of agonist (ED_{84}) and the effect on the tail flick response was measured. An ID_{50} value (dose that decrease the effect of agonist by 50%) was determined. Acute tolerance developed to agonists such as (+)- and (-)-nicotine isomers, m-nicotine, isonicotine and ABT-418 with ID_{50} values that did not produce agonists effects when administered alone. On the other hand, tolerance did not develop to other agonists such as DMPP, (+)- and (-)-epibatidine, lobeline and N-MCC. Cross-acute tolerance to nicotine was investigated by pretreating mice with different nicotinic ligands and then challenging them with nicotine. Interestingly, cross-tolerance was seen only with agonists which developed acute tolerance by themselves. However, no relationship was found between receptor affinity and degree of acute tolerance. Finally, although acute tolerance developed to (+)-BN. a rigid analog of nicotine with low affinity to [^{3}H]-nicotine binding sites, cross tolerance to nicotine was not observed. These results suggest that multiple mechanisms are involved in the cholinergic desensitization of spinal nicotinic responses in mice.

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ALTERED COGNITIVE TASK-INDUCED BRAIN ACTIVATION DURING NICOTINE WITHDRAWAL: A HUMAN FMRI STUDY

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Chronic use of nicotine products such as cigarettes produces physiological and/or psychological dependence. Smoking cessation is associated with a withdrawal syndrome consisting of alterations in mood along with an impairment of attention and cognitive performance. To better understand the biological substrates of nicotine dependence, we examined the time course of nicotine withdrawals effects on brain activation induced by cognitive tasks using functional magnetic resonance imaging (FMRI). Chronic smokers (ages 24 - 43) agreed to abstain from nicotine use for three weeks. They performed three different cognitive tasks (delayed match to sample, visuospatial working memory and concept formation) while undergoing whole brain FMRI scanning. Scanning was performed prior to smoking cessation and at one day, one week and three weeks of abstinence. While each task produced a characteristic activation pattern, all tasks produced activation in frontal cortex and strong activation in parietal and visual cortical areas. While the FMRI signal magnitude. did not change, the area of activation and task performance were decreased at day one of withdrawal. Brain activation and task performance returned to pre-withdrawal levels at one week, suggesting that the decrease in cognitive performance during nicotine withdrawal may be related to localized associated decreases in brain activity.

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TREATMENT OF NICOTINE DEPENDENCE WITH FLUOXETINE, NICOTINE PATCH, AND GROUP THERAPY

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Smoking cessation attempts are often complicated by dysphoria/ depression, weight gain, craving, and other nicotine withdrawal symptoms. Fluoxetine's antidepressant and anorectant properties, along with its capacity to attenuate compulsive behavior, suggest that this medication might facilitate smoking cessation treatment. In this pilot study, we examined the effect of pretreating smokers with fluoxetine and maintaining them on the medication throughout a standard, state-of-the-art smoking cessation program including group cognitive-behavioral therapy (6 weeks) and transdermal nicotine patches (10 weeks). Ten daily-smokers were assigned to either placebo (n=3), 20mg (n=4), or 40mg fluoxetine (n=3). Only 50% of subjects correctly guessed whether they had been taking fluoxetine versus placebo. Fluoxetine was well-tolerated by all subjects. All 7 fluoxetine subjects achieved initial abstinence; only one had relapsed just prior to 3 month follow-up; and 3 of 7 (43%) remained abstinent by 6 month follow-up. Of those on placebo, 2 failed to achieve initial abstinence. although, after 1 week on patch, 1 was able to achieve and maintain abstinence up to 3-month follow-up. The third placebo subject relapsed just prior to discontinuation of nicotine patch treatment (9 weeks post quit-date). At six months, 1 of 3 assigned to placebo remain abstinent (33%). Confirmation of fluoxetine's apparent efficacy to facilitate smoking cessation and the mechanisms underlying this effect await availability of a larger sample size.

QUITTERS AND NONQUITTERS DIFFER IN THEIR PRETREATMENT REACTIVITY TO SMOKING

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We examined whether pretreatment reactivity to smoking cues differed between quitters and nonquitters who completed 8 weeks of nicotine patch treatment. Smoking status was determined by self-report of the number of cigarettes smoked on weeks 8 and 9 using the Time-Line Followback method. Smokers were categorized as quitters if they reported smoking no cigarettes, and nonquitters if they reported smoking at east 10 cigarettes on each of weeks 8 and 9. Self-reports were confirmed with week-9 urine cotinine levels which were lower than 100ng/kg for all quitters and higher than 500ng/kg for all nonquitters. Although quitters and nonquitters did not differ in demographic characteristics, pretreatment smoking characteristics (e.g., Fagerstrom score, Shiffman and Jarvic withdrawal scales) and incidence of Axis I diagnoses, they differed in pretreatment reactivity to smoking cues. ANOVAs showed that although both quitters and nonquitters reported increases in "craving", and "withdrawal" in response to the smoking cues, quitters showed a larger increase. Furthermore, the nonquitters reported less "high" following the smoking cues than at the beginning of the session, while the quilters did not exhibit a similar reduction. Given that smokers bad been required to smoke a cigarette prior to the pretreatment session, the quitters' report of strong "high" following the cues indicates that the cues helped preserve a nicotine-like effect. These results corroborate similar findings with cocaine addicted patients.

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PRELIMINARY EXPERIENCES WITH OPIATE ABUSERS SEEKING SMOKING CESSATION TREATMENT

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The prevalence of tobacco smoking among opiate abusers is extremely high, with estimates ranging from 70-100%. There is evidence that tobacco smoking is correlated with illicit substance abuse, through biological mechanisms as well as social and behavioral linkages. This study describes preliminary experiences with opiate abusers participating in a smoking cessation trial evaluating Relapse Prevention and Contingency Management in conjunction with transdermal nicotine patches. Comparing study applicants who were randomized to participate in the trial with applicants who did not complete screening procedures we found a greater likelihood of opiate use among unsuccessful applicants ($\chi^2(1)=5.71$, $p<.05$). In addition. unsuccessful applicants showed significantly higher urine cotinine values ($t(39)=2.37$, $p<.05$). suggesting greater severity of nicotine dependence. By the end of the 12 week treatment episode, 7 (31.82%) of the first 22 study participants were confirmed non-smokers. Criteria consisted of serum thiocyanate below 100 UMOL/L, expired carbon monoxide below 8ppm, and self-report of non-smoking for the last week of treatment. In treatment. urine toxicology data suggest a strong association between cocaine use and inability to stop smoking tobacco. Replicating our findings from a previous pilot study subjects that did not stop smoking were much more likely to be using cocaine compared to subjects confirmed to be non-smokers at the end of treatment ($\chi^2(1)=4.02$, $p<.05$). These findings suggest that opiate abusers are able to use available methods for smoking cessation and achieve similar preliminary success as found in the general population. Our findings support common pathways involved in tobacco and other substance abuse.

THE EFFECT OF SUBSTANCE ABUSE TREATMENT HISTORY, CURRENT ALCOHOL USE, OR MARIJUANA USE ON SUCCESS IN QUITTING SMOKING

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Previous research suggests higher rates of smoking, and smoking cessation failure, in alcohol and drug abusing populations. The relationship is not as clear in a non-abusing population. The present study examined the relationship of alcohol/drug treatment history and current alcohol and marijuana consumption with success in smoking cessation treatment in a smoking clinic population. Subjects were 199 smokers participating in a smoking cessation clinical trial. Subjects were 55% female. Mean age =40.7 years. Mean daily cigarettes = 22.5. Mean years smoking = 22.2. History of alcohol/drug problems, treatment. and current use was assessed prior to study entry. Any potential subject reporting current alcohol or drug problems was excluded from the study resulting in a population with low to moderate levels of alcohol and marijuana use. Current alcohol/drug consumption was also reported at monthly intervals during treatment and at follow-up assessments. Twenty three percent reported a history of an alcohol/drug problem and 12.6% reported a history of drug treatment. Seventy-eight .7 percent reported alcohol use and 21.3% reported marijuana use during treatment. Analyses examined abstinence rates at the end of treatment and 3. 6, and 12 months post-treatment as well as continuous abstinence. Results indicate no significant differences in abstinence rates at any assessment based on history of alcohol/drug problem or treatment. Differences were found for any current alcohol use but not marijuana use. Both alcohol use at baseline and any alcohol use during treatment predicted abstinence at all follow-up points with alcohol users having significantly lower quit rates than those reporting no use. Neither use of marijuana at baseline or during treatment predicted outcome. Although past alcohol/drug problems do not appear to predict treatment outcome, these findings suggest that even low to moderate levels of alcohol consumption during smoking cessation may decease treatment success. Contrary to an earlier report, marijuana use was not related to relapse.

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ORAL COMMUNICATIONS II

THE EARLIEST STAGE OF MARIJUANA INVOLVEMENT: INITIAL OPPORTUNITY TO USE

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A renewed American interest in marijuana has coincided with our research group's focus on the earliest stages of drug involvement. Here. we have studied the transition from an initial opportunity to try marijuana to the subsequent use of this drug. We analyzed self-report interview data gathered from nationally representative samples of the United States National Household Surveys on Drug Abuse, 1979-94. The evidence indicates that the estimated prevalence of initial opportunities to try marijuana has been rather stable for 15 years. However, there are recent increases in the probability of rapidly progressing from first marijuana opportunity to first marijuana use, among persons given an opportunity to use. As age of first marijuana opportunity increases, the likelihood of marijuana use decreases. Also, male-female differences in marijuana use appear to be due to differences in opportunity to use rather than differences in likelihood of use once an opportunity has occurred. This epidemiological evidence on the transition from marijuana opportunity to marijuana use, the first to be published based on a nationally representative U.S. sample, highlights directions for future research and a focus for prevention efforts.

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PREDICTORS OF CESSATION OF MARIJUANA USE

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In contrast to the initiation of marijuana use, little is known about the predictors of cessation. Event history analysis was applied to monthly life and drug histories of a representative community sample of 706 marijuana users, followed from ages 15-16 to 34-35, to investigate factors associated with cessation of marijuana use from adolescence to adulthood. In addition to gender, the most important determinants of cessation are the phenomenology of marijuana use, social role participation, depressive symptoms and deviance. Frequent users, those who started using early and those who use illicit drugs other than marijuana are more likely to continue using marijuana. Using marijuana for social reasons accelerates cessation, using to change one's mood reduces cessation for women only. Becoming a parent is the most important social role leading to marijuana cessation. There is also a very important experimental effect of the interview itself on the reported timing of cessation. One-third of the effect of age observed at the univariate level is explained by the factors included in the model. The effect of social context favorable to marijuana use. appears to reflect a selection effect rather than social influence. Postponing onset into marijuana use. reducing extensiveness of use, increasing commitment to conventional social roles, and reducing delinquent participation are likely to be important interventions that would shorten a marijuana-using career.

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ASSESSMENT AND TREATMENT OF ADULT MARIJUANA DEPENDENCE: COMPARISON TO COCAINE AND OPIOID DEPENDENCE

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The prevalence rate of marijuana dependence is the highest of any illicit drug in the general population, yet clinical research on marijuana dependence is sparse. The aim of the present research is to extend prior findings regarding the characteristics of individuals who seek treatment for marijuana-related problems and examine the efficacy of three behaviorally-based interventions, (1) brief motivational enhancement, (2) motivational enhancement plus behavioral coping skills therapy, and (3) motivational enhancement, behavioral coping skills therapy plus reinforcement contingent on marijuana abstinence. Marijuana-dependent individuals (n=62) averaged 21.8 ± 9.9 days of marijuana use during the 30 days prior to treatment and smoked 4.0 ± 3.5 times per day. This marijuana group reported drug-use histories and impairment comparable to cocaine- and heroin- dependent individuals seeking treatment in the same clinic. Notable significant differcences observed between groups included more education, less employment problems, less depressive symptomatology. and lower prevalence of cigarette smoking among the marijuana abusers. A readiness-to-change measure suggested that marijuana abusers may enter treatment less motivated to discontinue their use than cocaine or heroin abusers. To date, 33 marijuana-dependent individuals have entered the clinical trial. Preliminary outcome data indicate that 58% completed treatment, and 42% reported a greater than 50% reduction in days of marijuana use at the end treatment. In summary, these data suggest that marijuana abusers present for treatment with substantial psychosocial problems. Clinical research focused on the development of efficacious treatments for this population appears warranted.

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THE EFFECTS OF A MONETARY ALTERNATIVE ON MARIJUANA SELF-ADMINISTRATION

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Availability of alternative reinforcers can reduce drug self-administration. This 21-day study investigated the effect of monetary alternatives on marijuana self-administration. Seven participants (3F, 4M) performed computer tasks (baseline) in the morning prior to smoking a sample marijuana cigarette (0.0, 1.8, or 3.9% THC) and receiving the sample alternative ($5 voucher). In the afternoon, participants had five opportunities to choose to receive either of the earlier alternatives. Participants were required to meet a criterion level of task performance to obtain each choice. The monetary performance criterion varied from day to day (80, 100, or 120% of baseline); the marijuana performance criterion remained constant at 100% of baseline. Choices were delivered in the evening, after task completion. Marijuana choice varied as a function of THC concentration and criterion to earn money. Active marijuana was always chosen more often than placebo, and active and placebo marijuana were chosen over money when the criterion to earn money was high. Task performance improved when criteria were imposed, even after participants had smoked the sample marijuana cigarette. Subjective ratings of drug effects increased with increasing THC concentration, but did not predict choice. Results indicate that the availability of a monetary alternative was effective in shifting choice to self-administer marijuana, and that marijuana choice was sensitive to contingency manipulations. Results further suggest that contingency manipulations may override the performance-impairing effects of marijuana.

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CHANGES IN AGGRESSIVE BEHAVIOR FOLLOWING DISCONTINUATION FROM LONG-TERM MARIHUANA USE

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Most studies investigating the relationship between marihuana smoking and aggression have concluded that acute administration of marihuana decreases aggressive behavior in humans (Myerscough *et al.,* 1985). However, there are no published studies on the effects of withdraw from chronic marihuana use on aggressive behavior in humans. This represents a serious omission in the research literature because it has been shown that the abrupt discontinuation of marihuana after long-term use can result in a syndrome characterized by insomnia, restlessness and irritability within 24 hours after discontinuation of the drug (Compton *et al.,* 1990; Mendelson *et al.,* 1984). Our study was conducted to characterize the duration and pattern of changes in aggressive behavior in long-term marihuana users after a 28-day abstinence period verified by daily urines. Our subjects were 4 women and 13 men who had smoked marihuana on at least 5,000 occasions (the equivalent of smoking daily for approximately 14 years) and who were smoking regularly when recruited. Subjects were studied on day 0 (when they were still smoking), day 1 (during acute withdrawal), days 3, 7 and 28 of a 28-day detoxification period. Aggression was measured with the Point Subtraction Aggression Paradigm (PSAP, Cherek, 1981). There was a significant increase in aggressive responding on days 3 and 7 of withdrawal as compared to day 0. These increases in aggressive responding returned to pre-withdrawal levels after 28 days. Our findings confirm previous reports of an abstinence syndrome associated with chronic marihuana use and suggest that aggressive behavior should be an additional component of this syndrome.

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MARIJUANA SLOWS SMOOTH PURSUIT EYE TRACKING AND REDUCES LIGHT REFLEX

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Marijuana continues to be the most commonly abused illicit drug in the United Slates. Because many people abuse marijuana during the evening and on weekends and then go to work or school the next day, more research is needed on the residual effects of marijuana. The current study sought to examine both acute and residual subjective, physiologic, and performance effects of smoking a single marijuana cigarette. Ten healthy male volunteers who reported recent use of marijuana resided on a residential research ward. On three separate days, subjects smoked one NIDA marijuana cigarette containing either 0%, 1.8%, or 3.6%Δ^9-tetrahydrocannabinol (THC) according to a paced puffing procedure. Subjective, physiologic, and performance measures were collected prior to smoking, five limes following smoking on that day, and three times on the following morning. Smooth pursuit eye tracking was measured at 15°/sec through the central (0-22°) and peripheral (22-45°) visual fields. The response to a sustained light stimulus at two intensities (8 and 20 ftcd) were recorded using a computer-based video system. Subjects reported robust subjective effects following both active doses of marijuana which returned to baseline levels within 3.5 hr. Heart rate increased and the pupillary light reflex decreased following active dose administration with return to baseline on that day. The mean constriction amplitude of the light reflex decreased from 1.8 to 0.9 mm (8 ftcd) and 2.8 to 1.8 mm (20 ftcd). Marijuana smoking produced decrements in smooth pursuit eye tracking that persisted for 1.75h after smoking. Tracking speed was reduced from 11.5 to 6.5 °/see (central field) and 6 to 2 °/sec (peripheral field). Although robust acute effects of marijuana were found on subjective and physiologic measures, and on smooth pursuit eye tracking performance, no effects were evident the day following administration indicating that the residual effects of smoking a single marijuana cigarette are minimal, the acute effects of marijuana to impair smooth pursuit tracking and the light reflex may be involved in workplace and traffic accidents associated with its use.

MOTOR COORDINATION AND BALANCE ARE IMPAIRED BY ACUTE MARIJUANA ADMINISTRATION

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In two studies. we investigated the effect of smoked marijuana on four standardized field sobriety tests (FST) that are used to determine whether a person can safely operate a motor vehicle. Subjective effects and Δ^9-tetrahydrocannabinol (THC) plasma concentrations were also measured to correlate with behavioral impairment. In a residential study. 12 volunteers participated in six experimental sessions. At each session, subjects smoked ad lib two half-cigarettes containing 0 or 3.58% THC. Placebo, low, and high doses consisted of two placebo half-cigarettes, one placebo and one active half-cigarette, and two active half-cigarettes, respectively. Subjects received each marijuana dose twice in random order. Marijuana impaired performance on only one FST, the One Leg Stand, by increasing number of hops and times the elevated foot touched the floor to maintain balance. In a nonresidential study. 20 subjects participated in three experimental sessions. At each session, subjects smoked two cigarettes (16 paced puffs) containing 0, 1.75, or 3.55% THC. Marijuana impaired performance on two FST, One Leg Stand and Finger to Nose. The number of times subjects put their foot down and raised their arms to maintain balance and amount of body sway were increased by marijuana in the One Leg Stand test. A dose-dependent increase in number of misses was observed in the Finger to Nose test. In both studies, marijuana produced orderly dose-relaled increases in subjective ratings of intoxication. THC plasma concentrations peaked immediately after smoking and bad declined to 15-28 ng/ml at time of FST testing (15 min postsmoking). These data suggest a threshold plasma THC level in the 20-25 ng/ml range for marijuana to impair behaviors critical for safe driving.

MARIHUANA AND ETHANOL EFFECTS ON COGNITION, HEART RATE AND SUBJECTIVE MOOD

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Researchers using electrophysiology as a measure of cognitive processing following ethanol and maribuana challenges have suggested that the N100 and P300 event-related (ERP) components can reflect two aspens of selective attention, stimulus set and response evaluation, respectively. However, few have studied ERP responses to combined ethanol and marihuana Eighteen healthy male recreational drug users were randomly assigned to one of three groups: placebo marihuana (0.001%Δ^9-THC), low-dose marihuana (1.26%Δ^9-THC) and high-dose marihuana (2.53%Δ^9-THC). the marihuana dose was held constant and each subject drank three different doses of ethanol on three different days: placebo, 0.35 g/kg or 0.70 g/kg. Thirty minutes after drinking they smoked a maribuana cigarette. Subjects were presented with an auditory "oddball" ERP task and measurements were obtained at baseline and at 20, 40, 60 and 80 minutes after smoking. Blood samples, heart rate and subjective mood ratings were also analyzed. A MANOVA revealed a reduced P300 amplitude 70 minutes after drinking and at 60 minutes after smoking, a high dose of maribuana and ethanol produced a longer P300 latency. Both high and low dose maribuana produced longer N100 latencies at 80 minutes after smoking. Heart rate remained increased for an hour after smoking. Subjects reported feeling "high" until 50 minutes after smoking, and "drunk" until 90 minutes after drinking. these findings suggest that an acute dose of marihuana and ethanol may alter cognitive processing in healthy individuals long after the physiological and subjective states have disappeared.

ACKNOWLEDGMENTS: Supported by NIDA Grants DA00115 and DA00115

ORAL COMMUNICATIONS III

CONSERVATION OF CONFORMATIONAL TOPOGRAPHY AT FIVE GABA$_A$/BENZODI-AZEPINE RECEPTOR SUBTYPES

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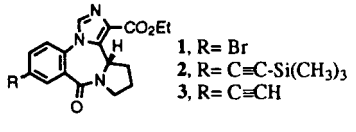
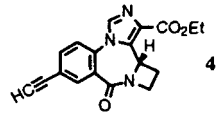
The synthesis and *in vitro* affinities of a series of optically active pyrrolo or azetidinylimidazobenzodiazepines at five recombinant GABA$_A$/BzR subtypes expressed from human cell lines are described Examination of *in vitro* binding data indicates thaat (S)-enantiomers of these ligands are much more potent than their corresponding (R)-isomers. Binding affinities of three framework constrained (rigid) ligands provide evidence for the first time which indicates the conformational preference for BzR ligands is highly conserved at these five recombinant receptor subtypes. The contigurational preference for (S)-enantiomers in both series of ligands suggests that pharmacophoric descriptors H_1, H_2 and L_1 are the same in these five receptor subtypes in agreement with previous modeling studies. In addition, these framework constrained (S)-pyrroloimidazobenzodiazepines 1, 2, 3, and azetidinyl analog 4, were 45 to 57 times more selective for the $\alpha5\beta3\gamma2$ subtype in comparison to the $\alpha1\beta3\gamma2$ isoform. Data from the present study should be useful for understanding conformational requirements of GABA$_A$/BzR subtypes as well as providing some insights into the conservation of binding site topography across a series of BxzR subtypes.





4

APPARENT pA_2 VALUES OF PARTIAL AND SELECTIVE $GABA_A$ ANTAGONISTS WITH MIDAZOLAM IN MONKEYS

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Drugs that bind to benzodiazepine recognition sites of $GABA_A$ receptor complexes may function as agonists in some behavioral assays while functioning as antagonists in other behavioral assays. The present studies compared the effects of the imidazodiazepines midazolam, Ro 41-7812, and Ro 42-8773 and the β-carboline β-CCt under two different procedures of schedule-controlled responding. One group of squirrel monkeys (N=4) responded under a multiple fixed-ratio schedule of food presentation involving suppressed and nonsuppressed behavior. Another group of monkeys (N=3) responded under a fixed-ratio (FR30) schedule of stimulus-shock termination. Midazolam (0.03 - 0.3 mg/kg) and Ro 42-8773 (0.01-1 mg/kg) dose-dependently increased rates of suppressed responding, and flumazenil (0.3 mg/kg) surmountably antagonized these antisuppressant effects. Ro 41-7812 and β-CCt bad no effects on behavior maintained under the suppressed- responding schedule. Under the schedule of stimulus-shock termination, only midazolam decreased responding (ED_{50} = 0.3 - 0.1 mg/kg), and these effects were surmountably antagonized by Ro 41-7812 (0.3-10.0 mg/kg), Ro 42-8773 (0.1-3 mg/kg), and β--CCt (3-30 mg/kg). Schild plot analysis revealed tbe following mean values (with 95% C.L.): Ro 41-7812 pA_2= 7.06 (5.67, 8.44) witb a slope of -0.76 (-1.31, -0.20); Ro 42-8773 pA_2= 6.81 (6.26, 7.37) with a slope of -1.11 (-1.66. -0.57). Apparent pA_2 values were not calculated for β-CCt because the confidence limits of the slope of the Schild plot included positive values, these results demonstrate that Ro 42-8773 has both agonist and antagonist properties in squirrel monkeys, whereas β--CCt and Ro 41-7812 have predominantly antagonist effects in monkeys. Furthermore. these results indicate that apparent pA_2 values can he obtained for benzodiazepine ligands that are either full antagonists or partial agonists.

ACKNOWLEDGMENTS: Supported by USPHS Grants DA 03774, DA 05653. MI-I 07658 and RR 00168.

DISCRIMINATIVE STIMULUS EFFECTS OF FLUMAZENIL IN RHESUS MONKEYS TREATED CHRONICALLY WITH DIAZEPAM

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One consequence of long-term treatment with benzodiazepine agonists is the development of physical dependence. The purposes of the current study were to establish a procedure for evaluating benzodizepine dependence and withdrawal in nonhuman primates and to assess the effects of other drugs for their ability to modify dependence or withdrawal. Four thesus monkeys were treated daily with 5.6 mg/kg of diazepam (p.o.) while discriminating 0.32 mg/kg of flumazenil (s.c.) from vehicle under a fixed ratio 5 schedule of stimulus-shock termination. Flumazenil (0.0032-0.32 mg/kg) dose-dependently increased responding on the flumazenil lever with doses larger than 0.1 mg/kg producing ≥80% flumazenil- appropriate responding. Discriminative stimulus effects of 0.32 mg/kg of flumazenil were evident 10 mm after injection and bad a duration of 60 min. The benzodiazepine receptor inverse agonist Ro 154513 produced ≥ 80% flumazenil- lever responding in all monkeys whereas the benzodiazepine receptor inverse agonist ethyl β-carboline-3-carboxylate and the GABA receptor antagonist pentylenetetrazole produced ≥80% flumazenil-appropriate responding in only some monkeys; drugs from other pharmacological classes produced vehicle-appropriate responding. Temporary suspension of diazepam treatment resulted in a time-related switch in responding to the flumazenil lever; 75 hr after the last dose of diazepam, flumazenil-lever responding was reversed by 1.0 mg/kg of diazepam. In diazepam-treated monkeys, there was no apparent change in effectiveness of the training dose of flumazenil even when it was administered daily. This procedure appears to be pharmacologically selective for antagonists and inverse agonists at the benzodiazepine $GABA_A$ receptor complex. To the extent that the discriminative stimulus effects of flumazenil are related to benzodiazepine withdrawal, this procedure should prove useful for studying dependence and withdrawal in a manner that will be predictive of subjective effects in humans.

ACKNOWLEDGMENT: Supported by USPHS Grant DA09157.

ZOLPIDEM PHYSICAL DEPENDENCE ASSESSED ACROSS INCREASING DOSES UNDER A ONCE-DAILY DOSING REGIMEN

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Zolpidem (ZLP) is an imidazopyridine hypnotic with selectivity for BZ_1 receptor subtypes. Previously, discontinuation of ZLP after chronic self-administration suppressed food intake indicating that baboons may have been physically dependent (Griftiths *et al.* 1992). The current study examined the behavioral effects and possible development of physical dependence after once-daily bolus doses of ZLP (0, 1, 3.2, 10, 32 mg/kg) in 3 baboons. Each dose was administered i.g. for 17 days and then the dose was increased. Chronic dosing was discontinued after the 32 mg/kg condition. Baboons had access to pellets for 20 h/day beginning 15 min after dosing. Baboons were presented with a motor task 1 h after dosing, and tremor, incoordination, and time to complete the task were recorded. Behavioral observations were conducted 1 h after dosing on days 1, 10, 12 and 14 of each dose and after dosing was terminated. On days 10 and 14 of each dose, vehicle and flumazenil (FLZ, 5 mg/kg) were administered i.m., respectively. ZLP increased pellet intake in 2 of 3 baboons. At 3.2 and 32 mg/kg ZLP, 1 baboon vomited and a 2nd baboon showed head-lower-than-torso posture (often associated with nausea and vomiting). Time to complete the motor task was increased in 3 baboons, and incoordination was observed at 10 and 32 mg/kg ZLP. FLZ produced behavioral signs of withdrawal including vomit/retch (2 of 3 baboons) and tremors/jerks (3 baboons) at 32 mg/kg ZLP. Discontinuation of ZLP resulted in suppression of pellet intake for 15 days in 2 baboons, and signs of withdrawal in all 3 baboons. These data indicate that ZLP produced physical dependence under once-daily dosing conditions. References: Griffiths, R.R.; Sannerud, C.A.; Ator, N.A.; Brady, J.V. (1992) Zolpidem behavioral pharmacology in baboons: self-injection, discrimination, tolerance and withdrawal. J Pharmacol Exp Ther 260: 1199-1208.

ACKNOWLEDGMENT: Supported by NIDA grant DA01147.

SELECTIVE EFFECTS OF ZOLPIDEM ON HUMAN MEMORY FUNCTIONS

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Zolpidem (ZOL) is an imidazopyridine hypnotic with selective affinity for the ω_1 benzodiazepine receptor subtype. It has been suggested that ZOL may produce less memory impairment than classic benzodiazepines due to its relatively low affinity for the ω receptor subtypes found in areas of the brain which are involved in learning and memory. The present double-blind, placebo-controlled study evaluated the effects of orally administered ZOL (15 mg/70 kg) on a battery of memory tasks with word and picture stimuli in 16 normal human volunteers. Relative to placebo, ZOL significantly impaired memory for material presented after drug administration when memory was assessed directly by referring subjects back to the prior study episode (explicit memory: recall and recognition) but not when memory was assessed indirectly by evaluating subjects' ability to identify degraded versions of studied stimuli (implicit memory: fragment completion). ZOL did not impair explicit memory for material presented before drug administration or memory for previously acquired knowledge (semantic memory: categorization). There was evidence suggesting that ZOL enhanced explicit and implicit memory for material presented before drug administration and that ZOL produced a specific deficit in the acquisition of contextual information about material presented after drug administration. The results of the present study document selectivity in the memory-impairing effects of zolpidem. The extent to which zolpidem's selectivity differs from that of classic benzodiazepines remains to be explored.

ACKNOWLEDGMENT: Supported by NIDA grant DA03889.

CHRONIC BENZODIAZEPINE THERAPY DOES NOT RESULT IN BRAIN ABNORMALITIES AS MEASURED ON COMPUTERIZED TOMOGRAPHY (CT) SCANS

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Studies on the association between chronic benzodiazepine use and chronic brain abnormalities have yielded conflicting results. The computerized tomography (CT) scans of 20 chronic benzodiazepine users (65% male; age, ± SD [range] = 42.2±12 yrs [23-59], mean daily benzodiazepine dose, diazepam equivalents = 21±18 mg, [2.5-70], mean cumulative benzodiazepine exposure = 55.2 g, [1.8-198]) were compared to 36 age (±2 yrs) and sex-matched controls. Controls were prospectively recruited from 120 patients attending a neurology clinic, and interviewed to screen for alcohol and substance use disorders and other conditions possibly leading to brain atrophy. Three neurologists blindly assessed each CT scan for atrophy and measured ventricles (V1, V2, V3), sulci, fissures, cisterns and folia. Reliability among raters ranged from 0.92 to <0.1, in which case, deleting one rater raised all reliabilities to >0.45. No difference in atrophy was found between benzodiazepine users and controls, V1 measures were significantly higher for benzodiazepine users than controls (x±SD = 12.1±1.3 vs. 11.1±2.0, p=0.02) but measures of 3rd and 4th largest sulci were significantly higher in controls than in benzodiazepine users. Right 3rd and 4th largest sulci (x±SD) were: controls, 0.72±0.4 and 0.74±0.7; benzodiazepine users, 0.51±0.3 and 0.46±0.3 p<0.02). Left 3rd and 4th largest sulci were: controls, 0.77±0.6 and 0.65±0.3; benzodiazepine users, 0.53±0.3 and 0.5±0.3 (p<0.02). Chronic benzodiazepine therapy does not result in brain abnormalities.

FLUNITRAZEPAM ABUSE POTENTIAL IN RELATION TO RATE OF ONSET OF EFFECTS AND DOSE ADMINISTERED

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Drug abuse potential seems to be related to intensity and rate of onset of effects. Thus, benzodiazepines with fast absorption might be preferred by drug abusers because of rapid and intense obtention of pleasurable feelings, the manipulation of rate of delivery has been a useful method to study differences in onset of effects. For diazepam 20 mg, a fast administration schedule showed higher ratings in ARCI-MBG scale, more behavioral signs of intoxication, and greater psychomotor impairement than a slow administration. In a previous study, we failed to demonstrate differences between fast and slow 2 mg flunitrazepam (FNZ) administration. Twelve male healthy volunteers participated in a randomized, double-blind, double-dummy, crossover study. Drugs were administered in 6 capsules, ingested at 30-min intervals over 2.5 h. Conditions were: placebo, FNZ SLOW (6 doses of 0.25 mg), and FNZ FAST (5 doses of placebo and a single last dose of 1.25 mg). Variables included: vital signs, subjective effects (VAS, ARCI, POMS), psychomotor performance (simple reaction time, DSST. Maddox-wing) and blood samples. Both active conditions induced an impairment of performance tasks and sedative effects, and produced increases in scales related to pleasurable effects ("high", "good effects") compared to placebo. Both active conditions produced similar psychomotor impairment and sedative effects, while FAST administration induced significantly increases in drug-related euphoria ("high", "good effects", "liking", ARCI-MBG) in comparison to SLOW. Peak plasma concentrations were similar between both FNZ conditions. This results, taken together witlh the previous study with FNZ 2 mg, seems to support the influence of rate of onset of effects and dose in drug abuse liability.

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EXPECTANCIES IN BENZODIAZEPINE (BZ) DEPENDENCE

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***University of Texas - Houston HSC and [&]Allegheny University HSC**

Thirty-seven males and females with iatrogenic BZ dependence were enrolled in an outpatient treatment program providing clonazepam substitution and gradual dose reduction under double-blind conditions. Over the course of weekly clinic visits, patients initially were stabilized on their intake BZ (Wk#1) and then were stabilized on an equivalent dose of clonazepam (Wks #2-4). Thereafter, clonazepam doses were reduced weekly by 1/2 of a log, unit. We assessed patient expectations regarding treatment, BZ use, and self-efficacy with questionnaires and attempted to experimentally manipulate expectations through a dose-reduction instruction that was given prior to Wk #5 of treatment. The manipulation involved a balanced-expectancy design in which withdrawal instructions were balanced with the actual dose reduction condition. A 2x2 factorial design generated 4 differ-em groups wherein patients either were or were not informed that their doses were being reduced (2 levels of Instruction) when they in fact were or were not aetually being reduced (2 levels of dose reduction). Symptoms of anxiety/BZ withdrawal were assessed over the next 3 weeks. After Wk #8, subjects, previously maintained at constant clonazepam doses, also began dose reduction. Outcome measures were treatment retention, achievement of placebo dose, and anxiety/withdrawal symptom levels. Counter to our hypothesis, the withdrawal instructions had no consistent effect on anxiety symptoms in the initial 3-week period or on ultimate treatment outcome. However, initial "desire to quit" predicted longer retention in treatment and intake assessments of general self-efficacy, low "fears of withdrawal", and greater ratings of "ability to manage anxiety without medication" predicted success in achieving placebo doses. Thus, we failed to gain experimental control over anxiety levels and expectation but did find that initial assessment of patient self-efficacy and expectation may be useful predictors of treatment outcome.

ACKNOWLEDGMENT: Supported by NIDA Grant DA-07431.

ORAL COMMUNICATIONS IV

COCAINE TREATMENT AGENTS: SYNTHESIS AND PHARMACOLOGY OF N-METHYLPHENIDATE ANALOGS

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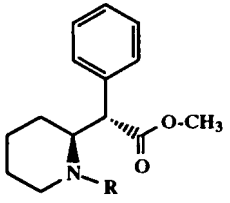
The long term objective of this research is to develop treatment agents for cocaine abuse. An important site of the molecular action of cocaine is the binding site associated with the dopamine transport complex. The specific aim of this work is to make drugs which will selectively attenuate the effects of cocaine at this site, but minimally Interfere with the transport of dopamine. A number of N-substituted analogs of methylphenidate have been synthesized and evaluated for inhibition of [^{3}H]WIN 35,428 binding and [3H]dopamine uptake and in various animal behavioral tests. Whereas N-aLkyl and N-aIkenyl groups uniformity lower the binding affinity, some N-benzyl groups actually increase the binding potency. Analysis of the *in vitro* data by looking at the ratio of inhibition of uptake to binding indicated that the some of these compounds might have potential as possible cocaine partial agonists or antagonists. The results of drug discrimination and locomotor stimulation testing in rats, and the synthesis and pharmacology of compounds will be discussed in detail.



R = alkyl, alkenyl, alkynyl and benzyl

Methylphenidate
R = H

TRANSPORTER AFFINITY OF HYDROXYLATED DERIVATIVES OF COCAINE AND THE PHENYLTROPANES β-CIT AND FP-CIT

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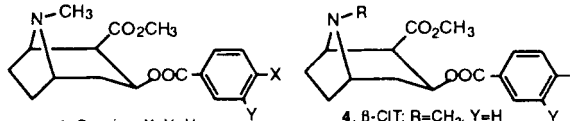
ADARC and MRC, McLean Hospital—Harvard Medical School, Belmont, MA; and *Research Biochemicals International (RBI), Natick, MA

The 3'-hydroxy (2) and 4'-hydroxy derivatives (3) of cocaine (1) have been identified as metabolites but their neuropharmacology remains poorly characterized.β-CIT (4) and FP-CIT (6) are stable phenyltropane analogs of cocaine with high affinity for the cocaine binding site on cerebral dopamine transporter (DA_T) that can be used for imaging the DAT with PET or SPECT, and might also undergo aromatic hydroxylation *in vivo.* We synthesized the hydroxy metabolites of cocaine (2,3) and potential hydroxylated metabolites of the phenyltropanes (4, 6, 5, 7) and evaluated their affinity to DAT as well as transporters for serotonin ($5\text{-}HT_T$) and norepinephrine (NET) in corpus striatum tissue from rat forebrain, in comparison with the parent compounds (1, 4, 6). Synthesis of the compounds and modification of transporter affinity and selectivity by hydroxylation will be reported.



1. Cocaine; X=Y=H
2. 3'-OH-1; X=H, Y=OH
3. 4'-OH-1; X=OH, Y=H
4. β-CIT; R=CH_3, Y=H
5. 3'-OH-4; R=CH_3, Y=OH
6. FP-CIT-1; R=$(CH_2)_3F$, Y=H
7. 3'-OH-6; R=$(CH_2)_3F$, Y=OH

ACKNOWLEDGMENTS: Supported by grants MH-34006, MH-47370, MH-49533 and DA-04060 and an award from the Royal Danish School of Pharmacy (to A.A.).

COCAINE ANTAGONISTS FROM DIRECTED COMBINATORIAL CHEMISTRY

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The dopamine transporter (DAT) and related modulation of dopamine function have been identified as the relevant bio-macromolecules for initiating cocaine self-administration behavior. A correlation has been observed between the drug potency al inhibiting ligand binding to DAT and replacing cocaine in a self-administration paradigm. Previously, others have proposed that binding to and uptake inhibition of the DAT was highly correlated. As part of a comprehensive program to develop antidotes to cocaine abuse, we used high yield solution phase chemical synthesis to create chemical libraries that were screened for inhibition of DAT binding, dopamine uptake and release. In addition, the selectivity of action of the antagonists for the dopamine receptor versus the DAT was examined in the presence of rat dorsal striatal membranes. From a modest sized library, one sublibrary was chosen for more extensive study and individual members were chemically synthesized. For the chemical sublibrary that was examined as individual members, a very poor correlation between binding and uptake inhibition at the human DAT was observed. For the sublibrary examined, one member showed essentially no binding to the DAT but significant inhibition of uptake. The data suggest that binding and inhibition of [^{3}H]-DA uptake may have different mechanisms. The use of chemical libraries in drug discovery of medications to combat drugs of abuse overuse may provide unique entities that may otherwise not have been anticipated.

ACKNOWLEDGMENT: Supported by NIDA grant DA00269

8-OXATROPANES: POTENT NON-NITROGEN INHIBITORS OF MONOAMINE TRANSPORT SYSTEMS

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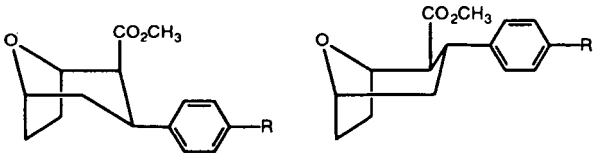
Cocaine is a potent stimulant of the mammalian central nervous system. Its reinforcing and stimulant properties have been associated with its propensity to bind to the dopamine transporter (DAT). The binding interaction between the tropanes and their biological target at the molecular level is still uncertain, It has always been assumed that an 8-amino nitrogen is required for binding between the DAT and ligands in the tropane series, We now report that substitution of the amine by an ether can result in potentligands for the DAT. We now describe the design, synthesis, and biology of a family of potenl inhibitors: 2-catbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes. In this family of 8-oxa compounds, a 3,4-dichloroaryl compound has proved to be a particularly potent inhibitor of the dopamine and serotonin transporters (DAT= 3.08 ± 0.07 nM and SERT=64.5 ± 10.3 nM). An interesting aspect of the binding of the 8-oxa compounds is that they are potent in both the chair and boat conformations.



ACKNOWLEDGMENTS: Supported by NIDA (DA4-8309; DA09462; DA06303) (RR 00168).

A 3α-(DIPHENYLMETHOXY)TROPANE BASED PHOTOAFFINITY LABEL FOR THE DOPAMINE TRANSPORTER

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The dopamine transporter (DAT) is believed to play a central role in cocaine addiction. Many cocaine analogs are known to bind to the DAT. inhibit the reuptake of dopamine and demonstrate a cocaine-like behavioral profile in animal models. In contrast, while 3α--(diphenyhnethoxyhropane analogs show analogous binding and uptake characteristics they demonstrate a non-cocaine-like behavioral profile. The structural and behavioral distinctions between these classes of dopamine uptake inhibitors suggest a dissimilarity in their binding interaction with the DAT protein. Recently, it was reported that photoaffinity labels based on the structures of GBR 12909 and RTI 55 bound to different regions on the DAT. Based on this information, we have prepared a photoaffinity label containing the 3α-(diphenylmethoxy)tropane core to explore its interaction with the DAT. Our studies to date have revealed that the N-(4-n-butylphenyl)-4',4"-difluoro-3α-(diphenylmethoxy)tropane demonstrates potent DAT binding affinity (K_i = 8.3 nM). The phenyl ring in this ligand may serve as an anchor in which an azido and ^{125}I group can be attached. The butyl azido/iodophenyl tropane photoaffinity label may be a useful ligand that will further reveal structure / function relationships at the DAT.

BRIDGED PIPERAZINES AND PIPERIDINES RELATED TO GBR12909 AS DOPAMINE UPTAKE INHIBITORS

Y. Zhang, R. B. Rothman, C. M. Dersch*, J. S. Portilla*, D. B. Joseph, W. D. Bowen, and K. C. Rice*

LMC, NIDDK, NIH, Bethesda, MD and *Clinical Psychopharmacology Sect., IRP, NIDA, NIH, Baltimore, MD

Current studies on the treatment of cocaine abuse have focused on the development of selective dopamine transporter (DAT) ligands as dopamine uptake inhibitors. Among the different classes of ligands identified, the disubstituted piperazines including GBR12909, have demonstrated high affinity and selectivity for the transporter, A drug ad food self-administration study showed that GBR12909 suppresses the cocaine-maintained responding without affecting normal food intake in rhesus monkeys. Recent studies on a decanoate ester of a benzylic hydroxyl derivative of GBR12909, a prodrug formulated To be a long acting dopamine uptake inhibitor, showed that a single dose resulted in a sustained and selective decrease of cocaine self-administration for almost 30 days in rhesus monkeys (J. R. Glowa, *et. al.,* I. Med. Chem., 39, 4689-91). As a continuation of the SAR study, we have modified the piperazine moiety and the ether linkage of the diphenylmethylether of GBR analogs, In the first series, the diphenyhnethylamine derivatives of bridged piperidine GBR analogs, all 6 compounds showed moderate to low aftinity for the dopamine transporter, indicating that an ether linkage is probably necessary to maintain a high binding affinity for the transporter. The second series of compounds is composed of N-methyl and N-(3-phenyl)propyl derivatives of bridged homopiperazine GBR analogs. The synthesis of this series requires the preparation of a bridged homopiperazine moiety via a Schmidt reaction on 3-tropinone followed by an LAH reduction of the lactam. Biological studies of this series is currently underway.

4-PHENOLIC ANALGOS OF NALTRINDOLE AS DELTA-SELECTIVE OPIOID LIGANDS

A. Coop, J. Pinto, C. M. Bertha, K. McCullough†, C. Dersch†, H. Xu†, R. B. Rothman†, and K. C. Rice

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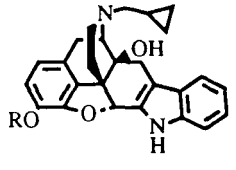
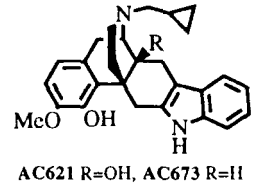
Naltrindole **(1),** a δ- selective opioid antagonist (μδ= 150 in binding assays), is widely used as a pharmacological tool and has many potential clinical applications. The 6,7-fused indole group is known to be essential for delta selectivity, however changes in functionality in the opioid nucleus have been shown to have a marked effect on selectivity. We decided to systematically introduce groups known to lessen μ affinity into the opioid nucleus of **1,** with the aim of discovering a group which would lessen μ affinity but not δ.. It was shown that masking the 3-phenol of **1** as a methyl ether gave **JP45** which had reduced aftinity at both μ and δ,, however the loss in affinity at μ was far greater than at δ,. giving an increased selectivity (μ/δ= 576). Introduction of a 4-phenolic group into **1** gave a compound **(AC621)** of both reduced affinity and selectivity (μδ= 117). The corresponding compound lacking a 14-hydroxy group **(AC673)** also showed reduced affinity compared with 1, but like **JP45,** μ affinity was reduced to a far greater extent than δ,, giving the most selective morphinan based ligand yet described **(AC673,** μδ: >950).



1 R=H, JP45 R=Me



AC621 R=OH, AC673 R=H

DESIGN AND SYNTHESIS OF DERIVATIVES OF THE δ-SELECTIVE OPIOID ANTAGONIST NALTRINDOLE

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Naltrindole is a nonpeptide δ-selective opioid receptor antagonist which has become a very useful pharmacological tool in opioid research. The conformationally rigid indolic benzene moiety of the naltrindole affords higher δ-selectivity by increasing δ-affinity and reducing affmity for μ opioid receptor sites (Portghese 1990). Recent studies have shown that 14-alkoxy substituents on morphinans increase δ-selectivity (Schmidhammer 1997). Also, unpublished biological dam of our group showed that replacing me A ring 3-phenol with a 3-methoxy group greatly increases the δ-selectivity. As part of our program to develop δ-selective opioid ligands, we synthesized 14-isopentylhydrocodeinone indoles and 14-isopentylhydromorphone indole with different substituents on indolic benzene ring. Preliminary binding studies indicated that 14-isopentylhydrocodeinone indole wilhout substituents on indollc benzene ring provided higher δ-selectivity (μ/δ ratio = 1050) than those with substituents on indolic benzene ring (R =Me, μ/δ ratio = 65.4 and R= F, μ/δ ratio = 14.5). Also, 14-isopentylhydrocodeinone indole had the same δ binding affinity as and higher δ-selectivity than 14-isopentylhydromorphone indole (IC50 = 5.85 nM and 5.36 nM; μ/δ ratio = 1050 and 63.2). On the basis of our results, we propose that a 3-methoxy group in A ring decreased the μ-affinity and increased δ-selectivhy (3-OMe/3-OH = 16) and the 14-isopentyl group may interact with an active binding site for the δ receptor (μ/δ ratio of 14-isopenlyl/14-OH = 2).

DESIGN AND SYNTHESIS OF SNC80-BASED AFFINITY LABELING ANALOGS FOR DELTA OPIOID RECEPTORS

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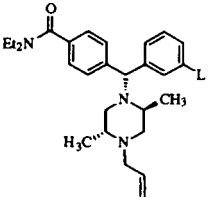
Affinity labels are useful pharmacological tools to study receptor structure and function. As part of our program to develop highly selective, nonpeptide δ opioid receptor ligands, we recently designed and synthesized a series of affinity labeling analogs based on the structure of SNC80, (+)-4[(α*R*-α-{(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl}-3-methoxybenzyl]- *N,N*-dietbylbenzamide). We utilized a stereoselective version of Katritzky's tertiary amine synthesis to prepare an amino analog of SNC80 (L=NH_2). Different electrophilic labeling moieties (i.e. isothiocyanate and α-haloacetamide) were then introduced via the amino functionalized aromatic ring. The binding affinities of the new analogs **1-3** for μ and δ receptors were determined by inhibition of binding of [^{3}H]DAMGO and [^{3}H]DADLE at rat brain membranes. Compounds with the stereochemistry same as that of SNC80 showed higher potency and selectivity for the δ receptors than their enantiomers. Compounds **2** and **3b-c** were found to produce wash-resistant inhibition of [^{3}H]DADLE binding at δ receptors. Further pharmacological studies of these compounds are in progress.



1. L = NH_2
2. L = NCS
3. L = NHCOX
3a. X = H
3b. X = Cl
3c. X = Br

PHARMACOLOGICAL PROPERTIES OF THE STEREOISOMERS OF A 14β-CINNAMOYL-AMINO CODEINONE DERIVATIVE

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In an attempt to determine whether codeinone derivatives, containing a 14-cinnamoylamino group, bind covalently to the opioid receptor, the cis and trans isomers of 14beta-[cinnamoytamino]-7,8-dihydro-N-(cyclopropyl-methyl)norcodeinone (N-CPM-H-CACO) were evaluated for their affinity. selectivity, and ability to produce wash-resistant inhibition of opioid binding to bovine striatal membranes. The trans isomer produced wash-resistant inhibition of mu and kappa binding, but not delta binding, to membranes pretreated with the compound. At least a It-fold higher concentration of the cis isomer was needed to obtain wash-resistant inhibition binding. Saturation binding experiments showed a decrease in the B_{max} value for both mu and kappa radioligands in membranes that had been treated with the trans isomer. These *in vitro* results suggest that the trans isomer of N-CPM-H-CACO preferentially binds covalently to both the mu and kappa opioid receptor in comparison to the cis isomer. The trans isomer was about 50-fold more potent than the cis isomer in producing antinociception in the mouse 55° warm-water tail flick test. Surprisingly, both compounds were equipotent in producing long-term antagonism of morphine-induced antinociception.

ACKNOWLEDGMENTS: Supported by NIDA grants DA03742 and DA01674.

ORAL COMMUNICATIONS V

EFFECT OF THE "CRACK" COCAINE PYROLYSIS PRODUCT, METHYLECGONIDINE, IN SHEEP

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Methylecgonidine (MEG) is a component of "crack" cocaine smoke and a noncompetitive antagonist of acetylcholine possessing biologic activity in guinea pigs and squirrel monkeys. Since crack cocaine continues to be consumed by pregnant women, one concern is the effect of crack upon the mother and its fetus, Since sheep are most appropriate for reproductive toxicology studies, we investigated the systemic effects of MEGfumarate (MEG) on blood pressure, heart rate, skin temperature, and core temperature and compared these responses to cocaine HCI in the same nonpregnant sheep. After implanting polyvinyl catheters in the femoral artery and vein of two sheep, MEGfumarate was administered intravenously on alternate days at 3.0, 5.6, and 10.0 mg/kg. After MEG administration, there was a dose-dependent, transient decrease in mean arterial blood pressure and heart rate, followed by a marked increase above baseline in both measures. The transient decrease in blood pressure after MEG was not observed after intravenous cocaine HCI, 1.8 mg/kg, however, marked hypertension and tachycardia occurred. Skin temperature was elevated after MEG with no alteration in core body temperature. In contrast, skin temperature decreased after cocaine administration, reflective of vasoconstriction, and core temperature increased. These results demonstrate that MEG has characteristics of an initial vasodilatative action not seen with cocaine atone.

ACKNOWLEDGMENT: Supported by NIDA grant DA05080.

PET IMAGING IN AWAKE RHESUS MONKEYS: EFFECTS OF COCAINE ON REGIONAL CEREBRAL BLOOD FLOW (rCBF)

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Positron emission tomography (PET) imaging techniques were used in awake rhesus monkeys as an innovative approach to investigate cocaine-induced functional changes in CNS activity. An effective restraint device was developed that attaches to a commercially-available primate chair to facilitate immobilization, and subsequently attaches to the end of a scanning table to allow for proper orientation in the tomograph. Function changes in regional cerebral blood flow (rCBF) were characterzed with the positron-emitting tracer ^{15}O water following acute i.v. administration of cocaine (0.1, 0.3 and 1.0 mg/kg). Regions of interest were defined on MRl scans and then transformed into the coordinate system of the PET scans with a high degree of accuracy. Cocaine had pronounced dose-related effects on blood flow at 5 min postinjection that diminished markedly by 25 min postinjection. The most obvious regions of increased blood flow were localized to the frontal lobes and corresponded tolimbic areas. This study documents the successful development of an effective restraint device that will allow for the acquisition of reliable PET images in awake monkeys following acute administration of cocaine.

ACKNOWLEDGMENTS: Supported by USPHS grants DA-05346 and RR-00165.

EFFECTS OF COCAINE AND AMPHETAMINE ON EXTRACELLULAR DOPAMINE IN THE MACAQUE

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The present study utilized intracerebral microdialysis techniques to determine to what extent locally administered cocaine HCl (COC) and d-amphetamine (AMP) increase extracellular dopamine levels in the awake macaque. 2-3 mictodialysis probes were acutely placed into the caudate nucleus, nucleus accumbens and anterior cingulate cortex of two unanaesthetized cynomolgous monkeys via implanted guides during each of several different sessions. Eight dialysate samples of 40 min duration were collected during a given experimental session, and analyzed via HPLC-EC for concentrations of dopamine and its metabolites 3-MT, DOPAC and HVA. Changing the perfusate to 50 μM AMP for a single 40 min sample produced pronounced increases over baseline dopamine and 3-MT concentrations in caudate (1,500%; 400%) and nucleus accumbens (2.700%; 400%) followed by a gradual return to baseline levels. 50 μM COC produced similar increases in caudate (1, 100%; 300%) followed by a return to baseline levels. Modest and unreliable increases in dopamine concentrations were observed in anterior cingulate cortex. DOPAC and HVA concentrations did not change after AMP or COC perfusion in any brain region. Chronic daily administration of Haloperidol (0.03 mg/kg. i.m.; n=1) or Risperidone (0.03 mg/kg. i.m.; n=1) had a tendency to enhance the response of DA and 3-MT to infused AMP or COC in the caudate after 12 (Hal, Risp) and 21 (Risp) days. This study demonstrates the feasibility of measuring increases in extracellular dopamine following local administration of dopamine indirect agonists in the awake monkey. This preparation provides an assay for changes in dopamine availability following chronic systemic administration of neuroleptic drugs in a subject population that is similar to man in terms of the dopamine system anatomy, receptor subtype distribution and structure as well as similar in pharmacokinetic parameters of drug clearance and penetration.

ACKNOWLEDGMENT: Supported in part by U.S.P.H.S. grant MH 19934.

GENETIC VARIATION IN COCAINE- AND AMPHETAMINE- REGULATED TRANSCRIPT (CART) EXPRESSION BETWEEN LEWIS (LEW) AND FISCHER (F344) RATS

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Cocaine- and Amphetamine-Regulated Transcript (CART) is a brain enriched cDNA that encodes for a novel protein. Its regulation by psychostimulants, distribution in the brain and putative protein sequence suggests that it may be involved in drug reinforcement and reward. We have started examining CART's expression pattern in the histocompatible inbreed Fischer (F344) and Lewis (LEW) rat strains because they show differential behavioral sensitivities to drug of abuse. Furthermore, in comparison to LEW rats, the F344 strain exhibits a depressed hypothalamic-pituitary-adrenal axis responses to stress, a higher susceptibility to arthritis and a depressed immune system. CART mRNA levels from 60 day old male rats were measured by Northern blot analysis. CART mRNA was undetectable in the hippocampus of F344 rats but present in the hippocampus of LEW rats. F344 rat CART mRNA levels were 14% lower ($p<0.03$) in the nucleus accumbens (nAcc), 75% higher in the hypothalamus ($p<le-5$). and 50% higher ($p<0.01$) in the thalamus. The pituitary of F344 rats exhibited 29-fold less CART mRNA than that of LEW rats. No differences in CART mRNA levels were noted in the olfactory bulb, caudate putamen. cortex, and midbrain; CART was not detected in the cerebellum of either strain. The genetic variation in nAcc CART expression strengthens previous data on a role of CART in drug reinforcement and reward. We also have data demonstrating an effect of CART peptide(s) and CART antisera on cocaine-induced locomotor activity and feeding behaviors. CART expression in LEW and F344 brains and pituitary is strikingly different in selected areas. These areas implicated in immune function, HPA axis and responses to drugs where LEW and F344 exhibit differences. It is plausible that CART may mediate some of these differences and is therefore physiologically relevant.

"BINGE" COCAINE ADMINISTRATION ALTERS PREPROENKEPHALIN mRNA LEVELS IN THE GUINEA PIG BRAIN

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An initial study in this laboratory on the effects of "binge" cocaine administration on gene expression in the guinea pig brain suggested that preproenkephalin mRNA levels were altered by seven days of cocaine administered in a "binge" paradigm (three daily i.p. injections, spaced at hourly intervals with the first injection given 30 min. after the start of the light cycle). We have repeated and extended these studies in this report. Male Hartley guinea pigs were administered saline or cocaine (45 mg/kg/day) in the "binge" paradigm for seven days. Animals were sacrificed 30 min. following the final injection, and mRNA isolated from dissected brain regions of individual animals, Solution hybridization-RNase protection assays were performed on the isolated RNA to determine preproenkephalin MRNA and total RNA content. Data from this and the previous study were combined to provide increased statistical power. Differences between cocaine and control groups were analyzed by two-way analysis of variance unless a significant Group by Study interaction was observed; in this case, a t-test was performed to assess statistical signiftcance. In the cocaine-treated animals, we observed increased levels of preproenkephalin mRNA in the frontal cortex [$F(1,31)=23.5$, $p<0.00004$] and amygdala [$F(1.31)$-10.7, $p<0.003$] when compared to saline-treated animals. Preproenkephalin mRNA levels were lower in the nucleus accumbens [$F(1.33)=5.61$, $P<0.03$] and hypothalamus [$F(1,32)=9.84$, $p<0.004$] of the cocaine group. No differences between preproenkephalin mRNA levels were observed in the caudate putamen, hippocampus, thalamus or cerebellum. These findings differ from similar studies performed in the rat and underscore me importance of studying more than one species.

ACKNOWLEDGMENTS: Supported by NIDA grants P50-DA05130 and DA00049.

THE ROLE OF CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE II IN BEHAVIORAL SENSITIZATION TO COCAINE

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Repeated injections of amphetamine-like psychostimulants result in an enhancement in the ability of these drugs to increase behavioral activation and extracellular dopamine in the medial nucleus accumbens. Calcium plays an important role in this process, suggesting that the repeated drug treatment regimen induces a calcium requirement for the augmented dopamine release. This represents a shift in the mechanism of action of amphetamine since the increase in exttacellular dopamine induced by this drug is normally calcium-independent. The following experiments assessed the potential role of calcium/calmodulin-dependent protein kinase II (CaM-KII) in the enhanced increase in extracellular dopamine induced by amphetamine in the medial nucleus accumbens of rats sensitized to cocaine. In addition, the behavioral relevance of these changes in the mechanism of action of amphetamine were assessed. The results indicate that the CaM-KII inhibitor, KN-93, eliminated the amphetamine-induced enhanced increase in accumbal dopamine in cocaine-pretreated rats, while having no influence on the ability of this drug to increase dopamine in saline-pretreated animaIs. Consistent with these data, the intra-accumbal microinjection of KN-93 produced a dose-dependent reduction in the sensitized behavioral response to a cocaine challenge in rats previously administered repeated daily cocaine, while having no effect on the behavioral response to cocaine in control animals. Taken together, these results indicate that CaM-KII plays a critical role in the expression of behavioral sensitization to cocaine.

ACKNOWLEDGMENTS: Supported in part by the Washington State Alcohol and Drug Abuse Program and U.S. Public Health Service grants MH-40817, DA-03906, Research Career Development Award DA-00158 (P.W.K.) and National Research Service Award DA-05589 (R.C.P.).

EFFECTS OF ANTI-COCAINE ANTIBODIES UNDER DIFFERENT COCAINE SELF-ADMINISTRATION CONDITIONS

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In a recent report (Fox *et al.,* 1996), 4 mg of an anti-cocaine monoclonal antibody (mAb) were shown to extinguish responding maintained by 1 mg/kg/infusion cocaine over a 5-day block of daily 2 hr sessions in rats. Drug delivery was controlled by a second order schedule and infused at a rate of 0.6 ml/min, resulting in a baseline average of 8 infusions per hr. For the present study, reinforcement schedule, drug delivery rate and mAb dose were varied in separate groups of rats in order to more clearly define the range of conditions for antagonizing the reinforcing effects of cocaine by passive transfer of an anti-cocaine mAb. Under a fixed-ratio 1 schedule, cocaine infusions (14 per hr) were not altered after treatment with 4 mg of the anticocaine mAb in the four rats tested. Under the secondorder schedule when drug delivery rate was increased to 1.2 ml/min, cocaine infusions (8 per hr) were extinguished over 5 days in only one of four rats. By increasing the dose of the anti-cocaine mAb to 12 mg under these same conditions, cocaine infusions (9 per hr) were extinguished for 3-5 days in five of the six rats tested. These findings suggest that the cocaine antagonizing effects of the anti-cocaine mAb can be blunted by increasing the frequency and rapidity of cocaine delivery. Under these conditions, a larger dose of antibody was necessary to obtain an effective blockade. Active immunization with a cocaine vaccine will need to induce a high titer antibody response in order to be capable of long-term blockade of the reinforcing effects of cocaine under a wide range of conditions.

ACKNOWLEDGMENT: Supported by NIDA grant DA08979.

ORAL COMMUNICATIONS VI

ANTINOCICEPTIVE PROPERTIES OF A SERIES OF 2-CHLOROACRYLAMIDO DERIVATIVES OF 7,8-DIHYDROMORPHINANS

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The purpose of this study was to identify compounds that act as short-term κ-selective opioid agonists and long-term μ-selective antagonists; such compounds have been shown to exhibit substantially less drug abuse potential and may prove effective in treating addiction. Antinociceptive effects of 6β-(2chloroarrylamido)-4,5-epoxy-3-hydroxy-17-methyl(cyclopropylmethyl)morphinan (N-CPM-6-CLAMO), its N-cyclobutylmethyl analog (N-CBM-6-CLAMO), and its tetrahydrofurfuryl analog (N-FURAN-6-CLAMO) were studied in the mouse tail-flick and acetic-acid writhing assays. In the acetic-acid writhing test. the compounds had D_{50} values ranging from 4.9-5.4 nmol, after i.c.v. administration. The antinociception induced by the compounds was blocked by the κ antagonist nor-BNI, but not by μ or δ antagonists. Pretreatment of mice with the compounds produced a time- and dose- defendent antagonism of morphine-induced antinociception but failed to antagonize antinociception induced by κ and δ agonists. The μ antagonistic effect of 1 nmol of the compounds appeared at 60 min and lasted up to 72 hr, with a maximal effect at 16 to 24 hr after i.c.v. administration. In summary, N-CPM-6-CLAMO, N-CBM-6-CLAMO, and N-FURAN-6-CLAMO are all short-term κ--selective agonists of equipotency and long-term p-selective antagonists in the mouse antinociceptive tests.

ACKNOWLEDGMENTS: Supported by USPHS grants DA03742 and DA01674.

FUNCTIONAL EVIDENCE OF *KAPPA* OPIOID RECEPTOR SUBTYPES IN RHESUS MONKEYS: *IN VIVO* APPARENT pA_2 ANALYSIS

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The potency of naltrexone (NTX) in displacing the specific binding of [^{3}H]U69,593 (putative k_1-selective ligand) was approximately 10-fold higher than [^{3}H]bremazocine (non-k_1-selective ligand) in monkey brain membranes. This led us to test the hypothesis that NTX could display *in vivo* antagonist selectivity for k_1- versus non-k_1-mediated effects. Six opioid agonists were characterized by *in vivo* apparent pA_2 analysis in the warm water (50°C) tail-withdrawal procedure in rhesus monkeys. Naltrexone constrained pA_2 values (95% C.L.) in this assay were: alfentanil, 8.66 (8.5-8.9); EKC, 7.97 (7.9-8.0); U69,593, 7.64 (7.5-7.8); U50,488, 7.55 (7.4-7.7); bremazocine, 6.92 (6.7-7.1); CL-977(enadoline). 6.87 (6.7-7.1) (n=4). Naltrexone apparent pK_B values obtained from another group of three subjects were similar to the range of pA_2 values reported above. Clocinnamox (C-CAM), an irreversible mu opioid antagonist, shifted the dose-effect curves of alfentanil, a *mu*-selective agonist, and EKC by 10- and 3-fold, respectively; but it did not shift those of U69,593, U50,488, bremazocine, and CI-977. In the presence of C-CAM, the pK_B value for NTX in combination with EKC was reduced to 6.89 (6.8-7.0) (n=7). Together with previously obtained data, results of this study suggest that U69,593 and U50,488 produced antinociception by acting on k_1 receptors, hut bremazocine and CI-977 probably on non- k_1 receptors. In addition, both mu and *kappa* receptors mediate the antinociceptive effect of EKC. The current study provides functional evidence of *kappa* opioid receptor multiplicity in primates.

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BEHAVIORAL EFFECTS OF THE NOVEL DELTA OPIOID AGONIST SNC80 IN RHESUS MONKEYS

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The behavioral effects of recently developed non-peptidic delta opioid agonists were examined in assays of schedule-controlled behavior and thermal nociception in rhesus monkeys. In the assay of schedule-controlled behavior, monkeys were trained to respond for food under a FR30 schedule of reinforcement. The putative delta agonists SNC86, SNC67, SNC80, SNC121 and SNC162 produced dose-dependent decreases in response rates. The potency of these compounds in decreasing rates of responding correlated with their affinity for delta but not mu opioid receptors. The effects of SNC80 were reversibly antagonized by the delta-selective antagonist naltrindole (1.0 mg/kg) but not by the mu-selective antagonist quadazocine (0.1 mg/kg) or the kappa-selective antagonist nor-BNI (3.2 mg/kg). In the assay of thermal nociception, latencies to tail-withdrawal were measured following immersion of the tail in water heated to various temperatures (42, 46, 50 and 54°C). SNC80 produced weak but dose-dependent and naltrindole-reversible antinociceptive effects. BW373U86 was ineffective in this assay of nociception; however, BW373U86 antagonized the effects of SNC80, suggesting that SNC80 has higher efficacy than BW373U86 at delta receptors. Moreover, in contrast to BW373U86, doses of SNC80 up to 32 mg/kg did not produce convulsions. These results suggest that SNC80 is a relatively safe, selective and high efficacy agonist at delta opioid receptors in primates.

ACKNOWLEDGMENTS: Supported in part by grants DA02519, DA04059 and DA00101.

INVESTIGATING THE ROLE OF DELTA RECEPTORS IN THE REINFORCING EFFECTS OF HEROIN USING 5'-NTII

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Recent evidence suggests that some of the pharmacology of heroin may be mediated through delta-opioid receptors as well as mu-opioid receptors. This study investigated the role of delta-opioid receptors in the reinforcing effects of heroin using a selective delta-opioid receptor-alkylating antagonist. Rats were trained to self-administer heroin (5.4, 9, 18 or 30 µg/infusion) under an FR10 schedule of reinforcement and given either 0, 1, 5, 10 or 40 nmol of 5'-NTII i.c.v. 5'-NTII attenuated heroin self-administration in a dose-dependent manner. Administration of 5 or 10 nmol of 5'-NTII decreased the number of infusions taken at the lower doses of heroin, whereas administration of 40 nmol attenuated the self-administration of all doses. Administration of vehicle or 1 nmol 5'-NTII was without effect. The effects of 5 and 10 nmol 5'-NTII lasted for 4 days, and the number of infusions gradually returned to control levels from days 4 to 10 after i.c.v. administration. The effects of 40 nmol 5'-NTII persisted for 11 days, and the number of heroin infusions gradually returned to control values from days 14 to 18 after 5'-NTII administration. Examination of the full dose-effect curve for heroin following 5'NTII demonstrated that 10 nmol icv shifted the dose-effect curve approximately 0.5 log units to the right with a slight downward shift. Administration of 40 nmol of 5'NTII produced a dramatic downward shift and shifted the dose-effect curve approximately 1.25 log units to the right. Administration of 40 nmol of 5'-NTII i.c.v. to rats trained to self-administer cocaine (0.17, 0.33 or 0.67 mg/inf) had little effect. Therefore, delta-opioid receptors appear to be involved in the reinforcing effects of heroin. The effects of these doses of 5'-NTII on delta- and mu-opioid receptor binding are currently being assessed to compare with the effects on heroin self-administration.

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STUDIES OF SELECTIVE OPIOID ANTAGONISTS AND AGONISTS AFTER SPINAL ADMINISTRATION IN AMPHIBIANS

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The pharmacological effect of β-FNA (an irreversible mu opioid antagonist), naltrindole (NTI, delta selective antagonist) and norBNI (kappa selective antagonist) was tested against *mu, delta,* and *kappa* selective opioids after spinal administration in unanesthetized leopard frogs, *Rana pipiens*. Analgesic effects were measured using the acetic acid test. Acute β-FNA (20 nmol) did not produce analgesia, and concurrent injection of the mu opioid. fentanyl (30 nmol) and β-FNA (20 nmol) produced a significant block of fentanyl analgesia. Fentanyl analgesia was antagonized for up to 10 days after β-FNA pretreatment. Twenty-four hour pre-treatment with β-FNA also blocked morphine, but not *delta* (DADLE, DSLET) or *kappa* (bremazocine, U50488) opioid analgesia. NTl (0.1 nmol/frog) was selective for DPDPE antagonism and concurrent injection blocked DSLET, DPDPE, and morphine analgesia. NTI potentiated fentanyl and DADLE effects and had no effect on DELT, DAMGO or *kappa* selective opioids. norBNI (0.1 nmol) was selective for GR89696 (*kappa*) analgesia and concurrent injection blocked equieffective doses of U50488, but also blocked morphine, fentanyl, DPDPE, and DELT, norBNI potentiated DADLE analgesia but bad no effect on DSLET. In light of previous studies showing that systemic, spinal and icv administration of *mu, delta,* and *kappa* opioids produces analgesia in amphibians in the same rank order of relative potency as in mammals but that binding studies show only one predominant *kappa-like* opioid site, these present results suggest that norBNl may block analgesic effects of mu, delta, and *kappa*-selective opioids in amphibians and support a "unireceptor hypothesis" of opioid analgesia which may be relevant to opioid analgesia in humans.

ACKNOWLEDGMENTS: Supported by NIH-NIDA (DA07326) and the Whitchall Foundation.

THE d-ISOMER OF METHADONE HAS NMDA RECEPTOR ANTAGONIST ACTIVITY

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dl-Methadone and its *d*- and *l*- isomers exhibit low micromolar affinities for the [^{3}H]MK-801-labeled noncompetitive site of the NMDA receptor in both rat forebrain and spinal cad synaptic membranes, with K_i values and displacement curves similar to those of dextromethorphan, an established NMDA receptor antagonist (Neurosci, Lett., 223: 5-8, 1997). To determine whether d-methadone has "functional" NMDA receptor antagonist activity, rats were pretreated with d-methadone prior to the formalin test, a model of central sensitization. d-Methadone in a dose of 32, 160, or 320 ug/rat or saline in a volume of 10 ul was administered intrathecally (IT) 15 minutes prior to intraplantar formalin. In the saline-pretreated rats, formalin produced stereotypical nociceptive behaviors. d-Methadone dose dependently reduced the phase 2 flinching, with the 320 ug/rat dose producing a 68% decrease. Phase 2 licking and the phase 1 behaviors were not dose dependently affected (phase 1 licking was reduced only at the highest dose). d-Methadone did not alter the tail-flick response. These results demonstrate that IT d-methadone is antinociceptive. This activity may be a consequence of itsNMDA receptor antagonist activity.

ACKNOWLEDGMENTS: Supported in part by NIDA Grants DA01457, DA00198, DA07274, DA00255 and the VZV Foundation.

SEX DIFFERENCES IN MORPHINE ANTINOCICEPTION

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Several investigators have shown that male rodents are more sensitive than female rodents to morphine's antinociceptive effects. The present study was conducted to de&mine the generality of this sex difference by examining morphine's effects in female and male rats on two different thermal nociception assays, using three different stimulus intensities, either acute or repeated dosing, and in females at various stages of the estrous cycle. In the first experiment, a time course of antinociception was obtained on the 50, or 52 or 54°C hotplate and warm water tail withdrawal tests. Acutely administered morphine produced greater antinociception per given dose - greater peak and/or longer duration antinociception -- in males than in females at all three stimulus intensities on each assay. In contrast, when rats were tested on all four dose conditions (one dose/week for four weeks), there were no sex differences in morphine's effects on either assay (52°C stimulus), suggesting that female and male rats may develop tolerance at different rates. This hypothesis was tested in a separate experiment; however, there was no sex diifference in rate of tolerance development in rats tested daily with 10 mg/kg morphine on the 52°C hotplate. In a separate experiment. female rats in proestrus, estrus or diestrus-1 were tested with saline or 5.6 mg/kg morphine; preliminary results indicate that morphine produced the least antinociception in diestrus-1 females. Thus, the fact that no sex differences were obtained when rats were tested repeatedly may be attributable to variability of morpbine antinociception across the estrous cycle, in addition to morphine-induced changes in estrous cyclicity.

ACKNOWLEDGMENT: Supported by NIDA grant DA 10284.

STUDIES ON THE ANTIPRURITIC POTENTIAL OF AGONISTS AT MU, KAPPA AND DELTA OPIOID RECEPTORS

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Pain and itch are probably independent sensory modalities. The pharmacological bases of itch remain ill-defined Scratch behavior is specific for itching and differentiates itch from pain. Kuraishi *et al.* (1995) recently described an animal model of itch which involves Compound 48/80-induced scratching in mice. We have validated and standardized this model, and studied the effects of morphine (mu), enadoline (kappa), ICI 204,448 (peripheral kappa), SNC 80 (delta), naloxone (opioid antagonist) and saline on scratching over 30 min caused by 50 μg (100 μl) of Compound 48/80 injected s.c into the back of the neck of albino Swiss male mice (24-27 g; n=7-10). Antiscratch-50 values were obtained by nonlinear regression analysis (KaleidaGraph) for morphine (0.25-2 mg/kg s.c. given 10 min before Compound 48/80), enadoline (2.5-20 μg/kg s.c. at -5 min), ICI 204,448 (2.5-10 mg/kg s.c. at -20 min), SNC 80 (0.25-25 mg/kg s.c. at -30 min) and naloxone (0.3-3 mg/kg s.c. at -10 min). The values were 0.38, 0.004, 2.82, 2.73 and >3 mg/kg, respectively. Enadoline is very potent against icv bombesin (another scratch-inducing agent) in rats; we have therefore focused on the role of kappa receptors in mediating the sensation of itch. Kappa receptors seem to be involved since pretreatment of mice with a behaviorally neutral dose of norbinaltorphimine (20 mg/kg s.c. at -15 h) antagonized the antiscratch activity of enadoline (0.01 mg/kg) (76±4% to 37%±12%, s.e. mean). Also, our demonstration of activity for ICI 204,448 against Compound 48/80 (in contrast to the bombesin model) affords another endpoint for structure-activity studies with peripheral kappa agonists.

REFERENCE: Kuraishi, Y. *et al.* (1995) Eur J Pharmacol 275, 229-233.

ACKNOWLEDGMENT: Supported by NIDA grant DA-07237.

ORAL COMMUNICATIONS VII

A PILOT STUDY OF THREE DOSE SCHEDULES FOR THRICE WEEKLY ADMINISTRATION OF BUPRENORPHINE

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Thrice weekly buprenorphine (BUP) dosing has been proposed as an altemative to daily dosing for treating opioid dependence. To determine the optimal regimen, we compared 3 thrice-weekly BUP dose schedules (DS) (mg/70kg) - A: 16, 16, and 32; B: 22.22, and 40; and C: 34, 34, and 44. Opioid dependent subjects were maintained on each DS for two three-week periods during the 18 week study. Subjects and investigators were blind 10 the DS. The outcomes were: urine toxicology (UTOX) and self reported opioid use and withdrawal symptoms. Subjects (N=21) included 11 males and 10 females and 66% (14/21) completed the study. No complications were noted. Between the 3 DS (A v B v C), there were no significant differences in % UTOX positive for opioids (66% v 70% v 66%) or cocaine (33% v 30% v 36%). Similarly, mean use of opioids (bags/week) (2.5 v 2.6 v 2.9) and cocaine (0.7 v 0.5 v 1.3) did not differ across DS. Opioid use tended to be higher in all 3 DS when patients went 72 hours without BUP. Finally, mean daily opioid withdrawal symptom scores (range: 0-88) did not differ significantly (4.6 v 3.7 v 4.5). In conclusion, thrice weekly BUP was well tolerated. High opioid use in our subjects may be based on the short duration of treatment and frequent DS changes. No significant differences were noted between the 3 BUP DS studied. Our future research will compare thrice weekly to daily dosing.

DOSE COMPARISON OF LAAM DURING MAINTENANCE THERAPY

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LOAM is the most recently approved pharmacotherapy for opioid dependence. To date, there have been no clinical trials assessing dose effectiveness of LAAM during maintenance therapy. **Purpose:** To assess the effectiveness of three LAAM doses during maintenance therapy. **Methods:** Patients (N=180) were stratified and randomly assigned to a 203 day double-blind clinical trial comparing three, thrice-weekly (M/W/F) LAAM dose conditions. Of the 180 patients initially enrolled, 142 entered the *a priori* identified maintenance phase (days 36-119). Patients in the low (N=50), medium (N=50), and high (N=42) dose conditions recrived 25/25/35, 50/50/70, and 100/100/140 mg oral LAAM, respectively. Urine specimens were collected and tested 3x/week. Outcome measures were: retention in treatment, percent of opioid negative urine specimens, percent of patients who submitted 12 consecutive opioid negative urine specimens, and self-reported heroin use (past 30 days). **Results:** There was no overall main effect on retention in treatment; however, there was a trend ($p<.07$) for greater retention in the high dose compared to the low dose condition. Overall, patients in the high dose condition submitted 46% opioid-negative urine specimens, as compared to 35% in the medium, and 26% in the low dose condition ($p<.05$, high vs. low). Similarly, 44% of the patients in the high dose condition submitted 12 consecutive opioid negative urine specimens, as compared to 18% in the medium and 13% in the tow dose condition. ($p<.05$, high vs. low). Patients in the high dose condition reported using heroin 3.4 out of the past 30 days, compared to 6.2 days for the medium and 9.2 days for the low dose condition, ($p<.05$, high vs. low). No difference between groups was observed for cocaine use. **Conclusion:** The effectiveness of LAAM during maintenance therapy is positively related to dose.

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EFFECTIVE MAINTENANCE TREATMENT OF OPIOID DEPENDENCE WITH TWICE WEEKLY LAAM DOSING

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The NY VA Opioid substitution Program has been prescribing LAAM since October 1994. Current prescribing guidelines recommend three times a week dosing. In the course of regular use of LAAM, we noted that some individuals missed a dose and returned to the clinic with no evidence of withdrawal or complaints of discomfort. Based upon clinical observation, in September 1996. we offered twice weekly dosing to LAAM patients, **Method:** Patients dosed with LAAM 3 times a week, who reported no Sunday withdrawal symptoms and demonstrated 8 consecutive random urine drug screens negative for opiates, were invited to reduce the frequency of clinic visits to twice/week. Total weekly LAAM doses guided adjustment of the 2 doses. During the 1996-97 Christmas and New Year Holidays, all LAAM patients were given the option of twice-weekly dosing. Results: In January 50 LAAM patients requested twice weekly dosing, and 28 were placed on the new schedule. One of the September and 2 of the January volunteers returned to 3 times/week due to somnolence on the 96 hour dose or Withdrawal discomfort.) April 1997 review indicates that 26 (18%) of all LAAM patients were on twice weekly dosing. Review of urine drug screens demonstrated that 13 (50%) used no illicit drugs, 13 used an illicit drug at least once in the previous 4 months. Urine drug screens of the twice weekly group were compared to methadone maintained patients (N 20) and 3 times/week LAAM maintained patients (N 20). We found that 7% of the twice weekly LAAM group used heroin at least once compared to 21% of the methadone group and 13% of the 3x week LAAM group. We conclude that a selected population of motivated addicts can be successfully maintained on twice weekly LAAM dosing.

RELAPSE TO HEROIN USE AMONG STABLE METHADONE MAINTENANCE PATIENTS

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Use of illicit opioids is high among methadone maintenance treatment (MMT) patients, and such use brings with it continued involvement in illegal activities and the risk of HIV infection. We studied psychological variables predicting relapse to illicit opioids among 74 MMT patients, all of whom had been in treatment for 3-18 months. This time period was selected because it allowed for completion of the induction phase of treatment, and also excluded subjects who had remained in treatment for such an extended length of time that relapse would be unlikely Sixty percent of the subjects were men. Sixty-one percent were Caucasian, 20% were African-American, 12% were Latino, and 7% were members of other racial groups. At induction into the study, all subjects reported at least two weeks of abstinence from opioids. All subjects also maintained biochemically verified abstinence two additional weeks, and were abstinent during the baseline data collection week of the study which followed. Based on social learning models. and previous work by our group, we predicted that: (1) more stringent abstinence goats. higher positive moods, greater optimism, and higher frequency of pleasant events would predict abstinence from illicit opioids; (2) lapses to heroin would be followed by retrospective reports of poor mood, and more life stress, but these variables would not prospectively predict lapses. All subjects were assessed on withdrawal symptoms, dispositional optimism, and mastery at baseline. All variables except optimism and mastery were reassessed at follow-up meetings during weeks 2-8. The prototypical data analysis method will be proportional hazard regression. As predicted, a stringent abstinence goal predicted abstinence from heroin. Poor mood was reported concurrent with lapses, but neither mood nor stress predicted abstinence from heroin. Use of cocaine, marijuana, and benzodiazepines predicted subsequent lapse to heroin. but alcohol use did not.

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PREDICTION OF 7 MONTH METHADONE MAINTENANCE TREATMENT RESPONSE BY 4 MEASURES OF ANTISOCIALITY

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Simultaneous regression analyses were performed to ascertain the comparative validity of four measures of antisociality for predicting the initial seven month treatment response of 193 male methadone maintenance Veterans Administration patients. The predictor variables were the number of childhood antisocial personality disorder behaviors (CD), number of adult antisocial personality disorder behaviors (A-ASPD). the total revised Psychopathy Checklist (PCL-R) score, and the revised California Psychological Inventory- Socialization scale (CPI-So) score. The outcome measures evaluated were completion/noncompletion of the initial seven months of treatment, percent positive during-treatment cocaine, opiate, and benzodiazepine urine toxicologies, and relative change from baseline to seven month follow-up in the seven Addiction Severity Index (ASI) composite scores. Only the PCL-R score entered into the regression model for completion/noncompletion. No variables significantly predicted opiate use and only the PCL-R predicted cocaine toxicologies. Although both the PCL-R and CPI-So measures were significantly correlated with benzodiazepene use, neither variable was significant in the regression model. None of the predictor variables were significantly correlated with baseline to follow-up composite score change in any of the Seven ASI areas.

ACKNOWLEDGMENTS: Supported by NIDA Center Grant # DA05186, NIDA Grant # DA-05858, and the Department of Veterans Affairs.

NTORS: THE NATIONAL TREATMENT OUTCOME RESEARCH STUDY (UK)

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The National Treatment Outcome Research Study (NTORS) is the largest study of treatment outcome for drug abusers ever conducted in the UK. and plays an important role in the development and guidance of UK national drug treatment policy responses. The NTORS cohort of 1075 clients were treated in four modalities: specialist inpatient units, residential rehabilitation units, methadone maintenance and methadone reduction programs. NTORS investigates the impact of these treatments on drug-related problems, health and social functioning. The project was established to advise the Department of Health's Task Force on the effectiveness of existing national drug treatment services and preliminary findings from NTORS were given to the British Government in 1996. NTORS results have also been used by the Department of Health to formulate guidance to treatment purchasers. The early findings show marked improvements in key problem behaviors after treatment. Some of the main findings obtained six months after starting treatment, and especially those relating to substance use problems, are reported in this paper. The extension of NTORS to permit the continuing follow-up of clients over a 5-year period will enable its findings to provide further assistance to the direction of services within the UK.

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METHADONE TREATMENT REDUCES HOSPITAL UTILIZATION: PRELIMINARY ANALYSIS OF A CONTROLLED TRIAL

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Objective: To describe the relationship between methadone maintenance (MM) treatment and medical care utilization in injection drug users (IDUs). **Method:** This is a preliminary analysis of medical care utilization by the first 55 of an eventual 112 opioid dependent tuberculin skin-test positive IDUs. Subjects participated in a 6 month controlled trial of MM vs. routine care. Routine care consisted of referral to TR Clinic and 21-day methadone detoxification. but no methadone maintenance, (No-MM). MM was either Standard MM with counseling (S-MM) or Minimal MM with no counseling (M-MM). Nineteen participants were assigned to No-MM, 17 to S-MM and 19 to M-MM. 26 (47%) were women, 19 (35%) were African -American, 10 (18%) were Latino(a), and 26 (47%) were white. All were HIV seronegative. Mean age was 42 (± 5.8) yrs. Mean years of heroin use was 17.2 (±9.1). All were patients at San Francisco General Hospital (SFGH). Utilization data was obtained from computerized SFGH records. **Results:** In the No-MM group, mean annualized medical charges totaled $9841/pt-yr (± 2661) prior to entry into the study and $9047/pt-yr (± 3703) after entry. For the two MM groups, the mean annualized medical charges decreased from $14069/pt-yr (± 2997) prior to entry into the study to $4869/pt-yr (± 1428) after entry. The two MM groups had a greater reduction in total medical charges compared to the no-MM group (repeated measures ANOVA. F=3.51, p=.067). **Conclusion:** MM treatment is associated with major reductions in medical care utilization.

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SUBSTANCE ABUSE TREATMENT NEED AMONG ARRESTEES-ADULTS

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To evaluate rates of current drug or alcohol use and dependence among adult arrestees and to evaluate the social and psychiatric comorbidity, criminal history, prior treatment history, and treatment needs of dependent arrestees, we used structured interviews and urine toxicology testing to assess 278 mates and 200 females, ages 21 or over from detention centers in two CT cities. Utox was performed on 157 mates and 71 females. Estimated rates of use within 72 hours preceding arrest (based on self-report or positive Utox) for mates and females respectively were 72%, 84% for any drug; 48% 48% for cocaine; 18.6%. 15.8% for heroin; and 27.3% 18.6% for marijuana. Rates of current drug or alcohol dependence were 53.2%, 60.8%; 27.4%, 38.2% for cocaine; 16.9%, 18.6% for heroin; 12.5%, 7.4% for marijuana, and 36.3%, and 25.7% for alcohol. Compared to their counterparts without drug dependence, heroin dependent arestees had lower rates of arrest for violent offenses and higher rates for property offenses, while cocaine dependent females had tower rates and cocaine dependent mates had equivalent rates of arrest for violent charges. Compared to drug free arrestees, drug dependent arrestees had lower rates of employment, more income from illegal sources, and higher rates of current depression, anxiety, and recent suicide attempts, and engage in more HIV risk behaviors. While 80-92% of those dependent on heroin or cocaine reported a need for treatment, only 9% of males and 19.1% of females were enrolled in treatment at the time of arrest. Despite long duration and severity of dependence and interest of drug dependent arrestees in treatment, few are currently in treatment and most have never received treatment other than detoxification. Treatment services for drug dependent arrestees need to address their educational and vocational deficits, HIV risk, and psychiatric comorbidity.

ORAL COMMUNICATIONS VIII

SYNTHESIS AND BIOLOGICAL EVALUATION OF ANANDAMIDE ANALOGS

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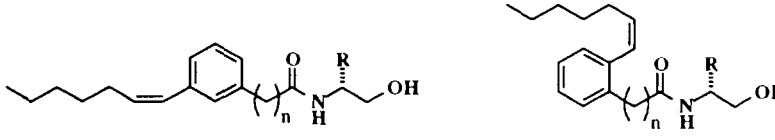
The discovery of an endogenous ligand, anandamide, for the cannabinoid neurochemical system by Devane *et al.* in 1992 introduced a structurally unique cannabinoid agonist: the ethanolamide of arachidonic acid. A number of SAR studies followed shortly thereafter that primarily involved either changing the alkyl group at the amide nitrogen or increasing or reducing the degree of unsaturation in the arachidonyl chain. These initial SAR studies left open the question of which conformations of anandamide were biologically relevant. The flexibility of the arachidonyl chain makes the determination of the biologically active conformations of anandamide by computational methods a great challenge. We wished to address the question by preparing a number of conformationally restricted anandamide analogs. Analogs were prepared that incorporated a phenyl ring in the arachidonyl portion of the molecule as shown in the structures. We then measured their affinities for the cannahbinoid (CB1) receptor. All analogs had CB1 receptor affmities in the range of low to high μM in rat brain membranes which are three orders of magnitude smaller than anandamide



n = 0-2; R = H or Me

EVIDENCE FOR PERIPHERAL-TYPE CANNABINOID RECEPTORS (CB2) ON RAT MICROGLIAL CELLS

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Modulation of immune cell function by cannabinoids is believed to be mediated by the peripheral cannabinoid receptor (CB2). The CB2 receptor has been shown to decrease adenylyl cyclase, activity through a pertussis toxin sensitive G-protein. Microglia are immune competent cells of myeloid lineage which reside in the central nervous system and have been implicated in several pathologies including AIDS dementia complex. We investigated the hypothesis that microglia express the CB2 receptor. Microglia were isolated in >98% purity from confluent cultures of 2 day old rat pups using standard techniques. RT-PCR was used to amplify the mRNA for the CB2 receptor from total RNA. Sequencing of the 694 bp amplicon showed 94% identity with the mouse CB2 transcript, and 82% identity with the human CB2. The CB2 agonist CP55,940 elicited a dose dependent decrease in cAMP accumulation in IBMX treated microglia stimulated with one micromolar forskolin. The EC50 for CP55,940 was 1.98 nM and 100 nM CP55,940 decreased stimulated adenylyl cyclase activity by 95%. In light of the relationship between microglia and AIDS dementia complex, further work is needed to elucidate the effects of cannabinoid agonists on microglial function.

ACKNOWLEDGMENTS: Supported by the Cancer Center of the Medical College of Wisconsin, NIDA grant DA-08098, and NIDA-Office on AIDS Travel Award.

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 1,1-DIMETHYLHEPTYL ANANDAMIDES.

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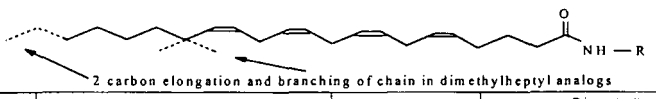
We have proposed, based on a previously reported pharmacophore alignment between anandamides and classical and nonclassical cannabinoids, that extension of the pentyl side chain of anandamide to a dimethylheptyl side chain should result in increased binding affinity and pharmacological potency. In order to test this hypothesis, we have synthesized and assayed a series of 1,1-dimethylheptyl anandamides for comparison to their pentyl side chain analogs. We have found that while the binding affinity of each dimethylheptyl analog was improved over that of its pentyl side chain analog (Table 1), their potency in the isolated mouse vas deferens (EC_{50}'s) preparation did not increase as predicted. In this tissue, the dimethylheptyl compounds exhibited decreased potency and efficacy when compared to their pentyl side chain analogs. On the other hand, the *in vivo* potency of the dimethylheptyl compounds (mouse tetrad) was greater than that seen with their pentyl analogs and paralleled their increased binding affinity. Therefore, the data supports the relevance of the side chain equivalence postulated in our original pharmacophore model and suggests that the cannabinoid receptor population in the mouse vas deferens differs from neuronal (CB1) receptors. Supported by NIDA: DA 10063-01A1, DA03672-09.

Table 1. K_i values (nM) of Anandamide Analogs vs [^{3}H]CP-55940



	Arachidonyl					Dimethylheptyl			
R =	K_i	Std Dev	% C.V.	N =	R =	K_i	Std Dev	% C V	N =
CH_2CH_3OH	25.0	15 1	60.5	4	CH_2CH_3OH	1.90	1.24	85 6	4
$CH(CH_3)CH_2OH$	22 2	8.48	38.2	3	$CH(CH_3)CH_2OH$	1.66	0.961	57.9	4
$CH_2CH_2OCH_3$	43 8	11.5	28.3	3	$CH_2CH_2OCH_3$	3.91	0 881	22 5	4
$CH_2CH_2CH_3$	2.58	2 46	95.6	3	$CH_2CH_2CH_3$	1 47	0 487	33.2	4
$CH_2CH(CH_3)OH$	58.8	8.56	15.1	3	$CH_2CH(CH_3)OH$	5 05	1 11	22.0	4

EFFECTS OF Δ9-THC, R-METHANANDAMIDE, SR 141716, & *d*-AMPHETAMINE BEFORE & AFTER DAILY Δ9-THC DOSING

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We examined the effects of Δ9-THC, R-methanandamide, SR 141617, and *d*-amphetamine on fixed-ratio responding maintained by food in rats before and after daily dosing with Δ9-THC. Rats responded under a schedule with 4 five-minute periods of FR 10 food reinforcement separated by 15-minute time-outs during which responding had no consequences. Cumulative dose-response curves for the various drugs were determined before and during daily Δ9-THC administration by giving ascending doses of the drug at the beginning of consecutive time-out periods. All four drugs dose-relatively deceased responding both before and during daily dosing with Δ9-THC (18 mg/kg/day). The dose-response curves for both Δ9-THC and R-methanandamide were shifted to the right with daily dosing with Δ9-THC. In other words, there was tolerance to the effects of Δ9-THC and cross-tolerance to the effects of R-methananadamide. The doses of *d*-amphetamine examined produced similar effects both before and during daily dosing with Δ9-THC. We determined the effects of SR 141716 twice during daily Δ9-THC administration. On the first occasion, the SR 141716 dose-response curve was shifted to the left of the curve determined before daily Δ9-THC administration began. The second SR 141716 curve. however, approximated the SR 141716 curve determined before daily Δ9-THC administration. These two results indicate that if sensitization occurrs to the effects of SR 141716 with daily Δ9-THC administration, it is labile. This finding is not simply a result of the instability of the dose-response curves, because we determined the Δ9-THC curve at two points during daily Δ9-THC administration and both of these curves demonstrated similar degrees of tolerance.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 09064, DA 00253, DA09158, & DA 03801.

SR141716A PRECIPITATES SUPPRESSION OF OPERANT RESPONSE RATES IN THC CHRONICALLY TREATED RATS

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Prior to the availability of cannabinoid antagonists, we had demonstrated that chronic, i.v. infusion of delta-9-tetrahydrocannabinol (THC) can induce behavioral dependence in rhesus monkeys as reflected by the suppression of food-maintained lever pressing rates upon termination of THC infusion. In the present studies, we attempted to systematically extend this demonstration to rats treated s.c. with THC and in which withdrawal effects were precipitated with the cannabinoid antagonist, SR141716A. Adult male Long-Evans rats were trained to lever press according to VI-10 sec schedules during daily experimental sessions composed of six, 3-min food-reinforcement periods which alternated with six, 10-min time-out (TO) periods. Following training, separate groups of rats were treated b.i.d. for 6 days with either vehicle or escalating dosage regimens terminating with either 30, 40, or 50 mg/kg of THC. On days 7 and 8, tests with cumulative doses of SR141716A (3 and 9 mg/kg, respectively) were conducted. SR141716A dose-dependently suppressed response rates only in rats with THC histories and did so as a positive function of THC dosage regimen. Subsequently, rats were administered an escalating 6-day b.i.d. THC treatment terminating with 30 mg/kg and then were tested with vehicle or 1, 3, or 6 mg/kg SR141716A. Again, SR141716A dose-dependently suppressed response rates only in rats with THC histories. These data suggest that SR141716A can precipitate withdrawal effects in THC-treated rats and are consistent with inferring that THC can induce behavioral dependence.

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EFFECTS OF Δ^{9}-THC AND R-METHANANDAMIDE ON OPEN-FIELD BEHAVIORS IN RATS

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This study compared the effects of R-methanandamine (RM), an analog of the mammalian brain constituent amandamide, and Δ^{9}-THC; on the open-field (O-F) behavior of male Sprague-Dawley rats. Before testing. rats were individually housed with free access to food and water. Groups of rats (n=10; N=80) were tested with 0, 1, 3, and 5.6 mg/kg THC given i.p. 30 min. pre session, and 0, 3, 10, and 18 mg/kg RM, 15 min. pre session. The O-F arena was a gray painted wooden box (60 x 60 x 50 cm) with an open top and a white floor divided into 16 squares (15 x 15 cm) and a circle (diameter 19 cm) marked in the center of the field. The squared floor was covered with an acrylic plate (60 x 60 cm), which was cleaned between trials. The behavioral categories recorded were ambulation (the number of squares crossed). rearing (the number of times the rat stood erect on its hind-legs), latency (the time in sec to leave the starting area, the circle in the center of the field), circling (the number of times the animals turned around its vertical axis, 0.5 point given for each 180 degrees turn), grooming (the number of cleaning bouts). urination and defecation (the number of urination spots and fecal boli deposited during the 5 min. observation period). THC was more potent than RM, but otherwise the effects of THC and RM were similar with one exception. While THC produced dose related increases in circling. RM did not increase circling over the doses examined. This may indicate that there are qualitative behavioral differences in the effects of THC and RM. In order to determine if the THC-induced circling was a cannabinoid mediated effect, two doses of the CB1 selective antagonist SR141716 (1 and 5.6 mg/kg) were examined in combination with 3 mg/kg THC (N=15; n=7 and n=8). Only the higher dose prevented circling.

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THE CANNABINOID ANTAGONIST SR141716A ENHANCES RADIAL ARM MAZE PERFORMANCE IN RATS

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The putative endogenous cannabinoid system has been proposed to be tonically active in a variety of processes including learning and memory. In the present study, we examined whether blockade of this system with the specific cannabinoid antagonist SR141716A would enhance spatial memory as assessed in a variation of the 8 arm radial maze task. Rats were given an i.p. injection of either vehicle or SR141716A (3 mg/kg) and given access to seven run-way arms, the eighth arm was blocked off (phase 1). After all of the available arms were visited and food pellets consumed, the subjects were removed from the maze for either a 1, 10, 30, or 60 min delay. After the delay. the subjects were placed in maze again with all eight arms available (phase 2). The number of entries to obtain the food reinforcement in the eighth arm was scored. SR141716A signhicantly decreased the number of trials required to visit the previously unavailable arm. At the 30 min delay, for example, the subjects committed 2 ± 0.5 reentries when given vehicle, but only 0.6 ± 0.2 reentries after drug administration. In an additional experiment, rats were given an i.p. injection of Δ^9-THC (0, 1, 2, 4, or 6 mg/kg) 20 min prior to phase 1. Δ^9-THC significantly impaired maze accuracy in both phases. Our results are consistent with those from a recent report in which SR141716A enhanced memory in a social recognition task. These findings suggest that antagonism of a tonically active cannabinoid system may enhance some forms of memory.

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ORAL COMMUNICATIONS IX

REVERSAL OF COCAINE-INDUCED CHANGES IN BRAIN BLOOD FLOW BY ISRADIPINE

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Using a new quantified technique for measuring absolute brain blood flow (BBF) with Single Photon Emission Computerized Tomography (SPECT), we studied the effects of intravenous (IV) cocaine (0.325 mg/kg and 0.65 mg/kg dissolved in 25 ml of 0.9% NaCl) and IV cocaine and isradipine (10 mg orally) in two recently abstinent cocaine dependent subjects. We found that cocaine administration was associated with a significant reduction in total BBF, and in induced perfusion to areas rich in dopaminergic innervation (e.g. putamen, superior temporal lobe, prefrontal cortex). Importantly; however, these cocaine-induced reductions in BBF were completely reversed by isradipine. These results show that isradipine, a L-type calcium channel blocker, can antagonize the ischemic effects of cocaine. We postulate that the effects of isradipine is achieved via the inhibition of dopaminergic activity.

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OPEN TRIALS AS A METHOD OF SCREENING POTENTIAL MEDICATIONS FOR THE TREATMENT OF COCAINE DEPENDENCE

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Objective: This study describes the use of open trials with a historical control group to rapidly identify promising medications for the treatment of cocaine dependence The following medications were compared: propranolol, nefazodone, phentermine and fenflutamine (phen/fen), and a multivitamin control. **Methods:** Each medication was evaluated sequentially in an open trial. Propranolol (n=15) was given for 8 weeks at a dose of 60-100 mg daily. Nefazodone (n=17) was given for 8 weeks at a dose of 100-300 mg daily. Phentermine 30 mg and fenfluramine 80 mg (N=16) were given for 7 weeks. Finally, a multivitamin (N=17) was given for 7 weeks as a control. Outcome measures and psychosocial treatment were standardized in all groups. Primary outcome measures included treatment retention and urine toxicology screens. Secondary outcome measures included the Addiction Severity Index (ASI). **Results:** Retention at 7 weeks was significantly better in the propranolol group. Defined as completion of 7 weeks of treatment with 4 weeks of documented abstinence from cocaine, treatment success was better in the propranolol group. Forty percent of propranolol group achieved success, whereas only 24% of the multivitamin group, and less than 20% of the nefazodone and phen/fen group achieved success. Among completers in all 4 groups, there was a significant decline in ASI Composite Drug Scores. The propranolol anl nefazodone groups also had significanl declines in ASI Composite Alcohol Scores. Treatment retention of patients with high ASI Composite Alcohol Scores was significantly better in the propranolol and the nefazodone groups. **Conclusions:** Propranolol may be helpful in assisting cocaine dependent outpatients stay in treatment and attain abstinence. Propranolol and nefazodone may be especially useful in cocaine dependent patients who also abuse alcohol. Open trials may be useful in rapidly identifying promising medications for the treatment of cocaine dependence.

MOTIVATIONAL ENHANCEMENT TO INCREASE TREATMENT READINESS AMONG STIMULANT USERS: A PILOT EVALUATION

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This was a pilot study to assess the effect of Motivational Enhancement (ME) (Miller and Rollnick, 1991) with cocaine dependent people not actively seeking treatment. It employed a 3-group design with two waiting lit controls and follow-up interviews at 1 and 2 months. Participants, recruited in street contacts by outreach workers, were 57% male, and 90% African American. At initial interview, the ME group (n=21) completed a structured assessment administered by research staff and feedback using ME techniques. Feedback was delivered by outreach workers trained in ME for this project or by a psychologist with background in ME. The Assessment Only (AO) ($\underline{n}$ =14) group received an assessment initially and received feedback after the follow-up assessment at 1 month. The Assessment at Follow-up Only (AFO) ($\underline{n}$ =7) group, a control for the effects of assessment, completed only consent and locator at initial, a follow-up assessment at 1 month, and assessment and feedback at 2 months. There was differential study attrition at 1 month, with the ME group returning at a greater rate (85%) than the AO (46%) or AFO (57%) groups. The ME group showed greater reductions than the AO group in self-reported cocaine use at 1 month (Group X Time $F = 3.19$, $df = 1.21$, $p = .088$). The groups differed at 1 month in readiness to change (University of Rhode Island Change Assessment questionnaire) with the ME group showing the greatest readiness. There was also some indication, although not significant that ME participants increased the number of days in which they sought help for their drug problem. Self-efficacy did not seem to be improved by ME.

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AN OUTPATIENT COCAINE DETOXIFICATION PROGRAM USING MOTIVATIONAL ENHANCEMENT THERAPY

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Achieving initial abstinence from cocaine is considered to be an important prerequisite to the application of Relapse Prevention (RP) strategies and techniques. Complete abstinence prior to RP treatment may increase motivation and decrease early dropout rates commonly reported in cocaine treatment outcome studies. In order to inmate abstinence in cocaine-dependent patients prior to their entrance into an RP maintenance treatment study, the authors developed and evaluated a brief, outpatient detoxification program. The "detox" program included daily clinic visits (2-6 hrs), the viewing of educational videotapes, completion of assessment procedures, provision of urine samples, and a physical examination including EKG, HIV and TB tests. Entrance into the 12-week RP treatment was contingent on the submission of five consecutive cocaine-free mines within a 10 day period. A brief motivational component was developed and implemented to promote compliance and abstinence during the detox period. Motivational Enhancement Therapy (MET) based on the principles and techniques of Miller and Rollnick's Motivational Interviewing was provided in a two-session format and included personalized feedback. To evaluate the efficacy of this component. participants were randomly assigned to MET or a detox-only control group. A detailed description of the detox program will be presented along with outcome data related to the motivational therapy component. Stages and Processes of Change data will also be reported. To the authors' knowledge, this outpatient detoxification program represents a novel adjunct to traditional outpatient treatment of cocaine dependence and may have important implications for future treatment research and clinical practice in this area.

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COCAINE/CRACK USE AND TREATMENT RETENTION IN A NATIONAL TREATMENT SAMPLE (DATOS)

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Clients who enter treatment with cocaine problems are diffcult to engage and retain in treatment. In the NIDA-funded Drug Abuse. Treatment Outcome Study (DATOS), approximately 25% of the 10,010 clients reported daily cocaine or crack use before admission to treatment. This study addressed the question of whether crack users have lower retention rates than noncrack cocaine users. The sample focused on 900 clients enrolled in 13 long-term residential (LTR) treatment programs. It was limited to cocaine dependent clients as defined by those who met DSM III-R criteria and also were at least weekly cocaine-crack users. Hierarchical linear model regression analysis (HLM) was used to examine the relationship between 90-day retention, cocaine use. client attributes, and program characteristics. Results indicated that 51% of the sample dropped out of treatment within 90 days, and these early dropouts were more likely to prefer crack (over cocaine), not be dependent on alcohol, have lower motivation, be adressed, have more lifetime arrests, be married, and have less education. Further research into the characteristics of these difficult-to-treat cocaine users, especially crack users. is important to the development of new treatment and engagement strategies.

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USING FEE REBATES TO REINFORCE ABSTINENCE AND COUNSELING ATTENDANCE IN COCAINE ABUSERS

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Voucher-based reinforcement therapies are effective for reducing cocaine use in outpatient cocaine abusers. However, fmancing voucher programs may be problematic for many community-based treatment providers. Thus, researching cost-effective and practical techniques for using voucher-based technology in general clinical practice is important. One solution may be to examine clinic fee structures and rebate portions of client's fees contingent on their performance in treatment. This ongoing study investigates the use of fee rebates for treating cocaine abuse. Cocaine-dependent outpatients were randomly assigned to Rebate (n=5) or Control (n=4) groups for 11 weeks. A matched Historical Control (HC) group was constructed from records of nine previous patients. Rebate and Control groups received an individual evaluation, 10 weekly group sessions using modules from the NIDA "Recovery Training" model and weekly, random urine testing. Treatment fees were based on a sliding scale for low income and averaged $33/week. Each cocaine-negative urine sample provided and each counseling session attended by the Rebate Group was reinforced with a fixed weekly rebate averaging $2.99. In addition, bonus rebates averaging $8.37 reinforced *continuous* cocaine-abstinence and/or counseling session attendance during weeks 1-3, 4-7 and 8-11. Under this schedule, clients with perfect performance earned back 25% of their total fee. Data collected from the first 5 weeks of study participation (and the first 5 weeks of treatment for the HC group) are presented. Missed urine samples were considered drug-positive. Rebates appear to increase (a) treatment retention (Rebate:100%, Control:50%, HC:44%), (b) counseling session attendance (Rebate:60±14%, Control:35±22;, HC:42±14%). (c) cocaine-negative urines (Rebate:53±7%, Control:30±24%, HC:26±11%) and (d) fee payments (Rebate:68±16%, Control:55±21%, HC:30±10%). Finally, for the Rebate group, the probability of retrieving the rebate increased linearly as the rebate amount increased, suggesting that rebates functioned as positive reinforcers. Fee rebates appear to be a viable, practical, cost-effective and easily managed positive reinforcement strategy for improving substance abuse treatment outcomes.

A COMPARISON OF TWO AFTERCARE TREATMENTS FOR COCAINE DEPENDENCE: RESULTS AT 6 AND 12 MONTHS

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As the duration and intensity of primary rehabilitation programs for drug and alcohol abusers are reduced due to funding constraints. there is likely to be a greater emphasis on the use of aftercare services to prevent relapse. In the case of cocaine abusers, however, them is a lack of information on both the relative effectiveness of different approaches to aftercare and on patient by treatment matches that might improve outcomes. In the present study, 98 male cocaine-dependent patients who completed an intensive outpatient program (IOP) were randomly assigned to either standard group counseling (STND) or individualized relapse prevention (RP) aftercare. Outcome analyses indicated that the conditions did not differ on percent days of cocaine use in months 1-6. However, fates of complete abstinence during months 1-6 were higher in STND than RP. whereas RP was more effective in limiting the extent of cocaine use in those who used any cocaine. These treatment group main effects were also observed in months 7-12. Matching analyses indicated that patients who failed to achieve remission from cocaine dependence during IOP and those with a commitment to absolute abstinence at entrance to aftercare did better in RP than in STND in months 1-6, whereas patients with other abstinence goals did better in STND than RP. During months 7-12, patients who had not achieved remission from cocaine dependence during IOP continued to have much better outcomes in RP than in STND, whereas the two conditions were equally effective for those who had achieved cocaine abstinence during IOP.

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ENHANCED AND BASIC ADDICTION OUTPATIENT TREATMENT FOR CRACK-COCAINE DEPENDENT MOTHERS

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The treatment of cocaine dependent women with young children is complicated by special psychosocial factors such as limited financial resources, histories of physical and sexual abuse, and co-existing emotional disorders, This special population has historically been difficult to retain in treatment. This study compared two types of psychosocial treatment in a sample of cocaine dependent females who were pregnant or had a child less than 4 years old. Subjects were randomly assigned to either basic addiction treatment (BAT) or psychosocial-enhanced treatment (PET). PET was designed to address some of the special problems of women dependent on cocaine. This comprehensive program consisted of group addictions counseling as well as outpatient individual psychotherapy, vocational training, parenting classes, family therapy, and psychiatric monitoring, all available on site. In contrast, BAT treatment consisted of group addictions treatment and case management in which additional services were obtained by referrals to community resources. The individual therapy was based on compliance enhancement techniques (Volpicelli, Pettinati, McLellan and O'Brien, 1997). Results for the first 12 weeks of treatment revealed that for those who remained in treatment, there was improvement in their drug and alcohol severity scores on the Addiction Severity Index (ASI), for both PET and BAT conditions. However, treatment attendance was improved by assignment to the PET condition. Good attendance (attending more than 10 sessions by 12 weeks) was higher in the PET group (63%) than in the BAT group (37%) (chi square = 4.74, df = 1. $p < 0.05$). Improved attendance in the PET condition interacted with initial readiness to change. For those subjects with high levels of readiness to change, good attendance was high for both the PET and BAT group (61% versus 52%)(chi sq = .33, df = 1, p = .57). In contrast, for those subjects with low readiness to change, good attendance was only 25% in the BAT gmup and improved to 65% in the PET group (chi square = 6.46. df = 1, $p < 0.05$). In sum. treatment attendance in the first 12 weeks of outpatient addiction treatment was improved for cocaine dependent mothers who scored low on a "readiness-to-change" measure at treatment entry if they received enhanced psychosocial support.

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EFFECTIVE TREATMENT FOR HOMELESS COCAINE ABUSERS: ABSTINENCE VS. REHAB OUTCOMES

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Day treatment/work therapy with abstinent contingent housing (DT+) was compared to day treatment without housing or work therapy (DT). In a randomized control outcome study for homeless, dually diagnosed, cocaine abusers, addiction severity was measured by ASI composite scores at baseline, 2, 6 mo. and bi-weekly urine toxicologies. Better DT+ outcomes were hypothesized. Independent "blind" interviewers assessed 110 randomly assigned subjects. DT and DT+ used unique goals established during assessment, random urines 2/wk., individual and group counseling 6 hr./day for 2 mo., vouchers reinforcing non-drug related social/recreation activities, and weekly goal reviews reinforcing rehabilitation indicants. Transportation to/from shelters and lunch were provided. DT+ subjects worked refurbishing housing and had housing available for modest rent, both abstinence contingent. Results: Baseline ASI's and toxicologies did not differ. Both groups substantially improved ASI scores baseline to 6 mo., Med $p < .02$, Legal $p < .01$, others $p < .0001$ (F test Mixed Model df=2, 189) with consistent trends favoring DT+. Toxicologies show robust, differences favoring DT+. At 2 mo. 75% vs. 31% were abstinent ($p < .001$) at 6 mo. 50% vs 17% abstinent ($p < .034$, Chi Sqs.=15.1, and 4.5, df=1). Similar robust effects favoring DT+ were found for consecutive weeks abstinent: at 6 mo. DT+ averaged 10.12 vs. 5.45 consecutive wk. abstinent ($p < .0001$ Wilcoxon Rank). Results suggest behavioral day treatment is effective, with abstinence contingent housing and work therapy differentially impacting drug abuse outcomes relative to other rehabilitation outcomes.

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ORAL COMMUNICATIONS X

AIDS-RELATED DRUG AND SEXUAL RISK BEHAVIORS: WHAT DRUGS AND WHICH ROUTES?

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Injection drug use (IDU) and unprotected sexual behaviors are the two major determinants of HIV transmission among drug abusers, though only 7% of AIDS cases in LA County are due to IDU behaviors. Thus, in LA County, sexual risk behaviors are the primary concern for HIV transmission risks. We describe drug use and sexual risk behaviors across 3 cohorts of treatment-seeking drug abusers (primary cocaine dependent (PCD), n=74; primary opiate dependent (POD), n=106; dual dependent (DD), n=58) at baseline and at 13-or 16-week follow-up to provide an initial evaluation of drug treatment episodes for reducing AIDS-related drug use and sexual behaviors in these cohorts. Findings (mean (standard deviation) indicated that cocaine abusing subjects rarely used needles in a 30-day reporting period ($PCD_{Baseline}$=0.2 (0.2) times, $PCD_{FollowUp}$=0.0 (0.2) times), and opiate abusers significantly reduced injection behaviors with treatment ($POD_{Baseline}$=16.4 (27.7) times, $POD_{FollowUp}$=2.7 (5.0) times; $DD_{Baseline}$= 10.5 (14.4) times, $DD_{FollowUp}$=7.8 (14.4) times; F=16.84, df=2.232, p<.001). Sexual behaviors were more resistant to change. With treatment, fewer cocaine abusers reported trading xx for money, drugs, or gifts ($PCD_{Baseline}$=5.4%, $PCD_{FollowUp}$=1.4%) compared to opiate abusers ($POD_{Baseline}$=1.9%, $POD_{FollowUp}$=0.0%; $DD_{Baseline}$=3.4%, $DD_{FollowUp}$=3.4%). Implications are that drug abusers engage in specific AIDS-related risk behaviors that are dependent upon drug used and route of administration. Drug and sexual AIDS-risk behaviors change consequent to drug treatment at statistically and clinically significant levels.

CHANGES IN HIV RISK BEHAVIORS AMONG COCAINE-USING METHADONE PATIENTS BEFORE AND DURING TREATMENT

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Methadone patients who were also dependent on cocaine (N=207) provided information on their current (past 30 days) HIV risk behaviors and their behaviors 30 days prior to entering treatment. DSM-III-R diagnoses for Axis I disorders and Anti-Social Personality (ASPD) were obtained by the SCID. Significant differences ($p < .05$) between the two times were determined with paired t-tests. Multiple regression analyses were conducted to determine predictors of changes in risk. Subjects were 59% male; 53% Hispanic, 36% African-Am.; mean age = 38; mean methadone dose = 67 mg; and mean months in methadone treatment = 28. Significant decreases occurred for heroin frequency (27.9 vs. 3.2 days/mo.), injection frequency (17.6 vs. 4.5 injections/mo.), needle-sharing risk index (7.5 vs. 3.7), multiple partners (3.8 vs. 1.6 partners/mo.), sexual risk partner in&x (0.21 vs. 0.12), unprotected sex index (3.0 vs. 2.5). However, needle hygiene practices for those continuing to share did not change. Injection frequency during treatment was independently predicted by heroin frequency pre-tx, current bipolar and current ASPD. Needle sharing during treatment was predicted by HIV-positive, violent offenses, female gender and cocaine frequency pre-tx. Overall, these results support the growing recognition of methadone treatment as a harm reduction modality; even methadone patients who continue to use cocaine and have poor psychosocial functioning significantly reduced their drug- and sex-related HIV risks when compared with their pre-treatment behaviors.

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HIV RISK BEHAVIOR AMONG A COHORT OF OLDER, MALE HEROIN ADDICTS

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This study examined the prevalence of HIV risk behavior among a cohort of male heroin addicts who are currently being interviewed as part of a longitudinal study of the natural history of heroin addiction. The subjects are part of a sample of 581 males who participated in the California Civil Addict Program in the 1960s. Of the original sample, approximately one-half have died, one-third have recently been interviewed, and about 20% have not been located or are unable to be interviewed. The average age of men in the current sample is 57 years and the ethnic distribution is 36% white, 57% Hispanic, and 7% African American. Of the current sample, 58% reported injection heroin use at the previous interview ten years ago. and 33% reported current injection heroin use. The subgroup of long-term heroin injectors (n=51) was more likely than current non-injectors to be Latino, unemployed unmarried, in unstable housing, under legal supervision; to report symptoms of depression; to have been incarcerated in the last ten years; and to use cocaine, marijuana amphetamines, tobacco, and alcohol. About one-quarter of the current heroin injectors reported having two or more female sex partners without always using condoms, 20% reported having a sex partner who was an injection drug user, and one-third relaxed using others' injection equipment without always cleaning. Although the leading causes of mortality among the original sample were accidents, heart disease, and liver disease, a small subgroup of current injectors was at risk for HIV infection.

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HIV RISK BEHAVIORS OF CRYSTAL METHAMPHETAMINE USERS CONTACTED THROUGH STREET OUTREACH

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This presentation describes the HIV risk behaviors of 908 gay and bisexual mate drug users contacted through a street outreach HIV risk reduction program in Hollywood, CA. in 1996. Individuals received a brief drug use and HIV risk assessment, referrals for needed services, free bleach, condoms and hygiene kits. Over one-third (37%) of the contacted individuals reported using crystal methamphetamine in the previous 30 days. Compared with the non-methamphetamine users, methamphetamine users were more likely to be Caucasian/white ($p<.001$), be younger ($p<.001$), engage in sex work ($p<.0001$), have an IDU sex partner ($p<.0001$), receive referrals for long-term and immediate needs ($p<.01$), and were less likely to always use condoms when having sex with other men ($p<0.01$), or with an IDU sex partner ($p<.01$). Methamphetamine users were also more likely than non-methamphetamine users to report use of heroin, crack, ecstacy, cocaine, marijuana, and alcohol within the previous 30 days (all differences, $p<.01$). Approximately 58% of the crystal users reported injection drug use within the previous 30 days; 29% reported that they shared injection equipment with others, and the majority (65%) stated that they never used bleach to clean equipment prior to injection. Methamphetamine use is an emerging drug problem within gay and bisexual male communities which compounds preexisting HIV risks. HIV interventions to this population should address both high-risk drug and sexual behaviors.

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PSYCHOSOCIAL RISK AND PROTECTIVE FACTORS AND COPING IN FEMALE IDUS

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We studied the psychosocial determinants of coping ability in a cohort of HIV-positive and HIV-negative female injection drug users (IDUs). We hypothesized that conventionality and family and peer support were related to greater adaptive coping. Cross-sectional data were collected using a structured questionnaire with 249 female AIDS clinic or methadone clinic patients in an urban municipal hospital, of whom 43.4% were HIV-positive. Data were analyzed using Pearson correlation analyses, t-tests, and multiple hierarchical regression analyses. Coping ability was associated with conventionality, greater control of emotions, and less psychopathology, as well as family cohesion in both HIV-positive and HIV-negative patients. Different mediational models best depicted the pathways by which psychosocial factors affected coping in HIV-positive and HIV-negative subjects. The findings supported the presence of risk/protective interactions in both groups: for the HIV-positive subjects, less significant other marital harmony was offset by high maternal emotional support, leading to better coping ability. For the HIV-negative group the adverse effects of paternal risk factors were offset by high maternal identification and maternal attachment. The findings confirm the importance of the interplay between personality factors and external support on coping ability in female IDUs.

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A MULTISITE STUDY OF REAL AND PERCEIVED HIV RISK BY COUNTY POPULATION DENSITY

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The purpose of this study was to contrast real and perceived HIV risk among 2,566 out-of-treatment drug users in a multisite sample of low-, medium-, and high-population density counties in Kentucky, Maryland, Missouri, North Carolina, Texas, Virginia, and Washington, DC. It was hypothesized that respondents in lower population density areas would be less likely to see themselves as being at risk of acquiring HIV/AIDS-despite the high rates of risk behaviors reported by this sample as a whole. As predicted, the perception of having zero risk of acquiring HIV/AIDS was indeed more common among respondents in the low- and medium-population density areas than among those in the high-density areas. Likewise, a logistic regression model predicting the likelihood of perceiving no HIV risk revealed that population density, in addition to needle use and having multiple sex partners, was negatively associated with the likelihood of perceiving no risk of HIV. In other words. drug users in the lower-density areas were more likely to perceive themselves as having no risk of ever acquiring HIV/AIDS, regardless of their actual risk levels.

HIV SEROPREVALENCE AND RISK BEHAVIOR CHANGES IN HIGH RISK DRUG USERS: ENCOURAGING TRENDS

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Introduction: HIV infection was first documented among injection drug users (IDUs) in NYC in 1979; seroprevalence rates reached 50% by 1990. A variety of prevention efforts were mounted. This study was undertaken to assess trends in HIV seroprevalence and changes in risk behaviors among IDUs and crack smokers (CSs) in East Harlem from 1992-1995. **Methods:** IDUs/CSs participated in baseline interviews, interventions, and six month follow-up interviews. Analyses conducted: trend analyses of seroprevalence for annual recruitment cohorts of IDUs; analyses of behavior changes, by serostatus. **Results:** Trend analyses(450 IDUs):Seroprevalence from 1992 to 1995 was 48%. 38%. 34%. and 21%, respectively ($p<.0001$). Analyses of behavior change [245 IDUs (33%HIV+) and 338 CSs (15%HIV+). For subjects who had sex at baseline and follow-up, unprotected sex decreased from 50% to 35% among seropositives and 69% to 63% among seronegatives (time effect $p<.01$; timeXserostatus interaction, ns). For those who reported injecting drugs at both points, indirect sharing (of cookers/ cotton/ rinse water) reduced from 41% of seropositives at baseline to 9% at follow-up, and from 24% of seronegatives to 16% (time effect, $p<.0001$; timeXserostatus, $p<.01$). **Conclusions:** HIV among IDUs declined from 1992-1995. Both HIV positive and negative subjects reported reductions in risk behaviors over time, with HIV+ subjects reporting greater risk reductions for selected behaviors. Community-wide prevention efforts contributed to these declines, and are needed to maintain declines. Further research, particularly among those who continue to engage in risk behaviors, is indicated.

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ORAL COMMUNICATIONS XI

IMPACT OF ILLICIT AMPHETAMINE USE ON NEUROPSYCHOLOGICAL FUNCTIONING

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The purpose of this study was to assess the impact of illicit amphetamine use on cognitive functioning. A neuropsychological test battery (Wechsler Memory Scale-Revised and the Digit Symbol. Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scale-Revised) was admired to 78 amphetamine users (mean age = 22.5 years, 45 males. 33 females). Regression analysis was used to adjust for premorbid intelligence, other drug use. drug positive urinalysis and other potentially confounding variables. Severity of amphetamine dependence was found to be associated with worse performance on the WMS-R indices of Attention/Concentration ($p < .05$) and Delayed Recall ($p < .01$). while the Visual Memory index was negatively correlated with both severity of amphetamine dependence and extent of amphetamine use ($p <.05$). A secondary analysis was carried out on data from 26 subjects with drug free urine. Subjects were divided into two groups ($n = 13$) based on severity of dependence (low vs high). Groups did not differ significantly in terms of age, other drug use, or premorbid intelligence. The high severity of dependence group performed significantly worse than the low group on the WMS-R indices of Verbal Memory ($p < .01$). Attention/Concentration ($p <.05$) and Delayed Recall ($p <.05$). The high severity of dependence group also showed a non-significant decrement on the Visual Memory Index ($p < .10$). These results suggest that heavy illicit amphetamine use, particularly severe dependence on amphetamine, is associated with cognitive impairment. It is not clear whether this impairment is due to amphetamine neurotoxicity or other factors associated with amphetamine use.

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EVOKED POTENTIAL EVIDENCE OF ABNORMAL CORTICAL SUBCORTICAL INTERACTION IN COCAINE WITHDRAWAL

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Somatosensory EP (SEPs) were measured on 40 male and 16 female subjects in locked residential treatment for cocaine dependence. Peak latencies were normal for brainstem and cortical components of the SEP, however significant relative reductions in cortically generated SEP peak amplitudes were observed which correlated with length of exposure to cocaine and persisted into 6 months of continuous drug abstinence. SEP amplitudes in the central cortical region contralateral to the side of stimulus delivery correlated with length of exposure ($R=-0.36$, $p<=.01$) and also with subjects length of slay in treatment ($R=-0.28$, $p<=0.04$). In view of reasonably reliable data regarding the anatomical localization of SEP components, these results suggest that the pathophysiology of cocaine withdrawal involves a disturbance at the level of the cortex. The possible clinical significance of these findings with respect to the compulsive self administration of cocaine is considered in the context of the "incentive sensitization" model of T.E. Robinson and others, and the role of descending cortical regulation of striatal activity as a determinant of behavioral output.

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ABNORMAL METYRAPONE TESTS DURING COCAINE ABSTINENCE

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Metyrapone testing was performed in chronic cocaine addicts admitted to the GCRC at the inpatient unit of the Rockefeller University Hospital, to assess the response of the hypothalamic-pituitary-adrenal axis to an acute cut-off of glucocorticoid negative feedback, in the setting of abstinence from cocaine. Nineteen subjects were studied (15 males, 4 females, age: mean 34.1 yrs. range 22.8 - 42.1 yrs), 10 were in methadone maintenance treatment, and 9 were not opiate dependent Subjects were free of active major active medical problems on admission other than substance abuse. and were HIV-1 antibody negative. Patients were administered 2.25 g of melyrapone in a single oral dose al 9:00 A.M. Blood was drawn 30 to 120 minutes prior to, and immediately prior to metyrapone administration, and 1.2.4 and 8 hours afterwards. Plasma levels of β-endorphin were determined by RIA. Subjects were tested after a period of abstinence from cocaine ranging from 1 to 155 days, and 7 subjects had a repeal test after sustained abstinence, totaling 26 tests. Results of individual tests were expressed as the ratio of the highest post-metyrapone level of β-endorphin to the lowest pre-metyrapone level, this ratio having previously been determined to range from 2 to 4 ("normal") in normal volunteers. Seventeen out of 26 tests yielded "highest-post"/ "lowest-pre" ratios that were abnormal: 15/26 (57%) were "high, (> 4) 2/26 (8%) were "low" (< 2). Upon examining levels of β-endorphin at individual the points, it appeared that "high" responders had lower than normal pre-metyrapone, and higher than normal post-metyrapone levels. There was not a significant difference in the rates of abnormal tests in methadone treated vs. non-opiate dependent patients The results of this study suggest that during abstinence from cocaine following chronic addiction, there is a hyper-responsivily to an acute cut-off of the usual negative feedback exerted by endogenous glucocorticoids, which persists long into abstinence.

ACKNOWLEDGMENTS: Supported in part by grants: DA-P50-05130, DA00049 and M01-RR00102

COCAINE-INDUCED CEREBRAL VASOSPASM IN HUMANS: DETECTION WITH MAGNETIC RESONANCE ANGIOGRAPHY

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Cocaine has been suggested to induce cerebral vasospasm based on clinical case reports in cocaine abusers. However, no study has determined whether acute cocaine administration, in the absence of other factors (e.g. polydrug abuse, underlying disease), induces cerebral vasospasm. This study used magnetic resonance angiography (MRA) to detect the effects of acute cocaine on cerebral arterial blood flow. Subjects were 24 males aged 29±5 years (mean±SD) reporting casual cocaine use (10±12 lifetime exposures). MRA was conducted on a 1.5 Tesla scanner with a 3D Time-of-Flight sequence. Axial MRAs were obtained at baseline and 17 minutes following intravenous double-blind placebo or cocaine (0.4 or 0.2 mg/kg) administration. Two raters, interpreting MRAs independently and blindly, concerdantly determined that 5 of 8 and 3 of 9 subjects administered 0.4 or 0.2 mg/kg cocaine, respectively, experienced MRA changes indicative of cerebral vasospasm, compared to 1 of 7 subjects administered placebo. This suggests that cocaine induces cerebral vasospasm in a dose-related manner(p =0.041). Stratification of the data by self-reported lifetime cocaine use strengthened the statistical significance of this relationship (p <0.001). These results, that low dose cocaine promotes acute cerebrovascular abnormalities, particularly in persons with other risk factors, may help explain the complication of vasospasm associated with chronic cocaine abuse.

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BRAIN IMAGING DURING CUE-INDUCED OPIATE AND COCAINE CRAVING

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Powerful drug incentive ("craving") states are cardinal features of addictive disorders, and can fuel the relapse tendency which charactetirizes addictions. We recently studied the brain substrates of cocaine craving by monitoring brain activity (indexed by regional cerebral blood flow, rCBF) during video cues which reliably induce the state. Based on preclinical data showing limbic activation both to cocaine and to cocaine cues, and on the salient emotional and motivational properties of cocaine craving, we hypothesized and subsequently confirmed increases in limbic activity (amygdala, anterior cingulate and temporal pole) during cue-induced cocaine craving. Comparison regions (cerebellum, dorsolateral prefrontal cortex, basal ganglia, occipital cortices, and thalamus) did not show differential activation. Cocaine-naive controls neither craved nor showed differential limbic activation during the cocaine videos. We are now testing the generalizability of these llmbic findings to a sample of opiate patients (n=3 thusfar) imaged during cue-induced opiate craving. As in the prior study, imaging of rCBF is accomplished with PET (Positron Emission Tomography) scans, using radioactively-labeled (0-15) water as the flow tracer. PET scans for each subject are co-registered with an MRI (magnetic resonance image) to permit anatomical localization of radioactivity. Findings from the opiate sample will test the hypothesis that limbic activation is a shared feature of drug incentive states.

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BRAIN MU-OPIOID RECEPTOR BINDING BY PET SCANNING DURING EARLY AND PROLONGED COCAINE ABSTINENCE

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Upregulation of brain mu-opioid receptors (mOR) has been reported in animals and humans shortly after cessation of chronic cocaine administration. We evaluated the time course of this change using positron emission tomography (PET) scanning with ^{11}C-carfentanil (GE 4096 scanner, FWHM resolution 7 mm) in 12 chronic (mean 6.6 years of use) heavy cocaine users (10 male, mean age 32 years) with no other recent drug use and 25 nondrug using healthy controls (12 male, mean age 30 years). Regions of interest were localized by MRI. Cocaine users had 90 days of monitored abstinence on the DIR closed research ward. during which they had 5 PET scans: #1 within 48 hours of last cocaine use (1 day after admission), #2 and #3 (on the same day) about 7 days later, and #4 and #5 (on the same day) about 90 days after admission. Cocaine (80 mg intranasal) was given during scans #3 and #5 5 minutes after IV carfentanil to achieve plateau plasma cocaine concentrations (100-300 ng/ml) during the period of scan acquisition. Compared to controls, cocaine users bad significant ($\geq$ 20%) increases in mOR binding in putamen, cingulate, temporal, and frontal cortex at scan #1, which persisted through scan #4 except in temporal cortex. Thalamus, caudate, amygdala and parietal cortex showed increased binding only at scan #2. There was a significanl positive correlation between plasma cocaine concentration and the change in regional mOR binding between the pairs of scans without and with cocaine challenge. There was also a significant correlation between the decrease in mOR binding between scans #2 and #4 and the time to relapse to cocaine use after ward discharge. These findings suggest that increased regional mOR binding persists during prolonged cocaine abstinence (possibly mediated by cocaine-induced decreases in endogenous opioid neurotransmission) and may influence relapse to cocaine use.

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ORAL COMMUNICATIONS XII

THE ROLE OF CORTICOTROPIN-RELEASING FACTOR IN RELAPSE TO HEROIN-SEEKING

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Background: We have shown previously that brief footshock stress and priming injections of heroin reinstate heroin-seeking after prolonged drug-free periods. Recently we have found that adrenalectomy appears to potentiate the reinstatement effect of footshock, and that acute administration of a synthesis inhibitor of corticosterone. metyrapone, potently reinstated heroin-seeking. Based on these observations, we have examined whether corticotropin-releasing factor (CRF) is involved in reinstatement of heroin-seeking. **Methods:** Three groups of rats (n=10-14) were trained to self-administer heroin (100 g/kg/infusion, IV) for 12-14 days. Extinction sessions with saline were given for 4-8 days. We then compared the effect on reinstatement of heroin-seeking of acute intracerebroventricular (ICV) injections of CRF (0.3 and 1.0 µg) to those of intermittent footshock stress (15 and 30 min, 0.5 mA) and priming injections of heroin (0.25 mg/kg, SC). We also tested the effect of ICV injections of the CRF antagonist, alpha-helical CRF (3 and 10 µg) on reinstatement induced by saline priming, heroin priming and footshock. Results: Acute exposure to CRF reinstated heroin-seeking compared with a vehicle ICV injection ($p<0.05$). This effect of CRF; however, was somewhat weaker than the reinstatement effects of stress and heroin priming. In addition, the CRF antagonist, alpha-helical CRF, significantly attenuated stress-induced reinstatement ($p<0.05$). The effect of the CRF antagonist on reinstatement by heroin was less consistent, **Conclusions:** These results suggest that CRF, a major brain neuropeptide involved in the stress response, contributes to relapse to heroin-seeking induced by stressors.

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A METHOD FOR TESTING THE SPECIFICITY OF MANIPULATIONS ON DRUG SELF-ADMINISTRATION

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Drug self-administration may be modified with pharmacologic (e.g., methadone) and environmental (e.g., footshock) interventions. whether such interventions modify behaviors other than drug use is less well characterized. We describe a model of choice behavior that provides a sensitive and realistic assay of the specificity of pharmacologic and environmental manipulations on drug self-administration. Twelve male Sprague-Dawley rats were trained to orally self-administer fentanyl HCL (56 µg/ml) dissolved in tapwater on an FR schedule using a sucrose fading procedure. After eliminating sucrose, a second lever reinforced with 45 mg food pellets was activated, with rein forcement for responding on each lever controlled by separate but concurrent VI schedules. After responding on the levers stabilized. a series of within-subject ABA design studies were used to evaluate the sensitivity of dipper responding (as a percentage of all responding) to changes in available contingencies. When the feeder was placed under extinction, responding shifted to the dipper lever, $F(1,11)=50$, $p<.001$. When the dipper was placed under extinction, and when the dipper was empty, responding shifted to the feeder lever, $F(1,11)=28$ and $F(1, 10)=64$, both $p<.001$. Effect sixes were large accounting for 72% to 86% of variance in responding. Despite this sensitivity, no changes were noted in dipper responding when water was substituted for fentanyl for 2 weeks. Therefore, we cannot conclude that responding was maintained by fentanyl more than for the water vehicle alone. The concurrent VI paradigm appears useful for assessing the specificity of interventions designed to modulate drug self-administration. In particular, by using Matching Law principles to adjust base rates of responding for drug vs an alternative reinforcer, this paradigm offers the promise of greater control over pre-intervention response ratios, a factor that might decisively influence post-intervention response ratios. Furthermore, choice paradigms provide a good model of human drug use. since drug abusers typically have nondrug-reinforced responses available to them.
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DEPRENYL PREVENTS LONG-TERM BEHAVIORAL AND NEUROCHEMICAL CHANGES THAT FOLLOW OPIATE WITHDRAWAL

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Because of evidence for decreased dopaminergic function during the withdrawal syndromes associated with opiates and other medications with potential for abuse, we investigated the effects of treatment with deprenyl on *in vitro* measures of dopamine release during opiate withdrawal. Forty-eight male Wistar rats received injections of either saline or morphine, 3 times per day, with the dose of morphine gradually increased to 120 mg/kg-injection. During withdrawal, morphine treated animals received daily subcutaneous injections of either saline (WS) or 2.0 mg/kg-day of deprenyl (WD). Control subjects initially received an identical pattern of saline injections to morphine treated subjects, which was then followed by a daily injection of deprenyl (SD) or saline (SS). Behavioral and neurochemical measures were obtained 17 to 24 days after the onset of withdrawal. Deprenyl treatment prevented increases in stress immobility that occurred in saline treated withdrawn subjects (values of 6.59 ± 0.60 minutes for group SS, 5.40 ± 0.69** for SD, 7.50 ± 1.06* for WS, and 5.64 ± 0.78** for WD [group means and standard deviation, *P<0.05 and **P<0.01 relative to group SS]). In addition, effects of morphine withdrawal on *in vitro* dopamine release by brain slices obtained from the nucleus accumbens were not observed in deprenyl treated animals (percent decline in fractional dopamine release between an initial and subsequent 4-aminopyridine exposure was 40.5 ± 11.5 for group SS, 31.5 ± 18.5 for SD, 52.5 ± 7.00 ** for WS, and 39.9 ± 10.8 for WD [**P<0.01]). Similar effects were observed for in vitro release for brain slices obtained from the striatum. In conclusion, opiate withdrawal is followed by long-term effects on both the behavioral response to stress and the functional reserve for dopamine release. Both behavioral changes and deficits in dopaminergic function can be prevented through depenyl treatment

DISCRIMINATIVE STIMULUS EFFECTS OF DEPRIVATION-INDUCED AND PRECIPITATED WITHDRAWAL IN LAAM-TREATED RHESUS MONKEYS

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The purpose of the current study was to characterize the behavioral effects of withdrawal in monkeys (n=4) treated with 1.0 mg/kg/12 hr s.c. of 1-alpha-acetylmethadol (LAAM). Monkeys discriminated between 0.0178 mg/kg of naltrexone and saline while responding under a fixed-ratio schedule of stimulus-shock termination. Monkeys responded on the saline lever after injections of LAAM; 0.1 mg/kg of naltrexone increased drug-lever responding to more than 90% and elicited signs of opioid withdrawal (e.g., emesis). Naloxone and quadozocine substituted, whereas, morphine, nalbuphine and ketamine did not substitute, for the naltrexone discriminative stimulus. Acute injections of morphine or nalbuphine, and not ketamine, dose-dependently shifted the naltrexone dose-effect curve to the right. Compared to precipitated withdrawal, deprivation-induced withdrawal occasioned less naltrexone-lever responding and fewer withdrawal signs. Maximal naltrexone-lever responding occurred between 24 and 48 hr after the discontinuation of LAAM treatment. Similarly, the magnitude and frequency of withdrawal signs peaked between 24 and 48 hr after the discontinuation of LAAM treatment. Partial naltrexone-lever responding occuned for up to 10 days following the discontinuation of LAAM treatment; during this time, naltrexone did not further increase either naltrexone-lever responding or signs of withdrawal. Although the partial naltrexone-lever responding that occurred following the discontinuation of LAAM might suggest that LAAM, or one of its metabolites, has a very long duration of action, the inability of naltrexone to increase drug-lever responding or elicit signs of withdrawal indicate that the discriminative stimuli associated with deprivation-induced withdrawal are qualitatively different from the stimuli associated with precipitated withdrawal.

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THE EFFECTS OF NALOXONE ON RESPONSES REINFORCED BY ORALLY DELIVERED METHADONE

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The relationship between methadone reinforced behavior and naloxone dose was studied with three monkeys and under three schedules (Not all monkeys were studied under each schedule). Unlike most other studies, the methadone was taken orally; however, like other studies methadone did serve as a positive reinforcer. The three schedules wae all concurrent schedules with waler and methadone available. The schedules were a fixed-interval 15". a mutually exclusive fixed-interval 15", and a fixed-ratio (FR) 16. Under the mutually exclusive FI schedule, the monkey could obtain one liquid delivery from either of the two spouts. In general, naloxone doses from 0.0125 to 0.2 mg/kg were presented in an ascending and then descending order. Blocks of sessions with daily naloxone injections alternated with blocks of daily saline session. Naloxone and saline were administered by IM injection 10 min prior to the session. In the ascending series, low naloxone doses produced slight increases in responding, except for M-JS under the mutually exclusive FI 15" schedule. At higher doses, naloxone decreased responding under all three schedules, except for M-ED under the FI 15" schedule. During the ascending series, responding was usually greater than during the descending series, suggesting an order effect. Analysis of the time course showed that the duration of naloxone's effects were a direct function of dose and occurred within the first hour of the session. In the third hour of the session responding rebounded In the second part of experiment, the dose of naloxone (0.1 mg/kg) was held constant and the methadone concentration was varied (0.05, 0.2, 0.4 and 0.8 mg/ml). The responding maintained by the methadone concentrations was differentially affected by the 0.1 mg/kg naloxone dose. Naloxone's effects also varied among monkeys. Theses experiments confirm and extend earlier results by demonstration that methadone reinforced responding is sensitive to naloxone pretreatment and that the effects of naloxone are as a direct function of dose.

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DISCRIMINATIVE STIMULUS EFFECTS OF NALTREXONE FOLLOWING ACUTE MORPHINE PRETREATMENT

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Opioid antagonists such as naltrexone (NTX) have few documented behavioral effects in otherwise drug-free subjects, but have prominent effects in subjects receiving morphine (MOR) chronically or acutely. The present experiments characterized the discriminative stimulus effects of an acute MOR⇒ NTX combination. Adult male Sprague-Dawley rats (N=6) were trained to discriminate between two drug treatments in a discrete-trial avoidance/escape procedure -- MOR (10 mg./kg. s.c., 4 hr) ⇒ NTX (0.3 mg/kg, s.c., 15 min.) vs. SAL (1 m/kg, s.c., 4 hr) NTX (0.3 mg/kg, s.c., 15 min.). Subjects acquired the discrimination within 69 (± 9.1) sessions and responded almost exclusively only on the SAL ⇒ NTX-appropriate lever when SAL was given 3.75 hr after MOR or 3.75 hr before any dose of NTX (0.3 - 100 mg/kg). In contrast, responding occurred on the MOR ⇒ NIX-appropriate lever dose-dependently when small doses of NTX (0.01 - 0.1 mg/kg) followed MOR, with complete substitution occurring at the training dose of 0.3 mg/kg (ED_{50} = 0.03 mg/kg). Holding other parameters constant, full MOR =) NTX-appropriate responding was also dependent on the pretreatment dose of MOR (ED_{50} = 2.19). Further, at the training doses of MOR and NTX, stimulus effects were dependent on the duration of the MOR pretreatment, with full effects seen only at 34 hr. At MOR pretreatment times less than 3 hr (1 hr), NTX ($\leq$ 30 mg/kg) did not engender full stimulus effects, although it did result in partial responding on the MOR ⇒ NTX-appropriate lever (ED_{50} = 7.72). Therefore, a qualitatively unique "withdrawal" stimulus that is dose- and time-dependent appears to be the basis of this discrimination.

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NMDA RECEPTOR ANTAGONISTS ATTENUATE TOLERANCE TO MORPHINE'S DISCRIMINATIVE STIMULUS EFFECTS

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Adult male Long-Evans rats were trained to discriminate 3.2 mg/kg of s.c. morphine from water under a standard two-lever fixed ratio 10 schedule of food reinforcement. Cumulative dose-effect functions for morphine were determined before and after repeated treatment with water or morphine. Treatment with morphine (10 mg/kg; 14 days, b.i.d.) had little effect on morphine's discriminative stimulus properties but induced tolerance to its response rate effects. Increasing the treatment dose of morphine to 20 mg/kg resulted in more than a 4-fold rightward shift in the dose-effect curve for morphine's discriminative stimulus effects and tolerance to its response rate effects. Sensitivity to both stimulus and response rate-altering effects returned to initial levels when rats were tested 2 weeks after morphine's repeated treatment. Separate groups of rats were treated with a combination of 20 mg/kg morphine or its vehicle and the non-competitive NMDA receptor antagonist dizocilpine (MK-801; 0.1 mg/kg, i.p.), the competitive antagonist d-CPPene (3 and 5.6 mg/kg; i.p.), the polyamine site antagonist eliprodil (17.3 mg/kg; i.p.), or the partial agonist at the strychnine-insensitive glycine site (+)-HA-966 (10 mg/kg; i.p.). The development of tolerance to morphine was attenuated only by eliprodl and d-CPPene. Because earlier reports have described inhibition of the development of tolerance to morphine analgesia by dizocilpine, these results suggest different mechanisms underlying the development of tolerance to analgesic and discriminative stimulus effects of morphine.

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BEHAVIORAL AND PHYSIOLOGICAL EFFECTS OF BUPRENORPHINE AND MORPHINE IN NON-DRUG ABUSING VOLUNTEERS

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Buprenorphine is an opioid with putative partial mu agonist and kappa, agonist effects, and kappa, antagonist effects. In the present investigation, we characterized, in non-drug abusing volunteers, the subjective, psychomotor, and physiological effects of a range of intravenous doses of buprenorphine [B], up to and including doses that would be used for post-operative pain. We also compared me effects of one of the doses of B to that of morphine [M]; our hypothesis was that the two drugs at equianalgesic doses would have a similar profile of effects given the similarity of their actions at the mu receptor. An IRB-approved, crossover, Latin-square, double-blind, placebo-controlled trial was conducted; sixteen nondrug abusing volunleers (mean age: 26 yrs, 5 females) were injected in an upper-extremity vein with 0, 0.075, 0.15, and 0.3 mg/70 kg B, and 10 mg/70 kg M, and saline, 0.3 mg B is considered clinically to be equianalgesic to that of 10 mg M. Results indicated that 0.3 mg B and 10 mg M produced a similar spectrum of subjective and physiological effects, but that the intensity of effects (including VAS ratings of dizzy, sleepy, high, difficulty concentrating, and me physiological measure of miosis) was significantly greater with 0.3 mg B. Psychomotor performance [e.g., Digit Symbol Substitution Test] was impaired and the VAS rating of nauseous was increased by 0.3 mg B, but not by 10 mg M. Seven subjects vomited during 0.3 mg B sessions, but none did so during the 10 mg M sessions. In general, B effects were dose-related, and, consistent with the pharmacokinetic profile of this drug, were long-lasting (> 5 h). We conclude that a clinically-relevant dose of B produces a greater intensity of behavioral and physiological effects. overall, than does an equianalgesic dose of M.

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SUBJECTIVE RESPONSES TO DYNORPHIN A(1-13) IN NORMAL CONTROLS AND METHADONE MAINTENANCE PATIENTS

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Twelve normal healthy controls, 5 stabilized methadone maintenance patients (MMPs), and 5 MMP's with ongoing cocaine abuse participated in a placebo-controlled single-blind study of the subjective response to acute i.v. administration of dynorphin A(1-13),# a synthetic kappa opioid agonist. Subjects were tested on three separate days for the response to low (120 μg/kg) and high (500 μg/kg) dynorphin compared to placebo (saline) injection. Each subject completed 100 mm visual analog scales (VAS) for "Drug Effect" (0 for "sick/cold turkey" to 10 "euphoric/high") and general "Mood Effect" (0 for "terrible" to 10 "terrific"). The patient groups also completed a drug craving VAS. The results for the controls showed that postinjection (10 min), mere were significantly higher ratings of "Drug Effect" (euphoria) for both me high and low dose of dynorphin compared to placebo ($ps<.05$), with no significant dose-dependent differences. For general "Mood Effect," the MMP's with ongoing cocaine use showed greater "terrific" mood ($p<.05$) after low dynorphin compared to controls. Preliminary results on drug craving in the cocaine-abusing MMP's show a directional dose-dependent increase in craving (placebo craving=4.8/10, low dynorphin=6.4/10, high dynorphin=7.7/10). In contrast to cocaine-abusing MMP's, stabilized MMP's did not significantly differ from the controls in mood response to either dose of dynorphin, although craving was augmented after high dynorphin (placebo craving=2.2/10, high dynorphin=5.5/10). The results show that dynorphin was well-tolerated and that normal subjects can discern the effects in a euphoric direction of both low and high dynorphin compared to placebo. Cocaine-abusing MMP's, in contrast to well-stabilized MMP's, have a variable subjective response to dynorphin with potential dose-dependent increased craving.

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EFFECTS OF ANTISOCIAL PERSONALITY DISORDER (APD) AND PROVOCATION ON AGGRESSIVE RESPONDING

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Recent research suggests that drug abusers with APD may exhibit greater aggressive behavior in a laboratory model (Point Subtraction Aggression Procedure) than those without APD. This study validates and extends this model in relation to clinical state. Methadone-stabilized clients (50-80 mg/day) diagnosed with APD and matched non-APD Controls participate in this inpatient study (target n= 18/group). On three consecutive days, subjects are tested before and after receiving their fixed methadone dose. Across sessions, three widely varying provocation levels are presented. Eleven APDs and 6 Controls have completed testing. Initial results show trends for a Group effect (APD > Control) and Group x Provocation interaction on mean aggressive responding, which increases with provocation level more for APDs than Controls. Number of aggressive behavioral responses at the high provocation level is significantly correlated with Buss-Perry Physical Aggression scores for APDs (r =0.56) but not Controls. APDs also exhibit greater negative mood shifts with increasing provocation (decreases in Profile of Mood States Positive Mood scale). As their aggressive responding increases, APDs decrease responding for money; money-reinforced responding (and money earned) significantly increases with less provocation, more so for APDs than Controls. Escape responding (from money loss) tends to be greater overall for APDs and unrelated to provocation level. At present, no clear effects of time since methadone dose (possibly related to early withdrawal signs) on aggressiveness have emerged. These results suggest that APDs are more aggressive generally and more sensitive to repeated provocation than their non-APD counterparts, and suggest important new avenues for investigating parameters and treatment of aggressiveness in this high-risk population.

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ORAL COMMUNICATIONS XIII

IMMUNE ALTERATIONS IN MICE LACKING THE MU-OPIOID RECEPTOR GENE

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It has been well established that opiates alter immune functions. In order to study μ-opioid receptor (MOR) implication in modulation of immune responses by endogenous opioid peptides and opiates alkaloids. we used mice where the MOR gene has been disrupted by homologous recombination. We determined the weight and cellularities of thymus and spleen. as well as splenic macrophage content and Natural Killer activity. To assess T cell activity, we analyzed the percent of CD4 and CD8 cells in thymus and spleen, 4s well as *in vitro* Concanavalin A-induced proliferation. In order to evaluate B cell activity, we measured serum immunoglobulin (Ig) levels, *in vitro* lipopolysaccharide-induced proliferation and Ig production. Our results show that disruption of the MOR gene does not produce any overt immune abnormalites in mice. We also assessed the contribution of MOR in morphine-induced immunosuppression by comparing alterations of immune responses after chronic morphine treatment *in vivo.* Spleen and thymus cellularities as well as NK activity were altered by morphine in wild type but not in MOR knock-out mice.

CHANGES IN KAPPA OPIOID RECEPTOR EXPRESSION DURING MATURATION OF MOUSE IMMUNE CELLS

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Recent initiatives combining flow cytometric analysis with indirect immunofluorescent labeling have been successful in demonstrating κ opioid receptor expression on mouse immune cells. This sensitive method employs amplification of labeling by a κ–selective opioid, fluorescein-conjugated arylacetamide, with the addition of biotinylated anti-fluorescein IgG and extravidin-R-phycoerythrin, along with double-labeling by various fluorophore-conjugated monoclonal antibodies for phenolypic analysis of immune cells. Immature (>80% $CD4^+/CD8^+$) T-cells isolated from thymi of 6-8 week old C57BL/6ByJ mice demonstrated greater than 50% specific κ opioid recetor labeling. as assessed in the presence of the K-selective antagonist nor-binaltorphimine. Likewise, mature splenic T-cells ($CD8^+/CD3^+$ or $CD4^+/CD3^+$) and B-cells ($CD45R^+$), as well as resident, peritoneal macrophages demonstrated specific κ opioid receptor labeling. Interestingly, the relative percentage of T-lymphocytes expressing the κ opioid receptor appears to change upon phenotypic maturation. decreasing from approximately 60% of the immature, double-positive thymocytes to less than 25% of the mature, single-positive splenic T-cells showing labeling for the receptor. Likewise, only 15% of splenic B-cells show labeling for the κ opioid receptor. Taken together, these findings demonslrate the diversity in the expression of the κ opioid receptor on immune cells at varying stages of differentiation.

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POTENTIATION OF T CELL PROLIFERATION WITH NOVEL NON-PEPTIDIC OPIOID LIGANDS

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Although the central nervous system mediated indirect effect of opioids has been shown to suppress immune function (see Suo and Weber, Gomez-Flores and Weber; Weber, *et. al.,* abstracts this meeting), the direct effect of certain novel opioid derivatives on cells of the immune system has been shown to induce immunopotentiation in vitro. Naltrindole (NTI), selective for the δ opioid receptor, and benzylidenenaltrexone (BNTX), selective for the δ_1 opioid receptor, have been shown to act as antagonists in classical neuronal opioid receptor systems. We have identified a class of novel NTI derived non-peptidic opioid receptor ligands with direct immunopotentiating effects on mitogen stimulated lymphocytes. *In vitro,* the NTI analogues SoRI 9331 and 9340 consistently produced a dose dependent (10^{-7} to 10^{-6} M) potentiation of lymphocytes following mitogen stimulation. BNTX related compounds SoRI 9334 and 9336 produced no significant effect on T-cell proliferation. Future studies will address structure/activity relationships of these and other compounds and investigate the cellular mechanisms of immunopotentiation. This series of novel non-peptidic opioid ligands could serve as immunotherapeutic agents with potential use in the treatment of infectious diseases including AIDS, and cancer.

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MORPHINE ENHANCES MACROPHAGE (Mϕ)) APOPTOSIS

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Clinical reports suggest that heroin addicts are prone to infections. We studied the occurrence of apoptosis in peritoneal (P) Mϕ (harvested from control and morphine treated rats), murine (M) Mϕ (J774.16) and human monocytes (HM, isolated from healthy volunteers). Subconfluent Mϕ were incubated in media containing either buffer alone (control) or variable concentrations of morphine (10^{-10} to 10^{-4}M) for variable periods (12 to 48 hours; n= 4 to 6). Subsequently, Mϕ were either stained with H-33342 and propidium iodide or underwent DNA isolation, ^{32}PdCTP labeling and gel electrophoresis. To determine whether this effect of morphine is opiate receptor mediated, Mϕ were treated with morphine with or without naloxone. We also evaluated the effect of L-NAME (a nitric oxide synthase inhibitor) with or without morphine on macrophage apoptosis, nitric (NO) production, and accumulation of inducible NO synthase, (iNOS). We also examined the dose response and time course effect of morphine on macrophage p53 accumulation. Morphine enhanced Mϕ apoptosis in a dose and time dependent manner. Morphine treated Mϕ showed integer multiples of 180 base pair (ladder pattern). Naloxone, an opiate receptor inhibitor, attenuated morphine-induced Mϕ apoptosis. Morphine also stimulated Mϕ NO production in a dose dependent manner. Morphine promoted the accumulation of iNOS and p53. Since L-NAME attenuated morphine-induced Mϕ apoptosis, iNOS expression, and NO production it appears that morphine may be causing Mϕ apoptosis through the activation of Mϕ iNOS and the generation of NO. We conclude that morphine-induced Mϕ apoptosis is mediated through opiate receptors and nitric oxide and associated with the accumulation of iNOS and p53.

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CHRONIC EXPOSURE TO MORPHINE, NOT ETHANOL, ATTENUATES THE EXPRESSION OF INTERLEUKIN-1β CONVERTING ENZYME IN RAT SPLEEN

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Interleukin-1 β (IL-1 b) is generated from an inactive precursor by IL-1β converting enzyme (ICE). IL-1β exerts its effects directly by acting on immune cells and indirectly through the neuro-endocrine regulatory system. Exposure to ethanol has been shown to decrease the plasma level of IL-1β in human subjects (Muzes *et al.* 1989). IL-1β reverses the suppression of antibody response in the rats given chronic morphine (Bussiere *et al.* 1993). Recently, we reported that chronic exposure to morphine attenuates IL-1β immunoreactivity in the rat hippocampus (Patel *et al.* 1995). and preliminary data show that chronic exposure to morphine attenuates the expression of ICE in the rat brain (Chang *et al.* 1995). In this study, we examined the expression of ICE in the rat spleen after chronic exposure to morphine or ethanol. Twelve adult male Harlan Sprague-Dawley rats were implanted subcutaneously with 2 pellets of morphine sulfate (75 mg/pellet) with or without 1 pellet of naltrexone or 2 pellets of placebo with or without 1 pellet of naltrexone on Day 1 and 4 pellets of morphine sulfate (75 mg/pellet) with or without 1 pellet of naltrexone or 4 pellets of placebo with or without 1 pellet of naltrexone of on Day 2. On Day 5, the rats were sacrificed, the spleens were collected, frozen on dry ice and stored at -80° until RNA isolation. Four male rats were randomly assigned to receive a liquid Lieber-DeCarli diet or a control diet with an isocaloric amount of dextran for 16 weeks. At the end of the treatment, the spleens were collected as above. Total RNA was isolated from each spleen and subjected to RT-PCR procedures. Following chronic ethanol treatment, the expression of ICE in the spleen of rats was equivalent to those given placebo. The expression of ICE in the spleen of rats given chronic morphine was less than that of the animals given placebo. This attenuation was reversed by cotreatment with naltrexone. These data suggest that chronic use of morphine, but not ethanol, attenuates the expression of ICE in the spleen. Naltrexone reversibitity suggests specificity for the mu opioid receptor. Although both morphine and ethanol alter the actions of IL-1β, morphine may act through an ICE cascade mechanism, while ethanol does not.

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THE EFFECTS OF PRENATAL COCAINE EXPOSURE ON IMMUNE FUNCTIONING

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We have recently reported that pups born of dams exposed to cocaine prior to and during pregnancy displayed decreased mitogen-induced lymphocyte proliferation in whole blood relative to pups born of pair-fed or vehicle-treated dams or darns exposed to cocaine only during pregnancy (Pellegrino *et al.,* Soc. Neurosci. Abstr. 22:1886; 1996). The presenl study extended this analysis by examining such exposure on a functional immune response, specifically, delayed-type hypersensitivity. Adult female rats were exposed to cocaine (40 mg/kg. daily; sc) 30 days prior to pregnancy, during Gestation Days 7 - 19 or both prior to and during pregnancy. Vehicle-injected controls were pair-fed to the cocaine-exposed subjects. All pups were reared by untreated lactating dams. On Day 60, subjects were injected with Primary Bovine Serum Albumin (BSA). One week later, subjects were injected with BSA into the left or right hind paw and equivolume saline into the other paw. On the next day, the left and right paws were measured for swelling induced by BSA (relative to saline). There was a significant reduction in swelling in female pups born of dams receiving cocaine both prior to and during pregnancy, indicating a reduced immune reaction. Male pups born of dams receiving cocaine (independent of when cocaine was given) displayed significantly reduced swelling in response to BSA. These results are consistent with our prior work reporting reduced lymphocyte proliferation and suggest that prenatal cocaine exposure compromises immune functioning.

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ELEVATED SPLENIC CATECHOLAMINES AND IMMUNOSUPPRESSION FOLLOWING MICROINJECTION OF MORPHINE INTO THE PAG

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Central nervous system mediated morphine-induced immunosuppression has been hypothesized to be due to activation of either the hypothalamic-pituitary-adrenal (HPA) axis or the sympathetic nervous system (Weber and Pert; Science 245:188-190, 1989). Studies in our lab, (see Sue and Weber, abstract this meeting), demonstrate that bilateral injection of morphine into the ventral-caudal periaqueductal gray (PAG) matter of the mesencephalon results in elevated plasma levels of adrenocorticotrophic hormone (ACTH) and corticosterone, as well as suppression of natural killer (NK) cell activity, T cell proliferation and macrophage phagocytic activity (see Gomez-Flores and Weber, abstract this meeting). However, the glucocorticoid antagonist, RU486, is ineffective in blocking either the suppression of NK ceil activity or T cell proliferation. Consequently, we examined the role of the sympathetic nervous system in the observed immunosuppression. Catecholamine levels were measured kinetically and continuously in splenic microdialysates in freely moving Fischer 344N rats, both before and after bilateral administration of morphine into the PAG. Our results indicate that morphine induces an increase in norepinephrine (NE), dopamine (DA) and serotonin (5-HT) levels but does not alter 5-hydroxyindolacetic acid (5-HIAA) levels within the spleen. The elevated levels of NE, DA and 5-HT reach a maximum level between 15 to 30 minutes after injection of morphine, and then gradually decline. Both NE and 5-HT levels return to a basal level approximately 150 minutes after morphine injection, while DA and levels remain elevated for more than 15 hours post injection. Our findings indicate that morphine injection into the ventral-caudal PAG, leads to a subsequent increase in catecholamine levels within the spleen, and is correlated with changes in splenic lymphocyte function.

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EFFECTS OF ENDOGENOUS CORTISOL LEVELS ON NATURAL KILLER CELL ACTIVITY IN HEALTHY HUMANS

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Natural killer (NK) cells are large, unprimed lymphocytes which have a direct, immediate cytolytic activity against tumor and virus infected cells. NK activity can be modulated by a variety of humoral substances including endogenous opioids, lymphokines and hormones. Cortisol is a potent inhibitor of NK activity in vitro. However, there are conflicting results in human studies after either exogenous cortisol administration or during physiologic conditions in which endogenous plasma cortisol is elevated, such as in physical or emotional stress. There are no data on the effects on NK activity *in vivo* of cortisol levels in a lower than normal physiologic range. The present work examined the effects of manipulating endogenous cortisol level on NK activity *in vivo*. Normal healthy volunteers were studied on separate days: baseline (n=27), metyrapone test (n=10), dexamethasone suppression test (n=10) and ACTH stimulation test (n=8). Each subject served as his own control. NK activity and plasma cortisol levels were measured at 9 a.m., just before the challenge drug administration. and at 10a.m, except for the dexamethasone study in which only the 9 a.m. blood was drawn, 10h after dexamethasone administration. On the baseline study day. a significant decrease in plasma cortisol levels was found from 9 to 10 a.m. ($p<0.02$) along with a significant increase in NK activity ($p<0.001$). In the metyrapone test, plasma cortisol levels were significantly reduced at 10 a.m. ($p<0.005$) as expected, while NK activity at the same time point was not affected and was increased to an extent equivalenl to me baseline study day. In the dexamethasone test, plasma cortisol concentrations were significantly decreased ($p<0.0001$), without any significant change in the NK activity. In the ACTH test, plasma cortisol rose significantly at 10a.m. ($p<0.02$). with no change in NK activity. We conclude that plasma cortisol alone has no significant effects on NK activity *in vivo*.

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NITRIC OXIDE LIBERATED BY ISOBUTYL NITRITE IS NOT RESPONSIBLE FOR THE INHALANT'S IMMUNOTOXICITY

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Isobutyl nitrite is an inhalant abused by male homosexuals and adolescents. We have shown that inhaled isobutyl nitrite severely depressed immunity, including macrophage function and decreased blood and spleen cellularity. Immunosuppression by nitrite inhalants could explain epidemiological correlations of inhalant abuse with HIV seropositivity and with Kaposi's sarcoma. To determine if the inhalants produced their immunotoxicity by liberating nitric oxide ($NO^{\bullet}$), we first measured $NO^{\bullet}$ release from isobutyl nitrite. An immunotoxic dose of isobutyl nitrite (900 ppm) liberated 115 ppm $NO^{\bullet}$. To determine whether $NO^{\bullet}$ was responsible for the immunotoxicity, mice were exposed to 115 ppm authentic $NO^{\bullet}$ using the same exposure regimen used for isobutyl nitrite exposures (45 min/day, 14 days). At this dose, $NO^{\bullet}$ did not affect peripheral blood cell counts, peritoneal macrophage tumoricidal activity, or spleen cell mitogen responses. Inhalation exposure to authentic $NO^{\bullet}$ did reduce spleen cellularity by 35% and increased spleen cell reactivity in mixed lymphocyte cultures and macrophage induction of $NO^{\bullet}$ by LPS + interferon- γ. It is, thus, likely that immunotoxicity is mediated by direct nitration of critical mediators or by other radicals, such as peroxynitrite.

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COCAINE AND TUMOR NECROSIS FACTOR-α INCREASE INULIN AND HIV-1 PERMEABILITY ACROSS THE BLOOD-BRAIN BARRIER

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The blood-brain barrier does not fully protect the brain from some viruses, in particular HIV-l which penetrates into the brain early after the infection. We constructed a model of the blood-brain barrier with human brain microvascular endothelial cells (BMVEC) and fetal astrocytes on a matrix-coated porous membrane to evaluate the effects of abused drugs on molecular permeability and HIV-l penetration. In basal state, the permeability was modulated by the matrix. Collagen I/fibronectin was optimal for construction of a tight model with the permeability coefficient for ^{14}C-inulin as low as 0.0014 (BMVEC passage 2). Cocaine (10^{-5}M) treatment (1 hr) increased the coefficient for ^{14}C-inulin 1.31 to 2.17 fold and, in comparison, TNF-α treatment (100 ng/ml for 4 h) increased the coefficient two-fold. Infectious HIV-1 was placed in the upper chamber and its penetration into the lower chamber was measured by p24 antigen assay after amplification in CEM cells. Using this assay, the unmanipulated model leaked less than measurable amount of HIV-1 (<7 pg/ml) for a variable interval ranging from 1 to 6 days post-infection. Cocaine (10^{-6} M for 24 h) treatment of the model enhanced penetration of infectious HIV-1 an average of five-fold (range 1.5 to 8 fold in 4 experiments) and TNF-α (100 ng/ml) up to 12.8 fold (range 4 to 12.8 fold in 3 experiments). Cocaine (10^{-4} M to 10^{-8} M for 24 hr, max 10^{-5} M) also increased migration of monocytes across the BBB model by 136 to 202%. In rats chronic exposure to cocaine (20 mg/kg twice a day for 19 days) significantly increased rolling WBC flux and leukocytcendothelium adhesion (LEA). We postulate that cocaine's effects on increased cell migration are due to upregulation of cell adhesion molecules (CAM's), intercellular adhesion molecule 1 (ICAM-1). vascular cell adhesion molecule 1 (VCAM-1), and platelet/endothelial cell adhesion molecule 1 (PECAM-1), on endothelial cells. CAM upregulation was shown by cell ELISA, and in the case of ICAM-1 *in vivo,* by RT PCR. In cocaine-addicted subjects enrolled in a therapeutic study, i.v. cocaine administration increased cytokine responses associated with strong Th1 responses (IFN-γ, IL-12, and TN~α) by peripheral blood mononuclear cells. Since *in vitro* secretion of inflammatory cytokines, IL-6, IL-12 and TN·α, by monocytes was greatly increased by their coculture with endothelial cells, the upregulation of adhesion molecules could potentiate further the vicious circle of cocaineinduced adhesion and inflammation These results show that cocaine abuse increases immune cell migration. which could cause vasculitis and increase the BBB permeability for cell-free HIV1.

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ORAL COMMUNICATIONS XIV

SEROTONERGIC AGENTS IN RATS TRAINED TO DISCRIMINATE ETHANOL FROM SALINE

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Different serotonergic agents - including 5-HT-uptake inhibitors, 5-HT_{1A}-agonists and 5-HT_2- and 5-HT_3-antagonists -have been described to reduce the consumption of alcohol in a variety of animal models. In the present study, it was evaluated whether the alcohol reducing properties of these serotonergic agents may be related to an interference of these compounds with the discriminative stimulus properties of ethanol. Rats were trained to discriminate 1000 mg/kg ethanol from saline (IP, at 15 min prior to testing) in a two-lever food reinforced drug discrimination test procedure. After training, generalization and antagonism trials were performed. The test compounds were given SC. at 1 h prior to testing. The ED_{50} (95% confidence limits) of ethanol for stimutus generalization in the ethanol trained rats was 933.5 (680.5-1280.6) mg/kg. Partial generalization to the ethanol cue was obtained with buspirone and fluoxetine (80%), 8-OHDPAT, DOM, ipsapirone and TFMPP (60%), mCPP (40%) and mianserin and fluvoxamine (20%). No generalization was measured with citalopram, paroxetine, ritanserin and ondansetron. In terms of antagonism of the ethanol cue, a limited antagonism was only observed with fluoxetine and TFMPP (40%) and ipsapirone (20%). These results indicate that stimulation of the 5-HT system with 5-HT_1 or 5-HT_2 agonists and with some 5-HT-uptake inhibitors produces in some rats cueing properties analogous to 1000 mg/kg ethanol.

THE EFFECTS OF NALTREXONE AND OTHER OPIOID ANTAGONISTS ON ORAL ETHANOL-REINFORCED RESPONDING IN RHESUS MONKEYS

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These experiments examined the effects of naltrexone (NTX) and μ-, κ-, and δ- selective antagonists on the oral-reinforced responding for ethanol. The effects of NTX were also examined in the presence of specific μ- and κ-antagonists. Six rhesus monkeys were given daily 3 hr opportunities to respond for ethanol (1% or 2%) or water on independent, concurrent FR4 schedules of reinforcement. On some test days, the monkeys were pretreated with an i.m. injection of saline or NTX at 0.032 - 0.32 mg/kg. On other test days, they received injections of the δ-antagonist, naltrindole at 1 - 3.2 mg/kg. the μ-irreversible antagonist, clocinnamox (CCAM) at 0.1 mg/kg, or the κ--antagonist, nor-binaltorphimine (nBNI) at 3 mg/kg. CCAM and nBN1 were administered atone and in conjunction with NTX (0.32 mg/kg). When NTX alone was tested, only 0.32 mg/kg significantly reduced ethanol, but not water, fluid deliveries when compared to saline (SNK, $p<.05$). There was no effect of any NTI dose. CCAM when tested alone, had no effect. When NTX was given in the presence of CCAM, ethanol fluid deliveries were significantly less that that when given saline (SNK, $p<0.05$). When nBNI was tested alone, and when NTX was tested in the presence of nBNI, them were significant reductions of ethanol fluid deliveries (SNK, $p<0.05$). The reduction by nBNI was observed only on the day of injection. In other behavioral situations nBNI exerts k-antagonist effects for more than 2 weeks in rhesus monkeys. Thus. in these experiments. NTX exerted similar behavioral effects under circumstances where μ- and κ-receptors were significantly altered.

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EXTINCTION AND REINSTATEMENT OF ORAL ETHANOL SELF-ADMINISTRATION IN RATS

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Extinction is a useful procedure for assessing drug seeking behavior and is an important aspect for treatments of drug abuse. However, time is known about the processes and patterns of extinction in rats trained to self-administer ethanol. The present study was conducted to characterize the behavioral response to the removal of ethanol (extinction) and its subsequent reinstatement (availability of ethanol restored). Male Wistar rats were trained in a limited access paradigm (30 min/day) to respond for ethanol (10% w/v) in a two-lever free-choice condition using a saccharin fading procedure. Responding to one lever resulted in delivery of an ethanol solution, while responding to the other lever resulted in either delivery of water or nothing (i.e., a blank lever). Extinction was conducted for 3 days using operational extinction (responding to either lever resulted in nothing) or water substitution procedures. Operational extinction procedures resulted in a rapid decrease in responding that was influenced by the training condition. Water substitution significantly prolonged extinction, with a greater resistance to extinction observed in animals trained with water when compared to those trained with a blank lever. The reinstatement of ethanol resulted in a return to baseline levels of ethanol intake for the operational extinction groups, whereas an increase in ethanol consumption above previous baseline levels was observed in animals receiving water substitution. These results suggest that ethanol acts as a classic reinforcer and that partial substitution of cues associated with ethanol self-administration (e.g., oral fluids) prolong or prevent extinction.

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EFFECTS OF ACUTE ETHANOL AND COCAINE ADMINISTRATION ON MOTOR COORDINATION AND BALANCE

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We investigated the effects of ethanol and cocaine on four standardized field sobriety tests (FST) that are used to determine whether a person can safely operate a motor vehicle. Subjective and physiological effects and drug plasma concentrations were also measured to correlate with behavioral effects. In a nonresidential study, 20 community volunteers participated in 6 experimental sessions on separate days. At each session, subjects were administered a single dose of either oral ethanol (0, 0.28, 0.52 g/kg) or intranasal cocaine (4, 48, 96 mg/70 kg). Ethanol increased body sway in the Romberg Balance lest and number of misses in the Finger to Nose test. In contrast, cocaine produced a trend toward improved performance. Cocaine decreased number of arm raises needed to maintain balance in the One Leg Stand test ($p=.08$) and decreased number of misses in the Finger to Nose test compared with placebo ($p=.09$). Ethanol and cocaine produced orderly dose-related increases in subjective ratings of drug strength and drug liking. Cocaine increased blood pressure and produced a more robust heart rate increase than ethanol. Peek ethanol plasma concentrations for low and high doses were 24 and 54 mg/dl, respectively, and occurred at time of FST testing (15 min postdosing). Peak cocaine plasma concentrations for low and high doses were 81 and 201 ng/ml, respectively, and occurred at 45 minpostdosing, which was at the end of FST testing. These data indicate that ethanol impaired balance and motor coordination at doses that produced ethanol plasma concentrations below legal intoxication limits. Cocaine did not impair FST performance at doses that significantly increased subjective and physiological measures.

CHARACTERIZATION OF SIGNS OF ALCOHOL WITHDRAWAL DURING ACUTE AND PROTRACTED PHASES

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Alcohol withdrawal in humans is most severe in the first live days, but symptoms have been reported to persist for weeks following cessation of drinking. Most reports on the intensity and duration of alcohol withdrawal are primarily cross-sectional, and often employ non-standardized subjective measures of withdrawal severity. This study used an ambulatory monitor to provide objective, 24 hour recording of skin temperature, sweating and sleep restlessness, all of which vary during alcohol withdrawal. Monitors were worn for 24 hours on days 2, 3 and 4 (acute withdrawal phase) and days 14, 42 and 70 (protracted withdrawal phase) following cessation of drinking. Subjects were 30 patients presenting to an m-patient unit for treatment of alcohol withdrawal and were matched with 30 controls who also wore the monitor for 24 hours. Withdrawal subjects received standard clinical treatment including monitoring of withdrawal severity using the CIWA-Ar, with diazepam dosing when scores were greater than 10. Data were analysed using a mixed model analysis of variance. Results showed that alcohol withdrawal subjects experienced disruption to temperature rhythms in the acute phase, which persisted into the protracted phase. Sweating was prominent at night during acute withdrawal, and during the day in the protracted phase, lasting for at least 70 days. Sleep disturbance was a significant feature of withdrawal in both the acute and protracted phases, also persisting for at least 70 days. Results from this study show that the withdrawal syndrome was most severe during the acute phase. but that most symptoms persisted for at least 70 days following me last drink. In contrast with many studies, the ambulatory monitor allowed alcohol withdrawal symptomatology to be measured objectively, and also generated data on night withdrawal severity. These results provide a baseline of alcohol withdrawal severity, which has the potential to be useful in evaluation of novel therapies.

THE USE OF CUE EXPOSURE TO OBTAIN A GOAL OF CONTROLLED DRINKING

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Mild-to-moderately dependent out patient problem drinkers (n=100 were randomly allocated to receive a standard behavioral self management treatment (BSMT) or moderation oriented cue exposure treatment (MOCE) with a goal of learning to drink in a controlled manner. Following assessment and, if necessary, an outpatient detoxification, subjects received a mean of 7 (+ 3) sessions. The MOCE Involved administration of a priming dose of the subject's preferred alcoholic beverage (PAB; typically 1-2 standard drinks), followed by exposure to the PAB. Thus, each session consisted of exposure to alcohol effects, the interoceptive cue, and to the visual, tactile and olfactory cues associated with the PAB. During the MOCE sessions, subjects rated their desire to drink for its pleasant effect, their desire to drink to take away an unpleasant feeling or mood and intoxication on a ten point scale at four minute intervals. The BSMT consisted of self monitoring of alcohol consumption, training in drink refusal skills, alternatives to drinking and relaxation training. Seventy eight per cent of the sample were followed up at approximately 8 months. Preliminary analyses indicate that, irrespective of treatment condition, there were significant decreases in total alcohol consumption, mean number of stardard drinks per day, severity of dependence and alcohol-related problems. Further analyses will determine whether them was an additional beneficial effect of moderation oriented cue exposure.

THE EFFECT OF DEPRESSION ON RETURN TO DRINKING: A PROSPECTIVE STUDY

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Background: The effect of depression on return-to-drinking among individuals with alcohol depndence is controversial. Between 1993 and 1996, we recruited 40 women and 61 men hospitalized for alcohol dependence, and followed them monthly for one year to assess the effect of depression on subsequent drinking behavior, and to determine whether such an effect would differ by gender. **Methods:** We conducted structured interviews during hospitalization and then monthly following discharge for one year to determine whether depressive symptoms or a current diagnosis of major depression al treatment entry affected the likelihood of return to drinking, and whether this effect differed by gender. Using survival analysis, we examined the effect of both depressive symptoms and a diagnosis of current major depression at treatment entry on men's and women's time-to-first drink and time-to-relapse during the 12 months of follow-up. **Results:** A diagnosis of current major depression at the time of entry into alcohol treatment was associated with shorter time-to--first drink [hazard ratio 2.03, (95% CI 1.28-3.21), P =.003] and shorter time-to-relapse [hazard ratio 2.12, (95% CI 1.32-3.39), P =.002]. There was no significant difference between women and men in this effect. Depressive symptoms as measured by the BDI did not predict time-to-first drink or time-to-relapse in either women or men. **Conclusions:** A diagnosis of current major depression at entry into inpatient treatment for alcohol dependence predicted shorter time-to-first drink and time-to-relapse in both women and men. These results differ from earlier reports that men and women differ in the effect of depression on return-to-drinking.

GENETIC AND ENVIRONMENTAL FACTORS SHARED BY ALCOHOL DEPENDENCE AND ANTISOCIAL PERSONALITY

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The twin method was used to examine whether alcohol dependence (AD) and antisocial personality disorder (ASP) share underlying genetic and environmental factors. The sample consisted of 56 MZ and 66 DZ male twin pairs, recruited through alcohol and drug dependence programs (Pickens *et al.* 1991). To increase power, quantitative measures (symptom counts of DIS-III diagnoses of AD and ASP) rather than diagnoses were used. Because of reports on differences in magnitudes of genetic and environmenlal influences on juvenile and adult ASP, relations with AD were analyzed separately for the two types of ASP. Structural equation modeling approaches were used to estimate shared genetic and shared environmental variation in alcohol dependence with juvenile and adult antisocial behavior. While the majority of variation in AD (83%) was found to be independent of juvenile ASP, 17% was estimated to be shared with juvenile ASP (7% additive genetic, 6% common environmental, and 4% specific environmental). Shared variation was somewhat higher between AD and adult ASP (30%, of which 5% was of additive genetic, 15% of common environmental, and 10% of specific environmental origin). Conclusion: juvenile ASP and AD, and to a greater extent adult ASP and AD share genetic, but also environmental influences. These influences are mostly smaller than genetic and environmental influences contributing to AD and ASP separately.

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ALCOHOL, DRUGS AND RISK OF DYING IN THE BALTIMORE ECA COHORT, 1981-1995

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We tend to assume that alcohol and drug dependence shorten human life and harm our chances for survival. Nonetheless, there is surprisingly little evidence on this matter, except for cases of alcohol and heroin dependence severe enough to have been treated. To add new evidence, we have conducted a 14-year follow-up of adult community residents with and without these disorders - the vast majority of our cases had never sought treatment. This community sample consisted of 3481 adult participants in the Baltimore Epidemiologic Catchment Area study. At baseline in 1981, psychiatric diagnoses, levels of drug use and smoking, and other characteristics were assessed via an interview that included the Diagnostic Interview Schedule (DIS). After tracing age at death from 1981-95, we used survival analyses to estimate median age at death and the relative risk of dying for persons with and without these disorders. When compared to non-cases, DIS/DSM-III alcohol dependence cases were 40% more likely to have died within 14 years (relative risk estimate, RR = 1.4. p=.01), and DIS cases of the other drug disorders were 220% more likely to have died (RR=2.2, $p<0.05$), after statistical adjustment for age, sex, race, and tobacco smoking. Median age at death was substantially lower for cases with DIS alcohol and drug diagnoses, as compared to non-cases ($p<0.0001$). This epidemiologic study provides important quantitative estimates on the excess risk and life-shortening effects of alcohol dependence and other drug disorders. The evidence also indicates that information captured by the DIS diagnoses for alcohol and drug disorders help to account for 148-year mortality, over and above information captured by assessments about level of drinking or drug use. Limitations of this study and its implications for future research are discussed.

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ORAL COMMUNICATIONS XV

EFFECTS OF CHRONIC COCAINE TREATMENT ON PREPRODYNORPHIN mRNA LEVELS AND NEST BUILDING BEHAVIORS IN PREGNANT FISCHER RATS

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Previous studies showed that preprodynorphin mRNA levels are induced persistently in the caudate putamen by "binge" cocaine administration in male Fischer rats (Spangler *et. al.* 1993, 1996). To determine if similar changes occur in pregnant females, we administrated cocaine from gestation days 8 to 17 in pregnant Fischer rats. Similarly to male rats, preprodynorphin mRNA levels were significantly ($p<0.05$) increased in the caudate putamen of pregnant rats following 10 days of "binge" cocaine administration (15mg/kg/injection/3 times/day). No changes in the levels of preprodynorphin mRNA were observed in the thalamus, frontal cortex, and hypothalamus of cocaine treated animals when compared to saline treatment. The alteration of preprodynorphin mRNA levels by cocaine during pregnancy may have significant implication for the regulation of different aspects of pregnancy. Cocaine exposed animals incorporated less material into their nests and built fewer fully completed nest than control animals. The overall quality of the nest was significantly lower than that of control. Thus, cocaine exposure impairs maternal nest-building behaviors in pregnant animals. Furthermore, cocaine exposed dams gained less weight than contro1 dams. No differences in the number of pups, weight or lengths of pups was observed between groups. The effect of cocaine in the nest building behavior could be mediated by changes in the hormonal and neurochemical factors that regulate. the stimulation and/or maintenance of the maternal behaviors. The interaction between the alteration of preprodynorphin mRNA levels by cocaine, other cocaine induced neurochemicand hormonal alferations, and maternal behaviors remain to be elucidated.

ACKNOWLEDGMENTS: Supported by NIDA grant P50-DA05130 (MJK), NIDA K05-DA0049 (MJK) and an Altman Foundation Fellowship (VQJ).

FETAL COCAINE EXPOSURE AND NEUROBEHAVIORAL BIRTH OUTCOMES: BIOLOGIC AND SELF-REPORT MEASURES

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In 404 infants (211 cocaine-exposed and 193 non-exposed) recruited into a longitudinal study at birth, standardized clinical interviews, urine screens, and meconium assays were used to assess the relationship of cocaine and polydrug exposure to infant birth and neonatal neurobehavioral outcomes using the Gardner Neurobehavioral Assessment. Meconium assays measured cocaine and its metabolites; cocaine (COC), benzoylecgonine (BEN), M-O-H benzoylecgonine (MOH), and cocaethylene (COCETH); and marijuana (THC). In regressions controlling for alcohol. marijuana, and tobacco use, and GA if warranted, maternal self report of cocaine use predicted lower infant GA, head circumference, and birth length. An interaction effect of cocaine and tobacco was found for GA. Ng THC was related to higher GA. Higher levels of BEN were related to lower birthweight and length. Heavily exposed infants had more attentional, movement and tone abnormalities and jitteriness than lightly or non-exposed infants. Maternal report of tobacco use was the only self report measure to correlate with ND total score. Higher levels of COCETH were related to more attentional abnormalities and sensory asymmetries on the NB assessment; higher levels of BEN and MOH, to poorer head control, and higher COC and BEN to total abnormality score. These data support a dose-response effect of in utero cocaine exposure on birth outcomes and neurobehavioral functioning.

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SENSORY MOTOR DEVELOPMENT IN COCAINE EXPOSED INFANTS

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This longitudinal study investigated effects of prenatal cocaine exposure on infant sensory-motor development through 12 months of age. One hundred and sixty-seven infants (74 cocaine exposed and 93 non-exposed) were assessed using the Bayley Scales of Infant Development (BSID). Ninety-seven of the 12-month-olds had previously been evaluated on the Movement Assessment of Infants (MAI) and the Test of Sensory Functioning of Infants (TSFI)) at age 4 months. On the BSID, the cocaine exposed group performed significantly less well on both Mental (103.8 vs. 107.9, $p<.05$) and Psychomotor Development (100.6 vs. 105.0, $p<.05$) Indices. The mean scores of both groups; however, were within the average range. Cocaine exposed infants were also more frequently rated as behaviorally suspect. Separate MANOVA's found significant group differences for the four-month-old subset of infants, with cocaine exposed group performing significantly less well on both motor (MAI risk scores 8.9 vs 6.3, $p<.05$) and sensory (TSFI 36.2 vs 38.6, $p<.01$) measures. When the groups were combined, early motor performance, but not sensory performance, predicted 12 month MDI and PDI scores. Correlations between maternal drug use and child outcomes showed significant relationships between prenatal cocaine exposure and 12 month Mental ($r=.21$) and Psychomotor ($r=.18$) and Behavioral Suspect ($r=.22$) scores, and a relationship between cigarette use and Mental ($r=23$) scores. Findings suggest that it is possible to detect early delays in sensory motor development related to prenatal cocaine exposure.

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COMPARISONS OF THE BAYLEY SCALES (BSID-I and-II) ACROSS NORMAL, COCAINE-EXPOSED AND CNS-INJURED INFANTS

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The Bayley Scales of Infant Development (BSID) are widely used for research and clinical purposes in the evaluation of both normal and risk infants. We present comparisons between initial (BSID-I) and revised (BSID-II) versions involving 3334 tests on 1032 infants. The BSID-II was administered with additional items given from the BSID-I, when necessary, so that both BSID-I and -II mental and motor scores could be calculated. Normal nursery and NICU Infants were recruited as part of research protocols for infant follow-up in which testing was scheduled every 3 months between 4 and 25 months (corrected ages). Normal term nursery infants were divided into 2 groups - cocaine-exposed (CE) or not (no-CE). NICU infants were divided into 3 groups according to varying degrees of CNS pathology as diagnosed by brainstem auditory evoked responses and cranial ultrasonography. Results indicate inflated scores for younger infants on the BSID-I, but depressed scores for infants over a year of age on the BSID-II. For term no-CE infants, the standard deviation of me BSID-II showed a restricted range compared to the BSID-I (12 vs 15). The BSID-I showed better differentiation across groups (Fmax 1.5-3.0) and better inter-age correlations. especially at younger ages. The BSID-II tended to designate more normal infants as abnormal. After correction for non-linear age trends, no prenatal care, and minority status, normal CE infants showed declining BSID-I and II mental scores after 10 months comparable to mild/moderate CNS-injured infants, but higher than strong/severe CNS-injured infants. We would advise caution in changing from the BSID-I to BSID-II, since both age at test and estimates with respect to CNS pathology or neurotoxicity might differ and not be as differential.

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AROUSAL AND MODULATION IN E-WEEK-OLD INFANTS AS A FUNCTION OF GESTATIONAL AGE AND PRENATAL DRUG EXPOSURE

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We investigated homeostasis in a sample of 155 8-week-old infants as part of a longitudinal study of the differential effects of prenatal drug exposure on full term and preterm healthy infants. Developmental outcome was assessed on the mental (MDI) and motor (PDI) scales of the Bayley Scales of Infant Development -II. Concurrently, physiological measures of arousal and arousal modulation were collected. (behavioral state, heart rate [HR], HR variability, respiratory ram [RR], and RR variability). No significant differences were found on either PDI or MDI between infants prenatally exposed to cocaine and/or alcohol and controls, nor between preterms and full terms. The ability of infants to regulate their physiological state differed based on both gestational age and prenatal drug exposure. The findings that prenatal exposure to drugs and gestational age at birth interact suggest that preterm delivery may modulate me effects of prenatal drug exposure, perhaps as a protective mechanism. Neither variable, however, directly influences developmental outcome suggesting that me ability to modulate arousal may be a significant factor later in develpment.

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SUBSTANCE MISUSE DURING VERY EARLY PREGNANCY: RELATIONSHIP TO MATERNAL PROGNOSIS AND FETAL OUTCOME

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Previous studies of the prevalence of substance, including nicotine misuse during pregnancy, have screened subjects at ante-nalal clinic attendance, and thus are likely to underestimate the prevalence of misuse around the time of conception and implantation when much of the potential foelal damage is likely to have occurred. In the present study, the frequency of substance misuse was determined by urine analysis in positive pregnancy test samples in a multi-ethnic socially deprived community in South East London. Eight hundred and seven consecutive positive pregnancy tests were analysed for substance misuse by immuno assay (positives confirmed by GC), enzymatic and HPLC analysis, as appropriate. Positive tests for cotinine were present in 34.3%, for cannabinoids in 14.5%, opiates in 1.3%, with multiple drug misuser in 1.1%. Pregnancy outcome was traced in 288 subjects, 36 of whom were drug (predominantly cannabinoid) positive. There was no significant difference in the frequency of ante-partum haemorrhage, pre-eclampsia or still birth in the drug positive and negative sub-groups. In terms of foetal outcome. no infant in the drug positive group had congenital abnormalities and 5 minute Apgar scores were similar in both subgroups. There was, however, a highly significant risk of prematurity ($p=0.02$), reduced birth weight ($p=0.002$) and lower gestational age ($p=0.005$) in the new-born of cannabis using mothers. Maternal cigarette use was associated with reduced birth weight ($p=0.05$) but not gestational age ($p>0.5$). This study indicates that one in six women in South London are using drugs around the time of conception and suggests that cannabinoids, as well as cigarette use, is associated with impaired foetal outcome.

ASSESSMENT OF DIETARY PRACTICES IN A POPULATION OF COCAINE-DEPENDENT PREGNANT WOMEN

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This continuing investigation is aimed at assessing the nutritional status of cocaine-dependent pregnant women who are participating in a comprehensive treatment program designed to decrease cocaine use and increase compliance with the treatment regimen. Subjects are pregnant women who are 28 weeks gestation or less, with a primary diagnosis of cocaine dependence, or opiate dependent with secondary cocaine dependence. They are randomly assigned to one of 3 treatment groups. Patients in all 3 groups receive baseline treatment which includes: behaviorally-based individual counseling twice a week, group therapy/ parenting skills class, HIV pre- and post-test counseling and testing. and prenatal care once a week. Patients are required to attend the Substance Abuse parental Clinic once a week and the Treatment Research Clinic (TRC) twice a week, providing a urine sample at each of these visits. All subjects are also required to complete a nutrition questionnaire which includes a 24-hour dietary recall and a food frequency at beginning and end of the study. Results indicate that a significant proportion (over 70 percent) derive their caloric needs from fast food and processed foods including hamburgers, pizza, tacos, fried chicken, etc. Consumption of vegetables was often limited to small amounts of lettuce and tomato on sandwiches. preliminary results reveal that a significant number of patients (greater than 25 percent) have less than adequate levels of serum albumin, hematocrit and hemoglobin. Analysis of 24-hour dietary recalls shows deficiencies of several essential nutrients. The need for nutritional intervention in this population cannot be overemphasized.

EFFECTIVENESS OF INTENSIVE SERVICES FOR SUBSTANCE-USING WOMEN WITH COCAINE-EXPOSED INFANTS

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The increase in substance abuse is making new and growing demands on the child welfare system. One initiative aimed at addressing substance abuse in the context of clients' family needs is New York City's Family Rehabilitation Program (FRP), a multi-site, comprehensive services program for families with cocaine-exposed infants. Preliminary outcome data from an ongoing evaluation study based on 73% of the baseline sample of 253 clients indicate that at 12-month post-admission follow-up, 40% of clients are still enrolled in the program; median length of enrollment is 10 months. Seventy-eight percent of clients report no crack/cocaine use in the past month and 36% test negative for cocaine by hair analysis (estimated time window = 1 month). Overall, retention time in FRP (mean= 9 months and counting) appears excellent compared with traditional outpatient drug treatmentcor special treatment/intervention programs for pregnant or parenting women using cocaine crack. Cocaine/crack abstinence- between 3640% of all clients- at one year follow-up is encouraging. Clients completing or still enrolled in FRP displayed significantly lower levels of cocaine/crack use than dropouts at one year follow-up, as measured by quantitative hair levels in a multivariate analysis. Employment and participation in school/training increased and probation/parole status decreased between baseline and follow-up for the sample as a whole (although there is no significant difference among FRP enrollment status categories). Thus the FRP, which offers an integrated mix of treatment and social services where parental recovery is addressed in the context of the family's total needs, appears to be beneficial to substance-abusing parenting women.

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ORAL COMMUNICATIONS XVI

DEVELOPMENTAL COMPARISON OF G-PROTEIN COUPLING TO MU-OPIATE RECEPTORS IN THE RAT BRAIN

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Changes in the ability of μ-receptors to couple with G-proteins may play an integral role in the development of tolerance to opiates. Studies from our laboratory demonstrated that neonatal rats were relatively refractory to the development of tolerance to morphine (Windh *et al.,* 1995; Little *et al.,* 1995). The purpose of the present study was to determine the degree of G-protein coupling to μ-receptors in neonatal (10 day old) and adult rats. First, the ability of GppNHp to regulate n-opiate binding was tested. Second, the ability of the u-selective agonist, DAMGO to stimulate GTP-γ-S binding was determined. In thalamic membranes from adult tats, GppNHp shifted 19% of the μ-receptors from a high to low affinity state. In contrast, GppNHp failed to shift the affinity of μ-receptors in membranes from neonatal rats. DAMGO (0.01-10 μM) stimulated GTP-γ-S binding in a concentration-dependent manner in membranes from adult rats. A maximal stimulation of 55-60% was observed. In neonatal rats, DAMGO also stimulated GTP-γ-S binding in thalamic membranes. However, the maximal degree of stimulation of GTP-γ-S binding was only 26%. Using two different indices of μ-receptor coupling to G-proteins, it appears that the coupling of μ-receptors to G-proteins is not fully functional in the neonatal thalamus. Therefore, it is possible that adaptations which reflect changes in u-receptor coupling to G-proteins (i.e. desensitization) would differ between neonatal and adult rats.

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MU AND KAPPA OPIOID-STIMULATED [^{35}S]CTPγS AUTORADIOGRAPHY IN MONKEY BRAIN

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Receptor-stimulated guanylyl 5'[γ-[^{35}S]thio]triphosphate([^{35}S]GTPγS) binding was recently applied as an *in vitro* autoradiographic tool to identify anatomically receptor-activated G proteins in tissue sections from a control cynomolgus monkey. In this study, mu and kappa, opioid-stimulated [^{35}S]GTPγS binding was examined with [^{3}H]DAMGO and [^{3}H]U50,488H, respectively. Receptor specificity was verified by blocking agonist-stimulated binding with CTOP or nor-BNI. Autoradiograms indicated that mu binding was highest in the amygdala, cingulate cortex, caudate, putamen and nucleus accumbens. Kappa$_1$-stimulated binding was dense in the deep layers of neocortex and periamygdaloid cortex, amygdala, nucleus accumbens, caudate, putamen and claustrum. [^{35}S]GTPγS binding was also assessed in tissue from two rhesus monkeys: one food control and one that had self-administered cocaine for 5 days. Both of these monkeys were part of a metabolic mapping study to determine the effects of cocaine on cerebral metabolism using the 2[^{14}C]deoxyglucose method. It was determined that the [^{14}C] from this study did not interfere with the [^{35}S]GTPγS binding study. Preliminary findings indicated that kappa$_1$-slimulated [^{35}S]GTPγS binding appeared to be increased in cingulate cortex, caudate, putamen and nucleus accumbens following cocaine as compared to a food control. Further studies are underway to expand on these results. These findings demonstrate that opioid-stimulated [^{35}S]GTPγS autoradiography can be successfully applied to non-human primate tissue. This technique is useful for identifying receptor populations that are functionally activated.

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RESOLUTION OF TWO [^{35}S]GTP-γ-S BINDING SITES AND THEIR RESPONSE TO CHRONIC MORPHINE TREATMENT

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The mechanisms by which prolonged exposure to morphine leads to tolerance are not fully understood. We investigated the effects of etorphine (ET) on [^{35}S]GTP-γ-S binding in brains of rats made tolerant to morphine via the implantation of morphine (or placebo) pellets. Binding surface analysis was used to characterize the interactions of ET, Gpp(Np)H and GTP-γ-S with sites labeled by [^{35}S]GTP-γ-S. Data sets were fi to one- and two-site binding models using the nonlinear least squares curve fitting program MLAB-PC. Two binding sites were readily resolved:

	Placebo-ET	Placebo+ET	Morphine-ET	Morphine+ET
BH	2920±360	6800±540*	5000±764$^{\#}$	3020±290*
BL	39000±4800	6800±540*	46000±11400	31000±8500
KDH	11.4±1.2	8.0±0.6	16.7±2.2$^{\#}$	5.2±0.5*
KDL	275±50	281±58	605±232$^{\#}$	545±213

Chronic morphine significantly increased the Bmax and Kd of high affinity binding site. ET increased [^{35}S]GTP-γ-S binding in PLACEBO membranes via an increase in the Bmax. In contrast, ET produced a net stimulation of [^{35}S]GTP-γ-S in chronic MORPHINE membranes via a large decrease in the Bmax of the high affinity site. These results suggest that G-proteins coupled to opioid receptors respond differently to etorphine-stimulation in chronic MORPHINE membranes than PLACEBO membranes. Since proper G-protein/receptor coupling would be expected to stimulate [^{35}S]GTP-γ-S binding via an increase in Bmax values, these results suggest that opioid receptors in chronic MORPHINE membranes are not normally coupled to G-proteins. These findings corroborate earlier studies that reported changes in G-protein function in morphine tolerant animals.

THE CELLULAR MECHANISMS UNDERLYING THE PREVENTION OF MORPHINE ANTINOCICEPTIVE TOLERANCE BY NITRIC OXIDE SYNTHASE INHIBITORS

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A single i.c.v. pretreatment of mice with morphine (3 nmol, -140 min) produced an acute antinociceptive tolerance to subsequent i.c.v. morphine. When co-administered with morphine the nitric oxide synthase inhibitors, L-NAME, 3-bromo-7-nitroindazole, 7-nitroindazole, and L-NMMA, blocked the development of morphine antinociceptive tolerance. Also, the guanylyl cyclase inhibitors, LY-83,583 and methylene blue, blocked the development of morphine tolerance. The cellular mechanisms of this prevention of tolerance development were investigated using the human neuroblastoma SH-SY5Y cell line, differentiated with retinoic acid. Culturing cells with 1 μM morphine for 18 hr. followed by extensive washing, produced a down regulation of μ opioid receptors, as measured by a significant reduction in the Bmax value for the binding of the p-selective peptide [^{3}H]DAMGO. L-NAME (100μM) did not affect this down regulation when included along with the chronic morphine treatment. Culturing of cells with 10 μM morphine for 18 hr, followed by extensive washing, produced a desensitization DAMGO-induced inhibition of forskolin-stimulated adenylyl cyclase activity. This desensitization was prevented when 100 μM L-NAME was included along with the chronic morphine treatment. D-NAME at the same concentration did not produce this effect. These results suggest that inhibition of nitric oxide synthesis prevents the desensitization of μ opioid inhibition of adenylyl cyclase activity, but not down regulation of μ opioid receptors following chronic exposure of SH-SY5Y cells to morphine. Blocking desensitization of the μ opioid receptors may be the mechanism by which L-NAME blocks the development of antinociceptive tolerance in mice.

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EFFECTS OF OPIOIDS ON PROTEIN KINASE C (PKC) TRANSLOCATION: EVIDENCE FOR PKC INVOLVEMENT IN OPIOID RECEPTOR DOWNREGULATION

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Prolonged exposure to opioid agonists leads to loss of opioid receptor function. Desensitization is a rapid loss of agonist affinity and function produced by an uncoupling of the receptor from its effector system. Longer periods of exposure produce a physical loss (downregulation) of receptor binding sites. Despite their differences, both desensitization and downregulation appear dependent on pbosphorylation of some portion of the receptor-G-protein-effector system. The specific kinases that promote opioid receptor phosphorylation, and initiate the loss of receptor function, have not been identified. Protein kinase C (PKC) has been shown to be involved in the phosphorylation and desensitization of several GPCRs, suggesting that PKC activation could play a similar role in opioid receptor regulation, and previous reports have provided some evidence for opioid receptor phosphorylation by PKC. Using cultured SH-SY5Y neuroblastoma cells. we observed that μ-opioid agonists have a dual effect on cellular PKC activity. PKC translocation and opioid receptor density were quantified by ^{3}H-phorbolester and ^{3}H-diprenorphine binding, respectively. to washed cell membrane homogenates. Short-term exposure (3-12 hours) to morphine or DAMGO promotes the translocation of PKC from the cytosol to the plasma membrane. Longer periods of exposure (>12 hr.) decrease membrane-bound PKC density. During both periods, there is a decrease in membrane opioid binding sites, the opioid antagonist, naloxone, the PKC inhibitor, chelerythrine chloride, and the L-type calcium channel antagonist, nimodipine, all reversed agonist-mediated opioid receptor downregulation and PKC translocation. Conversely, a 60 minute pre-exposure of cells to the phorbol ester, 12-myristrate 13-acetate (PMA), accelerated the loss of ^{3}H-diprenorphine binding sites by DAMGO. Interestingly, downregulation of total diacylglycerol-sensitive PKC, by 24-hr. exposure to PMA, does not modulate DAMGO's ability to decrease the number of opioid binding sites. This raises the possibility that non-conventional PKC isozymes are involved in this regulatory process.

ORAL COMMUNICATIONS XVII

DOES ADHD IMPACT ON THE DEVELOPMENTAL COURSE OF DRUG AND ALCOHOL ABUSE AND DEPENDENCE?

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Objective: The co-occurrence of ADHD and substance use disorders (SUD) in adults has been the focus of much clinical and scientific inquiry. In this study, we examine the effects of ADHD on the transitions from substance abuse to dependence and between different classes of agents of abuse. **Methods:** An ADHD sample of 239 consecutively referred adults of both genders with a clinical diagnosis of childhood-onset and persistent DSM-III R ADHD confirmed by structured interview were compared with 268 non-ADHD healthy adults. Cox proportional hazard models evaluated the association between age at onset of a PSUD subtype following the earlier onset of another. **Results:** ADHD was associated with a two-fold increased risk for PSUD. ADHD subjects were significantly more likely than comparisons to transition from an alcohol use disorder to a drug use disorder (HR=3.8) and were significantly more likely to continue to abuse substances following a period of dependence (HR=4.9). **Conclusions:** ADHD is associated with a sequence of PSUD in which early alcohol use disorder increases the risk for subsequent drug use disorder and early substance dependence increases the risk for subsequent substance abuse. If confirmed, such developmental pathways might lead to preventive and early intervention strategies aimed at reducing the risk for PSUD in ADHD subjects.

PSYCHIATRIC COMORBIDITY AND SUBSTANCE ABUSE TREATMENT OUTCOME IN METHADONE MAINTENANCE PATIENTS WITH A HISTORY OF ADHD

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Objective: The relationship between the diagnosis of attention-deficit/hyperactivity disorder (ADHD) and drug abuse treatment outcome was assessed over nine months in 100 new admissions to a community-based methadone substitution treatment clinic. **Method:** Opioid dependent patients stabilized on methadone were evaluated for ADHD using a modified structured interview (the ADHD module of the Diagnostic Interview Schedule: DIS). Patients received an extensive assessment battery including the SCID I and II to assess for other psychiatric disorder. Urine toxicology and treatment retention data were also collected. **Results:** Twenty one percent (21/100) met childhood criteria for ADHD, 52% (11/21) of these had clinically meaningful current symptoms, and 19% (4/21) met criteria for a current diagnosis. Patients with a lifetime diagnosis of ADHD were compared to patients who did not have the diagnosis (Non-ADHD). There were significantly higher rates of current psychiatric comorbidity in the ADHD vs. Non-ADHD groups (76% vs. 45%; p=.01) including antisocial disorder (62% vs. 25%; p<.001), and Axis I disorders (52% vs. 19%; p=.01). Rates of anxiety disorders (29% vs. 8%; p=.06) and mood disorders (29% vs. 13%; p=NS) were higher in the ADHD group. but did not reach significance. Fifty-two percent of those diagnosed with ADHD were female, which is two to four times the expected rate in the community. No differences between ADHD and Non-ADHD patients were observed for substance abuse diagnoses or urine toxicology positivity rates for abused drugs. There was a trend for ADHD patients to be better retained in treatment over the 9 month assessment period (90% vs. 72%; p=.08). **Conclusion:** Twenty-one percent of patients entering methadone treatment had a history of ADHD, and comorbidity with antisocial personality, mood, and anxiety disorders was common. Substance abuse diagnoses and urine toxicology results did not differentiate the groups. The high percentage of women with a history of ADHD was unexpected. Surprisingly, patients with a history of ADHD were retained as well or better than Non-ADHD patients over the first nine months of treatment.

ADHD : PARENT REPORTS AND STIMULANT TREATMENT

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ADHD may contribute to substance problems in conduct-disordered (CD) adolescents. However, such adolescents may underreport ADHD symptoms and prior stimulant treatment. **Hypotheses:** Parent and child reports may differ with regard to: (1) ADHD symptoms and diagnoses and (2) stimulant treatment. Youths with a history of stimulant treatment will have (3) more ADHD symptoms and (4) may differ in rates of DSM-III-R cocaine, amphetamine, or methylphenidate abuse or dependence. **Methods:** During treatment adolescents received the Diagnostic Interview Schedule for Children version 2.1 (DISC) and CIDI-SAM to assess their psychiatric and substance use. Parents of 26 boys and 4 girls (ages 13-17) were subsequently interviewed with the ADHD section of parent DISC 2.1 and additional lifetime questions. **Results:** (1) Parents report in their children significantly more ADHD symptoms (10.3 vs. 6.1; $p<.0005$) and diagnoses (60% vs. 6.7%; $p<.0005$) and (2) significantly more stimulant treatment ($p<.03$) than their children. Youths with a history of stimulant treatment did not have more (3) ADHD symptoms or (4) differ in their rate of cocaine, amphetamine, or methylphenidate abuse or dependence. **Conclusions:** In CD/SUD adolescents, parent reports indicate that adolescents may underreport ADHD symptoms and treatment. History of stimulant treatment was unrelated to current ADHD symptom count or stimulant abuse or dependence.

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SUBSTANCE ABUSE TREATMENT NEEDS AMONG ARRESTEES-JUVENILES

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To evaluate rates of illicit drug and alcohol use and dependence and treatment needs among juvenile arrestees, we interviewed 127 males and 103 females 13 to 21 years, sampled at random from detention centers in 3 CT cities. The interview included DUF questions, SCID substance use disorders sections, and questions regarding AIDS risk behaviors, social and vocational functioning, and history of drug treatment. Utox was performed on 82/127 males and 51/103 females. Reported use within 72 hours preceding arrest for males and females, respectively, were 67.5%, 49% for any illicit drug or alcohol; 54.8%, 27.5% for marijuana; 6.4%. 2.0% for cocaine; 1.6%, 1.0% for heroin. Cocaine positive Utox for 18.6% of males and 7.4% of females led to estimated rates of current cocaine use of 22% for males and 9.3% for females. THC-positive Utox was found in 82.9% of males and 40.7% of females. Based on SCID, 35.2% of juveniles are currently dependent on alcohol or an illicit drug; 30% on marijuana, 3% on cocaine, and 2% on heroin. Only 37% of drug dependent juveniles reported a current need for treatment, compared to 80-92% of drug dependent adult arrestees; 7% were in treatment at the time of arrest, and 72% had no prior treatment. Drug dependent juveniles also reported high rates of persistent depressive symptoms (55.7%). suicide attempts (20%). school dropout (35%). and high risk sexual activity (90% are currently active; 63% had multiple partners in the past 3 months, and 54% engaged in unprotected sex). Rates of drug use are higher among juveniles 18-21 compared to those 13 to 17, but sexual behaviors did not differ. Drug dependent juveniles report higher rates of drug or alcohol problems in a parent compared to juveniles not dependent (OR=2.24, $p<.01$). High rates of psychiatric, educational, vocational and family comorbidity and increased risk for HIV point to the need for interventions targeting these areas. Despite the presence of family pathology, 98% of parents contacted gave permission for their children to be interviewed, suggesting their interest in finding treatment for their children.

GENDER DIFFERENCES IN SUBSTANCE USE AND PSYCHIATRIC SYMPTOMS IN SCHIZOPHRENICS WITH COCAINE ARUSE/ DEPENDENCE

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Gender differences in substance use patterns and psychiatric symptomatology in adults dually-diagnosed with schizophrenia/schizoaffective disorder and cocaine abuse/dependence are underreported. Participants were 59 (20 females) adults who met DSM-III-R criteria for Schizophrenia or Schizoaffective Disorder and Cocaine Abuse or Dependence who were being assessed prior to entry into an outpatient treatment study of cocaine dependence. Results revealed no statistically significant gender differences in age (M =32.9), years of education (M=11.5), or race (73% AA, 19% Caucasian. 3% Hispanic). With regard to psychiatric symptoms, there were no group differences on the Hamilton Rating Scales for Depression (M=6.4) and Anxiety (M=4.3), Global Assessment of Functioning (M=44.0), and the Brief Psychiatric Rating Scale (BPRS) total score (M =26.6). However, males scored statistically significantly higher than females on two items of the BPRS that assess negative symptoms of schizophrenia (Emotional Withdrawal: Males=1.5 vs. Females=1.1; Motor Retardation: Males= 1.5 vs. Females=1.1). With regard to cocaine use patterns, there were no gender differences with regard to age of onset of use (M =24.3 yrs), age of onset of problem use (M =28.1 yrs), years of lifetime use (M=5.6). and recent use (M=5.5 days/month). Females did report more intense cocaine cravings at time of assessment as measured on the 0-10 point Cocaine Craving Scale compared to males (M=4.2 vs. 2.6, respectively). There were no group differences on the Addiction Severity Index Severity Scores (Psychiatric M=6.5, Drug M=6.9, and Alcohol M=3.1). Results indicate the need for further assessment of gender differences in this dually-diagnosed population, with treatment implications.

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RELATIONSHIP BETWEEN PSYCHIATRIC COMORBIDITY AND FAMILIAL INFLUENCE FOR DRUG DEPENDENCE

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A family history interview (FHI) was conduced on 142 adults with DSM-IIIR opioid dependence (85 males, 57 females; mean age 37.5 yr). Excluded were probands with current diagnosis of alcohol dependence, major depression, bipolar disorder, or schizophrenia. FHI reliability was estimated from reports on 39 common relatives by 7 pairs of probands. Internal consistency was K = .84 for alcohol dependence and K = .62 for other drug dependence (excluding nicotine). FHI validity was estimated by comparing proband FHI reports to DIS diagnoses of relatives also participating in the study (N=33). FHI sensitivity for detecting alcohol and /or drug dependence in relatives was 96.4% (K=.89). Agreement between FHI and DIS drug diagnoses in probands was 97.8%. After exclusion, 37.2% of probands were comorbid for an Axis I mental disorder or ASP. Opioid dependent probands with comorbid mental disorder (N=51) were over twice as likely to have a parent with substance dependence disorders (OR=2.5, 1.2-5.1) as was opioid dependent probands without a comorbid mental disorder (N=86). The effect was significant only for female probands (OR=3.8, 1.0-13.6), and only for the mother being substance dependent (OR=3.9, 1.4-10.5). In addition, probands with comorbid mental disorder were over three times more likely to have any sibling with substance dependence (OR=3.2, 1.5-6.9), which was also significant only in female probands (OR=5.2, 1.5-18.2). Mean density of substance dependence in siblings (for probands who had siblings) was greater for opioid dependent probands with comorbid mental disorder (.44) than opioid dependent probands without comorbid mental disorder (.20) ($p<.001$). The results suggest a relationship between psychiatric comorbidity and familial influence of substance dependence.

PSYCHIATRIC COMORBIDITY IN COCAINE ABUSERS IN OUTPATIENT SETTINGS OR A THERAPEUTIC COMMUNITY

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Although researchers have noted high prevalence rates of psychiatric comorbidity among cocaine abusers seeking treatment, there is litlle information comparing the rates of psychiatric disorders in cocaine abusers entering therapeutic communities (TC's) to those entering outpatient settings. Treatment-seeking cocaine abusers in both types of treatment settings were given multiple assessments including: the SCID for DSM-IV, a SCID-like module for adult attention-deficit hyperactivity disorder and pattern of drug use questionnaires. One-hundred and eighty-one patients were interviewed: 158 within a TC and 123 within three outpatient settings, Individuals interviewed in the TC were more likely to be younger ($p<.001$) and male ($p<.001$). Compared to males in outpatient settings, males treated within the TC were mom likely to have antisocial personality disorder (ASP; 39% versus 27%). Females in outpatient treatment were more likely to have a major depression than females in the TC (33% versus 6%). Within the TC, 35% had substance-induced depression, 16% had adult attention-deficit hyperactivity disorder (ADHD) or subthreshold ADHD, 15% had specific phobia and 12% had social phobia. These rates were not significantly different than those found in the outpatient settings. Regardless of gender, cocaine abusers in the TC began using cocaine regularly at a younger age and had more frequent days of current cocaine use. Although abuse of multiple substances was common for both settings and for both genders, this was more so among individuals with adult ADHD; 67% of individuals with adult ADHD had at least two substance use disorders compared to 47% of individuals without ADHD ($p<.05$). These findings suggest that individuals within TC's, as well as outpatient settings, have a range of psychiatric disorders that may require targeted interventions.

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ATTENTION AND MEMORY IMPAIRMENT IN COCAINE ABUSING SCHIZOPHRENIC PATIENTS

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Two possible results concerning the effects of cocaine on schizophrenic (SZ) patients' neurocognitive functioning exist. The first is that psychostimulants may enhance prefrontal cortical D1 receptor activity and thereby improve SZ executive functioning, memory, and altentional performance. An alternative outcome is that the cerebral vascular constricting action of cocaine on frontal-subconical circuit functions will significantly women SZ cognitive functioning. Numerous reports have found rCBF brain abnormalities and cognitive deficits in cocaine abusing non-SZ individuals. In me present report. we examine executive, memory, and attentional functioning in a group of DSM-IV cocaine abusing SZ patients (n=15), cocaine nonSZ patients (n=15) and a comparison group of non-cocaine abusing SZ patients (n=15). We hypothesized that recent cocaine use by SZ patients would reduce SZ hypofrontality and improve cognitive performance. Attention and concentration was measured using the CPT. Memory was assessed using the CVLT and executive functioning was measured using the WCST and the Trailmaking Test. Contrary to expectations, results revealed cocaine abusing SZ and cocaine-only patients manifested significant long-term memory and attentional dysfunction. No differences were found on any demographic variable for SZ subjects including age, years of education or chronicity of illness or executive function tasks. These results suggest that cocaine abusing SZ patients, similar to their nonSZ cocaine abusing counterparts manifest striking cognitive impairment on tasks requiring sustained attention, concentration and verbal memory following acute cocaine use. Follow-up studies are needed to determine if these cognitive deficits persist after periods of prolonged abstinence.

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ORAL COMMUNICATIONS XVIII

METHADONE MAINTENANCE DURING PREGNANCY: DOES METHADONE DOSE RELATE TO INFANT OUTCOME?

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Methadone maintenance is recommended by NIDA and CSAT as the treatment of choice for opiate dependent pregnant women. The use of methadone during pregnancy; however, has been controversial, and the empirical literature regarding the relationship between dose and neonatal outcomes has yielded mixed results. The present study was a retrospective review of neonatal outcomes for 102 pregnant women maintained on methadone (15-70 mg) for at least eight weeks prior to delivery. AU infants' urine toxicology screens at birth were negative except for methadone. A 2 X 2 factorial design (Newborn Nursery (NN) vs. Neonatal intensive Care Unit (NICU) and treatment of neonates with opium drops vs. no treatment (-)) was utilized to minimize the effects of possible confounds. The groups were not significantly different in age, race, or education. The Neonatal Abstinence Scores (adapted) were obtained every 12 hours by nursing staff, and the NN- group received the lowest Neonatal Abstinence Scores over the first 96 hours. Time course analyses of withdrawal scores for the first 96 hours revealed linear effect curves for the untreated groups, with a increasing and no slope for the NN- and NICU-groups, respectively. Treated groups displayed increasing curvilinear functions over time. Mean maternal methadone doses were significantly higher for the NICU+ than for the NN- group. Some symptoms, especially vomiting and hyperactive more reflex, were dose related. Division of neonates into these four patient subgroups and me assessment of individual signs of withdrawal may be useful for interpreting methadone neonatal dose effects.

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METHADONE WITHDRAWAL DURING PREGNANCY, MATERNAL AND FETAL EFFECTS

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At the end of this project, 26 pregnant opioid-dependent women have undergone supervised withdrawals using methadone. The withdrawals were 10 days long. Fetal well-being and maternal welt-being were monitored. Three patients left against medical advise before the taper ended, two patients were referred to methadone maintenance because of fetal distress and one patient was delivered because of fetal distress. Twenty-three of the 26 patients showed no fetal distress on non-stress test and biophysical profile. While the study focused primarily on the immediate consequences of withdrawal, information about 13 of the offspring was available. One baby was delivered preterm; the average gestational length was 39 weeks, 3 days, which is well within the normal range. One baby was admitted to the NICU. The average weight at birth was 2797 grams, which is within the normal range. Four of the babies were treated for withdrawal. We conclude that withdrawal during pregnancy is not an inherently unsafe procedure, and that it can safely be used in judiciously-chosen circumstances.

BUPRENORPHINE MAINTENANCE IN PREGNANT OPIATE ADDICTS

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The use and effects of methadone during pregnancy have been well investigated. Alternative substances like morphine have been applied during pregnancies in opiate addicts and showed safety for the unborn child. Both, methadone and morphine improved the situation for mother and child in comparison to heroin exposure but yielded to art enhanced neonatal withdrawal syndrome. Reisinger reported, at the CPDD 1995, regarding low dose buprenorphine maintenance in pregnant opiate addicts that withdrawal syndrome did not occur in the newborn. At the drug addiction out-patient clinic in Vienna, seven opiate addicts with a mean duration of pregnancy of 28 weeks were maintained on sublingual buprenorphine during pregnancy. The subjects were switched from a mean daily dosage of 430mg slow-release morphine to a mean daily dosage of buprenorphine of 9 mg. The subjects were inregrated in an already established program with obstetricians and pediatricians and until delivery followed on an out-patients basis, observed 3 times a week. Supervised urine samples were examined weekly for toxicology to exclude illegal drug consumption. Buprenorphine was well tolerated in the females. Our preliminary results demonstrate that the newborns showed a decreazed opiate withdrawal syndrome in comparison to morphine or methadone exposure during pregnancies.

PREGNANCY OUTCOME AND SERUM NUTRIENT LEVELS IN WOMEN CONSUMING DRUGS AND VITAMIN AND MINERAL SUPPLEMENTS

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The lack of adequate prenatal care has been associated with negative pregnancy outcomes. Substance abusing subjects who receive little or no prenatal care have a greater risk for delivering infants weighing <2500g compared with those who do not consume drugs and receive prenatal care. However, women receiving no prenatal care and who abuse substances, are at a greater risk for delivering low birth weight infants. The data presented are from a subset of African American subjects (16-35 years old) who reported drug usage before and during pregnancy. In addition, the effects of vitamin and mineral supplement consumption on biochemical and pregnancy outcome variables were compared among the groups who respended "yes" (YDYS) or "no" (NDNS) to drug use and to vitamin and mineral consumption. In the YDYS and NDNS subjects, gestational age, birth length, head circumference, and birth weight were similar among those who reported drug use before or during pregnancy. Infant birth weights were <2500g for the YDYS women who consumed vitamin and mineral supplements before or during pregnancy. Among the women who received prenatal care, infant birth weight was 3242.5+27.7g which reflects the consumption of vitamin and mineral supplements. It appears that the consumption of vitamin and mineral supplements modulated the negative effects of birth weight.

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PREDICTORS OF DEVELOPMENT IN PRENATALLY DRUG-EXPOSED TODDLERS

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Because early play skills have been associated with children's later social development and because early cognitive development is associated with later learning, this study examined potential predictors of play and cognitive development in a sample of 86 children whose mothers used cocaine and other drugs during pregnancy. The sample was studied from pregnancy through 18 months of age. The hypothesis was thal both toddler's play behavior and cognitive development would be predicted by maternal pre- and post-natal drug use, maternal prenatal psychological status, birth weight, and caregiver behavior. A videotaped play assessment at 18 months was rated on the maturity and directedness of the toddlers' play. The Bayley Scales of Infant Development, Mental Development Index, was also administered at 18 months. Maternal drug use was measured prenatally by the ASI, a urine toxicology screen at delivery, and by the ASI at 6 months post-delivery. Prenatal maternal psychological status was assessed using the Million Clinical Multiaxial Inventory. Caregiver behaviors were rated by an observer in the home using a caregiver behavior rating scale at 6 months post-delivery. The results indicate that the prenatal ASI and the 6-month ASI did not predict either the play or the developmental outcome at 18 months. For the other predictors, no single measure, with the exception of the urine toxicology screen at delivery, predicted both play and developmental outcomes. However, a cumulative risk score, combining four individual predictors--prenatal psychological status, urine toxicology screen at delivery, birth weight, and care giving behaviors--more strongly predicted both play and cognitive outcomes at 18 months. Thus. both biological and environmental factors predict 18 month toddler developmental outcomes. Abstinence or decreased drug use by mothers who use drugs prenatally is not, by itself, sufficient to promote their children's developmental outcome.

DISTINCTIVE QUANTITATIVE EEG (QEEG) ABNORMALITIES IN CHILDREN EXPOSED TO COCAINE IN UTERO

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In a pilot study, six male children with histories of in utero exposure to crack cocaine were evaluated using QEEG. The QEEG obtained in these children were strikingly similar to those reported in adult cocaine dependence. However, while the adults show an anterior predominance of abnormalities, the children show a more posterior predominance, possibly reflecting Interactions between time of insult and specific developmenlal features. The significant overall similarities in QEEG profiles suggest that brain dysfunction reflected in the QEEG is not a result of transient changes in neurotransmission, but a more profound alteration persisting in the children at school age. In an extension to this study, QFEGs in children with attention deficit hyperactivity disorder (ADHD), specific learning disabilities (SLD), and normals (NL), [all without history of any in utero drug exposure] were compared to the crack cocaine exposed children (CCE), matched for age, sex and IQ. Significant differences from normative values were common in the CCE and ADHD children, less common in SLDs and rare in NLs. Several features distinguished the CCE children from the other groups. These QEEG inrergroup distinctions suggest differences in underlying pathophysiological etiology.

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SUBSTANCE USE RISK FACTORS: A BIRTH COHORT OF PREADOLESCENTS

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This study uses a birth cohort of 577 ten-year-olds who have been followed since their second trimester in utero. Mothers were interviewed about their drug use during pregnancy and ten years postpartum. Child variables in this analysis were: IQ, temperament, age, race, gender, attention, activity, delinquent behavior, anxiety, depression, self-esteem, and in utero exposure to substances. Current maternal tobacco, marijuana, and alcohol use was also included. Most of the children came from single parent homes of low socioeconomic status, and many of their mothers used substances prenatally and postpartum. Their mean age was 10.5 years; 53% were African-American. Regular substance use was rare among these children. However, 41% had experimented with alcohol and 6.2% with tobacco. Also, 23% had friends who smoked tobacco, drank alcohol (14%), and used marijuana (4%). The outcome variable was dichotomized as, use and no-use. The use group (5.5%) was made up of children who used and/or whose friends used any substances. The no-use group (45%) was those who did not use and whose friends did not use any substances. Bivariate analyses between outcome and each exploratory variable determined which variables were to be considered in the logistic regression model. The final model showed that children who were male, had a history of theft, were prenatally exposed to tobacco, were Caucasian race. and had lower self-esteem were significantly more likely to be in the use group. This is the first study to show that prenatal exposure to a substance, in this case. tobacco, is a significant risk factor for early substance experimentation among preadolescents.

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POSTER SESSION I

AMLODIPINE TREATMENT OF COCAINE DEPENDENCE

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Preclinical animal studies support the hypothesis that the reinforcing effects of cocaine are reduced by isradipine and nifedipine. In one human laboratory study, pretreating subjects with nifedipine decreased the subjective euphoric properties of IV administered cocaine. Amlodipine, a dihydropyridine type calcium channel antagonist and an analogue of isadipine and nifedipine, was administered in an open label trial to 16 mate and 3 female cocaine-dependent individuals aged 21-47 in doses of 5r mg/day of amlodipine for subjects <70 kg and 10 mg/day in subjects >70 kg. All subjects repotted having used over $1000 of crack in the past three months. Seventy Percent of subjects had positive urine drug screens for cocaine at the time of enrollment in the study. Flushing, headache, fatigue, nocturia, and lightheadedness were reported by four subjects. At 3-4 weeks on medication the proportion of positive urine drug screens had dropped to 50%. Subjects reported reduced cocaine craving, improved concentration, and clearer thinking. Calcium channel antagonists may act to improve the cardiovascular blood flow in cocaine addicts or act by some yet-undelineated neural mechanism.

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EFFECTS OF COCAINE PRIOR TO AND DURING BUPROPION MAINTENANCE IN COCAINE ABUSERS

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This pilot study examined the self-reported effects of cocaine prior to and during bupropion (BPP) maintenance in nonopioid-dependent cocaine abusers. Prior to BPP maintenance, subjects (n=6) underwent an experimental session during which each of the following was adminstered intranasally 90 minutes apart in ascending order cocaine placebo, cocaine at 50 mg/70 kg. and cocaine at 100 mg/70 kg. Subjects were then inducted onto BPP over a two week period. At both an intermediate (150 mg) and maximal (300 mg) BPP maintenance dose, participants underwent an experimental session during which the effects of cocaine (0, 50, 100 mg/70 kg) were reassessed. Assessments prior to and after each drug administration included the addiction research center inventory (ARCI), adjective ratings (ADJ), visual analog scales (VAS), and profile of mood states (PCMS). Results were that cocaine-induced "desire for cocaine" and "rush" ratings on the VAS appeared to be lower during BPP maintenance relative to no BPP. Also, cocaine-induced increases in POMS ratings of "friendliness", "arousal", and "vigor" appeared to be lower during BPP maintenance compared to no BPP. These preliminary findings suggest that chronic administration of BPP may reduce several positive subjective effects of cocaine in human subjects.

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EFFECT OF PHENYTOIN ON COCAINE SELF-ADMINISTRATION IN HUMANS

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In a recent double-blind, placebo-controlleded study, phenytoin treatment has been shown to decrease cocaine use in outpatient settings. The goal of this pilot study was to determine the effects of phenytoin on smoked cocaine-base self-administration, using our laboratory self-administration model. Self-administration session consists of work and cocaine-option periods. During the work period, subjects had the option to earn up to five tokens, worth $5 each, by doing simple arithmetic problems. In the cocaine option period, subjects were given the opportunity to exchange the tokens that they had earned earlier for doses of 0.4 mg/kg cocaine. A total of 12 patients were randomized, 6 to phenytoin and 6 to placebo treatment group. There were two phases in this 10-day inpatient study. During Phase 1, subjects underwent a cocaine self-administration session and those who administer all doses of cocaine while medication free were moved on to Phase 2. Subjects were randomized at the start of Phase 2, Day 4. Those assigned to phenytoin treatment received an oral loading dose (20 mg/kg) aimed at achieving plasma phenytoin concentrations of 10-20 mg/L. During Phase 2, subjects had self-administration sessions on Days 5, 7 and 9. Eighteen subjects enrolled in the study, 12 subjects were randomized, 6 to placebo and 6 to phenytoin treatment. Oral phenytoin loading was generally well tolerated, most of the side effects were short-lived. There were no differences between the two treatment groups in the number of tokens exchanged for cocaine. The subjective and the cardiovascular response to the sample dose of cocaine on Day 5 were comparable in the two treatment groups. This preliminary analysis of our study does not support efficacy of phenytoin in reducing cocaine self administration in a laboratory setting.

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BENZTROPINE PRETREATMENT MODIFIES THE PROFILE OF COCAINE'S EFFECTS IN MALE VOLUNTEERS

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In the search for new and improved pharmacotherapies for cocaine abuse, we studied a relatively non-toxic drug that inhibits the dopamine transporter with the aim of finding a "substitute" for cocaine that is not abused. Six healthy, male occasional cocaine users provided informed consent and volunteered to participate in this study. Each subject served as his own control and was tested under double-blind conditions on four separate experimental sessions during which they received either placebo, 1.0 or 2.0 mg of benztropine two hours before an intranasal dose of lactose (placebo) or cocaine (0.9 mg/kg). Studies were separated by at least one week. Dependent variables were measured for two hours after cocaine and included: heart rate; the Addiction Research Center Inventory; visual analog scales; subjective reports of drug detection, euphoria and dysphoria; and plasma cocaine and metabolite levels. Other than slight tachycardia benztropine produced few effects of its own. Compared to placebo pretreatment, benztropine slightly increased the intensity of the cocaine-induced "high", attenuated the "crash", increased the number of euphoric events, and prolonged the duration of cocaine's effects on heart rate in the absence of any changes in the kinetics of either cocaine or its metabolites. These data suggest that although it is unlikely that benztropine alone will be a useful medication to treat cocaine abuse, the strategy of using a drug that enhances some of cocaine's effects may he appealing because it could actually reduce the number of times cocaine is used during a binge.

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DEVELOPMENT OF A SUBJECTIVE RATING SCALE SENSITIVE TO ACUTE COCAINE ADMINISTRATION

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The epidemic of cocaine abuse has generated much research with the goal of understanding cocaine effects and finding effective treatments for cocaine addiction. Various instruments have been used to measure subjective effects produced by cocaine administration in the laboratory. This study evaluated responses to a list of subject-rated descriptors presented to inpatient volunteers (N=76) following intravenous cocaine (0 vs 40-50 mg) injections. Intravenous cocaine significantly altered scores of 21 adjectives, which were combined to form the Subjective Adjective Rating Scale. Sensitivity and specificity of this scale were assessed by examining the effects of psychoactive drugs administered concurrently with cocaine injections. Scale scores were not significantly altered by pretreatment with methadone, bromocriptine, fluoxetine, mazindol, buprenorphine, selegiline, or naltrexone. Compared to placebo, oral cocaine significantly lowered Subjective Adjective Rating Scale scores during i.v. cocaine administration. The adjective checklist described in this study is a sensitive and specific measure of subjective intravenous cocaine effects in humans under laboratory conditions.

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COCAINE-SEEKING BEHAVIOR AND DOPAMINE OVERFLOW IN THE AMYCDALA DURING COCAINE WITHDRAWAL

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Cocaine and cocaine-paired cues elicit craving in humans and reinstate cocaine-seeking behavior (CSB; i.e., lever pressing in the absence of cocaine) in rats. It has been suggested that craving and CSB may be. mediated by changes in dopamine (DA) neurotransmission that occur during the course of withdrawal. To examine this hypothesis, experimental rats received 14 3-hr daily sessions of cocaine self-administration training and control rats received yoked administration of saline. DA overflow in the amygdala was assessed following a 1-day (1D), 1-week (1W) or 1-month (1M) withdrawal period during 1) baseline (BL), 2) extinction of CSB and 3) cocaine reinstatement of CSB. BL measures revealed enhanced DA overflow in the amygdala in the 1M group relative to the control and 1W groups. During extinction, the pattern of changes in CSB did not correspond to changes in DA overflow. CSB was exhibited by the 1W and 1M groups, but DA overflow was only enhanced above BL in the 1M group. In contrast, during cocaine reinstatement, the pattern of changes across these variables was similar. CSB and DA overflow were enhanced in all cocaine groups and both effects were greater in the 1M group relative to the 1D and 1W groups. These findings indicate that CSB and DA overflow in the amygdala are enhanced following longer withdrawal periods.

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PREDICTIVE VALIDITY OF THE EXTINCTION/REINSTATEMENT MODEL OF DRUG CRAVING

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The effects of chronic desmethylimipramine (DMI) treatment on measures of incentive motivation for cocaine were assessed in order to investigate the predictive validity of the extinction/reinstatement model of drug craving. Rats were trained to respond for cocaine infusions (0.75 mg/kg/0.1 ml) or received saline infusions during daily 3-hr sessions. A light and tone were presented with the infusions. Following self-administration training, each group received daily injections of either saline or DMI (10 mg/kg, IP) for 21 days of withdrawal from the self-administration regimen. On days 12-21 of withdrawal, rats were allowed to respond in the absence of cocaine reinforcement (extinction phase). After reaching an extinction criterion of no responses for one hr, the cocaine-paired stimuli were presented rcpeatedly to reinstate responding (reinstatement phase). In controls, DMI treatment did not alter the responding during either test phase but increased the response latency during the extinction phase. In contrast, DMI treatment in the cocaine group decreased responding and increased the response latency during both test phases, and decreased the extinction latency during the extinction phase. Overall the effects of DMI were consistent with a reduction of incentive motivation for cocaine, lending support for the predictive validity of the extinction/reinstatement model of drug craving.

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EFFECTS OF PHENTERMINE AND FENFLURAMINE ON REACQUISITION OF COCAINE SELF-ADMINISTRATION IN RATS

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Clinical studies indicate that the administration of the dopaminergic agent phentermine (PHEN) together with the serotonergic agent fenfluramine (FEN) may be useful in the treatment of cocaine addiction. The aim of this study was to examine the effects of PHEN and FEN pretreatment on cocaine-seeking behaviour. Under 12-hr unlimited access conditions, four groups of male Sprague-Dawley rats (n = 5-6 per group) were trained to self-administer i.v. cocaine (0.66 mg/kg/infusion) under an FR-5 schedule of reinforcement. Once cocaine self-administration was stable, the behaviour was extinguished by replacing cocaine with saline. Following five days of extinction, cocaine was re-introduced until complete reinstatement of responding was achieved. Since the first day of extinction, four groups of rats received two injections a day of either PHEN (2.0 mg/kg IP), FEN (2.0 mg/kg IP), a mixture of both drugs (PHEN + FEN, 2.0 mg/kg of each IP) or saline (SAL, 1 ml/kg IP). administered 3 hours before and 3 hours after each session, until the end of the experiment. No significant changes of cocaine self-admtinistration responding were observed in the SAL or PHEN groups. However, rats pretreated with FEN or the mixture (PHEN + FEN) showed delayed rates of requisition; the changes were statistically significant ($p<0.05$) only for the FEN group. The present findings suggest that FEN is probably an effective substance in the PHEN-FEN mixture and support the hypothesis that serotonin dysfunction may contribute to craving elicited during withdrawal from cocaine.

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EFFECTS OF PHENTERMINE IN RHESUS MONKEYS PERFORMING UNDER PROGRESSIVE-RATIO SCHEDULES OF COCAINE AND FOOD DELIVERY

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Recent experiments employing multiple fixed-ratio (FR) schedules of cocaine and food delivery have shown that phentermine can selectively reduce cocaine-maintained responding in rhesus monkeys at doses that have no effect on food-maintained responding. The purpose of the present experiment was to examine further phentermine's effects on cocaine- and food-maintained behavior. Phentermine (0.1 to 5.6 mg/kg) was administered (i.m.) to groups of rhesus monkeys performing under progressive-ratio (PR) schedules of cocaine and food delivery that arranged a unit dose of cocaine and a magnitude of food delivery that were comparable in terms of their relative reinforcing efficacy (i.e., maintained similar breaking points). Two variants of the PR schedule, one that arranged one trial per ratio and another that arranged five trials per ratio, were used. Phentermine produced dose-dependent decreases in the number of reinforces earned under both variants of the cocaine and food PR schedules. In contrast to phentermine's dramatic and selective disruption of cocaine self-administration in prior studies using multiple FR schedules of cocaine and food delivery, only a slight behaviorally-selective reduction in cocaine self-administration was observed under the 1-trial PR, and no selective reduction in cocaine self-administration was observed under the 5-trial PR. This finding suggests that phentermine may produce less behaviorally-selective effects when the reinforcing efficacy of cocaine and food are comparable. Thus, taken together with findings from prior studies, the present results suggest that the relative reinforcing efficacy of cocaine and food may be a determinant of phentermine's behaviorally-selective effects on cocaine self-administration.

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STRESS RESPONSE AND STRESS-INDUCED CRAVING IN COCAINE ABUSERS

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Stressful situations and negative emotional states are commonly cited as reasons for drug use and relapse among substance abusers. Two pilot studies were conducted to examine the association between stressful situations and craving for cocaine among cocaine abusers. In the first study, we examined the effects of a speech stressor task and a personalized stressful imagery task on self-reported craving and emotional arousal in 10 cocaine abusers. Both stressors led to significant decreases in neutral and joyful feelings as compared to baseline ratings. The stressful imagery condition led 10 significant increases in sadness and anger ratings and led to significant increases in cocaine craving ($p<.01$). Thus, a personal stressful imagery task provides a useful method for examining the relationship between stress and cocaine craving. In a second ongoing study, we are examining the effects of stressful imagery as compared to neutral imagery on cocaine craving, emotional arousal, subjective anxiety and physiological responses. The stressful imagery task produced significant increases in heart rate. pulse transit time along with increases in cocaine craving and subjective anxiety ratings. These findings are consistent with preclinical data showing a significant association between acute behavioral stress and cocaine use.

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COCAINE CUE-REACTIVITY/CUE-INDUCED CRAVING IN A TRIAL OF FLUOXETINE FOR COCAINE DEPENDENCE

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Preclinical data suggest a link between stress reactivity, as measured by corticosteroid response, and cocaine self administration in rats. Serotonergic systems appear to modulate cue-reactivity for cocaine, a factor implicated in relapse to cocaine use. Twenty-two subjects in a double-blind, placebo-controlled trial of fluoxetine (flx) treatment for cocaine dependence participated in 2 cue reactivity sessions, 1 in the placebo run-in week and the other after approximately 5 weeks of flx or placebo treatment. The aim was to explore whether treatment with flx, a serotonin reuptake inhibitor, is associated with a decrease in rise in subjective cue reactivity and cortisol response to cocaine cues. Results: The effects of chronic fix pretreatment on cocaine cue reactivity were complex. Comparing cue reactivity sessions before and after medication, flx significantly increased a subjective measure of cocaine cue reactivity (likely to use). This finding is consistent with an earlier study (Satel *et al.* Am J. Psychiatry 152:778-83, 1995) in which a serotonin depletion diet attenuated cocaine cue reactivity. Other subjective responses were not significantly different between groups. In contrast, fix significantly attenuated cue induced activation of the adrenocortical (HPA) axis. These findings suggest that cue induced craving is not dependent on HPA activation. Any beneficial effects flx may have in the treatment of cocaine dependence are probably not attributable to suppression of cue-induced craving. Further study is needed to determine whether fluoxetine attenuates activation of the adrenocortical axis under other conditions (e.g., stress). However, given the literature linking the HPA axis with addiction and such mood states as anxiety and depression, flx's ability to attenuate HPA activation could have therapeutic implications.

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A NICOTINE ANTAGONIST, MECAMYLAMINE, REDUCES CONDITIONED COCAINE CRAVING IN COCAINE-DEPENDENT SUBJECTS

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Epidemiological studies have documented that cigarette smoking is significantly greater in cocaine dependent individuals. In a recent study, we demonstrated that nicotine (two 22 mg/day Nicoderm patches) enhanced cue-induced cocaine craving in cocaine dependent subjects suggesting that nicotine may have a direct psychopharmacological effect on conditioned cocaine craving. In the present study, cocaine-dependent, cigarette smoker patients were tested in a counterbalanced, double blind, placebo controlled design for the effects of a nicotine antagonist, mecamylamine (2.5 mg, p.o.). on cue-induced cocaine craving. Measures of cue-reactivity included self reported visual analog scales for cocaine craving, nicotine withdrawal and mood as well as physiological measures of skin conductance, skin temperature and heart rate. Subject were also asked to rate which test day they had the most craving. Cocaine conditioned cues included a 5 min video and the handling of crack cocaine paraphernalia Neutral cue controls were also performed. Cue-induced cocaine craving was significantly reduced by mecamylamine. In addition, more patients reported higher levels of craving during the placebo (16) versus mecamylamine (5) test day. Mecamylamine treatment also produced a mild reduction in cue-induced increases in skin conductance, while the skin temperature and heart rate responses were not affected. Analyses of the medication effects prior to cue testing indicated that the desire to smoke was also reduced by mecamylamine. These findings show that mecamylamine can reduce conditioned cocaine craving and suggest that this medication may be of therapeutic value in cocaine abuse treatment.

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EFFECTS OF BUTORPHANOL ON CUE-ELICITED COCAINE CRAVING

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There is considerable human laboratory evidence which has demonstrated that cocaine-dependent subjects, when re-exposed to environmental cues previously associated with cocaine use. exhibit a conditioned response (i.e., increased autonomic arousal and cocaine craving). An increase in CNS dopaminergic activity in response to cocaine cues is thought to underlie this phenomenon. Consistent with this hypothesis, our group recently demonstrated that the dopamine (DA) antagonist haloperidol blocked increases in plasma homovanillic acid, anxiety, and craving resulting from cocaine-cue exposure. However, haloperidol can produce a number of side effects, including drowsiness. parkinsonism, tardive dyskinesia and Neuroleptic Malignant Syndrome. Consequently, patient non-compliance is likely to be high with long-term use. This fact has been the impetus to search for DA modulating agents with fewer side effects. Presumably, drugs that indirectly interfere with DA release should blunt cue-induced DA elevations and craving without the side effects associated with complete antagonism of postsynaptic receptors. The opiate kappa agonist butorphanol seems well-suited in this regard. Data from several experiments indicate that opiate kappa agonists effectively attenuate CNS dopamine activity. We examined the effects of acute butorphanol (1 mg) administration on cue-induced cocaine craving in cocaine-dependent individuals. Our findings suggest that the conditioned cocaine response is dissociable and complex. Notably, butorphanol attenuated cue-induced euphoria. anxiety, and nervousness. without affecting craving or the desire to use now. Even though butorphanol was without affect on craving, the fact that are-induced euphoria was decreased suggests it may still be clinically useful. The effects of butorphanol on cocaine euphoria warrants further study.

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RELATIVE SENSITIVITY OF A LABORATORY CUE REACTIVITY PARADIGM

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Cue-reactivity has been studied in the laboratory with various substances including: cocaine, opiates, alcohol, and nicotine. The most studied cue modalities include: manual, visual, and audio. Thirty cocaine dependent subjects received the following cue types in a randomized fashion: 1) cocaine related, 2) neutral, and 3) arousal. Within each of the cue them were three cue-modalities which were presented in the following order: 1) audio, 2) visual, and 3) manual. Physiological measures consisting of skin conductance, temperature, and pulse was assessed continuously during the laboratory sessions. A repeated measures ANOVA was used to compare mean change response on physiological measures to cue-modality. We found that for cue-response, manual cues produced greater changes in all of the measures compared to audio and visual cues ($p=0.001$). Pulse was found to be relatively insensitive compared to skin conductance and temperature for the assessment of physiological responses. Our results demonstrate that the manual cue modality is the most sensitive measure for assessing craving in the cue-reactivity paradigm.

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CUE REACTIVITY AND SPECIFICITY

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Cue reactivity has been studied extensively in cocaine dependent subjects. The relationship between cocaine craving and cocaine stimuli remains unclear. The objective of this investigation was to examine the specificity of a cue-reactivity paradigm as a measure of cocaine craving. Thirty treatment seeking cocaine dependent subjects were exposed to three types of cues (cocaine-related, arousal, and neutral) in a randomized order. Change in subjective measures during the study and mood assessments were conducted. Physiological responses were measured cotinuously during the laboratory session. We found significant differences in craving responses between cocaine and neutral cues, and the cocaine and arousal cues; with the cocaine cues always producing the higher craving ratings. In contrast, both cocaine and arousal were associated with significant changes in general mood ratings. but there were no differences found between cocaine and arousal cues. We conclude that cocaine cues are specific to cocaine related stimuli, and are not simply a measure of general mood or arousal. Our findings suggests that the conditioned cue paradigm can be utilized as a relatively specific indicator of cocaine craving.

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ALTERNATE REINFORCER MODULATION OF COCAINE-SEEKING BEHAVIOR FOLLOWING COCAINE STIMULI EXPOSURE

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This study was designed to examine the effect of an alternative reinforcer on cocaine-seeking behavior following exposure to cocaine-related stimuli. Six healthy females and males who reported using crack cocaine at least two times a week for 6 months, and at least 1 g of crack in a 4-6 hr period, were recruited for an inpatient study. Three experimental sessions were held on separate days, during which subjects were exposed to cocaine-related external stimuli in a within-subjects design. The stimuli comprised a 5 min video of scenes showing cocaine use, followed by handling cocaine-related paraphernalia. After exposure to the stimuli, subjects worked on concurrently-available fixed-ratio tasks either for tokens that could be exchanged for money ($0.25, $5, or $15) or for tokens that could be exchanged for deliveries of cocaine (0.4 mg/kg). The order of exposure to money token value was counterbalanced across subjects, with each subject exposed to one money token value within a session and all money token values across the three experimental sessions. Any combination of a total of 7 tokens could be earned each day and tokens earned for cocaine deliveries were administered immediately following the work period. The results showed that craving for cocaine increased significantly from baseline rates following stimuli exposure. However, significantly fewer cocaine tokens were earned when the token value was either $5 or $15, compared to $0.25. This laboratory model may prove useful in examining the effect of treatment medications on craving and cocaine-seeking behavior,

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CRAVING AND WITHDRAWAL SYMPTOMS DURING AN AMBULATORY COCAINE DETOXIFICATION PROGRAM

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The phenomenon of cocaine craving is discussed extensively in the literature, and is believed to be a withdrawal symptom related to relapse/drug use. The exact role of craving during initial cessation of cocaine in currently dependent subjects is unknown. This ongoing investigation is designed to examine daily craving, withdrawal symptoms, and drug use in subjects participating in an outpatient detox program. It is hypothesized that craving intensity will decrease as the number of days of abstinence increases. Subjects attend the detox program daily for 10 days or until they submit 5 consecutive cocaine-free urine samples. Subjects complete self-report instruments assessing: craving, withdrawal symptoms, substance use, and identify events/triggers surrounding craving and/or drug use episodes. Urine samples are also collected each day to verify abstinence. To date, the majority of subjects (78%) who started the detox program have successfully abstained from cocaine use for 5 consecutive days. Preliminary analysis suggests an association between craving intensity and number of days abstinent. The most frequently reported withdrawal symptoms included: fatigue, anxiety, and agitation. This presentation will report on multivariate analyses comparing craving and withdrawal symptoms between drug users versus non-users, as well as compare cocaine only and cocaine/depression subjects during the detox program.

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VALIDITY AND UTILITY OF CRAVING ASSESSMENTS IN COCAINE TREATMENT

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This study evaluated several measures of cocaine craving including visual analogues (Multiple VAS); an one-item, likert-type scale: the multidimensional, 45-item, Cocaine Craving Questionnaire (CCQ-Now); and a new, 14-item brief version of the CCQ-Now. Participants were 13 volunteers who had completed at least three weeks of a 12-week program of cognitive-behavioral-inlerpersonal counseling for the treatment of cocaine abuse and dependence. The Multiple VAS detected significant decreases in craving and wanting, and increased needing cocaine among participants at the end of the three week monitoring period. The craving VAS and the likert-type craving scale were superior at predicting positive urines and self-reported cocaine use over the short-term (one week before or following monitoring), although the strongest association was found between use in the last seven days and current intensity levels of cocaine craving. Baseline scores on the four factors (dimensions of craving) from both versions of the CCQ-Now were the best predictors of future use over the long-term (entire three weeks), with partial correlations indicating that Compulsivily (Factor 3, "obsessive craving") represented the greatest independent contribution to this relationship. Significant intercorrelations existed among all craving measures, although each questionnaire was tapping different aspects of cocaine use. Researchers should consider using more than one measure of cocaine craving to assist in cross-study comparisons.

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COCAINE CRAVING: A REAL-TIME NATURALISTIC EVALUATION

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Craving is a popular term which has been poorly defined and measured. Most clinical data on craving in cocaine dependent patients has been collected retrospectively, and thereby subject to various methodological flaws. To overcome past limitations, the authors developed a method of collecting real-time descriptive data in the natural environment about immediate events surrounding cocaine craving episodes. The purpose of this study is to: 1) examine direct antecedents of cocaine use (both cognitive and behavioral), 2) identify various situational factors and their relationship to cocaine craving, and 3) explore the relationship between craving and baseline psychosocial variables (e.g., affect, coping skills, etc.). It is hypothesized that craving intensity will be the highest in cocaine dated situations versus non-cocaine-related situations. Subjects were given measurement booklets for recording craving, mood states, situations, and activities between the hours of 8:30 a.m. to 9:30 p.m. Subjects were instructed to record information at 5 randomly pre-selected times, in temptation situations, and after a cocaine using episode. Subjects call in their responses to a voice-mail telephone system that documents the time and date of the call. Data collected so far suggests good compliance, as indicated by a mean response time of 16 minutes (SD=24) following randomly scheduled time points. Data also reveal that subjects report greater craving intensity during temptations assessments versus random assessments. Pilot data utilizing an electronic pager to prompt recording will also be presented.

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RETROSPECTIVE ASSESSMENT OF DRUG AND NON-DRUG CRAVING STATES IN SUBSTANCE ABUSE PATIENTS

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Abused drugs act through brain substrates common to natural rewards such as food and sex, but the relationships among the "cravings" (learned incentives) for drug and non-drug rewards has not been systematically studied. The purpose of the ongoing study was to examine the relationships among drug, food, sexual cravings, and activities in patients seeking treatment for cocaine or alcohol dependence. We developed the Retrospective Assessment of Craving (RAC) interview to document these. cravings and activities over the six weeks prior to admission, using a timeline follow-back approach. Upon completion of the RAC calendar, patients (50 thusfar) were also asked to compare the pleasure states and craving states across all three categorie, and to rate the likelihood that craving a activity in one category could lead to craving or activity in another. Drug craving and drug use were commonly reported as co-occurring (on the same day). Across the six week period prior to admission, nearly half of the patients reported neither craving nor use on a given day. This pattern actually increased in the weeks closest to treatment admission. This may reflect a real decline in drug use for a subset of those planning to seek treatment, or possibly a demand effect of the interview situation. The demand effects of the instrument will be explored through prospective data collection with concomitant urinel/breathalyzer data. Men reported experiencing similarities between drug and sex-related states at double the frequency that women reported these experiences. Women reported that craving and use of cocaine or alcohol to be at its greatest at menses, while their sexual craving and activity were highest at the late luteal stage of the menstrual cycle.

FREQUENCY OF AVERSIVE EVENTS IN COCAINE-DEPENDENT OUTPATIENTS

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Behavioral theory posits that a low density of alternative non-drug reinforcement. and perhaps a high density of aversive events, increases vulnerability to drug abuse. while there is relatively extensive empirical support for this position from controlled laboratory studies, there is little evidence from studies conducted in naturalistic settings. In an initial study on this topic using the Pleasant Events Schedule (PES), cocaine-dependent patients reported engaging in a significantly lower frequency of potentially reinforcing events than controls (Van Ellen *et al.,* 1996). The present study was conducted using the Unpleasant Events Schedule (UES) to examine whether cocaine-dependent patients report a higher frequency of aversive events in their everyday lives than controls. The PES and UES are behavioral inventories originally developed to measure the density of potentially reinforcing and punishing events in the lives of depressives (Lewinsohn and Amenson, 1978). In the present study, the UES was administered to 53 cocaine-dependent adults 24 weeks after they entered outpatient treatment. We found little evidence that cocaine-dependent patients experience a higher density of unpleasant events than conlrol subjects. Cocaine-dependent patients differed significantly from normative controls on only 3 of the 9 UES subscales. Among those 3 subscales, only the scale dealing with legal issues clearly supported a greater frequency of aversive events for the cocaine-dependent sample, and even then the difference was only significant for younger subjects (i.e., age by group interaction). We only assessed the frequency of aversive events in this study and not the degree of aversiveness of the events. Prior studies in deposed individuals suggest that the latter may be important in distinguishing impaired subjects from controls. Overall, then, the present study found little evidence that cocaine abusers experience a greater frequency of unpleasant events than control subjects, but further research is needed to determine whether the degree of aversiveness of the unpleasanl events experienced might be greater in cocaine abusers.

SITUATIONAL CONFIDENCE QUESTIONNAIRE SCORES AS PREDICTORS OF TREATMENT OUTCOME AMONG COCAINE-DEPENDENT OUTPATIENTS

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Measures of patients' confidence in their ability to abstain from drug use in high-risk situations (i.e., situational confidence) have predicted treatment outcome across various types of drug abuse. We have been studying baseline situational-confidence as a predictor of treatment outcome among cocaine-dependent adults receiving therapy combining the community reinforcement approach (CRA) and vouchers. This report describes results from a recently completed clinical trial in which 70 cocaine-dependent adults were randomized to receive CRA-plus-vouchers contingent on cocaine abstinence or CRA-plus-vouchers delivered independent of cocaine use. A modified version of the Situational-Confidence Questionnaire (SCQ) was administered at 1, 6, 12, and 24 weeks after treatment entry. We examined (a) whether subject or drug-use characteristics at intake predicted baseline SCQ scores, (b) whether baseline SCQ scores predicted during-treatment cocaine abstinence, and (c) whether changes in confidence during the course of treatment predicted or were predicted by cocaine abstinence. Greater number of self-reported grams of cocaine used per week at intake and having ever smoked cocaine were the two predictors of baseline SCQ scores ($r = -.35$, $p<.001$; $r = -.28$, $p<.01$). Baseline SCQ scores did not predict cocaine abstinence for patients overall ($r = .22$, $p=.07$), but did so for those assigned to the contingent-vouchers group ($r = .51$, $p<.001$). Lastly, cocaine abstinence achieved during wks. 1-6, 1-12, and 1-24 was a stronger predictor of situational-confidence measured at the end of those specified periods than the converse. These results provide important new information on the dynamic relationships between situational confidence and cocaine use in cocaine-dependent outpatients.

DIFFERENCES IN PRE-TREATMENT SUBSTANCE ABUSE AND SYMPTOMS, TREATMENT DROPOUT AND RELAPSE IN COCAINE ABUSERS

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Differences in the number and nature of substances used in the thirty days prior to treatment entry among primary cocaine abusers (n=217) were examined in relation to differences in symptom expression, treatment dropout, and rates and patterns of relapse. The additional use of alcohol, or alcohol and marijuana by primary cocaine abusers was not related to increased symptom expression as measured by MCMI-II scales of Major Depression, Anxiety, and Bipolar Manic, higher rates of treatment dropout, nor higher overall rates of relapse. Cocaine only users (n=60), cocaine/alcohol users (n=94), and cocaine/alcohol/Marijuana (n=63) users evidenced subclinical symptom levels on MCMI-II scales of Major Depression (BR=69.69), Anxiety (BR=68.26), and Bipolar: Manic (BR=72.17). Treatment dropout rate averaged 22.6% across the three groups. Rams of relapse (34.3%) and lost to follow up (37.6%) were similar across the three groups over four, 3-month follow up periods (i.e. subjecls tracked 12 months post-treatment). Among relapsers, those classified as cocaine only users at treatment intake relapsed to alcohol (exclusively, prior to, or concurrent with first relapse to cocaine) much less frequently than cocaine/alcohol or cocaine/alcohol/marijuana users. Also among relapsers. those classified as cocaine only users at treatment intake relapsed to fewer substances than cocaine/alcohol/marijuana users.

CRACK COCAINE, ALCOHOL, AND OTHER DRUG USE PATTERNS AMONG HOMELESS PERSONS

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Alcohol or other drug use may be a trigger for cocaine use and a barrier to recovery. This study examined the co-Occurrence of cocaine, alcohol and other drug use among treatment seeking homeless persons to determine whether cocaine use occurred differently with alcohol than other drugs. It was hypothesized that less alcohol use is associated with less cocaine use among homeless persons and that there is a greater relation between crack cocaine and alcohol than between crack cocaine and other drugs. Subjects (N=49) participated in a treatment outcome study that measured alcohol and other drug use by the Addiction Severity Index (days used in the past 30 days) at intake. Subjects were 76.4% male and 82.7% African American with an average age of 38.2 (SD=7.4) years. Results from bivariate analyses revealed a moderate correlation between days alcohol and days cocaine use ($r=0.38$, $p<.006$) and low correlations between days marijuana use and cocaine use ($r=0.23$, $p<.10$) and days other drug use and cocaine use ($r=0.18$, $p<.20$). Multiple regression analyses showed that 14.6% of cocaine use frequency was predicted by alcohol use (R-squared=.146) and that adding other drug use (including marijuana) into the regression equation added little to the predictive power (R-squared=.148). These results suggest that crack cocaine use is positively related to alcohol use among homeless persons seeking treatment. Results also suggest that a greater association exists between crack cocaine and alcohol than between crack cocaine and other drugs. This supports the notion alcohol use can be a more important precursor to crack cocaine use than other drug use. These findings with crack smoking are consistent with recent studies showing alcohol use can be a precursor to intranasal and IV cocaine use as well.

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ABSTINENCE CONTINGENCY MAY POSITIVELY IMPACT HOMELESS CRACK ADDICTS' NON-DRUG RELATED ACTIVITIES

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A decrease in non-drug related activities and friendships is a drug use correlate and complaints of too much free time are common. Improvements in these domains are often predictive of rehabilitation. The Rehabilitation Checklist (RC), a six item questionnaire regarding activities, friendships, and time allocation, was administered al baseline and 2 month follow-up to 106 homeless crack cocaine using subjects who enrolled in a treatment program comparing the efficacy of day treatment (DT) (n=46) to day treatment with abstinent contingent housing (DT+) (n=60). It was hypothesized that all subjects would evidence improvement from baseline to two month follow-up on the major dimensions of the RC: number of friends, percentage of friendships with drug abstainers, number and frequency of non-drug related activities engaged in weekly, and satisfaction with activities and free time. Day treatment significantly improved the number of friendships, friendships with drug abstainers, weekly activities, satisfaction with activities, and satisfaction with free time for all subjects regardless of condition. Additionally, paired T-test revealed that DT+ demonstrated greater changes in weekly activities (DT + mean change = 2.3 vs. DT mean change = 1.4. p =.02). The DT+ group showed greater improvement on a composite variable requiring subjects to engage in at least 3 activities weekly, and report satisfaction with activities and bee time (48% change DT vs. 68% change DT+ p=.03). DT+ subjects demonstrated greater although not statistically significant improvements on most other dimensions. While day treatment alone (DT) positively impacts quality of life variables related to rehabilitation, such as friendships and activities, the addition of abstinent contingent housing (DT+) may increase this effect. especially with regard to number of activities engaged in and satisfaction with activities and free time. This implies that abstinent contingent housing may be useful for impacting variables associated with sustaining abstinence such as non-drug related activity and free time.

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MEASURES OF TEMPERAMENT AMONG DRUG ABUSERS IN TREATMENT

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Little information is available regarding temperament and relationship to outcome of treatment for drug abuse. We evaluated temperament using the NEO Personality Inventory. an instrument assessing dimensions of temperament in three primary domains: neuroticism, extraversion and openness. Each domain consists of 6 scales. Two additional domains are assessed, agreeableness and conscientiousness. but do not have subscales. Subjects were drawn from an oulpatienl community mental health treatment program and included a subgroup of subjects participating in a pharmacologic trial of desipramine, carbamazepine or placebo. The NEO was administered at treatment entry and at 6-month follow-up. Subjects participated in 10 hours of group and individual treatment weekly. The Addiction Severity Index was administered at treatment entry and al 6-month follow-up. Subjects in both groups had high scores on the Neuroticism (N) scale; in the psychosocial--treatment only group, high N scale scores correlated with higher ASI composite scores on drug use and treatment need at 6 month follow-up. Significant differences occurred at baseline among the pharmacotherapy groups on many of the NEO scales; these outcome data will not be presented al this time. Retention in treatment was generally not predicted by NEO scales.

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A THERAPIST ADHERENCE MEASURE FOR AN ANGER MANAGEMENT TREATMENT FOR SUBSTANCE ABUSERS

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We have developed a 12-week cognitive-behavioral anger management treatment (AMT) for substance abuse patients that produces reductions in the disposition to experience anger (Reilly *et al.,* 1995, 1996, 1997). The delivery of the AMT was manual-guided. We developed a therapist adherence coding method and we are currently using the method to assess therapist adherence in 10 cohorts of group participants. In this presentation, we discussed how the method for coding therapist adherence was developed and reported preliminary findings from two cohorts. The therapist adherence method assesses both the content and the process of patient-therapist interactions. Each treatment session consists of a structured didactic teaching component and a more open-ended check-in component where therapists deliver cognitive-behavioral interventions. An independent rater was trained to code audiotapes of AMT sessions. Rater "drift" was assessed by a study investigator who did not serve as a study therapist. Inter-rater agreement was adequate (r = .79). In the two cohorts that were rated, about 60% (58% and 52%) of the concepts prescribed by the treatment manual were delivered in the didactic teaching component, and about 30% (23% and 29%) of the patient-therapist interactions during the check-in component consisted of interventions prescribed by the treatment manual. We discussed procedures we have used to improve therapist adherence.

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ANGER MANAGEMENT TREATMENT: COMPARISONS AND FOLLOW-UP

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We demonstrated that a 12-week cognitive-behavioral anger management treatment (AMT) reduced levels of anger in cocaine abusing patients (Reilly *et. al.,* 1996). In addition to AMT. patients were enrolled in standard substance abuse treatment. It is possible; however, that standard substance abuse treatment may have produced the observed reductions in anger, rather than the AMT. To examine this hypothesis, we examined reductions in anger in a comparison group (n = 10) of patients enrolled in standard substance abuse treatment. Trait-anger and anger-expression were measured at baseline and at 12-week follow-up. Trait-anger did not change, while anger-expression actually increased, suggesting that AMT produced reductions in anger rather than mere enrollment in a substance abuse treatment program. A second issue we addressed concerned levels of bait-anger and anger-expression at a 3-month post-treatment follow-up. Trait-anger and anger-expression did not increase, and remained significantly ($p < .001$) lower than baseline. These findings suggest that an anger management treatment is an important component of sustance abuse treatment that warrants further study in controlled clinical trials.

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COCAINE-RELATED CHANGES IN BRAIN BLOOD FLOW

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Previous studies of cocaine-related changes in brain blood flow (BBF) have been conducted with semi-quantitative Single Photon Emission Computerized Tomography (SPECT). Semi-quantitative SPECT does not allow for measurement of absolute blood flow, and hence the correlation between reported changes in behaviors and BBF using this technique are not well characterized. Here, we present the results of a new quantified technique for measuring absolute BBF to specific brain regions during drug-taking. We found that in cocaine dependent subjects, cocaine in comparison with placebo was associated with reductions in total BBF, and in reduced perfusion to areas rich in dopaminergic innervation (e.g. putamen, superior temporal lobe, prefrontal cortex). These results demonstrate the development of a new quantified technique for measuring absolute BBF using SPECT, and some relatively specific blood flow changes during cocaine-taking.

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SPECT FOLLOWING IV PROCAINE IN COCAINE ADDICTION

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Previous investigators have suggested that a state of permanent limbic neuronal hyperexcitability may be present in cocaine addicts, such mat spontaneous or cue-related episodes of limbic neuronal discharge may result in craving. In order to explore this phenomena, we administered the limbic stimulus procaine to cocaine addicted patients and controls. **Methods:** Twelve healthy controls (9 men, 3 women) and twelve patients with only cocaine dependence (9 men, 3 women) were studied. Patients were 2-3 weeks abstinent. In two study sessions separated by 48 hours, saline (1st) and procaine (1.38 mg/kg) (2nd) were administered intravenously (single blind), immediately followed by the tracer ^{99m}TcHM-PAO. A SPECT scan was obtained 90 min. after injection. rCBF was assessed both by t-image analyses (Devous) and SPM (George). Subjective responses were assessed by analog scales (1-6). **Results:** Controls endorsed significantly greater drug effecf, "bad" drug effect, and "dislike" of drug compared to patients. Patients (n=5) demonstrated significantly ($p<0.01$) greater rCBF in anterior cingulate, inferior frontal, mesial temporal, brainstem, occipital, and cerebellar regions compared to controls (n=5). Total lifetime days of cocaine use was significantly correlated with brainstem (r=0.88) and right lateral temporal (r=0.69) procaine-induced activation. Areas of increased rCBF following procaine are distinctly different than those reported following cocaine. **Discussion:** These preliminary data suggest different biologic and subjective responses to procaine in cocaine addicted patients and controls. Greater limbic rCBF in patients offers tentative support for the sensitization hypothesis.

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[^{123}I]ß-CIT SPECT IMAGING OF DOPAMINE TRANSPORTER AVAILABILITY IN MAZINDOL-TREATED COCAINE ADDICTS

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The *in vivo* potency of mazindol for binding to striatal dopamine transporters (DAT) was assessed by [^{123}I]ß-CIT ([^{123}I]2ß-carbomethoxy-3ß-(4-iodophenyl)tropane) single photon emission computed tomography (SPECT). Cocaine-dependent subjects (n=6) underwent three SPECT scans, one before, between, and after subchronic (1 week) administration of 2 mg/day and 4 mg/day mazindol. For each scan, subjects were injected with [^{123}I]ß-CIT and imaged 24 h later under equilibrium conditions. Measurable reductions in the specific to nondisplaceable equilibrium partition coefficient, V_3" (which is proportional to DAT binding potential), were observed in only 4 of 6 subjects. A statistically significant effect for dose was found in this subset ($df = 2$, $F = 72.05$, $p < 0.001$, repeated measures ANOVA), but not in the entire group ($df = 2$, $F = 1.12$, $p = 0.37$). Regression analysis of the logit transformed data in the subset enabled estimation of the 50% displacement dose of mazindol ($ED_{50} = 21$ mg/day). These data suggest that low doses of mazindol (i.e., 2-4 mg) occupy a small percentage (i.e., < 25%) of DAT in human cocaine abusers and that much higher, potentially intolerable doses (i.e.,≥ 20 mg/day) may be required to antagonize cocaine binding *in vivo*.

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"BINGE" PATTERN ADMINISTRATION OF COCAINE ALTERS [^{11}C]ß-CIT BINDING IN THE RAT BRAIN AS MEASURED BY PET

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The effects of acute (2 days) and chronic (14 days) "binge" pattern cocaine administration, and also withdrawal from chronic cocaine, on the dopamine transporter (DAT) were evaluated in the living rat brain using a high resolution positron emission tomography (PET). Male Sprague-Dawley rats were injected in a "binge" pattern three times at 1-hr intervals with saline or cocaine (15 mg/kg) each day for 2 or 14 days. Furthermore, rats which received chronic "binge" cocaine were withdrawn 1, 10 or 21 days with no injections of cocaine. The *in vivo* binding of [^{11}C]ß-CIT, an analog of cocaine. in the striatum was measured by PET. Neither acute nor chronic administration of saline affected the [^{11}C]ß-CIT binding in any conditions. The binding of [^{11}C]ß-CIT was significantly reduced by either acute or chronic "binge" cocaine administration. In rats which received acute "binge" cocaine administration, the binding of [^{11}C]ß-CIT returned within 4 hr to basal levels as observed in saline administered rats. In contrast, in rats which received chronic "binge" cocaine, the binding of [^{11}C]ß-CIT was significantly lower up to 1 day after the last cocaine injection than in saline rats. During the withdrawaI period, the binding of [^{11}C]ß-CIT increased slightly, but significantly 10 days after the last cocaine injection, then returned to the basal level after 21 days of withdrawal. These results indicated that DAT availability in rat striatum was physiologically altered by chronic "binge" pattern cocaine administration and also by withdrawal from cocaine.

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EFFECTS OF WITHDRAWAL FROM BINGE PATTERN COCAINE ADMINISTRATION ON DOPAMINE D_1 AND D_2 RECEPTORS IN THE RAT BRAIN AS MEASURED BY PET

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Previous studies from our laboratories have shown that administration of cocaine to rats in a "binge" pattern for 14 days results in a significant decrease in binding of both D_1 and D_2 dopamine receptor antagonists in the striatum (Tsukada *et al.,* 1996). The present study investigated the effects of short-term and more prolonged withdrawal from cocaine on *in vivo* binding of [^{11}C]SCH23390 and [^{11}C]N-metbylspiperone to D_1 and D_2 dopamine receptors, using positron emission tomography (PET). Adult male Sprague-Dawley rats were injected with saline or cocaine HCl (15 mg/kg) three times daily, at 1-hr intervals, starting 30 min. after the start of the light cycle, for 14 days. PET scans were performed to measure D_1 and D_2 receptors on the 14th day of cocaine administration. and 1 and 10 days after the last cocaine injection. Fourteen days of binge pattern cocaine injections produced a significant reduction in D_1 and D_2 dopamine receptor binding, confirming our previous findings. After 1 day of withdrawal, a significant decrease in the binding potential of [^{11}C]SCH23390 was still found in the striatum. However, after 10 days of withdrawal, the binding potential of [^{11}C]SCH23390 returned to normal. After 1 day of withdrawal, a significant decrease in binding of [^{11}C]N-methylspiperone was also found in the striatum. Even after 10 days of withdrawal, the binding to D_2 receptor was still significantly reduced, showing that full recovery from the effects of cocaine on D_2 receptors had not yet occurred.

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EFFECTS OF LONG-TERM WITHDRAWAL AFTER CHRONIC BINGE COCAINE ON *IN VIVO* D_1 AND D_2 DOPAMINE RECEPTOR BINDING USING POSITRON EMISSION TOMOGRAPHY

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Our previous positron emission tomography (PET) studies detected a decrease of *in vivo* binding immediately following chronic (14 days) binge cocaine administration (CBC) for both [1C]SCH23390, a D_1 dopamine receptor antagonist, and [^{11}C]N-methylspiperone (NMSP), a D_2 dopamine receptor antagonist. The decrease in [^{11}C]SCH23390 binding levels returned to control levels after ten days of withdrawal from CBC, while the decrease in [^{11}C]NMSP binding was still observed after ten days withdrawal. The present study was designed to determine the effects of a longer, 21 day withdrawal period on [^{11}C]SCH23390 and espcially [^{11}C]NMSP binding, Previously studied timepoints, immediately following CBC and after 10 days of withdrawal, were also repeated for both [^{11}C]SCH23390 and [^{11}C]NMSP binding in the present study. The present study confirmed that both [^{11}C]SCH23390 and [^{11}C]NMSP binding were decreased immediately following CBC and that the decrease in [^{11}C]SCH23390 binding levels returned to control levels after ten days of withdrawal from CBC, while the decrease in [^{11}C]NMSP binding was still observed after ten days withdrawal. Furthermore, [^{11}C]SCH23390 binding was still at control levels after 21 days of withdrawal. The present data show that after 21 days of withdrawal from CBC [^{11}C]NMSP binding returns to control levels. This suggests that the change of *in vivo* [^{11}C]NMSP binding to D_2 dopamine receptors following CBC lasts longer than 10 days and therefore requires a longer period of abstinence for normalization. This finding indicates that the plasticity of *in vivo* D_2 dopamine receptor binding is different from that observed in D_1 dopamine receptor binding and may be important for development of pharmacotherapies for cocaine dependent patients. REFERENCES: Tsukada, H.; *et al.,* J. Neurosci., 16(23):7670-7677.

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COCAINE-INDUCED CEREBRAL BLOOD VOLUME REDUCTION IN FEMALES

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This study used dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) to dctermine the effect of intravenous cocaine on cerebral blood volume (CBV) in female subjects. Using data from a previous DSC MRI study of 9 age- and cocaine use-matched males, we also searched for gender differences. Healthy female subjects (N=8, aged 27±2 years) reporting casual cocaine use (7±3 lifetime exposures) participated during the follicular phase of their menstrual cycle. CBV was determined in an axial whole brain slice using a steady-state method with four injections of gradoteridol (0.075 mmol/kg). Baseline CBV was determined from the area under the third bolus curve. Cocaine (0.4mg/kg, i.v.) was administrered 10 minutes prior to the final bolus injection. Cocaine significantly increased heart rate (170%±8%) (mean±SE) and blood pressure (120%±5%), and reduced contrast arrival time (a measure of blood flow velocity) ($p<0.0001$). CBV was reduced following cocaine administration (29%±5%) ($p<0.008$). In males, CBV was also reduced (20%±5%) ($p<0.006$). The gender difference in cocaine-induced reduction of CBV was not statistically significant, suggesting that cocaine administration leads to comparable degrees of vasoconstriction in men and women. A gender difference in the severity of perfusion abnormalities in chronic cocaine-abusers has been reported, with females experiencing fewer defects than their male counterparts. The present finding suggests that these differences are not explained by differences in vasoconstriction.

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LONG-TERM DOWN-REGULATION OF DOPAMINE D2 RECEPTORS FOLLOWING COCAINE SELF-ADMINISTRATION IN MONKEYS

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The reinforcing effects of cocaine are believed to be mediated, in large part, through the dopaminergic system. Positron Emission Tomography (PET) studies in humans have shown a persistent decrease in D2 binding potential in cocaine abusers abstinent from cocaine for up to 4 months, compared to age-matched controls (Volkow *et al.,* Synapse, 1993, 14:169). The purpose of the present study was to 1) evaluate the effects of long-term cocaine exposure, using PET, in a monkey model of cocaine abuse, in which drug history could be controlled and 2) to extend the cocaine withdrawal period to better determine the long-term consequences of cocaine self-administration. PET studies using the D2 ligand [^{18}F]4-fluoroclebopride (FCP) (Mach *et al.,* Synapse, 1996, 24:322) were conducted in three adult mate rhesus monkeys with an extensive history of i.v. cocaine self-administration (mean total intake of 17 ± 3 g over - 3 years). PET studies were conducted at abstinence periods of 3 days to 302 days and all data were compared to baselines obtained from cocaine-naive controls (n=6). Baseline levels of D2 binding potential in control monkeys was 3.61 ± 0.58. There was a substantial and persistent decrease in D2 binding Potential throughout withdrawal: 3-7 days: 3.0 (± 0.17), 17-30 days: 3.13 (± 0.06), 90-110 days: 3.07 (± 0.2) and 200-302 days: 2.87 (± 0.05). These data are consistent with previous reports in humans suggesting that chronic cocaine abuse causes long-term alterations in central dopaminergic function and extend this finding to controlled experimental conditions and up to 10 months of withdrawal.

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COCAINE ABUSE ALONE (WITHOUT CONCOMITANT ALCOHOL ABUSE) DOES NOT CAUSE VOLUME CHANGES IN THE CEREBELLUM. COCAINE AND ALCOHOL CO-ABUSE IS ASSOCIATED WITH VOLUME LOSS IN THE DORSAL VERMIS AND THE CEREBELLAR HEMISPHERES: AN MRI VOLUMETRIC STUDY

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In alcohol abusers, brain volume loss has been reported primarily in the superior ventral Vermis and to a lesser extent in the dorsal Vermis and the cerebellar Hemispheres. Concurrent alcohol and cocaine abuse is common. There is no data on the. effect of cocaine abuse on cerebellar volume in humans. We used MRI to examine the effects on the cerebellar volume of chronic cocaine abuse with or without concurrent chronic alcohol abuse. The subjects were abstinent for an average of 20 weeks at the time of image acquisition. Results indicate that in the middle age chronic cocaine abuser who does not also abuse alcohol, no effect on the cerebellar volumes is evident. In the cocaine and alcohol coabuser, the volumes of the cerebellar Hemispheres and the dorsal Vermis are reduced. These findings suggest that cocaine alone has neither permanent nor independent effect on the cerebellar volume. Hither the metabolic and hemodynamic effects of cocaine on the brain are not translated into persistent volume changes in the cerebellum or such effects normalize over 20 weeks of abstinence. Our Cocaine/Alcohol group had a volume loss in the cerebellar Hemispheres and the dorsal but not the superior ventral Vermis. The dorsal Verrnis is preferentially affected by age and the effects in our study were largest in older subjects. Our results suggest increased susceptibility of the dorsal Vermis of the older cocaine/alcohol coabuser to age related volume loss. Absence of volume loss in the superior ventral Vermis in our cocaine/alcohol group could be explained if that region was less affected by age than the dorsal Vermis or has recovered during abstinence.

REFERENCES: Available upon request from the first author.

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MORPHOLOGICAL CHANGES IN OPIOID DEPENDENCE

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Cerebrospinal fluid (CSF) space enlargement has been demonstrated in substance-related disorders like alcohol and cocaine dependence. Experimental animal studies showed a reduction in shape and size of mesolimbic dopaminergic neurons after chronic morphine administration. Other studies indicated a change of neurofilament and glial fibrillary acid proteins after chronic opiate administration. Furthermore, frequent overdosing and toxicological effects of "street"-heroin may lead to CSF space enlargement in opioid dependence. In our study, the pericortical and ventricular CSF space of 21 male opioid-dependent patients was compared with an age- and sex-matched normal control group. Considering serious problems with ratio and proportion measures, we used a battery of linear (cella media index, Huckman number, frontal horn index), planimetric (cortical atrophy score) and stereological volumetric measures in order to detect differences in cranial computerized tomography scans. We found a significant ventricular and cortical brain atrophy in opioid-dependent patients. A higher degree of frontal lobe atrophy seemed to be associated with a shorter period of abstinence before relapse. However, the etiology of brain atrophy in opioid-dependent patients is still unclear, but experimental animal studies provide some evidence that long-term. chronic opiate exposure is associated with visible changes of specific structures in the brain.

EFFECTS OF *IBOGA* AGENTS ON NICOTINE PREFERENCE AND ON NICOTINE-INDUCED DOPAMINE RELEASE IN RATS

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Ibogaine, an alkaloid found in *Tabernanthe iboga,* is claimed to be effective in interrupting dependence on opioids. stimulants, alcohol and nicotine (smoking). While preclinical studies have examined its effects on opioid (morphine), stimulant (cocaine), and alcohol self-administration, only neurochemical interactions of ibogaine with nicotine have been reported. Ibogaine blocks nicotine-induced dopamine release in the nucleus accumbens, similar to its effect on dopamine release induced by morphine. 18-methoxy-coronaridine (18-MC), a novel *iboga* alkaloid congener, mimics ibogaine's effects on morphine and cocaine self-administration without producing typical side effects (e.g., tremor) of ibogaine. We have recently developed an oral self-administration model of nicotine preference in rats. In the present study we compared ibogaine and 18-MC in terms of their effects on nicotine preference and on nicotine-induced dopamine release. Both ibogaine and 18-MC produced dose-related decreases in rats' preferences for nicotine, and 18-MC, like ibogaine, blocked nicotine-induced dopamine release. 18-MC, and perhaps other *iboga* alkaloid congeners, may be potentially useful in smoking cessation programs.

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MATERNAL AND CHILD PREDICTORS OF THE ONSET OF CIGARETTE USE: DATA FROM THE N.L.S.Y. STUDY

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As part of an ongoing study conducted by the U.S. Department of Labor, the investigators of the National Longitudinal Survey of Youth (NLSY) collected data on persons aged 14-22 in 1979. This nationally representative sample has been interviewed annuatly with a retention rate of 89% as of 1994. In 1988, the study was expanded to collect information on the children of this cohort and are interviewed every two years starting at age ten regarding their substance use behaviors. As of 1992. (the most recent data available) there were 2,079 children interviewed for substance use. This sample is 52% male, 41% Black and 24% Hispanic with a mean age of 12.4 years. Nearly a quarter of these children had used cigarettes with their mean age at onset being 10.5. This study examines the risk and protective factors for the onset of cigarette use among children while controlling for both child and maternal variables. High religiosity was protective against the onset of cigarette use particularly for females. Having a close relationship with one's mother was protective for Black. Hispanic, and female children with those reporting a close relationship being half as likely to begin smoking compared to those with a more distant relationship. Non-Black. Non-Hispanic youth were at highest risk for the onset of smoking. Children with a higher number of behavioral problems were more likely to begin smoking. Males had no protective factors and maternal lifetime use of cocaine was the highest risk factor for males to begin smoking. A history of poverty status was a risk factor for the Non-Black, Non-Hispanic group. Maternal history of heavy alcohol use was a risk factor only for Hispanics. Both Non-Black Non-Hispanic children and Hispanic children whose mothers had smoked, were four times more likely to smoke compared to those with non-smoking mothers and as much as nine times more likely. The implications are mat preventive and intervention efforts should take into consideration the unique risk and protective factors for each ethnic and gender group.

SYNTHESIS AND NICOTINE ACETYLCHOLINE RECEPTOR BINDING PROPERTIES OF EPIBATIDINE ANALOGS, POTENTIAL PET AND SPECT LIGANDS

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(-)-Epibatidine [(-)-EB] is a naturally-occurring alkaloid with pM affinity for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nACbR). A new, efficient synthesis of (±)-EB has been developed. This synthesis as well as the syntheses of several EB analogs will be presented. The apparent affinity (K_{app}) of EB and the analogs for the $\alpha_4\beta_2$ nAChR was assessed in competition binding experiments using [^{3}H]norchloroepibatidine. Several analogs possessed affinity for the $\alpha_4\beta_2$ receptor comparable to that of EB. Norchlorofluoroepibatidine shows high specific binding to the nAChR and promise as a PET ligand for me neuronal nicotinic acetylcholine receptor.

ACKNOWLEDGMENT: Supported in part by a Tobacco Research Council grant.

RAT MODELS OF DRUG-SEEKING RELAPSE FOR ETHANOL OR NICOTINE

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The reexposure to drug-related stimuli or to the drug itself are important determinants of drug-craving. Therefore, it appears that the experimental manipulation of these factors is crucial for the induction of drug-seeking behaviour in laboratory animals. In a first set of experiments a tone was paired (600dB) with oral 8% ethanol (male Long Evans rats) or intravenous 0.03 mg/kg nicotine (male Wistar rats) self-administration. When stability of responding for drug self-administration was obtained, drug availability was discontinued and extinction developed (4-14 sessions). The reexposure to the tone, but not of the drug, induced a significanl reinstatement of responding for the drug-paired lever in me nicotine but not in the ethanol self-administration group. In a second set of experiments, with a similar protocol of between-session extinction, we tested me effect of drug reexposure to rats with extinguished responding for oral ethanol or intravenous nicotine. Reexposure to a limited amount of ethanol (0.18ml of 8% ethanol) caused resumption of responding on the drug-associated lever. This effect was reduced by single pretreatment with naltrexone 10mg/kg ip, a drug reported to be effective against craving for alcohol, We also observed that non-contingent nicotine priming induced reinstatement of responding. Reinstatement was not significant after priming with the 0.03 mg/kg training dose of nicotine. On the other hand, a marked and significant reinstatement was observed with lower doses (0.001, 0.003 or 0.01 mg/kg) of nicotine priming. Interestingly, nicotine priming after a within-session extinction did not induce reinstatement of responding (0.01, 0.03 or 0.06 mg/kg nicotine) suggesting a lack of responsiveness to the nicotine stimulus few hours after the end of me nicotine self-administration session (2-5 hrs). In conclusion, these studies show that the presentation of drug-related CS and drug-priming are able to induce drug-seeking in rats even after a long period of abstinence and suggest that the use of these models might predict the efficacy of novel anticraving therapies.

ACCU DROP: TESTING A SMOKING CESSATION AID

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A preliminary open trial examined the efficacy of a 6 week nicotine fading protocol using a non-pharmacologic agent, ACCU DROP in combination with cigarette tapering and brief motivational enhancement counseling. ACCU DROP is an FDA approved corn syrup based food additive which is purported to trap a proportion of the nicotine and tar when applied to cigarette filters. The subjects were 13 women and 5 men who smoked an average of 15 cigarettes daily (cpd). Subjects were seen weekly by a Ph.D. therapist for 20-30 minutes. The therapist used a motivational enhancement approach to encourage Ss to declare their own plan for smoking cessation while using the product, encouraged Ss to incrementally increase on a bi-weekly schedule the number of drops applied per cigarette, offered the suggestion of decreasing the cpd in combination with using the drops, and monitored adherence to the protocol. Sixty seven per cent (67%) of the Ss completed the six week protocol. Fifty per cent (50%) of the Ss (9/18) reported nonsmoking at the end of the projected six weeks of treatment and 39% (7/18) reported being continuously smoke-free one month later confirmed by CO readings <.009. There were no reports of increased craving. Subjects reported satisfaction with the treatment and adherence to smoking cigarettes treated with the ACCU DROPs. These preliminary findings support the potential utility of this alternative treatment approach.

TIME-OF-DAY OF RELAPSE DURING NICOTINE PATCH SMOKING CESSATION TREATMENT: ANALYSIS OF SUBGROUPS

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The overall results from a large scale (N=220), randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a nicotine patch (Nicotrol) have been presented by Sachs, *et. al.,* in Arch Int Med, 1993. Using these data, we have performed further analyses, on only those subjects who lapsed to evaluate, on the day of first lapse, the time-of-day when the first cigarette was smoked. Three predictors of lapse were studied: treatment condition (active or placebo patch), sex, and degree of nicotine dependence (FTQ score: high $\geq$ 7 or low $\leq$ 6). Prior to target quit day, mean time of first cigarette of the day was 07:23±148 min (±1 SD). On the day of first lapse, for the active group, time of first cigarette was 16:02±321 min for low dependency women; 11:53±309 min for high dependency women; 09:49±31 min for low dependency men; and 12:28±317 min for high dependency men. In the placebo group, time of first cigarette was 14:11±320 min for low dependency women; 13:45±309 min for high dependency women: 13:21±360 min for low dependency men; and 11:32±226 min for high dependency men. For all eight subgroups, time-of-day of first cigarette on day of first lapse was significantly later than prior to target quit day. Analysis of covariance of time of first cigarette on day of first lapse showed a significant three way interaction between treatment condition. sex and degree of nicotine dependence ($P < 0.05$). Furthermore, there was a near-significant three way interaction on the second lapse day ($P = 0.08$) and a significant three way interaction on the third lapse day ($P = 0.01$). Our results show that low dependency women ex-smokers receiving nicotine patch treatment lapse significantly later in the day than all other subgroups.

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CORTISOL SYNTHESIS INHIBITION IN HEAVY SMOKERS

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Animal studies strongly suggest an interaction of the stress hormone corticosterone with dopaminergic pathways in determining vulnerability to drug self-administration. Animals prone to self-administer drugs have a prolonged corticosterone response to stress, and administration of corticosterone to non-self-administering animals enhances the development of drug self-administration. Conversely, inhibition of corticosterone through surgical or pharmacologic intervention reduces drug/alcohol self-administration. In this study, the effects of ketoconazole on smoking behavior was evaluated in a double-blind crossover design with heavy cigarette smokers. Ketoconazole is a commonly used antifungal medication that also inhibits cortisol syntheses. Participants engaged in two (2), three hour sessions in which they completed inventories of mood and craving, gave carbon monoxide readings, and smoked ad-lib using a cigarette-holder device measuring number and duration of puffs taken. Active and placebo sessions were conducted two weeks apart (4 weeks for women) following one week of either placebo or ketoconazole medication. Subjects were five men and two women who were current smokers and smoked an average of 26.3 cigarettes/day. Five of the subjects received 400 mg. ketoconazole q.d. and two received 400 mg. b.i.d. (800 mg/day). Preliminary analyses indicate that ketoconazole had no significant effect on the number of cigarettes smoked, the number of puffs taken, total puff duration, or seconds per puff. Withdrawal as measured by the Schiffman scale did not differ on ketoconazole vs. placebo days, nor did the change in withdrawal, CO level, or craving from pre- to post-smoke. Inclusion of more subjects at the higher dose of ketoconazole may be necessary to fully evaluate the potential efficacy of cortisol synthesis inhibition in reducing cigarette intake. In line with animal findings, cortisol synthesis inhibition may be more useful in relapse prevention than in smoking or drug cessation.

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CIGARETTE SMOKING DURING EARLY COCAINE ABSTINENCE

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Some, but not all, studies have reported increased cigarette smoking for 1 to 3 hours after a single dose of a psychomotor stimulant, but there are no studies of smoking patterns during early cocaine abstinence. We addressed this issue by assessing, with computerized cigarette dispensers, the ad lib smoking behavior of 12 cocaine-dependent (DSM-III-R criteria) cigarette smokers (4 nicotine dependent no other current substance dependence, 11 with Fagerstrom Tolerance Questionnaire scores > 5) housed on a closed research ward for another study. Prior Studies validated that dispensing was an accurate reflection of actual cigarette smoking. Subjects (8 African-American men, 3 white men, 1 African-American woman) self-reported pre-admission mean [S.D.] daily 17.0 [10.3] cigarettes smoked, mean age of 33.8 [6.1] years, and a mean last cocaine use of 0.6 [0.7] grams 1.8 [1.3] days prior to admission. There was no significant difference between self-reported preadmission daily cigarettes smoked and the number of cigarettes dispensed daily on the research ward over the first 7 days (prior to start of other study). These findings suggest that early cocaine abstinence does not significantly alter ad lib smoking in a residential setting.

RECOVERING ALCOHOLIC VS NONALCOHOLIC SMOKERS

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Approximately 80% of recovering alcoholics smoke. Whether these smokers need more intensive or a different therapy for smoking cessation is unknown. To begin to answer this question, smokers with and without a history of alcoho1 dependence were compared (Pos Hx and Neg Hx, respectively). Subjects were recruited from prior studies and from ads. Inclusion criteria were (a) no current symptoms of alcohol dependence (last year SADD score $\leq$ 9; Davidson and Raistrick, 1986) and (b) an interest in quitting smoking in the next 6 months. Subjects with SADD scores $\geq$ 9 for the period prior to the last year were designated Pos Hx Ss and those with a prior SADD score of $\leq$ 9 were designated as Neg Hx Ss. The groups were age and sex matched. Each subject completed a 45 minute smoking history questionnaire. Pos Hx Ss scored higher on a nicotine dependence scale (FTQ; Fagerstrom and Schneider. 1989; 7.8 vs 6.2, $p < .001$), and on a Craving/Addiction scale (from the SCQ; Copeland, Brandon, and Quinn, 1995; 7.9 vs 7.2, $p < .05$). They also rated themselves as marginally more addicted than the Neg Hx Ss (9.2 vs 8.4 on a 10 pt scale; $p < .06$). However, they did not rate Addiction Barriers (from the BSC; MacNee and Talsma, 1995) as more important in contributing to the difficulty of smoking cessation than the Neg Hx Ss. Pos Hx Ss rated External Barriers (a measure of social support/intluences) as more important than did Neg Hx Ss. Pos Hx Ss did not have more smokers in their households than Neg Hx Ss. Results suggest Pos Hx Ss especially should receive nicotine replacement and will probably need more intensive therapy, particularly one that targets social influences and support.

REFERENCES: Available upon request from John Hughes.

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OPEN TRIAL STUDY OF TRANSDERMAL NICOTINE REPLACEMENT THERAPY IN SMOKERS WITH COMORBID MENTAL ILLNESS

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Nicotine dependence is more common in the mentally ill population than in the general population. However, there are few studies of smoking cessation in this population. This open label smoking cessation trial compares 36 subjects (PATCH) who chose eight weeks of transdermal nicotine replacement to 23 subjects (NO PATCH) not electing to use nicotine replacement at a community mental health center in an urban setting. All subjects received psychosocial treatment at least once per week. The schedule for transdermal nicotine replacement was 21mg/d x 4 wks, then reduced to 14 mgs/d x 2 wks, and finally 7 mgs/d x 2 wks. Variations from this schedule are noted and evaluated in the results. Subjects included fifty-nine smokers (68% female(n =41), 82% Caucasian (n=49), mean age=44.5) with comorbidity for either schizophrenia(n=19), depression(n =16), bipolar d/o(n=17), or schizoaffective d/o(n =7). No significanl difference was noted between the two study groups in age, race, or Fagerstrom scores. However, in the PATCH group there were 2.1 times the attempts at abstinence than the NO PATCH group (7.2 to 3.4 times respectively). Twenty two percent of the PATCH group bad achieved at least 3 months abstinence compared to only 4% of the NO PATCH group. In addition, only 8% of the PATCH group remained unchanged at the conclusion of the study compared to 48% of the NO PATCH group. Notably, there was little difference in treatment outcome between types of mental illness, however individual sample sizes were small. These results lend evidence for improved outcome with the use of nicotine replacement in this population.

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EFFECTS OF AN ALTERNATIVE REINFORCER AND VARYING RESPONSE REQUIREMENT ON SMOKING BY SCHIZOPHRENICS

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Cigarette smoking and drug abuse are more prevalent among schizophrenics than the general population. In the present study, we used a behavioral-economics approach to examine the effects of varying response requirement and availability of an alternative reinforcer on smoking by schizophrenics under controlled laboratory conditions. The behavioral-economics perspective predicts that smoking will decrease when its price (i.e., response requirement) and opportunity cost (i.e., forfeiture of an alternative reinforcer) are high. Six volunteers were recruited from a local mental health center and had initial carbon monoxide (CO) readings of at least 18 ppm, indicative of heavy smoking. Before each session, subjects went required to provide CO samples indicating recent (5-6 hrs) abstinence from smoking. Subjects responded for the opportunity to smoke by pulling a plunger which was interfaced with a microcomputer. The response requirement to obtain two cigarette puffs varied across sessions, ranging from 50 to 6400 responses. In half of the test sessions, subjects also were able to respond on another lever to earn a small amount of money. At high response requirements, response output and cigarette smoking decreased. Regardless of response requirement. smoking decreased when a competing alternative reinforcer was available. Combining both factors produced maximal decreases in response output and smoking. These results are similar to those observed previously in non-schizophrenic smokers, suggesting that smoking and perhaps other drug abuse by schizophrenics may be controlled by contingency-management and other behavioral interventions known to be efficacious in non-schizophrenics.

ACKNOWLEDGMENTS: Supported by NIDA grants RO1-DA-08076 and T32-DA-07232.

STUDIES ON ANALOGS OF THE DELTA-OPIOID AGONIST, SNC80: THE SEARCH FOR SELECTIVE DELTA ANTAGONISTS

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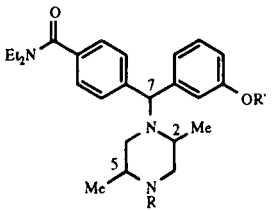
Delta (δ) opioid receptors have been reported to he involved in (a) mediation of analgesia. (b) the development of opioid tolerance and dependence, (c) regulation of the mesolimbic dopaminergic pathway, and (d) mediation of some effects of cocaine. SNC80 is a non-peptide opioid receptor agonist which has been shown to be highly selective for δ opioid receptors from *in vitro* binding assays and smooth muscle bioassays. Highly selective d antagonists are required to further study δ receptor function. Our goal in this study was to discover novel selective δ opioid receptor antagonists. Burroughs Wellcome reported that compound 5 which contains a *cis*2,5-dimethylpiperazine scaffold relative to the *trans*-2.5-dimethylpiperazine of SNC80 was a selective δ antagonist. We synthesized compounds **1-6,** and determined that they are all selective for the d receptor from *in vitro* binding assays with IC_{50} (μ/δ)) ratios of 4.3 to 2985. It was found that the most potent and selective compound in the series was compound **5.** Interestingly, compounds **1, 3,** and **5** have the same R stereochemistry at the dibenzylic center (C7) of SNC80 and are the most selective in each diastereomeric series.



SNC80	R=allyl, R'=Me, 7R, 5R, 2S
BW373U86	R=allyl, R'=H, 7R(S), 5R(S), 2S(R) (±)
1	R=H, R'=Me, 7R, 5R, 2R
2	R=H, R'=Me, 7S, 5R, 2R
3	R=Me, R'=Me, 7R, 5R, 2R
4	R=Me, R'=Me, 7S, 5R, 2R
5	R=Me, R'=H, 7R, 5R, 2R
6	R=Me, R'=H, 7S, 5R, 2R

A NOVEL SYNTHESIS OF A PHENYLDECAHYDROISOQUINOLINE RELATED TO MORPHINE

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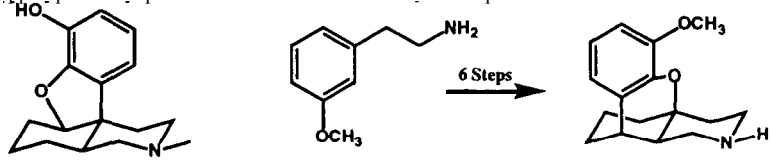
The oxide bridged 4a-phenyldecahydroisoquinoline ring system **1** is a morphine partial structure and drugs within this series exhibit potent agonist or antagonist profiles depending on the nitrogen substituent. We now report a novel synthesis of the isomeric ring system **2** in six steps from the commercially available 3-methoxyphenethyl amine. This approach for the synthesis of morphine related structures utilized an acid catalyzed inlramolecular cyclizadon in which the aromatic ring was tethered to an octahydroisoquinoline ring system via an oxygen atom. The structure of amine **2** was unambiguously established by single crystal X-ray analysis of the oxalate salt which revealed the *trans*-decahydroisoquinoline configuration. Compound **2** failed to show significant binding to mu, delta and kappa-opioid receptors and the brain cannabinoid receptor.



1 2

ANATOMICAL DISTRIBUTION OF A NOVEL KAPPA2 OPIOID RECEPTOR IN GUINEA PIG BRAIN VISUALIZED WITH [125I]IOXY

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Previous studies demonstrated unique opioid receptor distributions in guinea pig brain sections at the level of the caudate putamen. Mu, delta, and kappa, receptors were depleted by the irreversible ligands BIT, FIT, and UPHIT, and opioid receptors were labeled with the opioid antagonist [^{125}I]IOXY and subjected to autoradiographic analysis. The objective of this study was to characterize further these unique binding sites (designated kappa$_2$). Kappa$_2$ binding was quantitated by autoradiography in specific regions of four different levels of guinea pig brain (olfactory bulb, caudate putamen, hippocampus, and substantia nigra) for a total of 37 determinations across all levels. The kappa$_2$ distribution was then compared with the binding sites labeled by [^{125}I]DAMGO (mu), [^{125}I]deltorphin II (delta), and [^{125}I]IOXY under kappa$_1$ conditions to identical regions in adjacent guinea pig brain sections. The results are: (1) kappa$_2$ binding greatly exceeded mu and delta binding in all regions; (2) kappa$_2$ binding exceeded kappa, binding in all regions except the deep cortex at the level of the hippocampus; (3) the kappa, distribution was different than that of mu, delta or kappa, receptors. These results provide further evidence for the existence of a novel opioid binding site in guinea pig brain.

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MOLECULAR CHARACTERIZATION OF LIGAND-RECEPTOR INTERACTIONS OF RTI-4614-4 AND ITS FOUR STEREOISOMERS

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Previous data, obtained with cloned rat μ receptors, demonstrate that the "super-potent" opiates, RTI-4614-4 and its four stereoisomers differ in binding affinity, potency, efficacy and intrinsic efficacy. We speculate that this results from binding to different domains of the μ opioid receptor. Molecular modeling (Tang Yun *et al.,* 1995) of fentanyl derivatives binding to μ receptors indicated that important residues are Asp147, Tyr148, Trp318 and His319. Asp147 (TMH3) was required to interact with the positively charged opiate agonist in forming potent electrostatic and hydrogen-bonding interactions. In this study, the role of weak electrostatic and hydrogen-bonding π-π inceractions of the O atom of the carbonyl group and me phenyl ring structures of RTI-414-4 and its four stereoisomers with residues Tyr148, Trp318 and His319 were explored through site-directed mutagenesis. Tyr148, in the TMH3, Trp318, His319 in the TMH7 were individually replaced with phenylalanine or alanine. Mutation of Tyr148 reduced the binding affinities of the RTI-4614-4 and its stereoisomers (2-7 fold), but did not alter me aftinities of the peptide μ agonist DAMGO, the antagonist naloxone and the non-selective opiates etorphine and buprenorphine. Mutation of Ttp318 eliminated me ability to bind different opioid ligands (DADL, bremazocine and IOXY). TMH7 histidine substitution with alanine yielded a receptor with significantly reduced binding affinities for the opioid ligands tested. These results indicate the importance of these residues for the binding of fentanyl derivative to the μ receptor. Functional studies using the mutant receptors in transfected cos-7 cells will provide additional insight into the mechanism of action of RTI-4614-4 and its four stereoisomers.

ACKNOWLEDGMENTS: Generously supported by NIDA Intramural Research Program

EVIDENCE FOR INACTIVATION OF cAMP DEPENDENT PROTEIN KINASE IN SPINAL CORD BEING INVOLVED IN MORPHINE WITHDRAWAL IN RATS

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This laboratory has shown that inactivation of cAMP dependent protein kinase (PKA) within me spinal cord during the morphine withdrawal in rats cannot be explained by increasing intracellular cAMP levels, Additional studies are needed to identify whether inactivation of PKA in spinal cord mediates the morphine withdrawal. The present study was undertaken to examine the effects of Sp-cAMPS, a potent membrane-permeable inhibitor of PKA, Rp-cAMPS, a specific membrane-permeable inhibitor of activation of PKA. or calyculin A, an inhibitor of protein phosphatase by intrathecal injection on the morphine withdrawal. Catheterizalion of the spinal subarachnoid space was performed by inserting a length of PE10 tubing, terminated in me T11-T12 segments of the spinal cord. Male Sprague Dawley rats (n=7, in each group) were made morphine dependence after recovery from the surgical procedure Pretreamtent with 90 nmol/kg SP - cAMPS (i.t) or 100 pmol/kg calyculin A (i.t), the total rating of naloxone (4 mg/kg,ip) precipitated withdrawal signs across the session were 5.5±2.3 and 15.7±3.6, which were different significantly from that of placebo (27.8±5.9). while concurrent with 100 nmol/kg RP-cAMPS (i.t) could not inhibit the withdrawal symptoms. The observations showed that inactivation of PKA in the spinal cord may account for the activation of protein phosphatase and enhance of PKA holenzyme re-association, which mediate the morphine withdrawal.

PHOSPHORYLATION OF MU OPIATE RECEPTOR AND DOPAMINE TRANSPORTER

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Phosphorylation regulates the activities of a number of important brain proteins. The primary amino add sequences of the dopamine transporter (DAT) and μ opiate receptor (μOR) reveal consensus phosphorylation sites for several protein kinases. Phorbol esters that stimulate PKC activity regulate dopamine uptake and μ receptor desensitization. Phospho-DAT and μOR can be demonstrated in expressing cultured cells, brain slices and/or synaptosomes following incubation with [^{32}P]-orthophosphate, immunoprecipitation with specific antibodies, SDS-PAGE and autoradiography. Several lines of evidence support the specificity of labelling in each case. Pbosphorylation levels of both proteins are increased by PKC. Evidence for possibly-rapid turnover of phosphate incorporation comes from studies with and without phosphatase inhibitors. Mu receptor phosphorylation levels are also enhanccd by agonists in a fashion that is not blocked by the PKC blocker staurosporin, but relates to the potency and intrinsic activity of the agonist. Methadone, which stimulates phosphorylation better than morphine despite lower agonist potencies than morphine in two test systems, provides an exception to this relationship. Phosphorylation/dephospborytation events provide possible mechanisms for rapid regulation of circuits important for cocaine and opiate reward. Conceivably, these adaptive mechanisms could play roles in the activities of agonist replacement/substitution/blocking therapeutics for opiate and even cocaine dependence

DOSE-DEPENDENT EFFECTS OF HEROIN ON MESOLIMBIC MODULATION OF SYNAPTIC TRANSMISSION IN THE DENTATE CYRUS

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Conditioning stimulation of the VTA produces a robust facilitation of perforant path to hippocampal dentate population spike (PS) amplitudes that is inhibited by alcohol. Similar cellular substrate(s) for alcohol and opiates has been suggested. However, it is still unclear whether heroin has an effect on mesolimbic modulation of hippocampal function. Previous studies have shown that opioids, acting via μ receptors, generally enhances perforant path evoked activity in the dentate gyrus. Moreover, opiates and opioid peptides have been shown to enhance transmission of auditory sensory information from the entorhinal cortex to the dentate gyrus. To understand further the neuropharmacological substrates of opioid abuse, we sought to pharmacologically characterize the effects of heroin on VTA-induced facilitation of synaptic transmission in the dentate gyrus of anesthetized Sprague-Dawley rats. Stimulation of perforant path (0.1 Hz) produced typical evoked recordings in the dentate gyrus. High frequency stimulation (HFS; 400 Hz for 10 ms) of the VTA markedly increased PS amplitudes, but had no effect on perforant path to dentate population excitatory postsynaptic potentials. Our results indicated that systemic administration of a high dose of heroin (0.6 mg/kg) significantly increased VTA facilitation of perforant path to dentate responses. On the other hand, VTA facilitation was markedly reduced after administration of a lower dose of heroin (0.1 mg/kg). The fact that naloxone given systemically (5.0 mg/kg), but not locally into the dentate gyrus, markedly decreased baseline VTA facilitation of PS amplitudes indicate that endogenous opioids may mediate this modulation of dentate physiology via an extra-hippocampal mechanism(s). These results demonstrate the importance of opioid mechanisms on subcortical modulation of hippocampal function.

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ELECTROPHYSIOLOGICAL SUBSTRATES OF HEROIN SELF-ADMINISTRATION

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Mesolimbic dopamine (DA) neurons projecting from the ventral tegmentat area (WA) to the nucleus accumbens (NAcc) are a critical component of the neural substrates mediating opiate reinforcement. A recent study demonstrated that a DA-independent mechanism within the VTA itself mediates the rewarding properties of morphine only when animals were previously naive or in non-deprived opiate states. To understand further the neuropharmacological substrates responsible for opiate reinforcement, we are characterizng the neuronal responses of NAcc and VTA non-DA neurons during the acquisition of heroin self-administration. Our data suggest that during the initial sessions of heroin self-administration. an anticipatory increase in NAcc unit activity was observed seconds before the rat nosepoke for a heroin infusion. However, this anticipatory increase in NAcc unit activity was not present after seven sessions of heroin self-administration. As expected, non-contingent administration of heroin in freely-moving rats and systemic administration of heroin in anesthetized rats markedly suppressed spontaneously active VTA non-DA neurons. Administration of naloxone (5 mg/kg) not only reversed these effects, but produced a rebound excitation. During acquisition of heroin self-administration, lever pressing for a heroin infusion produced a marked suppression in the activity of VTA non-DA neurons. However, later in the same session (after 5 lever presses), we observed a marked desensitization of the heroin-induced suppression of VTA non-DA neuronal activity. These results demonstrate complex neurophysiologicat interactions in the NAcc and the VTA during the acquisition of heroin self-administration. Characterization of the neuropharmacological mechanisms responsible for these effects might provide us with valuable information on the basis for the addictive properties of heroin.

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MICROINJECTIONS OF CTOP INTO THE VENTRAL PALLIDUM BLOCK THE DEVELOPMENT OF SENSITIZATION TO CHRONIC MORPHINE

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The ventral tegmental area (VTA) is critical for the development of an opioid-induced sensitized motor response whereas the nucleus accumbens (NAC) is important for the expression of this behavior. Given the direct projections from the VTA and the NAC to the ventral pallidum (VP), and the probability of generalized system alterations following chronic drug exposure. it is likely that the VP plays a role in the opioid sensitization phenomenon. The following study investigated this possibility. Once a pretreatment baseline activity was determined for each subject, rats were randomly assigned to one of three groups: the Sat-Sal group (n = 6) received an intra-VP micminjection of saline (0.5 ml/side) 10 min prior to an ip saline injection; the Sal-Mor group (n = 6) received an intra-VP microinjection of saline (0.5 ml/side) to min prior to an ip injection of morphine (10 mg/kg), and the CTOP-Mor group (n = 6) received an intra-VP microinjection of the mu receptor antagonist, CTOP (2.1 mg/0.5 ml/side), 10 min prior to an ip injection of morphine (10 mg/kg). This procedure was repeated daily for 5 consecutive days. Two days after the final drug injection, all rats received an acute morphine (10 mg/kg. ip) challenge with no intra-VP treatment ANOVA analysis with planned contrasts revealed that only the rats in the Sal-Mor group displayed a sensitized motor response to the acute morphine challenge (400% increase over pretreatment baseline activity; $p < 0.001$). Scheffe's *post hoc* tests revealed that the Sal-Mor group was different from the Sal-Sal and the CTOP-Mor groups ($p < 0.001$, whereas the Sal-Sal and CTOP-Mor groups were not ditferent from each other ($p = .78$). Because opioid blockade in the VP inhibits the development of morphine-induced sensitization, it appears that the VP is important in the opioid sensitization phenomenon.

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DYNORPHIN RELEASE FROM THE PREOPTIC ANTERIOR HYPOTHALAMUS DURING INTERLEUKIN-1 FEVER

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We have demonstrated that μ-opioid receptor agonists induce hyperthermia when they are administered into the brain, while the κ-opioid receptor agonist dynorphn A1-17 (Dyn) induces hypothermia. The pyrogenic cytokine interleukin-1β (IL-1), injected into the brain, increases β-endorphin (β-E) release from the preoptic anterior hypothalamus (POAH) and produces fever. Because the IL-l-induced fever can be entranced by pretreament with the κ-opioid receptor antagonist nor-BNI, and there is a tonic basal release of bothβ-E and Dyn from me POAH, we postulate that there may be a functional balance, in terms of thermoregulalion, between the two peptides within the POAH. In the present study, we investigated whether Dyn release from this region changed during IL-1-induced fever. Microdialysis samples were collected from the POAH of freely moving S-D rats every 30 min at a rate of 4 μl/min for 4 hrs and analyzed for Dyn level by radioimmunoassay. Baseline release of Dyn was 0.3 - 0.58 fmol/fraction. Microinjection of IL-I (1000 LD induced a 130-180 % increase in Dyn release over baseline 60-90 min after injection. The Dyn increase occurs later than theβ-E increase (30 min) during IL-1 fever. Because the increase in Dyn release follows that of β-E and pretrearment with theκ-opioid receptor antagonist nor-BNI enhances the IL-1 fever, it suggests that an endogenous opioid peptide balance system and/or a feedback regulatory mechanism may exist in the POAH during cycokine-induced fever.

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MORPHINE DIFFERENTIALLY MODULATES HPA AXIS ACTIVITY IN RATS WITH OR WITHOUT WATER DEPRIVATION STRESS

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Acute administration of exogenous opioids (e.g., morphine) in the rat stimulates secretion of hypothalamic-pituitary-adrenal (HPA) hormones: adrenocorticotropin (ACTH), beta-endorphin and corticosterone (B). The present studies investigated the effects of morphine on the HPA activity under two different conditions: with or without water deprivation (WD) stress. Six injections of morphine (6.25 mg/kg/injection, s.c.) or saline were given every 2 hours during the light cycle. Animals were divided into 2 groups: one with water supply (morphine, n=12; saline, n=12); another with WD beginning 30 min before and during morphine or saline administration. Animals were sacrificed 30 min after the last morphine or saline injection. Plasma ACTH and B were measured by RIA. The levels of proopiomelanocortin (POMC) mRNA in both the anterior lobe (AP) and the neurointermediate lobe/posterior lobe of the pituitary gland, as well as in the hypothalarnus (Hypo) and amygdala were measured. **Results:** (1) Morphine alone caused significant elevations of both ACTH and B levels in the absence of WD; WD alone also significantly inreased ACTH levels. However, the WD rats treated with morphine failed to show any increases in ACTH or B levels. (2) Morphine alone significantly elevated CRF mRNA in the hypothalamus. However, the rats treated with morphine under WD condition did not show any CRF mRNA increases. (3) Morphine alone did not change POMC mRNA levels in the AP; WD alone significantly increased AP POMC mRNA. However, the WD-induced increase of AP POMC was attenuated by morphine. (4) In the Hypo, morphine alone significantly increased POMC mRNA; whereas WD alone had no effects. Further, the stimulatory effects of morphine on the Hypo POMC were also absent during WD. These observations suggests that the effects of morphine on the HPA activity may be altered by external stressors.

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DYNORPHIN A_{1-13} ELEVATES SERUM PROLACTIN LEVELS BY AN OPIOID RECEPTOR MECHANISM: CONTROLLED STUDIES OF NORMAL VOLUNTEERS

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In an earlier pilot study[1], we have shown that dynorphin A_{1-13} effects an elevation of serum prolactin levels in human subjects. Since prolactin release in humans is primarily under tonic inhibition by dopamine, dynorphin presumably acts to lower dopaminergic tone in the tubero-infundibular system. Therefore, placebo-cotrolled studies of dynorphin A_{1-13} effects was conducted in healthy normal volunteer subjects with no history of drug or alcohol abuse. 1) To study dosage effects, low (120 mgm/kg body weight) and high (500 mg/kg body weight) dose dynorphbin A_{1-13} were given iv. To determine if any effect is mediated by an opioid receptor mechanism. 2) naloxone (10 mg) a specific opioid antagonist, was given iv 30 minutes before iv low dose dynorphin A_{1-13}. 3) naloxone (30 mg) was injected 30 minutes before giving low dose dynorphin A_{1-13}. 4) nalmefene (30 mg), a different specific opioid antagonist with greater κ receptor activity was given 30 minutes before low dose dynorphin A_{1-13}. Blood specimens for prolactin levels were obtained over 6 hours, and assayed by RIA. As in the pilot study. we found that dynorphin A_{1-13} in normal volunteers causes a prompt, dose-dependent rise in serum prolactin ($p<0.05$), peaking at 10-40 minutes. Naloxone, a primary μ opioid receptor antagonist, had a modest effect at 10 mg ($pc<0.05$) and a greater, longer lasting effect at 30 mg ($p<0.001$) in attenuating dynorphin-induced elevation of serum prolactin. Nalmefene, also primarily a m opioid receptor antagonist but with more κ opioid effect also attenuated the dynorphin elevation of serum prolactin ($p<0.05$). These findings confirm that dynorphin affects the physiology of prolactin release, through an opioid receptor mechanism. [1]Kreck, M.J.; Ho, A.; and Borg, L. NIDA Res Monogr 141:108, 1994.

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RESPIRATORY STIMULATION DUE TO PRECIPITATED OPIOID WITHDRAWAL AND ITS INHIBITION IN RHESUS MONKEYS

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We previously reported that respiratory parameters, that is, respiratoryfrequency (f) and minute volume (Ve), were increased in μ-opioid withdrawal in rhesus monkeys (INRC, 1996, Long Beach, CA). Clonidine (alpha2-adrenoceptor agonist), MK-801 (NMDA antagonist) and diltiazem (Ca^{++} channel blocker) have been reported to suppress some opioid withdrawal signs. In this experiment we examined whether clonidine, MK-801 and diltiazem suppressed naltrexone-induced morphine and heroin withdrawal estimated by respiratory parameters in rhesus monkeys. Six adult rhesus monkeys were exposed to normal air and air mixed with 5% CO2: f, Ve and tidal volume (Vt) were measured using a pressure-displacement plethysmograph technique. To produce the acute dependence, monkeys were given morphine (10 mg/kg/day) or heroin (0.32 mg/kg/day) for two consecutive days, Twenty-four hrs later, naltrexone (0.001 - 1 mg/kg) was administered using a cumulative dosing procedure. Clonidine (0.01 and 0.1 mg/kg), MK-801 (0.1 mg/kg) or dilthiazem (40 mg/kg) was injected 30 min before naltrexone administration. In monkeys that were pretreated with morphine or heroin, f and Ve were increased dose-dependently following administration of naltrexone (antagonist-precipitated opioid withdrawal). Clonidine dose-dependently suppressed naltrexone-precipitated respiratory stimulation in both morphine- and heroin-pretreated monkeys. Alternatively, a large dose of MK-801 and diltiazem failed to alter the naltrexone-precipitated increases in respiration in these monkeys. These results suggest that drugs that are known to suppress some signs of opioid withdrawal not necessarily affect all aspects of the opioid-antagonist precipitated withdrawal syndrome in acutely μ-opioid dependent monkeys.

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DISCRIMINATIVE STIMULUS EFFECTS OF NALOXONE AND NALTREXONE ADMINISTERED S.C. AND P.O. IN MORPHINE-TREATED RHESUS MONKEYS

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The current study evaluated the discriminative stimulus effects of naloxone and naltrexone after oral and parenteral administration. Four morphine-treated (3.2 mg/kg/day) rhesus monkeys discriminated between s.c. injections of naltrexone (0.01 mg/kg) and saline while responding under a fixed-ratio 5 schedule of stimulus shock termination. Subjects were named in daily sessions consisting of several discret 15-min cycles, with each cycle comprising a 10-min time-out followed by a 5-min response period. The discriminative stimulus effects of naloxone and naltrexone were evaluated every 15 min over a 2-hour period. For p.o. administration, drugs were mixed in fruit punch. When administered s.c., naloxone or naltrexone produced greater than 90% drug-appropriate responding at a dose of 0.032 or 0.01 mg/kg, respectively. When administered p.o., naloxone or naltrexone produced greater than 80% drug-appropriate respondiug at doses of 3.2 or 1.0 mg/kg. respectively. When administered s.c., the onset of action was 15 min for both drugs; when administered p.o., the onset of action was 30 min for naloxone and 45 min for naltrexone. Although both drugs were at least 60 to 100-fold more potent s.c. as compared to p.o., there was little or no difference in the potency of naloxone and naltrexone overall. These results fail to support the view that naloxone might be especially useful for some therapeutics (e.g. Talwin Nx) because of its reduced bioavailability after p.o. administration.

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EVIDENCE OF PHARMACOLOGICAL SELECTIVITY IN PIGEONS DISCRIMINATING FENTANYL. BREMAZOCINE AND WATER

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The discriminative stimulus effects of opioids with activity at mu and kappa receptors were examined in pigeons discriminating the mu opioid fentanyl. the kappa opioid bremazocine and water in a three-choice discrimination task. Apparent pkB values obtained for naloxone as an antagonist of fentanyl were higher than those obtained against bremazocine. Morphine and *l*-methadone substituted for the fentanyl stimulus, U50,488 and U69,593 substituted for the bremazocine stimulus, and pentobarbital failed to substitute for either stimulus. Opioids with activity at both mu and kappa sites, including nalorphine, butorphanol, buprenorphine, nalbuphine, ethylketocyclazocine, (-)-ketoclazocine, (-)-n-allylnormetazocine (NANM) and levallorphan, produced fentanyl responding without producing bremazocine responding. At doses that did not substitute for the fentanyl stimulus, (-)-NANM, levallorphan, nalorphine and nalbuphine antagonized partially the bremazocine, stimulus. Butorphanol and buprenorphine antagonized bremazocine at doses that substituted for fentanyl, yet ethylketocyclaxocine and (-)-ketocyclazocine failed to antagonize bremazocine. The present findings indicate that in this three-choice task the fentanyl-like substitution patterns produced by these opioids are similar to those reported in pigeons discriminating either fentanyl or bremazocine from saline (i.e., two-choice tasks). In this task, however, the level of kappa antagonist activity observed was considerably less than that obtained in pigeons trained to discriminate bremazocine from saline.

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DISCRIMINATIVE STIMULUS PROPERTIES OF THE PARTIAL MU AGONIST DEZOCINE

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The purposc of this investigation was to evaluate the discriminative stimulus effects of the partial mu agonist dezocine. In pigeons trained to discriminate 1.7 mg/kg dezocine from saline, the mu agonists fentanyl, I-methadone, morphine, butorphanol, buprenorphine, nalbuphine and (+)-propoxyphene substituted completely for the dezocine stimulus. The (-)-isomers of cyclazocine, n-ahylnormetazocine and metazocine, but not their respective (+)-isomers, also produced high levels of substitution for the dezocine stimulus. Naloxone antagonized the stimulus effects of dezocine, (+)-propoxyphene and fentanyl in a dose-related manner, whereas doses of naloxone that antagonized fentanyl's rate-decreasing effects did not systematically alter the rate-decreasing effects of dezocine and (+)-propoxyphene. The mu-selective, noncompetitive antagonist beta-funaltrexamine was more effective against the stimulus effects of dezocine and nalbuphine than against morphine and fentanyl. The delta agonists BW373U86 ad SNC80 produced high levels of substitution for the dezocine stimulus, and these effects were reversed by a dose of naltrindole that had no effect on the dezocine stimulus. The kappa agonists bremazocine, spiradoline, U50,488 and U69,593, as well as various nonopioid compounds failed to substitute for the dezocine stimulus. The present fmdings indicate that dezocine shares similar stimulus effects with both mu and delta agonists, is less efficacious at the mu receptor than either morphine or fentanyl, and its rate-decreasing effects are not mediated by activity at mu, kappa or delta opioid receptors.

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DRUG DISCRIMINATION IN PIGEONS SUCCESSIVELY TRAINED TO DISCRIMINATE THE MU OPIOID BUTORPHANOL AND THE KAPPA OPIOID BREMAZOCINE

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In Phase 1, pigeons were trained to discriminate butorphanol(1.0 or 5.6 mg/kg) from saline using a standard, two key, food-reinforced, drug discrimination procedure. During substitution tests, the mu opioids morphine and fentanyl substituted completely for the butorphanol stimulus, whereas the kappa opioids bremazocine, U50,488 and U69,593 produced predominantly saline-appropriate responding. In Phase 2, the same pigeons were retrained to discriminate bremazocine (0.017 mg/kg) from saline. After this discrimination was established, tests revealed that (1) bremazocine, U50,488 and U69,593 substituted completely for the bremazocine stimulus, (2) as in Phase 1, complete substitution was obtained with butorphanol, morphine and fentanyl, (3) naloxone was more effective as an antagonist of the bremazocine stimulus than the butorphanol stimulus, (4) chronic administration of bremazocine produced tolerance to the bremaxocine stimulus but not to the butorphanol stimulus, (5) selected doses of butorphanol shifted the bremazocine curve to the left in an effect-additive manner, whereas selected doses of bremazocine shifted the butorphanol curve to the left in an effect-additive manner, and (6) one year of training with bremazocine did not alter the dose-effect curve for the butorphanol stimulus, the present findings indicate that the discriminative control produced butorphanol was retained during extensive training with bremazocine, and that discriminative control exerted by butorphanol and bremaxocine could be differentiated using various pharmacology probes.

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MORPHINE AND NALTREXONE ENHANCE GBRI2909-INDUCED ROTATIONAL BEHAVIOR

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In nigrally-lesioned rats, the mu-opioid receptor agonist morphine potentiated amphetamine- and cocaine-induced turning. To investigate further the relationship between brain opioid and dopamine systems, we examined the effects of morphine and opioid antagonists on turning induced by the selective dopamine uptake inhibitor, GBR12909. GBR12909 (3.0-30 mg/kg) dose-dependently produced turning that was potentiated by morphine (0.1-3.0 mg/kg) and the nonspecific opioid receptor antagonist naltrexone (0.3-3.0 mg/kg), but not by naloxone (0.3-3.0 mg/kg) or the selective opioid receptor antagonistsβ-funaltrexamine (mu) (3.0-10 µg), naltrindole (delta) (3.0-10 µg), and nor-binaltorphimine (kappa) (3.0-10 µg). These results leave unclear what, if any, role opioids have in GBR12909-induced turning. However, the observed effects of naltrexone and naloxone suggest a novel difference between the actions of these two drugs.

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STATE-DEPENDENT LEARNING: PERFORMANCE ON A COMPLEX MAZE TASK IS AFFECTED BY DRUG DOSE

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State-dependent learning (SDL) is a phenomenon closely associated with drug discrimination (DD) research. In SDL. a response learned in one chemical state fails to transfer completely to another chemical state. In most research to date, simple response topographies, such as operant conditioning lever-pressing or T-maze performance, have been used to evaluate SDL and DD effects. In this study, performance on a more complex task, completion of Small's (1901) Hampton Court maze, was evaluated. Thirty naïve adult male Long-Evens hooded rats were given injections of either saline or morphine solution and then introduced to the - for five trials per day until they reached criterion performance of three days with stable running time awl less than one error per day. Once the learning curve for the first state was established, subjects were switched to the other condition and a new learning curve was established. Results indicated that runtime increased at morphine doses of 10 mg/kg and 15 mg/kg, but not at 6 mg/kg, regardless of whether the switch was from saline to morphine or vice versa. Errors increased when animals initially switched from morphine to saline for all doses. The number of trials required for all groups to return to errorless performance was significantly less than in the initial drug state, indicating interruption of retrieval rather than loss of information. When subjects switched back to the original state, no significant performance decrements occurred. These results are consistent with a state-dependency interpretation.

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ROLE OF δ_2-OPIOID RECEPTOR IN NALOXONE-INDUCED PLACE AVERSION IN MORPHINE-DEPENDENT MICE

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It has been reportted that the expression of naloxone-induced place aversion can be measured using conditioned place preference (CPP) paradigm in morphine-dependent rats. The aim of the present study was (1) to establish a measuring method of naloxone-induced place aversion in morphine-dependent mice using the CPP paradigm, and (2) to examine the effects of δ_2-opioid receptor antagonists on the naloxone-induced place aversion. In the morphine-&pet&m mice, naloxone (0.3-3 mg/kg, s.c.) significantly produced a place aversion in a dose-dependent manner. The naloxone-induced place aversion was significantly suppressed by pretreatment with clonidine or diazepam. These fmdings are consistent with previous reports using rats, suggesting that the naloxone-induced place aversion in the morphine-dependent mice can be an index of the degree of physical dependence on morphine using the CPP paradigm. Therefore. we investigated the effect of δ--opioid receptor antagonists on the naloxone-induced aversion using this paradigm. Pretreatment with NTI (1-5 mg/kg, s.c.), a non-selective δ--opioid receptor antagonist, and naltriben (NTB; 0.05-0.5 mg/kg, s.c.), a selective $\delta_2$opioid receptor antagonist, but not with 7-benzylidenenaltrexone (BNTX; 0.3-3.0 mg/kg. s.c.), a selective δ_1 opioid receptor antagonist, during chronic morphine treatment suppressed the naloxone-induced place aversion. These findings suggest thatδ--opioid receptors, especially δ_2-opioid receptors, may be involved in the development of physical dependence in morphine-dependent mice.

GENETIC DIFFERENCES IN FOOD AND MORPHINE OPERANT REINFORCED BEHAVIOR IN FOUR INBRED RAT STRAINS

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It is well known that exists large individual variability in response to drugs of abuse. In a previous work (Ambrosio *et al.,* Behav. Pharmacol., 6(3), 1995), we have shown that there are significant differences in the rate of acquisition of morphine self-administration behavior in four inbred strains of rats(Lewis>>Fischer344,NBR and ACI). In order to determine if the genetic differences found could become extensive to natural reinforcers like food. we have studied that possibility in the above cited four inbred rat strains on a Fixed Ratio (FR) and a Progressive Ratio (PR) schedule of reinforcement. Eleven male rats of each inbred strain were trained to lever press for food pellets on a FR1 schedule in 60' sessions daily for 8 days. Following this acquisition period, subjects were put on a PR operant schedule in 3 h sessions over an additional 15 days period. Three months later, all these four inbred strain groups were surgically prepared to intravenous self-administer 1 mg/kg/injection of morphine on the previous PR schedule in 23 h sessions dally for 15 days, followed by two weeks of extinction period. On the PR schedule, the response requirements for each food pellet or i.v injection escalates according to the series: 2.3,5,7,11,15… The number of the reinforcers earned before responding ceased was defined as the breaking point. Rate of acquisition for food pellets on FRIschedule was significantly greater in Lewis and NBR rats compare to Fischer 344 and ACI rats. There were no significant differences in breaking points for food pellets on PR schedule between the four inbred strain tested. Breaking points for 1 mgl/kg/injection of morphine were significantly higher in Lewis rats compare to the other inbred rat strain. There were no significant differences during the extinction period. These results contirm a significant main effect of genotype in the reinforcing effects of morphine as measured by a PR schedule of reinforcement, but they also suggest that Lewis rats could have a high capability to learn or perform operant lever pressing tasks that might be interpreted as drug preference in operant conditioning paradigms.

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COMPARISON OF THE REINFORCING EFFECTS OF INTRAVENOUS AND INTRANASAL HEROIN IN HUMANS

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Eight heroin-dependent individuals, maintained on divided daily doses of oral morphine, participated in a 2.5-week inpatient study comparing the effects of intranasal (placebo, 12.5, 25, 50, 100 mg) and intravenous (placebo, 6.25, 12.5, 25, 50 mg) beroin. Each morning, participants received $20 and a sample dose of heroin, and each afternoon they had the opportunity to self-administcr all or part of the morning heroin dose or money amount. Participants responded under a modified progressive-ratio schedule (PR 50, 100, 200, …, 2800) during a 10-trial self-administration task. During each trial, participants could respond for 1/10th of the heroin dose or 1/1001 of the money amount. The PR value inreased independently for each option, the total amount of heroin and/or money chosen during the self-administration task was given at the end of the task. Participants received i.v. solution and i.n. powder simultaneously during each dosing; only one route contained active drug. Heroin produced dose-related increases in break point values by both routes of administration. The mean dose that maintained half-maximal responding (ED_{50}) for i.v. and i.n. heroin were 12.3 and 51.1 mg, respectively. Although i.v. heroin was approximately 4-fold more potent than i.n. heroin, the maximal break point values for both routes were not significantly different. A similar difference in potency between the i.v. and i.n. routes was also found for subjective effects ratings and physiological effects. Ratings of "nodding," were elevated after i.v., but not i.n. heroin. Correspondingly, task performance was more severely impaired after i.v. heroin. These results demonstrate similarities in efficacy, but differences in potency, for the reinforcing effects of i.v. and i.n. heroin.

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BEHAVIORAL ECONOMIC ANALYSES OF BUPRENORPHINE SELF-ADMINISTRATION IN BUPRENORPHINE-MAINTAINED OUTPATIENTS: EFFECTS OF AN ALTERNATIVE REINFORCER AND DISASSOCIATION OF SUBJECTIVE AND REINFORCING DRUG EFFECTS

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Eight buprenorphine-maintained, opioid-dependent outpatients participated in a two-phase study in which they first received low, standard, and high doses of buprenorphine in an exposure phase and then chose between doses of buprenorphine and amounts of money in a choice phase. When the amount of money available and cost of buprenorphine was low (e.g. $.30) in the choice phase, subjects self-administered the maximal doses of buprenorphine, available up to 32 mg/70 kg. As the amount of money available and cost of buprenorphine increased to $20, buprenorphine self-administration decreased to the standard maintenance dose or even lower. We applied a behavioral economic analysis to buprenorphine self-administration and found that demand for buprenorphine is inelastic. Thus, while subjects modified buprenorphine self-administration based on its price, changes in drug consumption were proportionally lower than changes in price. In the choice phase, subjective reports of opioid agonist and withdrawal symptoms did not vary whether subjects self-administered low or high doses of the drug. However. changes in subjective reports of opioid agonist and withdrawal effects increased over 200% when subjecis received high and low doses of buprenorphine. respectively, during the exposure phase. These results demonstrate that (1) buprenorphine self-administration varies with the presence of altemative reinforcers, (2) demand for buprenorphine is inelastic in buprenophine-maintained individuals, (3) the subjective and reinforcing effects of buprenorphine are not synonymous, and (4) the subjective effects of buprenorphine may depend on its administration.

EFFECTS OF SCOPOLAMINE ON MORPHINE REINFORCEMENT AND REINSTATMENT OF RESPONDING BY RHESUS MONKEY

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A naive rhesus monkey was trained to self-administer morphine (0.1 mg/kg/injection) which was paired with 5" red stirnulus tight for a daily 4 hour session under a FR1 schedule. Cumulative record of responding exhibited bursts of responding for morphine administration. 90% morphine infusions were taken in the first 2 hour. Five pre-session treatment of scopolamine decreased the total morphine intake and delayed the initiation of responding in a dose related manner (0.025 - 0.75 mg/kg). Response pattern was changed after scopolamine treatment at high doses (0.25 mg/kg). Few morphine infusions were taken at the beginning of session followed by a long delay (over 120 min) without responding. Chronic effect of scopolamine (0.25 mg/kg) was administered. The treatment causes 45% decrease of response rate by morphine priming compared with control. These results suggest that acute scopolamine treatment might decrease the total morphine intake, delay the initiation of responding in morphine self-administration, and chronic treatment inhibit the reinstatemenl of responding.

ROLE OF NMDA RECEPTOR IN THE EXPRESSION OF DIAZEPAM WITHDRAWAL SIGNS

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To clarify the role of NMDA receptor in the expression of diagram withdrawal signs, the present study investigated the effects of NMDA receptor antagonists on the DMCM-induced diazepam withdrawal seizure by subchronic treatment with diazepam in mice and on the abrupt withdrawal signs by discontinuation of the long-term treatment with diazepam in rats. In the experiment using mice, diazepam (16 mg/kg) was injected i.p. once a day for 6 days. The seizure threshold of DMCM was evaluated at 48 hr after the last injection of diazepam. NMDA receptor antagonists MK-801 and ifenprodil were injected s.c. and i.p., respectively, 30 min before the DMCM infusion. Withdrawal from subchronic diaazepam treatment elicited a significant decrease in the seizure threshold of DMCM. The decreasc in the seizure threshold of DMCM was abolished by pretreatment with MK-801 and ifenprodil. In the experiment using rats, rats were treated with diazepam-admixed food for 30 days. The concentration of diazepam in the food was gradually increased from 1 to 12 mg/g of food. Abrupt withdrawal was induced by substituting normal food for drug-admixed food, and withdrawal signs were observed at 27, 30, 33, 36, 39, 42 and 45 hr after withdrawal. MK-801 and ifenprodil was injected i.p. 30 min prior to the observation. After the last injection, withdrawal signs were observed over 6 days. Several withdrawal signs were induced by abrupt withdrawal signs. Pretreatment with MK-801 and ifenprodil drastically suppressed the abrupt withdrawal. These findings suggest that overactivation of NMDA receptor may be an important role in the expression of the diazepam-withdrawal signs.

RELATIONSHIP BETWEEN REINFORCING AND DISCRIMINATIVE EFFECTS OF GABAERGIC DRUGS IN BABOONS: A WITHIN-SUBJECT ANALYSIS

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Five baboons were trained to discriminate midazolam maleate (0.32 mg/kg, i.v.) under a two-lever, food-maintained drug verus no-drug procedure. Reliable dose-dependent generalization occurred in tests with i.v. chlordiazepoxide and zolpidem, less so with imidazenil and not with pentobarbital. The baboons then were trained under an i.v. drug self-administration procedure in which a drug injection depended upon completion of a fixed-ratio 160-response requirement on a third lever on the intelligence panel. Completion of the response requirement was followed by a 3-hour timeout; a maximum of 8 injections were available in each 24-hour period. Generalization to midazolam, chlordiazepoxide, zolpidem, imidazenil, and pentobarbiral then was studied under conditions in which the baboon self-administration drug dose and the drug discrimination session turned on automatically 10 or 15 min afterward. Generalization results were not consistently different from those when the doses had been delivered response independently. Greater drug reinforcement was found with midazolam, zolpidem, and pentobarbital than with chlordiazepoxide and imidazenil. With all drugs, doses that did not occasion midazolam-lever responding maintained self-injection, thus further indicating the functional difference in drug conlrol of behavior under the drug discrimination and the drug self-administration paradigms.

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COMPARISON OF THE ACUTE ACTIONS OF DIAZEPAM, LORAZEPAM AND ZOLPIDEM USING RADIOTELEMETRY

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Acute administration of benzodiazepines produces muscle relaxation, sedation, anxiolysis and, in rodents, hypothermia. The imidazopyridine zoipidem is a hypnotic non-benzodiazepine with high affinity for the BZ1 receptor. In humans it possesses only mild anticonvulsant, muscle relaxant and anxilytic properties. This study compared the acute actions of the benzodiazepines diazepam and lorazepam with those of the non-benzodiazepine zoipidem. Spontaneous locomotor activity (SLA), electromyographic activity (EMG) and body temperature were recorded by radiotelemetry. This is a new technique in small laboratory animals which enables the simultaneous gathering of multiple measures, without removing animals from their home cage and with minimal handling-related and restraint stress. Hooded Wistar rats, n=7 per group, were surgically implanted with radioelectrodes whilst fully anaesthetised. Transmitters were inserted into the abdomen and two electrodes were sutured into the left thigh muscle. One week after recovery. animals were administered either diazepam (5 - 20 mg/kg), lorazepam (6.25 - 25 mg/kg), zolpidem (2.5 - 10 mg/kg) or vehicle (1 ml /kg) via SC injection. SLA, EMG and temperature were recorded every 10 minutes for one hour after injection. Diazepam (10 mg/kg), lorazepam (12.5 mg/kg) and zolpidem (5 mg/kg) produced sedation and muscle relaxation of a similar magnitude. Hypothermia was greatest after administration of diazepam > lorazepam > zolpidem. Zolpidem produced little change in body temperature compared to vehicle controls. These data suggest that the imidazopyridine zolpidem has a similar profile of acute effects in comparison to the benzodiazepines diazepam and lorazepam. However, the relative magnitude of the effects differed, with zoipidem producing less muscle relaxation and hypothermia than the two benzodiazepines.

BEHAVIORAL EFFECTS OF DIAZEPAM: INFLUENCE OF GENDER AND MENSTRUAL CYCLE PHASE

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This study examined the effects of gender and menstrual cycle phase on the behavioral effects of diazepam. Six male and six female healthy adults, blind to the study drug, gave written consent and participated on three consecutive days per week over eight consecutive weeks (i.e., across successive menstrual cycles). Menstrual cycle activity was monitored prior to the study. On test days, subjects consumed a standard meal at 5:30 p.m., received drug at 6:30, and completed 20-minute sessions consisting of computerized performance tasks and visual-analog (VAS) ratings of drug effect 0, 0.5, 1, 2, 3, 4 and 5 hours after drug administration, and upon waking the next morning. Each of 3 doses (0, 5 and 10 mg/70 kg) of diazepam was administered orally 1 day each week in random order. Blood samples were collected prior to the first day of each week to monitor hormone levels. Study days coincided with four cycle phases (early follicular, late follicular, early luteal and late luteal). Diazepam altered visual-analog ratings of drug effect and several dimensions of task performance, including response rates during a psychomotor performance task and during both the acquisition and performance components of a learning task. The magnitude and tune-course of effects of diazepam were generally similar for females and mates. No evidence of residual next-day effects was obtained on any measure Interactions between the behavioral effects of diazepam and phase of the menstrual cycle were also observed on several measures, including response rates during the psychomotor performance task and on ratings of drug effect. These results indicate that the behavioral effects of diazepam in females vary across the menstrual cycle, but are similar between males and females when data from female participants are pooled across menstrual cycle phases.

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ROHYPNOL ABUSE IN FLORIDA

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Use of "roofies" has been widely reported in the media, in connection with sexual assault and also as a drug of abuse. The identity of "roofies" is reported or assumed to always be Rohypnol (flunitrazepam), a benzodiazeipine not marketed in the US, but smuggled in primarily from Latin America. We investigated patterns of "roofie" abuse in Florida among adolescents and young adults. Sixty-three interviews were conducted in the Miami area 9 in Gainesville and 20 in Tampa. A total of 62 interviewees (41 in Miami, 8 in Gainesville, and 12 in Tampa) reported having used "roofies," and of these persons, 66 percent (24 in Miami, 6 in Gainesville, and 11 in Tampa) provided at least one description of the tablets they took that were incompatible with any known dosage form of Rohypnol. An additional 45 % (17 in Miami, 5 in Gainesville, and 6 in Tampa) described tablets that were insufficiently detailed to determine whether the tablets they took were Rohypnol or another medication. Descriptions of tablets taken that were either positive or probable identifications of Rohypnol were provided by 29% of the users. (Many subjects provided multiple descriptions, and indicated that the appearance of "roofies" was variable.) Some of the descriptions raised the possibility that counterfeit preparations were also available, and one type of counterfeit tablet has subsequently been confirmed by forensic analysis. Our research suggests that in addition to ftunitrazepam, the pattern of "roofie" abuse includes a number of other drugs.

PKPD MODEL FOR STIMULATORY AND SEDATNE EFFECTS OF ALPRAZOLAM: TIMING PERFORMANCE DEFICITS

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Alprazolam increased the shorter (non-reinforced)-response rate (SRR) and decreased the reinforcement rate (RR) in a time- and dose-related fashion of a contingency-controlled timing behavior, differential reinforcement of low rate (DRL 45-s). We hypothesized that the rate changes observed were readily interpretable as functions of alprazolam concentration during 3-h session, a period for investigating the onset, peak and disappearance of alprazolam effect in rats. An integrated PKPD model was developed for three s.c. doses (1.25-7 mg/kg) and one i.v. dose (1.2 mg/kg) to study the pharmacokinetics (PK, n=4) and pharmacodynatnics (PD, n=7), respectively. The two peaks of SRR following s.c. alprazolam were. modeled as a stimulation-sedation PD model incorporating two opposing effect-link sigmoid Emax functions. This model suggested that alprazolam possesses both stimutatory and sedative effects in a continuous, but sequential fashion, which corresponded to low- (EC50 0.09 µg/ml) and high- (EC50 0.18 µg/ml) concentration effects, respectively. The i.v. dose identified the second peak as a transient, "rebound" phase in the recovery from drug effect, and the first peak (absent following i.v. dose) as the transition phase before onset of the sedative effect. The RR, characterized by the indirect response model (IC50 0.02 µg/ml), is an index for evaluating the deficit in timing performance. This model hypothesizes coexistence between stimulation and sedation components for alprazolam, which may help delineate possible mechanisms for rebound side effects and of tolerance in humans.

EFFECTS OF DRUGS OF ABUSE ON TEMPORAL DISCRIMINATION IN RATS

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The effects of drugs of abuse reprsentative of several pharmacological classes were examined in five rats trained to discriminate between two delay periods (3 s vs 10 s). Rats were first required to emit five consecutive responses upon a center lever after which one of two delay periods was presented. After a three second delay, rats were required to respond once on one of two levers, and after a ten second delay once on the other lever for food presentation. Upon completion of training rats responded with high accuracy (> 85%). Pentobarbital (0.1 - 13 mg/kg), diazepam (0.03 - 10 mg/kg), and phencyclidine (0.1 - 10 mg/kg) disrupted acuracy but at doses that also decreased response rates on the center lever. Amphetamine (0.01 - 5.6 mg/kg) and cocaine (0.3 - 13 mg/kg) did not produce significant disruption of accuracy up to and including doses that completely suppressed responding in some rats. The muscarinic antagonist scopolamine (0.003 - 1 mg/kg) dose-dependently reduced response rates and accuracy, whereas the quaternary analogue methscopolamine (0.003 - 1 mg/kg) did not disrupt accuracy up to and including rate suppressing doses. These results are consistent with those reported for the effects of drugs of abuse on measures of working memory and support the concept that drugs of abuse disrupt several aspects of cognitive function.

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MATCHING-TO-SAMPLE PERFORMANCE OF PIGEONS: EFFECTS OF SEDATIVE-HYPNOTICS AND RESPONSE BIAS

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To study the effects of pentobarbital, diazepam, and phencyclidine on both reference memory and working memory, 6 pigeons were trained under two matching-to-sample schedules. Under one schedule the ted-sample stimulus was presented 3 times more often than the green-sample stimulus. The ratio was reversed under the other schedule. It was hypothesized that such a training history would induce a response-bias model of reference memory useful for separating effects of drugs on reference and working memory. Drug testing was conducted under a no-bias condition: each sample stimulus was presented an equal number of tunes. Under both schedule conditions, pentobarbital (5.6 13 mg/kg), diazepam (1-5 mg/kg) and phencyclidine (1-3 mg/kg) decreased matching accuracy in an equivalent fashion. Likewise, no schedule dependent effects were observed on the rate of responding for any drug. Under the red bias condition, when doses of pentobarbital and diazepam were administered that decreased accuracy, an increase in ted-key responding was observed. A similar effect was not observed when the pigeons were biased toward green. Phencyclidine did not unmask a response bias under either training condition. These results suggest that these drugs have little effect on reference memory over the dose ranges studied.

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EFFECTS OF DRUGS OF ABUSE AND REINFORCEMENT SCHEDULE ON MATCHING-TO-SAMPLE PERFORMANCE

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The effects of pentobarbital, diazepam and phencyclidine were determined in 6 pigeons responding under a matching-to-sample schedule reinforced under a secondorder variable interval 100 sec (VI100) and, in a counterbalanced fashion, under a fixed-interval 100 sec (FI100) schedule of reinforcement. Under control conditions, overall matching accuracy was slightly higher under the VI100 schedule than the FI100 schedule, there were approximately 7 and 8 trials per food presentation under the FI100 and VI100 schedules, respectively, and the rate of responding to the sample stimulus presentation of each trial was slightly higher under the VI100 than the FI100 schedule. In spite of these differences, the effects of pentobarbital, diazepam and phencyclidine were similar under both schedules and little systematic difference was seen on overall percent matching accuracy or rate of responding. Likewise, the results were very similar to those previously reported in pigeons responding under matching-to-sample schedules in which every correct match resulted in food presentation. These results suggest that the effect of these drugs on working memory is not significantly altered by the schedule of reinforcement.

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EFFECTS OF SEDATIVE/HYPNOTICS AND STIMULANTS ON SYMBOLIC DELAYED MATCHING PERFORMANCE IN RATS

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Five rats were trained to respond under a delayed symbolic matching-to-sample baseline using a 3-sec delay. Baseline performance was characterized by approximately 80% matching accuracy and a 1.3 sec matching response latency. Experimental sessions terminated after 3600 sec or 60 trials in which the correct matching response was emitted. Pentobarbital, phencyclidine and *d*-amphetamine decreased matching accuracy at doses which did not significantly affect matching response latency or the number of trials completed per session. Still higher doses of pentobarbital (18 mg/kg) and phencyclidine (10 mg/kg) decreased matching accuracy and the number of trials completed per session, and increased matching response latency. Diazepam decreased matching accuracy andthe number of trials completed per session, and increased matching response latency at the same dose (10 mg/kg). Cocaine did not affect performance at doses up to and including 18 mg/kg. These results are similar to what has teen repotted in rats responding under both a 10-sec delayed alternation baseline and a matching-to-position baseline with delays of 3, 10 and 30 sec. Thus, there would appear to be less separation in the rat compared to the pigeon between doses which decrease working memory function and doses which decrease motor function.

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ANTECEDENT INFLUENCES ON HIV VULNERABILITY AMONG AFRICAN AMERICAN MEN

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This is a study of contributors to heterogeneity in HIV infectivity, i.e., differential vulnerability to HIV infection. Postulating that vulnerability derives from a complex of social and biological factors, it is focused on states anteceding exposure, particularly those related to the disadvantaged societal position of African Americans. The influence of social structural and psychosocial factors antecedent to exposure to HIV was tested with data from a prospective cohort study of 150 African American men, currently ages 35-41 who have been followed over 25 years and live study points since adolescence, using multivariate logistic analysis with three risk behaviors (IDU, male-male sex, heterosexual risk) controlled. Results showed that post adolescent demoralization, rather than temporally more proximal factors, had a significant effect. The effect was limited to, and conditioned, IDU risk. Specifically, IDUs with high demoralization had infection rates of 67% contrasted with 14% among earlier, low demoralized IDU's. Rigorous testing of potential confounders, including differences in injecting patterns and/or needle risk behaviors, general health status and depression did not reduce this effect. This evidence that psychosocial influences, antecedent to HIV exposure, modified risk infection for HIV among male IDU's underscores the urgency for early, i.e., adolescence and younger, drug prevention interventions for African American youth that includes attention to social contextual factors and youths' response to them.

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HIV AND RISK BEHAVIORS IN AFRICAN-AMERICAN PARTURIENT WOMEN

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Objective: To determine the relationship between HIV infection and behavioral risk factors among inner-city, African-American, partutient women. Methods: The study was part of a longitudinal investigation of the impact of *in utero* cocaine exposure on infant neurodevelopment. The sample included 1,802 African-American women delivering at ≥ 20 weeks gestation at the UM/Jackson Memorial Hospital. ELISA with Western Blot confirmation was used to assess HIV status. Tobacco, alcohol, marijuana, cocaine/crack, and other drug use; sexual behaviors; and physical and sexual abuse were determined by detailed maternal interviews. Toxicology assays were performed on maternal and infant urine and infant meconium, Logistic univariate and stepwise multivariate analyses were used. **Results:** 116 (6.4%) women were HIV-positive at delivery. 1,326 (74%) had no documented cocaine/crack use; 91(50%) used cocaine-crack before pregnancy only; 385 (21.4%) used cocaine/crack during pregnancy.

Demographics and Risk Behaviors	Adjusted O.R.	(95% C.I)
Cocaine/Crack Use During pregnancy	2.09	(1.29 - 3.39)
Physical Abuse Ever	1.97	(1.24 - 3.11)
# Sex Partners Past Year	1.38	(1.18 - 1.61)
Maternal Age at Delivery	1.06	(1.02 - 1.10)
Condom Use Past Year: Never vs. Always	0.42	(0.27 - 0.67)

Conclusion: HIV infection correlated significantly with cocaine/crack use during pregnancy, physical abuse ever, number of sex partners past year, and older maternal age. The results for condom use appear to be due to the large number of women (n--679) with no condom use and only one sexual partner in the past year.

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GENDER DIFFERENCES IN METHADONE MAINTENANCE PATIENTS

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An investigation of familial substance abuse and psychosocial variables in opiate and cocaine abusers was conducted during a 35-week outpatient pharmacologic and behavioral management treatment study at the Addiction Research Center. Of the three hundred seven participants, 37% (115) were female and 46% (142) were African-American. Fifty-one percent of the female enrollees were African-American. Drugs of choice were heroin (100%); cocaine (80%); benzodiazpines, marijuana, and alcohol (15%). Five percent of the participants reported using heroin only. Mean age was 37. Women differed from men on a number of characteristics: having a spouse/significant other IVDU (58-33%, p=.000); having a mother with a substance abuse history (30-19% p=.010); having sisters with substance abuse histories (53-34%, p=.013): later age of 1st regular drug use (mean =17.9-16.3, p=.022) and 1st regular use of heroin (mean=21.9-19.7, p=.0.37); less likely to be employed (37-18%, p=.000), and less stable occupation (33-15%, p=.000). There were no gender differences in the following characteristics: marital status, number of criminal charges and incarcerations, and life time number of sexual partners. This suggests some likelihood that women substance abusers may become vectors of HIV transmission which would spread to non-drug using sexual partners and unborn children. Transmission of HIV is entirely conceivable in light of the large number of sexual partners reported by participants in this study (43.95, SD 9.95), lack of regular condom use, and continued needle sharing with others in their social network, including IV drug using sexual partners.

PREVENTION OF HIV FROM UNPROTECTED SEX AND DRUG USE BY AFRICAN AMERICAN WOMEN THROUGH COMMUNITY AND CULTURAL INTERVENTION

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The increasing number of African Americans afflicted with HIV/AIDS give reason to direct attention to this segment of the population, Researchers and service providers need a better understanding of the role of culture, gender, and socioeconomic factors in the transmission of HIV among group. The study focuses on preventing the spread of HIV from unprotected sex and drug use by African American women via community and cultural intervention. Moreover, the study investigates the relationship between pre and post assessment relative to subjects attitudes regarding HIV, and the effectiveness of intervention for preventing the transmission of HIV. A cohort of women mostly African Americans from the lower socio economic stratum of Beaumont, TX agreed to volunteer as subjects. The subjects were identified by the health department for being at risk for transmitting HIV. Subjects took part in a day long program, sponsored by the health department and the university. The intervention encompassed education on the different ways of spreading HIV. The findings suggested that community and cultural intervention showed effectiveness and differences in attitudes regarding risky behaviors that contribute to me spread of HIV.

UNPROTECTED SEX WITH HIV INFECTED DRUG USERS

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Currently, injection drug users (IDUs) comprise 32% of AIDS cases reported to the Centers for Disease Control and Prevention. Unprotected sex with an HIV seropositive partner represents the greatest risk for contracting HIV among non-IDUs. The current study assessed the extent to which HIV seropositive drug users placed others at risk of infection through unprotected sex, and investigated demographic and behavioral factors contributing to risky sex behavior. Structured interviews were conducted as part of a three year, multi-site research project directed by the Health Resources and Services Administration and the National institute on Drug Abuse. Responses from 106 sexually active, HIV seropositive drug users in Denver, Detroit, New Orleans, St. Louis, and West Palm Beach were analyzed. Significant demographic differences across the five cities were controlled for in analyses of me predictors of unprotected sex. Results of a multiple logistic regression revealed that respondents having unprotected sex were more likely to be White, to have injected cocaine, to have teen told they had HIV/AIDS symptoms in the last six months and to have been told they were symptomatic more often than those not having unprotected sex. Implications are discussed with regards to future research needs and the educational needs of HIV seropositive drug users.

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PREVENTING HIV/AIDS AMONG MIDDLE-AGED AND ELDERLY PERSONS WHO USE INJECTION DRUGS

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Middle-aged and elderly persons are not immune from the hazards or consequences of excessive and abusive drug use, such as traffic accidents and fatalities, overdose, and in particular, contracting and spreading HIV/AIDS. As middle-aged persons of today become elderly in the beginning of the twenty-first century, it will become a health priority to provide HIV/AIDS outreach and treatment services for a segment of the population that is often mistakenly characterized as having low risk for contracting and spreading this disease. Injection drug use with dirty needles and promiscuity continue to occur in this nation's older populations, due in part to generational influences, via the permissive attitudes and openness to experience during the 1960s to the early 1970s, and enduring the horrors of the Vietnam War (war veterans). Current efforts to prevent HIV/AIDS target younger populations, fueling the misperception that HIV/AIDS is a scourge of the young. However, these same behavior choices are made by middle-aged and, to a lesser extnt, elderly people. Prevention efforts for older populations may include components from effective prevention protocols for younger populations: (1) social support groups that target issues of advanced age; (2) psychotherapy on an outpatient basis; and (3) education about safer injection drug use and sex practices.

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NEEDLE EXCHANGE AVAILABILITY AND PARTICIPATION AMONG INJECTION DRUG USING WOMEN

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Objective: To describe Needle Exchange Program (NEP) participation in women injection drug users (IDUs). **Methods:** NIDA/HERS substudy questionnaire was administered to all women enrolled in the multi-site HER Study who reported injection drug use within six months at semi-annual follow-up visits between January and December 1996. NEP administrators were contacted in all four cities. **Results:** Two hundred women reported injection drug use within 6 months; 71% were HIV positive; 39% reputed obtaining at least some syringes at a NEP. Women were more likely to use NEP in cities where needle exchange was more available (48% v. 14% p<.01). There was no difference between HIV positive and HIV negative women (43% vs 38% p= 0.6). NEP participants were more likely to inject within 2 days, (66% vs. 34% p<.01), to inject cocaine (71% vs. 55% p=.04). or to inject a speedball (79% vs. 54% p<.01). Daily injectors were more likely to participate in NEP than less frequent injectors of cocaine (63% vs 35% p=<.01), heroin (56% vs 30%,p<.01). and speedballs (66% vs 334%,p<.01). 19% reported using contaminated rinse water or syringes, of whom 61% did not use NEP. **Conclusions:** Sixty-one % of injection drug using women did not participate in needle exchange programs. Injection drug using women who reported heavier and more frequent drug use were more likely to participate in needle exchange programs. Availability of an established NEP is an important predictor of NEP use. Infrequent users may require more outreach. Further studies of obstacles to NEP use by injection drug using women are needed.

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TRENDS IN SELF-REPORTED HIV RISK BEHAVIOR: INJECTION DRUG USERS IN LOS ANGELES

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This paper reviews trends in HIV risk behaviors across serial samples of injection drug-using arrestees between 1987 and 1995. Current needle sharing and past-year needle sharing with strangers steadily declined. Past-year needle sharing at shooting galleries has remained low. Bleach use among needle sharers increased sharply. Through 1993, no increase had occurred in avoidance of needle sharing for as long as one year. In 1994-95, however, past-year needle sharing sharply declined, possibly as a result of new needle exchange programs. No change occurred in number of sex partners, but condom use became much more prevalent among nonmonogamous injectors. Needle exchange may have a unique role in reducing the risk of HIV transmission among Los Angeles drug users.

A TWO-WAY RELATIONAL MODEL BETWEEN DRUG USE AND HIV/AIDS

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The relationship between AIDS and drug abuse seems obvious to the commonsense public: the dire consequence of a bad behavior. Reflected in academic theorizing is an one-way model that traces AIDS to drug abuse through four routes. Fiit is intravenous drug use: drug users sharing needles in shooting galleries and other settings may contract and spread AIDS. Second is sex for drugs: drug users engaging in sex for or with drugs may contract and spead AIDS. Third is drug effects: drug users involved in impulsive and unprotected sex under the influence of drugs may contract and spread AIDS. Fourth is drug culture: drug users practicing antisocial behavior supported by a culture of deviance and rebellion may contract and spread AIDS. A two-way model is needed. When HIV infection becomes self-recognized, it may trigger drug abuse: if AIDS patients never abused drugs befor, use of marijuana and analgesic drugs for pain relief can initiate them into dependent drug use. It may worsen drug abuse: people with HIV may engage in high-risk drug use as a coping strategy. It may also terminate drug abuse: people with HIV may rediscover the meaning of life and be determined to live it free of drugs. Confinement in treatment terminates drug abuse for seriously ill AIDS patients as well. The two-way model treats HIV/AIDS as both a dependent and an independent variable and studies how HIV/AIDS influences and is influenced by drug abuse. With regard to the AIDS risk reduction model, the two-way model encompasses it since ARRM stands half-way in the AIDS-drug relationship by beginning with AIDS education, HIV knowledge, and AIDS fear rather than the verified infection of HIV or experienced effect of AIDS. ARRM may also branch out into risk reduction and risk augmentation models as HIV-negative drug users who have lived a risk lifestyle for years may perceive themselves as invulnerable and therefore continue or engage more in HIV-risk behavior.

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DOES KNOWLEDGE OF HIV RISK-REDUCTION STRATEGIES PRODUCE BEHAVIORAL CHANGE IN INJECTION DRUG USERS (IDUs)?

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The process by which knowledge about HIV risk-reduction strategies is translated into its behavioral counterpart was investigated in injection drug users (IDUs) in the context of an exploratory survey study. Twenty-nine opiate dependent IDUs in treatment at the Substance Abuse Treatment Center at the University of Vermont completed questionnaires designed to assess their 1) previous HIV/AIDS education, 2) level of accurate knowledge about HIV/AIDS, 3) estimated perceived risk of contracting AIDS, 4) estimated ability to refrain from engaging in HIV risk behaviors, and 5) degree of actual HIV-risk behaviors. Results indicated that IDUs typically have a high level of general knowledge regarding the prevention of the transmission of the AIDS virus (mean accuracy=84.62%; SEM=0.14%), which was significantly correlated with the number of days of their previous HIV/AIDS educational experiences ($\underline{r}$=0.385, $\underline{p}$<.05). No significant correlations between participants' level of accurate knowledge and their high levels of either drug-related ($\underline{r}$ =-0.167, ns) or sex-related HIV risk behavior ($\underline{r}$ =-0.272, ns) were evident. In addition, participants had a low perceived risk for contracting AIDS (mean =20.31%, SEM=3.57%), which did not correlate with either their high level of drug-related ($\underline{r}$=0.157, ns) or sex-related HIV risk behaviors ($\underline{r}$ =-0.046, ns). Findings suggest that HIV/AIDS education may promote the acquisition of accurate AIDS-related knowledge among IDUs; however, knowledge alone may he insufficient to produce behavioral changes. Rather, IDUs appear to dissociate their HIV-risk behavior from their personal perceived risk for contracting AIDS. As a result, interventions which train IDUs to accurately assess their likelihood of contracting AIDS based on their high-risk behavior may prove effective in promoting behavioral change.

ANTISOCIAL PERSONALITY DISORDER, SOCIOPATHY, AND RISK FOR HIV INFECTION IN INJECTION DRUG USERS

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A significant percentage of injection drug users (IDUs) have antisocial personality disorder (APD). APD has been found by some researchers to he an additional risk factor for human immunodeficiency virus (HIV) infection in IDUs. The present study evaluated the association of sociodemographic characteristics and substance abuse history from the Addiction Severity Index, and several measures of antisocially, to behaviors associated with HIV risk, a measured by the Risk Assessment Battery (RAB), in 289 opiate-dependent methadone-maintained subjects. The measures of sociopathy were the DSM-III-R diagnosis made by the Personality Disorder Examination, the California Psychological Inventory- Socialization Scale (CPI-So) and the Psychopathy Checklist- Revised (PCL-R). The presence of various risky behaviors was predicted with linear and logistic regression analyses more consistently by measures of personality traits associated with sociopathy (PCL-R and CPI-So) than by a diagnosis of APD. Personality traits of sociopathy may he more useful than an APD diagnosis in identifying at-risk patients for intensive HIV risk reduction interventions.

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ANTISOCIAL PERSONALITY DISORDER IS NOT ASSOCIATED WITH POOR IMPROVEMENT IN HIV RISK BEHAVIORS AMONG COCAINE USERS

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Previous work has documented that antisocial personality disorder (ASPD) is associated with increased rates of HIV risk behaviors and with worse substance abuse treatment outcomes. The question addressed by this paper is whether cocaine users with ASPD respond to an HIV risk-reduction intervention as well as cocaine users without the disorder. The study subjects were 333 cocaine users followed up at 18 months as part of a NIDA-funded treatment demonstration project. Improvement was found for the group as a whole across a wide range of HIV risk behaviors. Improving significantly ($p < .05$) from baseline to the 18 month follow up were several drug-related behaviors: current cocaine dependence, drug injection, injection equipment sharing, and use of syringes that were not cleaned. Several sex-related risk behaviors also improved significantly: having multiple sex partners, being intoxicated during sex, giving drugs for sex, receiving money for sex and receiving drugs for sex. When the sample was stratified by ASPD status, very similar improvement was seen in respondents with and without ASPD. To examine further the relationship of ASPD to change in HIV risk behaviors, separate logistic regression models of improving and worsening risk behaviors were tested. What we found was no association of ASPD with improvement (or lack thereof) in HIV risk behaviors but a possible association of ASPD with worsening HIV risk behaviors. It appears that cocaine users with ASPD improve their HIV risk behaviors just as much as those without ASPD hut are at higher risk for the development of such behaviors.

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RISKS FOR HIV SEROCONVERSION IN THE COLLABORATIVE INJECTION DRUG USERS STUDIES (CIDUS)

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Objectives: To *determine* risk factors for HIV seroconversion among injection drug users (IDUs) in six U.S. study sites (NYC [2], LA County, Chicago, San Jose, and Baltimore). **Methods:** Participants were street-recruited using word of mouth and "snowball" techniques interviewed with a standard questionnaire, and asked to return for follow-up. HIV serostatus was determined at baseline and at follow-up visits 6-12 months after. **Results:** At baseline, 3,775 IDUs bad been recruited in the CIDUS; 47% were re-recruited for at least one follow-up visit. At baseline, the mean age was 37 years, 36% were female, 39% African American, 33% Hispanics, 50% single, 57% homeless, and 55% bad less man a high school education. There were 19 seroconversions in 1323 "person-years" of observation (HIV incidence = 1.4/100 person-years). In a logistic regression analysis, risk independent factors for seroconversion included crack smoking; injecting "speedball;" injecting heroin; being an IDU from the East Coast: injecting more than they had six months previously; and, injecting at someone else's home; 80-100% of seroconverters bad at least one of these risks (all P-values <0.05). **Conclusion:** These preliminary data indicate seroconversion for IDUs in the CIDUS is multifunctional. Crack smoking plays an important role probably by increasing the number of unprotected sex acts. HIV prevention programs targeting IDUs should include "safe sex" as well as "safe injection" messages.

GENDER DIFFERENCES IN RECENT CRACK USE AND HIV RISK AMONG NON-INJECTING USERS OF HEROIN

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Introduction: Crack use has been found to be associated with HIV infection among both non-injectors and injectors. We examine, within gender, whether non-injecting users of heroin (NIUs) who report having never injected drugs and having recently used crack (in the prior 30 days) are more likely to be seropositive for HIV, hepatitis B and hepatitis C, and are more likely to engage in high-risk behaviors and have high-risk drug and sexual partners than NIUs not using crack. **Methods:** Two hundred sixty-nine NIUs recruited out-of-treatrnent in NYC who reported using heroin al least once in the last 30 days and having never injected drugs, were interviewed between March 1996 and April 1997 at intake into a cohort study on transitions to injecting. They were asked about their HIV risk behaviors and drug and sexual partners, and were counseled and tested for HIV, hepatitis B and hepatitis C. **Results:** The sample was 74% male, 26% female; mean age 34.3, S.D.= 8.2; 35% African-American, 31% Latino, 28% white, and 6% other race/ethnicity; 109 (41%) recently used crack (of whom 19 (17%) were women and 90 (83%) were men). Among women, but not among men, recent crack use was significantly associated with being infected with HIV (OR = 17.8; 95% CI = 3.3, 95.8) and HBV (OR = 4.6, 95% CI = 1.5, 14.2). and was a trend for HCV (OR = 2.9, 95% CI = 0.9, 10.1, $p < 0.10$). Among women, recent crack use was associated with exchanging sex for money or drugs (11% vs, 08, $p < 0.05$), and with having sex partners who were crack users (OR = 13.1, 95% CI 3.3, 50.9). Among men, recent crack use was associated with using heroin with current drug injectors (OR = 2.2, 95% CI = 1.1, 4.4) and at commercial multi-user settings (OR = 4.4, 95% CI 1.2, 16.6). **Conclusion:** Women NIUs who have never injected and who use crack have been and continue to be at high-risk for sexually transmitted HIV and HBV; they may also be a potential vector for the transmission of these pathogens. Among men, NIUs who have never injected and who use crack may be at high risk of becoming injectors. Interventions among NIUs should give increased attention to crack users within this group.

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INTERVENTION EFFECTIVENESS AMONG COCAINE SNORTERS AT RISK FOR HIV IN RIO DE JANEIRO, BRAZIL

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Established in 1993, by the National Institute on Drug Abuse, the *PROVIVA* Project has provided HIV risk reduction counseling to over 1,000 current cocaine users in Rio de Janeiro. The primary aims of this initiative are to reduce the spread of HIV/AIDS among street drug users, and to evaluate the efficacy of a controlled experimental intervention designed to decrease risky drug use and sexual behavior. All clients complete a detailed risk assessment interview at baseline. participate in standardized HIV pre-test and post-test counseling sessions, and are offered HIV testing. Participants are then re-interviewed in 3 months to determine whether reductions in HIV risk behaviors bave occurred. Through February 1997, complete data were available on 511 cocaine snorters who were primarily male (83.6%). young (median age 29 yrs.), poorly educated (84.7% had fewer than 8 years of schooling), and 9.0% tested HIV-positive. Preliminary analyses of pre- and post-intervention measures reveal a significant decrease in occasions of cocaine use, as well as a significant increase in occasions of protected vaginal sex for males. These data suggest that the intervention model, originally designed for drug users in the U.S., may have applications for reducing HIV risk among street populations in other nations.

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CONDUCTING RESEARCH ON THE AIR BRIDGE: HJV RISK BEHAVIOR AMONG PUERTO RICAN DRUG USERS

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High rates of seropositivity have been reported among Puerto Rican injection drug users (up to 50%) and crack smokers (10-20%) in PR and NYC, with significant differences in risk behaviors among drug users in both locations, yet there is a high rate of mobility between the two sites. Our previous research indicated that 88% of PR drug users in NYC have been to PR. This connection between the two locations which has been termed the "air bridge", provides the opportunity to study the impact of mobility, socioculturat factors and environment on risk behaviors in a single ethnic group. This paper will describe the qualitative methodologies developed to do the first phase of a multi-year qualitative and quantitative study of HIV risk behavior determinants among Puerto Rican drug users in Bayamón, PR and East Harlem, NY. New methodological approaches were needed to insure data collection for all key domains, and comparability between the two sites. Development and content of new guidelines for conducting mapping, field observations, focus groups and life history interviews will be described, including methods to standardize meanings between the two sites (e.g., rather than targeting shooting galleries as sites for observations, selecting observation sites based on behaviors (e.g., locations where drugs are used). Methodological problems and their solutions will be summarized, and preliminary findings of differences between the two sites will be presented.

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HIV PREVENTION WITH DRUG USERS: A DATABASE AND SYNTHESIS OF RESEARCH

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The effectiveness of behavioral methods of HIV risk reduction is a major public health concern. Efforts to reduce risk have been ongoing since the mid-80's. At present, a growing body of research must be synthesized, evaluated and made accessible for use by both researchers and practitioners. This poster describes a NIDA-funded project which, in the first phase, developed a database using information derived from efficacy studies of behavioral interventions which targeted high risk drug users for HIV prevention. Using information from this first phase, we will determine the feasibility of developing a range of products in later phases. Some products, (e.g., a citation database with descriptions of prevention strategies and critical, evaluative summaries) will be written in non-technical language to make the information accessible to those without research expertise. Other products (e.g., meta-analytic summaries) will be of interest primarly to researchers. Proocedures used to develop the database and extract information are described. Preliminary results of the first phase, consisting of an annotated bibliography, are available for distribution.

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POSTER SESSION II

IMPACT OF DRUG AND ALCOHOL TREATMENT AND A BRIEF COMMUNICABLE DISEASE INTERVENTION ON RISK BEHAVIORS

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This paper examined bow drug use and high-risk heterosexual behavior of substance abuse clients evolve during the first weeks of an outpatient, abstinence based. substance abuse treatment program, In addition, we aim to identify demographic and drug use correlates of sex trading through descriptive statistics and logistic regression. **Hypotheses:** Substance use will decrease with time in treatment; men will purchase commercial sex and trade drugs for sex with greater frequency than women; women will exchange sex for money and drugs with greater frequency; and crack cocaine will be the most important drug use correlate of sex trading. Design: Anonymous cross section of clients taken prior to STD/HIV education sessions from March 1996 to May 1997. **Methods:** Outpatients were surveyed with the Risk Assessment Battery (Metzger) and 167 questionnaires were analyzed. Simple cross tabulations were presented to illustrate the patterns of behavior by the exposure variable - - time in treatment. Logistic regression was used to estimate the strength of the association between various correlates of high-risk behavior. Data was presented as EXP (b) to estimate odds ratios and confidence intervals. ANOVA was used to analyze a summary measure of these behaviors plus multiple sexual partners. **Results:** Self-reported drug use and alcohol consumption decreased sharply with time in treatment. Commercial sex and sex trading varied by age, sex, and time in treatment. In this small sample from Chicago, snorting cocaine, not smoking crack, and sex were the only significant correlates of high-risk sexual behavior. **Conclusion:** With 10% to 22% of all clients engaging in some form of high risk sexual behavior during the course of their treatment, programs should continue to integrate substance abuse treatment with some form of HIV/STD education, screening, referral and/or therapy.

RETENTION AND HIV RISK-REDUCTION IN A NATIONAL TREATMENT SAMPLE (DATOS)

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The prevalence of HIV among injection drug users, particularly drug-using women, means intervention efforts directed at reducing injection and risky sexual behavior are increasingly important. However, clients must remain in treatment long enough to benefit from these efforts, This study examined HIV risk outcomes during the 1-year period after discharge, comparing early dropouts and longer-tenure clients from long-term residential (LTR). outpatient methadone maintenance (ONM), and outpatient drug free (ODF) modalities of the NIDA-funded Drug Abuse Treatment Outcome Study (DATOS). Analysis of covariance was used to assess the relationship among gender. treatment tenure, and post-treatment injecting, condom use, and number of sex partners (while holding pretreatment behavior statistically controlled). In both LTR and OMM, longer-tenure clients exhibited lower frequencies of injection at follow-up, and in LTR they also had fewer sex partners following treatment. Among women in LTR, early dropouts had more post-treatment sex partners than men, but longer-tenure women did not. Longer treatment especially for women, may be vital to reducing the spread of HIV and underscores the consequences of early dropout from treatment.

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DRUG ABUSE TREATMENT AND RISKY SEX

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This paper presents evidence regarding the possibility of a cumulative effect of drug abuse treatment on risky sexual behavior among a sample of 6,620 cases entering drug abuse treatment in the United States in 1991-93. These cases were participating in the Drug Abuse Treatment Outcome Study (DATOS). Analyses tested the relationship between lifetime treatment exposure and risky sex by drug users during the year before DATOS intake. Analyses controlled for age, drug use severity, history of antisocial conduct, and other factors that might have confounded the relationship between treatment exposure and risky sex. Results indicated that users with mote lifetime treatment exposure had significantly lower scores on risky sex. This finding is consistent with the hypothesis that treatment has long-term cumulative effects on drug users HIV risk behavior.

HIV SERVICES AMONG CLIENTS IN DRUG TREATMENT: DIFFERENCES BY GENDER, MODALITY, AND RISK STATUS

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This study examined the extent and type of services related to HIV risk reduction received by clients in the Drug Abuse Treatment Outcome Study (DATOS). Data was collected from clients after three months in long-term residential, outpatient drug-free and methadone maintenance treatment and after one month in short-term inpatient treatment. Clients in residential treatment were mosl likely to receive HIV-related services compared with the other modalities. Across all four modalities, men were more likely than women to receive HIV-related services regarding sex-risk reduction, health care options, and general knowledge about HIV, with no difference in services regarding needle-risk reduction. Individuals were classified into high and low sex-risk categories based on: whether they exchanged sex for drugs or money, had a high-risk sex partner (i.e., a sex partner who is HIV-positive. a man who has sex with men. an injection drug user, or a sex worker), or had more than two sex partners and did not consistently use condoms. High sex-risk males were more likely to receive sex-risk reduction services, although high sex-risk females were not. A logistic regression equation indicated that men. African-Americans, Hispanics, individuals who were alcohol dependent, and sex workers were more likely to receive HIV-related services, whereas individuals who were employed full-time or had health insurance were less likely to receive HIV-related services, controlling for type of drug treatment modality and other variables. These findings suggest that high sex-risk women may not be receiving needed services for HIV sex-risk reduction within drug treatment programs, particularly women who have a high-risk sex partner or multiple sex partners.

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EFFECTS OF STAGE OF CHANGE AND HIV RISK-REDUCTION COUNSELING ON BLACK CRACK/COCAINE USERS

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St. Louis' EachOneTeachOne (EOTO) Cooperative Agreement research project data are used to examine the effects of Stage of Change and Standard vs. Enhanced Counseling on the HIV risky behaviors of 861 out-of-treatment. black crack/cocaine users 3 months after intervention. Results show similar changes in HIV risky behaviors across four stages of change: the precontemplation stage, contemplation stage, action stage. and maintenance stage. Most study participants, regardless of their stage of change al baseline. improved by reducing or maintaining lower levels of HIV risky behaviors. Specifically, 57% reduced or maintained a low level of non-injection drug use; 93% abstained from injection drug use or reduced their level of injection drug use; 81% reduced their number of sex partners or abstained from sex; and 70% reduced the percent of times not using a condom when having sex or abstained from sex. The Standard Interrvention Group and the Enhanced Intervention Group had similar reductions in risk related to number of sex partners and injection drug use. The Enhanced Group had a statistically significantly higher percent of improvement in non-injection drug use (62% compared to 51% for the Standard Group), but less improvement in the percent of times not using a condom when having sex (66% compared to 75% for the Standard Croup). When Stage of Change is controlled, the precontemplators are more affected by the Enhanced Counseling than those in later stages of change. Implications are that street outreach, recruitment, and targeting out-of-treatment drug users at earlier stages of change for interventions may prove to be more effective than waiting until they reach later stages of change and/or enter treatment.

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NODE-LINK MAPS, AIDS-RISK LEVELS, AND RESIDENTIAL DRUG ABUSE TREATMENT

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The investigation examined the influence of pre-treatment AIDS-risk levels and node-link mapping on client ratings of treatment programs. Node-link mapping is a visual representation strategy that has been shown to reduce drug and needle use and facilitate group counseling. Probationers (n = 288) mandated to a 16-week residential drug abuse treatment program received either mapping enhanced (n = 149) or standard counseling (n = 139), and were classified on the basis of intake data to be at either high (n = 140) or low risk (n = 148) for AIDS. Participants completed a variety of measures at intake, midterm and endterm. A series of 2 (Counseling method: Mapping vs. Standard) X 2 (AIDS-risk levels: High vs. Low) multivariate analyses of variance were conducted. The dependent variable probationers' ratings of: a) their motivation to acquire certain life skills (i.e., emotional control, improved cognition. and life-management skills); b) their reported treatment self-efficacy and motivation; c) their evaluations of themselves in treatment (i.e., their treatment progress, success, and engagement, and affect toward treatment); and d) their psychological well-being (i.e., anxiety, depression, and self-esteem). Those at high AIDS-risk reported significantly (p < .05) lower treatment self-efficacy and motivation, and lower psychological well being (e.g., anxiety and depression) than those with low AIDS-risk. High AIDS-risk mapping probationers reported significantly (p < .05) higher motivation to acquire life-skills (e.g., emotional control and life management skills) than their counterparts in standard counseling. Low AIDS-risk probationers receiving mapping reported significantly (p < .05) higher treatment engagement and session participation than their counterparts who received standard counseling. The results suggest that AIDS-risk levels affect evaluations of drug abuse treatment programs, and that exposure to mapping-enhanced counseling may ameliorate some of the disadvantages that accompany high AIDS-risk levels while also providing benefits to those at low AIDS-risk.

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AIDS RISK BEHAVIORS, COCAINE USE, AND TREATMENT OUTCOMES

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HIV risk practices and relationships to treatment outcome were studied in 444 cocaine-dependent Ss in private chemical dependency treatment programs during 1989 - 1991. The hypothesis was that risky drug use and sexual practices are related and linked to an increased probability of relapse to cocaine use. Ss were recruited prior to treatment entry and provided data on drug and alcohol use. symptoms of cocaine dependence, and route of cocaine administration. They provided data on HIV risk drug use and sexual practices. Ss were followed for 12 months (4 quarters) following treatment entry and provided data about their cocaine use and urine specimens to confirm self-reports. There were 49 IVDUs in the sample, not all of whom injected cocaine. For non-injectors, smoking crack was significantly related to risky sexual practices. For IVDUs. risky sexual practices and needle risk were significantly and positively correlated. Notable differences between IVDUs and non-injectors in patterns of correlations were observed. There were no differences between IVDUs and non-injectors on the outcome variable, number of quarters of cocaine use post-treatment entry. This outcome measure was unrelated to all of the risk measures for IVDUs and non-injectors. Linear regressions were Performed regressing number of cocaine dependence symptoms, route of administration, sex risk scores, and for IVDUs, needle risk scores, on quarters of cocaine use. The models were not significant. The hypothesized relationship between risky needle use and sex practices was obtained, but there was no evidence to support a linear positive relationship of these behaviors to treatment outcome. Data reveal that IVDUs and non-injectors have different patterns of sexual practices and therefore they might benefit from differently targeted AIDS prevention interventions.

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DRUG USE/HIV RISK OUTCOMES BY TYPE OF DRUG TREATMENT

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Hypothesis: Participation in drug treatment will result in greater reductions in drug use and drug-related HIV risk when type of drug treatment is compared to no treatment. **Sample:** *Data source:* national database for NIDA Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program. **Eligibility:** Adults who used cocaine or heroin in previous 30 days and were not in treatment during 30 days prior to baseline; *sample:* Cocaine Users (CU) who did not use heroin (N=4,806, 91% no drug treatment; 8.3% HIV+), Heroin Injectors (HI) who did not use cocaine (N=690; 62% no drug treatment; 5% HIV+), and Dual Users (DU) who used both cocaine and heroin (N=3,156; 79% no drug treatment; 10.5% HIV+); 2/3 male, 2/3 African American. Methods: For each of the three drug user groups, comparisons were made between people who had not received any drug treatment between baseline and six months follow-up and those who participated in at least 14 days of either methadone detoxification methadone maintenance, outpatient treatment, residential treatment, or prison/jail-based treatment. **Results:** For CUs, outpatient treatment resulted in greater reductions in crack use compared to no treatment (10 vs. 6 days, $p<.0001$). Although residential treatment showed greater reductions in crack use (9 days), this was not significant. For HIs, methadone maintenance resulted in greater reductions in heroin use than did no treatment (14 vs. 7 days, $p<.0001$). Residential treatment was also associated with a 14-day reduction in heroin use. but due to an N of 12, this was not significant For DUs. methadone maintenance or outpatient treatment resulted in gteater reductions in heroin use man did no treatment (14 vs 10 vs 4 days, $p<.0001$). Reductions in sharing needles, cookers, or cottons did not differ significantly for any type of treatment for any group. **Implications:** AIDS outreach/intervention was effective in reducing drug use and drug-related HIV risk behavior. Some drug treatment modalities facilitated greater reductions in crack or heroin use beyond outreach alone, but did not produce greater reductions in other types of drug-related HIV risk. Greater emphasis on getting drug users into drug treatment, and enhancing HIV risk reduction education during treatment, may be needed.

HIV RISK REDUCTION AMONG HOMELESS CRACK SMOKERS COMPLETING DAY TREATMENT AND AFTERCARE

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Crack cocaine use has been directly linked to increased risky sexual behaviors, like trading sex and crack. Participants in a 2 group treatment outcome study completed the AIDS Risk Assessment for Crack Cocaine Users (ARA-C) at intake and treatment completion after 6 months. Information was collected related to crack and alcohol use, sexual behaviors, and sex and crack use behaviors. The ARA-C measures seven HIV risk constructs: Self Control (SCon), Sexual Negotiation (SNeg), Sex and Crack (SCk), Condom Use (CUse), Partners (P), IV Use (IV), and Sexual Behavior (SBeh) represented by a standardized risk value from 0 (lowest risk) to 100 (highest risk) for each construct. Subjects (N=68) were 71.2% male, 85.6% African American, with an average age of 37.7 (S D=6.97) years. Results using T-tests and McNemar's tests (past 6 months from baseline vs treatment completion after 6 months) were: daily crack use (62% vs 15%, p <.05); daiiy alcohol use (36% vs 17%, p <.05); number of different sex partners (9.7 vs 3.3, p<.05); number of sex partners with whom used crack (7.1 vs 1.8, p <.05); times traded sex for crack (8.2 vs 2.6, p<.05); times traded crack for sex (10.3 vs 1.2, p<.05); use condom with spouse/mate nearly every time (44% vs 56%); and use condom with dale/trick nearly every time (44% vs 50%). Significant reductions (p <.05, T-tests) from intake to treatment completion were found for the following HIV constructs: SNeg (53.1 vs 45.8); SCk (10.3 vs 3.3); CUse (37.0 vs 30.7); P (7.2 vs 2.0); SBeh (13.9 vs 7.6), and IV (20.6 vs 6.3). No significant change was shown for SCon (53.3 vs 47.4). Findings suggest important HIV risk factors associated with crack cocaine using Lifestyle were reduced after 2 months of day treatment and 4 months of aftercare. Implications for including HIV risk reduction intervention during drug treatment are made. Treatment group differences will be analyzed.

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EFFICACY OF A STRUCTURED MANUAL FOR IMPROVING DRUG COUNSELING AMONG SUBSTANCE ABUSERS WITH HIV

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Drug abusers with HIV have multiple and often severe problems with a host of issues, including housing, transportation, physical and psychiatric illnesses, substance use, and finances that can overwhelm even the most enthusiastic of counselors. Training programs that provide structured methods for working with substance abusers with HIV may help increase counselor efticacy and reduce burnout and consequent attrition of qualified personnel. This study evaluated the impact upon counselors of being trained to use a structured treatment manual for substance abusers with HIV. A total of 99 counselors from 34 clinics across the United States were randomly assigned to 'Immediate' or 'Delayed training. Counselors from clinics in the 'Delayed' condition were trained after six month foiiow up assessments. We hypothesized that counselors in the 'immediate' training condition would show higher self-efiicacy. lower bum-out, greater perceived clinic quality, a counseling style that is more cognitive-behaviorally oriented, and better HIV knowledge, when compared with counselors in the 'Delayed condition at six month follow-up. Findings suggest a limited impact of the training on counselor variables. Counselors in the 'Immediate' training group showed a mom cognitive-behaviorally oriented counseling style (t(71)=2.61, p<.05). No differences were found in self-efficacy, burnout perceived clinic quality, or HIV knowledge. Overall HIV knowledge was very low, with counselors in the 'Immediate' training condition answering 58.17% (S.E.M. = 1.97) of questions in a knowledge survey correctly. These findings imply that counselors who work with substance abusers with HIV need more intensive interventions than brief training and structured manuals.

DRUG TREATMENT STAFF AND AIDS: RESPONSE TO DEATHS IN PROGRAMS

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We examined reactions to deaths among clinical staff from drug treatment programs specializing in HIV disease. Subjects were 65 paraprofessional (PP) and 18 professional (PRO) staff in San Francisco programs. PPs (former substance abusers with BA/BS or less) were more likely to be men and nonwhites. Procedures involved individual interviews using quantitative measures of personality, job characteristics, exposure to deaths, and staff difficulties (distress about deaths, grief, burnout, stress, psychological symptoms, and records of absences from work). Focus groups provided qualitative information. Our hypotheses were that exposure to patient deaths predicts staff difficulties, and PPs display more staff difficulties. **Results:** Staff knew a mean of 14 people who died in the past year, including 10 who had died related to AIDS. PPs and PROs did not differ in exposure to deaths. In general exposure to deaths did not predict staff difficulties, although there were some moderate relationships with distress about deaths and absences from work. In general PPs and PROs were more similar than different on most measures of staff difficulties, although there were some differences in psychological symptoms, burnout, and stress that may be explained by background and personality differences between PPs and PROs. **Implications:** Exposure to patient deaths was substantial, but we did not detect an influence on level of staff difficulties. Staff expressed a need for better training in dealing with deaths.

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CASE MANAGEMENT OF SUBSTANCE ABUSERS WITH HIV INFECTION: SERVICE UTILIZATION AND COSTS

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We report on health service utilization among 190 substance abusers with HIV who were not in substance abuse treatment. Participants are in an on-going randomized controlled trial of a case management intervention. Pre-enrollment levels of medical, mental health, and substance abuse service utilization were assessed in preparation for a future cost effectiveness analysis of case management at one-year follow-up. Data was obtained from a review of computerized records at San Francisco General Hospital and the San Francisco County Health Department. Data was grouped into emergency, outpatient. inpatient, day service, residential, methadone detoxification. and methadone maintenance services obtained over a one-year period prior to enrollment in case management. Preliminary analyses show that in the year before study participation 92% of study participants used medical services, 18% used mental health services, and 65% used substance abuse services. The most frequently used services were outpatient medical services (82% of participants), inpatient medical services (72% of participants), and emergency medical services (60% of participants). Future analyses will examine the impact of case management on health outcomes at one-year follow-up. Case management may be helpful in increasing use of appropriate medical, mental health, and substance abuse services. It is important to develop cost-effective interventions for substance abusers with HIV infection.

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DRUG DEPENDENCIES AND PSYCHIATRIC ILLNESSES AMONG AIDS PATIENTS

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This was an exploratory study of 253 HIV infected patients admitted to a CMHS/SAMHSA funded AIDS/mental health speciality clinic. Baseline data revealed that subjects were 37 years old, 3/4ths mate, and 2/3rds African American; 52% were heterosexual; 41% homosexual, and 7% bisexual. Although heterosexual contact was the most frequent mode of transmission, 43% of cases were attributable to substance abuse. Rates for substance abuse were: 10% ETOH only, 24% drug only, 22% both ETOH and drug, and 44% neither. On the CIDI, co-morbidity was found for substance abuse and type 2 (vegetative) depression and for substance abuse and anxiety disorder. On the MCMI-III, comorbidity was found for schizoid personality (ETOH), ASP (ETOH and drug abuse), and BPD (ETOH and drug abuse). Personality "profiles" for 4 substance use subgroups (ETOH only, drug only, both, neither) reveal less psychopathology for non-substance abusers with more Axis I pathology for alcohol abusers and more Axis II pathology for polysubstance abusers. Finally, although no between groups differences were found with regard to cognitive functioning, MMHC patients evidenced neuropsych impairments of 2-3 times the magnitude found in the general public. Findings suggest the need for screening for co-morbid conditions in HIV infected patients applying for medical care.

DRUG ADDICTION AND TREATMENT CAREERS AMONG CLIENTS IN DATOS

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Considerable heterogeneity in patterns of addiction and treatment career histories was observed among the 10,010 clients participating in the NIDA-sponsored Drug Abuse Treatment Outcome Study (DATOS). First treatment entry was on aver-age Seven years after the initiation of use of heroin or cocaine, although clients differed in duration of addiction and treatment careers across modalities. Approximately one-half of the clients had no prior treatment experience. About one-half of DATOS clients with prior treatment had received treatment within the prior year and they utilized a variety of types of treatment modalities. Regression analyses demonstrated that prior drug treatment utilization was associated with being female and African American; having longer employment history, more severe drug dependence, and prior mental health treatment; injecting drug use, and engaging in sex work and criminal activities. Younger age at first treatment was associated with shorter duration of employment, more severe drug dependence, earlier onset of drug use. prior alcohol treatment, and fewer types of illegal activity. Approximately one-third of clients received additional or ongoing treatment during the one-year follow-up period, most frequently from outpatient drug-free programs. Analysis of cocaine users in outpatient drug-free treatment showed that individuals with prior treatment were more likely to be abstinent at follow-up if they received more services; similarly, individuals with prior treatment and longer duration in DATOS treatment were mom likely to be abstinent at follow-up than those with shorter treatment duration. Career-based research suggests that the drug treatment system needs to provide a range of approaches and services to address client heterogeneity.

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WE BUILT IT, BUT MOST DIDN'T COME: TREATMENT ENTRY AND RETENTION AMONG OUT-OF-TREATMENT INJECTION DRUG USERS

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The HIV epidemic and the rising number of injection drug users (IDUs) infected with the disease has led, increasingly, to calls for an emphasis on substance abuse treatment as a means to reduce its spread. Recommendations to enhance the attractiveness of treatment for out-of-treatment IDUs include elimination of waiting lists, rapid intake, and treatment on demand. In this study, we report findings on the comparative effects of two intervention strategies, each with a free and a payment condition, in increasing treatment entry and retention. Using a two-by-two factorial design, IDUs were randomly assigned to either motivational interviewing (focusing on entering treatment) or an HIV risk reduction intervention (focusing on changing HIV risk behaviors), with or without 90 days of free treatment. All participants were offered rapid treatment intake, transportation to the treatment facility, and a waiver of the intake fee at the clinic. Findings from nearly 200 IDUs showed that 39% entered treatment, including 38% assigned to motivational interviewing and 39% to HIV risk reduction. By payment condition, 50% of those receiving free treatment entered compared to 27% for those paying. Treatment retention at 90 days was as follows: motivational interviewing, 33%; harm reduction, 49%; free treatment, 59%, no free treatment, 15%. Predictors of treatment entry, other than free vs. paid treatment, included African American ethnicity, a perception of having a 50% or greater chance of getting infected with HIV, being in the "Determination" stage of change, prior drug treatment experiences, and not injecting or smoking cocaine. Predictors of treatment retention included free vs. paid treatment. These findings call for further efforts to enhance the perceived benefits of treatment.

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REACHING AND ENROLLING DRUG USERS FOR HIV PREVENTION: A MULTI-SITE ANALYSIS

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Since 1994, six additional sites participated in a NIDA-funded Cooperative Agreement aimed at examining rates of HIV risk behaviors and evaluating HIV risk reduction interventions among out-of-treatment drug injection and crack cocaine users. The St. Louis site recently showed gender and HIV risk behavior differences among those contacted by through street outreach and those who actually enrolled in the study (Cunningham, *et. al.,* 1996). The current study is a cross-site replication of fit year street outreach and study enrollment data from 2 other NIDA Cooperative Agreement Sites (San Antonio, TX and Durham/Wake County, NC). The following findings were replicated at least one site: **Recruitment:** 1) More eligible men than eligible women were contacted by CHOWS; 2) No striking racial differences were found among street contacts and eligible street contacts; 3) Over 1/2 of street contacts and over 1/2 of eligible street contacts were not current injectors; **Enrollment:** 1) Compared to eligible street contacts, fewer enrollees were HIV tested; 2) Compared to eligible women street contacts, a higher proportion of enrollees were women; 3) A smaller proportion of drug users without any previous drug treatment/treatment-seeking history were enrolled in the study. These findings indicate that we are reaching and enrolling our target population, but that the sites differ in the effectiveness and accuracy of the street outreach method. Street outreach alone may not be enough to recruit women and current injectors into HIV prevention studies.

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RE-ENGAGEMENT OF DROP OUTS FROM A DRUG TREATMENT PROGRAM

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Hypothesis: While it is well known that clients lend to cycle in and out of the drug treatment system, this phenomenon has not been well researched and little is known about those who drop out. Drop out rates for methadone treatment are typically 33% within 3 months and 50% within 6 months. There are very few studies in which an attempt has been made to reengage drop outs. despite the fact that it often lakes an addict several tries to be successful in a treatment program and that drug treatment (particularly methadone treatment) has been shown to be effective as HIV prevention. The present study hypothesis is that outreach and counseling techniques can be used to re-engage these drop outs, and they will show greater rates of treatment re-enrollment. HIV risk reduction and decreases in drug use than a randomly assigned control group. **Methods:** The project seeks to reengage persons who have recently dropped out of an MMTP. Initial client contact will be made by an outreach worker who will offer a "low-threshold" service. After the outreach contact. the client will be invited to participate in a variety of groups (recovery, support, relapse prevention) as well as individual counseling, at the project field site. The randomly assigned control group will be offered passive (paper) referrals to community services. Both groups will be assessed at: drug treatment intake, shortly after drop out, at 6 months, and one year post drop out. A total of 700 clients will take part in the study over a 4 year period. A description of the project components and preliminary findings for intake assessments will be presented.

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RELATIONSHIP BETWEEN RESISTANCE TO LEARNING ONE'S HIV SEROSTATUS AND DISCLOSING COCAINE USE

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Recent advances in the treatment of HIV-positive individuals, as well as efforts to reduce the spread of AIDS, have made early detection of HIV status even more important than formerly. Most drug abuse treatment clinics now encourage their patients to undergo HIV testing. but many patients avoid learning their serostatus by refusing to be tested or failing to obtain test results. This possible sign of denial may be related to others such as the underreporting of cocaine use and persistence in engaging in HIV-risky behaviors. In our population of inner-city cocaine abusers, 778 former patients were interviewed 9 months after being admitted to a 3-month intensive outpatient treatment program. Of these 21% reported never having been tested, and 9% having been tested but not knowing the results. In addition. 522 of the former patients claimed not to have used cocaine during the 30 preceding days, although 32% of these submitted urines which tested positive, a clear indication of underreporting. These data were related in that those who had avoided learning their serostatus were substantially more likely to conceal their recent use of cocaine than those who had obtained test results (41% vs. 29% $p < .01$. They also were al much higher risk of HIV infection (above the median on the RAB), (60% vs. 42%, $p < .001$). One practical implication of these results is that self-report data may give a distorted picture of the relationships among cocaine use. AIDS-risky behaviors, and HIV status.

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VALIDITY OF A BRIEF OPIOID ABUSE SCREEN FOR PREDICTING CURRENT HEROIN USE IN HOSPITALIZED HIV-INFECTED DRUG USERS

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Drug users [DUs] represent ≥ 25% of HIV-infected cases. In some metropolitan areas, HIV-infected DUs make up a large proportion of hospitalized patients as they are at risk for opportunistic infections. Discrimination between current and former DUs is necessary for targeting appropriate interventions. Clinicians lack guidelines for assessing reliably drug use histories. The CAGE Screen has been used effectively to elicit symptoms suggestive of alcohol abuse problems. Based on that model, we adapted an 8-item questionnaire from the National Household Survey on Drug Abuse for use as a Brief Opioid Abuse Screen [BOAS] to elicit current heroin use [CHU]. This study evaluates validity indices of 1) self-reported last heroin use for predicting an opioid-positive urine test; 2) the BOAS for predicting CHU in hospitalized HIV-infected DUs. Patients (N = 507) were admitted on 845 occasions to the inpatient AIDS service of an inner-city academic center, and were screened by questionnaire for heroin and cocaine use; urine samples were tested for opioids by OnTrak®. Of 495 responders, 359 (73%) self-reported use of heroin or cocaine and were considered DUs. Among these, 303 (84%) had used heroin (65% male, 92% African-American, mean age 39.4 ± 0.4 years); heroin users were classified as CHUs if they self-reported heroin use within the last month, or abstainers [no use in last month]; they were evaluated for opioid withdrawal. Only 84 (44%) were CHU; CHU were more likely to have opioid-positive urine ($p<.000$) (sensitivity 0.81, specificity 0.72, positive predictive value 0.76 [PPV], negative predictive value 0.85 [NPV]). Each item on the BOAS correlated with CHU ($p<.000$) (ranges for sensitivity: 0.66 - 0.82, specificity: 0.61 - 0.84, PPV: 0.72 - 0.86, NPV: 0.64 - 0.78). Clinical Institute Narcotic assessment withdrawal scores were high in CHU [5.4 ± 0.4] and low in abstinent DUs (2.8 ± 0.5) ($p<.000$). In hospitalized HIV-infected DUs, self-reported heroin use in the last month or a positive response on the BOAS is a reliable indicator of current use, and each correlates with opioid withdrawal.

A REVIEW OF THE UTILITY OF A NOVEL URINE HIV-1 TEST METHODOLOGY IN DUF POPULATIONS

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Berries *et al.* (1995) and MacGregor *et al.* (1994) have favorably reported on the safety, simplicity, and high subject acceptance of a urine test for HIV-1 antibodies in recovering alcoholics and subjects attending a methadone clinic, The epidemiologic utility of unlinked mine HIV-1 antibody testing in DUF populations was investigated by two NH- sponsored DUF sites in Manhattan and Los Angeles, and one multicounty CALDUF site sponsored by CSAT and California ADP. As expected, HIV-1 prevalence in Manhattan (17.1%, n= 1,615) was significantly higher than in two Los Angeles studies (2.9%, n = 2,900 and 1.7%, n = 359) and CALDUF (1.2%, n = 1,961). HIV-1 prevalence in self-reported lDUs was 1.8 times and 1.6 times higher than that of all arrestees in Manhattan and CALDUF respectively, and male:female prevalence rates were 1:1.5 and 1:1.9 in Manhattan and CALDUF respectively. Manhattan DUF data suggest that in unlinked epidemiologic studies. reliable prevalence data are possible without the expense of Western blot confirmation by employing an elevated cutoff value in the Urine HIV-1 EIA. The Calypte Urine HIV-1 EIA makes it possible to conveniently evaluate HIV-1 prevalence in a previously untestable population of high-risk DUF subjects, with no additional sample collection costs. References available upon request from senior author.

References available upon request from R. Van Maanen Fax: 510-814-8408.

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A PRELIMINARY INVESTIGATION OF LAMOTRIGINE FOR COCAINE ABUSE IN HIV-SEROPOSITIVE PATIENTS

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Theoretical considerations as well as preclinical data suggest a potential role for excitatory amino acid antagonists in the treatment of cocaine addiction. Here we report on results from a preliminary study in which eighteen HIV-seropositive cocaine dependent, opiate-agonist maintained patients received lamotrigine (300 mg/day), an indirect glutamate release inhibitor, on either a standard induction schedule (n=8; full dose beginning week 6) or accelerated induction schedule (n=10; full dose beginning week 3) for 12 weeks. Outcome measures included cocaine use assessed by three times weekly urine screens as well as pre- and post-treatment neuropsychological assessments. Results showed a significant 50% decrease in percent of cocaine positive urine screens in the standard induction group, but no decrease in the accelerated induction group. There were fewer reports of side-effects and fewer drop-outs in the standard-induction lamotrigine group compared to the fast induction group. Neuropsychological assessments showed decrements in the Trail Making Tests and improvements in the Controlled Oral Wad Association test in both groups, but no other changes in cognitive functioning. We conclude that standard-induction lamotrigine is well-tolerated and warrants further investigation for the treatment of cocaine abuse in this patient population.

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NEUROCHEMICAL CHANGES IN COCAINE USERS WITH HIV-1

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Introduction: Previous proton magnetic resonance spectroscopy (^{1}H MRS) studies in brains of HIV patients showed increased choline compounds (CHO) in the early stages and decreased N-acetyl aspartate/creatine (NA/CR) in the later stages of the disease. The aim of this study is to determine whether cocaine use has an effect on the neurochemical abnormalities of HIV patients. **Methods:** 18 HIV cocaine users and 17 HIV patients wee compared to 29 normal subjects. MRI and ^{1}H MRS were performed on a GE 1.5 T MR scanner. ^{1}H MRS voxels (3-50cc) were in the mid-frontal gray, frontal white matter and basal ganglia. Data were acquired using PRESS with TE/TR=30/3000 ms. Absolute quantitation including cerebrospinal fluid (QCSF) measurement were performed using brain water as an internal reference. **Results:** ANOVA showed significantly elevated %CSF ($p = 0.002$) in the gray matter of HIV patients compared to HIV cocaine users and the normals. In the white matter, both the HIV and HIV cocaine users showed lower NA/CR ($p = 0.04$) and higher CHO ($p = 0.002$) while the HIV patients showed higher MI/CR ($p = 0.003$) and higher MI ($p = 0.0001$) compared to normal controls. In the basal ganglia, both NA/CR ($p = 0.03$) and MI/CR ($p = 0.05$) were elevated in HIV and HIV cocaine users due to a lower CR. Furthermore, CD4 showed inverse correlation with % CSF (in HIV) and with MI (in HIV cocaine users) while AIDS dementia complex (ADC) staging positively correlated with CHO in HIV patients. **Discussion:** This study found abnormal metabolites in both HIV patients with and without history of cocaine addiction. Increased CHO suggests increased cell membrane turnover while increased MI suggests increased glial activities in HIV. No significant effects were observed in HIV patients due to cocaine use; however, the rate of progression of the disease may be different and remains to be evaluated.

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RHESUS MONKEY BEHAVIORAL BATTERY: ACQUISITION AND PERFORMANCE WITH DRUG AND VIRAL MANIPULATIONS

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A computerized behavioral battery based upon human neuropsychological tests has been developed to assess changes in cognitive performance of rhesus monkeys resulting from neurotoxicity produced by MDMA or infection with simian immunodeficiency virus (SIV). The battery addresses memory (delayed non-matching to sample, DNMS; spatial working memory, SWM), attention (intra-/extra-dimensional shift, ED/ID), motivation (progressive-ratio, PR), reaction time (RT) and motor coordination (bimanual task) [CANTAB, Cambridge Cognition, Cambridge, UK]. As with human neuropsychological batteries, different tasks are thought to depend on different neural substrates, and therefore performance profiles should assess function in particular brain regions. Monkeys are tested in transport cages and responding on a touch sensitive computer monitor is maintained by food reinforcement. Eighteen monkeys have been trained on the SWM (2-5 boxes), PR, and bimanual task. Twelve of these have also been trained on DNMS (0-64s delay) and 11 tested on ED/ID. Performance on all tasks has been reliable over a period of years, allowing for assessment of long-term behavioral changes, Increasing delays in the SWM and DNMS tasks reduces accuracy, as does increasing the number of boxes in the SWM task. The RT task is sensitive to impairment with dopaminergic or cholinergic antagonists, and PR performance is a function of reinforcer magnitude. Several tasks have been shown to he sensitive to the effects of SIV infection, including the bimanual motor, PR, ED/ID and SWM tasks. In summary, sensitivity to neuropharmacological manipulations and SIV infection, along with stability of performance, validate this battery as a measurement instrument for characterizing alterations in neuropsychological performance in rhesus monkeys.

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DISCRIMINATING COGNITIVE IMPAIRMENT FROM HIV VERSUS CHRONIC SUBSTANCE USE IN METHADONE MAINTAINED IVDUS

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The important role of neuropsychological tests for diagnosis, treatment, and research in the nervous system complications often accompanying HIV infection is largely based on data from non-IVDU groups, mostly gay or bisexual males. The presumptively high background rate of impairment in IVDUs as well as the cultural and educational assumptions underlying some neuropsychological tests suggest that a specialized testing strategy is needed for these patients. We administered standard neuropsychological and reaction time (RT) tests to 131 methadone maintained IVDUs (62 HIV negative, 43 HIV infected asymptomatics, 29 AIDS). Choice RT was sensitive both to neuropsychological impairment [$F(1,108) = 19.59$. $p < .001$] and specifically sensitive to impairments associated with advancing HIV infection lF(2.108) = 9.53, $p < .001$]. Simple RT was sensitive to neuropsychologicai impairment [$F(1.108) = 6.39$, $p < .02$] but not specifically sensitive to HIV associated impairments [$F(1.108) = .291$, ns]. On the standard tests, mere is an increasing rate of neuropsychological impairment with advancing HIV infection [$F(1.119) = 4.03$, $p < ,051$, however, only tests of memory were specifically sensitive to these impairments [$F(2,105) = 8.361$, $p < .001$]. Further analyses showed that IVDUs, irrespective of HIV status, have a higher impairment ram than demographically matched healthy controls [$F(3.140) = 5.35$, $p < .002$]. We conclude that IVDUs can be readily screened for HIV associated cognitive impairments by a battery taking less man to minutes to administer. The significance of our findings with respect to the cognitive impairments in both HIV infected and uninfected IVDUs will he discussed.

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DYNORPHINS MODULATE LIPOPOLYSACCHARIDE-INDUCED NEUROTOXICITY IN CORTICAL NEURON/GLIA CULTURES

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We previously reports that dynorphins inhibit the lipopolysaccharide (LPS)-induced production of nitric oxide RIO) and proinflammatory cytokines in glial cells from the brain without the participation of κ-opioid receptors. Because NO and the proinflammatory cytokines have been implicated in various neuropathological conditions, we hypothesized that dynorphins would reduce LPS-induced neurotoxicity. Therefore, we examined the effects and mechanizms of action of dynorphins on the LPS-induced release of lactate dehydrogenase (LDH), an indicator for cell injury or death, and morphological changes in mouse primary mixed cortical neuron/glia cultures. LPS induced a concentration-dependent increase in the level of LDH in these cultures. Dynorphin (dyn) A-(1-8) significantly inhibited the LPS-induced release of LDH and reduced the LPS-induced neuronal losses or morphological changes at ultralow concentrations of 10^{-14} to 10^{-12} M and at a high concentration of 10^{-6} M. Dyn A-(1-8) suppressed the LPS-induced production of NO at concentrations of 10^{-16} to 10^{-12} M. Ultralow concentrations (10^{-15} to 10^{-13} M) of des-[Tyr^{1}]dyn A-(2-17), a non-opioid peptide which does not bind to κ-opioid receptors, exhibited the same inhibitory effect as dyn A-(1-17). [Met^{5}]-enkephalin, β-endorpphin, or nociceptin did not affect the LPS-induced LDH release. These results suggest that dynorphins reduce the LPS-induced neuronal injury in the brain and their beneficial effect is not mediated by classical opioid receptors or the opioid receptor-like KOR-3 receptor. In addition, these results indicate that decreasing the level of NO alone is not sufficient to reduce the LPS-induced neuronal damages, which may provide new insights into the role of NO in the LPS-induced neurotoxicity.

EFFECT OF ACUTE MORPHINE INJECTION IN THE PERIAQUEDUCTAL GRAY MATTER ON MACROPHAGE FUNCTIONS

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Opioid action in the periaqueductal gray matter (PAG) is well known to suppress T cell proliferative responses and NK cell activity. We investigated the effect of acute microinjection of morphine into the PAG on nitric oxide and tumor necrosis factor-α (TNF-α) production, and its effect on phagocytosis of *Candida albicans* by resident and activated rat splenic macrophages. Fischer 344N male rats were injected bilaterally into the PAG with 10 nmol of morphine. Three hours following injection, resident splenic macrophages were obtained, and incubated overnight. Macrophage monolayers were then incubated for 3 days in the presence or absence of 25 ng/ml of lipopolysaccharide (LPS). after which supernatants were taken for nitrite (Griess reagent), and TNFα (L929 bioassay) determinations. For the phagocytic activity, resident macrophages were incubated with *C. albicans* (ratio yeast to macrophage, 10:1) for 1 hr. and then stained with Giemsa reagent; the phagocytosis of yeasts among macrophages was determined by visual inspection of at least 100 macrophages. Morphine treatment significantly ($P < 0.01$) suppressed nitrite release (39% and 50% reduction compared with untreated control and sham control, respectively), TNF-α production (21% and 28% reduction, respectively), and the phagocytic activity of macrophages (50% and 60% reduction, respectively). Further studies with acute and chronic injections of morphine in PAG may provide additional evidence of its effects on macrophage functions.

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IMMUNOSUPPRESSION FOLLOWING PAG MORPHINE INJECTION IS CORRELATED WITH ACTIVATION OF THE HPA AXIS AND IS NOT BLOCKED BY MIFEPRISTONE

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Central nervous system mediated morphine-induced immunosuppression has been hypothesized to be due to activation of either the hypothalamic-pituitary-adrenal (HPA) axis or the sympathetic nervous system (SNS). We investigated the effects of morphine injected bilaterally into ventral-caudal periaqueductal gray (PAG) matter of the mesencephalon on various parameters of immunocompetence. We found that injection of 20 nmol of morphine into the PAG resulted in a significant suppression of splenic NK cell activity, splenic and thymic T-lymphocyte proliferation, and peritoneal macrophage function. Furthermore, CD25, CD54, and CD71 activation markers on splenocytes and thymocytes from morphine treated animals were atso decreased after 24 hours culture with ConA. No changes in CD3, CD4, and CD8 or NKR-P1 positive cells of spleen and thymus were seen 3 hr after morphine injection. To assess the effects of morphine on the activation of HPA axis, plasma ACTH and corticosterone (CSO) levels were determined before and after injection of morphine in jugular catheterized Fischer 344N mate rats. A temporal increase in ACTH was observed which peaked at 40 minutes (9-fold) following PAG morphine injection. This was accompanied by a subsequent 2-fold sustained increase in CSO. Prior peripheral injection of mifepristone (RU 486, 20 mg/kg), a glucocorticoid receptor antagonist. was ineffective in blocking morphine-mediated suppression of NK cell activity and T cell proliferation, indicating alternative mechanisms involved in morphine-induced suppression. We have shown that the SNS may play a role in morphine-induced immunosuppression. In summary, we found that acute microinjection of 20 nmol of morphine bilaterally into ventral-caudal PAG results in suppression of immune function, which is accompanied by increases of plasma ACTH and CSO levels but is not blocked by prior administration of RU 486.

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SUPER- AND SUBADDITIVE INTERACTIONS OF MORPHINE AND DELTORPHIN IN INDUCING IMMUNOSUPPRESSION

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We have previously repotted that μ (morphine), κ (U50,488H) or δ_2 (deltorphin) agonists can suppress the secondary *in vitro* antibody response of mouse splenocytes to sheep red blood cells in a plaque-forming cell assay. Treatment of spleen cells with any one of these opioids induces a maximum of 50% to 60% suppression in the number of plaques at concentrations of 10^{-7} to 10^{-11} and the suppressive effects are no longer significant at 10^{-15}. To try to augment the suppressive effects, combinations of opioid agonists binding at the different receptor types were used. Morphine (M) and deltorphin (D) were combined in a molar ratio of 3 (M) to 1 (D). The combination was treated as a new compound and diluted in 100-fold increments. Pooled data from 11 experiments using this combination showed a dramatic alteration in the dose-response curve. At low concentrations, there was a strong indication of superadditivity that reverted to subadditivity at high concentrations. Pretreatment of spleen cells with CTAP, a selective m receptor antagonist, or naltriben (NTB), a selective $\delta_{,2}$ receptor antagonist, for 2 hours before addition of the 3(M):1(D) combination returned the dose-response curve to that observed with either agonist atone. A model is presented to explain the effects of the drug combinations.

TIME-DEPENDENT IMMUNOMODULATORY EFFECTS FOLLOWING NATURAL OPIOID WITHDRAWAL

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Although the consequences of chronic opioid administration and tolerance on immune status have been examined, few studies have investigated the immunomodulatory effects of opioid withdrawal. The current study utilized the chronic drinking method of drug administration and a subsequent natural withdrawal episode to investigate the effect of opioid withdrawal on several *in vitro* measures of immune status. Male Lewis rats were administered 0.6 mg/ml morphine in their drinking water for 20 days. Following this period, withdrawal was induced either 0, 6. 12, 24 or 48 hours prior to sacrifice and tissue collection. Measures of splenic T- and B-cell proliferation, γ-IFN production, and natural killer cell activity were performed. Immune measures in rats that drank morphine and did not experience withdrawal immediately prior to sacrifice were not significantly different from those measures in rats that drank tap water for 20 days. In rats that underwent natural opioid withdrawal; however, there was a time-dependent modulation of Con-A and TSST-1 stimulated splenic T-cell proliferation, Con-A stimulated splenocyte g-IFN production, and splenic natural killer cell activity. Immune measures were reduced within 12 hr of withdrawal induction but gradually recovered within 48 hr. Proliferation of splenic B-cells was not significantly modulated by opioid withdrawal. These data provided evidence to suggest that withdrawal from chronically administered opioids such as morphine or heroin may lead to alterations in the immune status of drug using individuals.

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DELTA OPIOID RECEPTOR LIGANDS MODULATE APOPTOSIS IN CULTURED LYMPHOCYTES

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Apoptosis, a form of programmed cell death characterized by disruption of the nucleus and chromosomal fragmentation, plays an important role in the homeostasis of both resting and activated lymphocytes. It is mediated, in part, by i) intracellular proteases, ii) bcl-2-related proteins, and iii) cell surface receptors, including ones for adhesion molecules, cytokines and members of the tumor necrosis factor receptor superfamily. We have initiated studies in 3 systems to define the effects of opioids and opioid antagonists on apoplosis. 1) thymocytes from 4-6 week old CD-1 mice were cultured with 0.5 ug/ml concanavalin A (Con A) and apoptosis was measured by DNA fragmentation or by FITC-Annexin V binding. The addition of the delta receptor antagonist, naltrindole (NTl), to the Con-A stimulated thymocyte cultures modulated the apoptotic response in a biphasic, dose-dependent manner. 2) In fetal thymic organ cultures NTI either enhanced or inhibited apoptosis depending on the gestational age of the thymic lobes. 3) The numbers of apoptotic cells in human Jurkat and NALM 6 cell lines incubated the delta agonist, DADLE (10^{-7}M), for 48h with and without dexamethasone were reduced, as measured by Hoechst dye and FITS-Annexin V binding. These studies show that the addition of delta receptor ligands to cultured lymphocytes results in a shift in the homeostatic processes that regulate apoptosis.

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RENAL INTERSTITIAL SCARRING (RIS): ROLE OF MORPHINE

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Renal interstitial scarring (RIS) is an important component of heroin-associated nephropathy (HAN). Kidney fibroblasts have been demonstrated to play a role in the development of renal scarring in a variety of renal diseases. We studied the effect of morphine on the proliferation of rat kidney fibroblasts (NRK-49). Growth arrested subconfluent NRK cells were incubated with variable concentrations of morphine (10^{-14} to 10^{-4} M) for variable periods (24 to 72 hours). Subsequently, cells were trypsinized and counted (n=4 to 6). [^{3}H]thymidine incorporation studies were also carried out under identical conditions. To determine the role of early growth associated genes in morphine-induced NRK proliferation, Northern blots were generated from control and morphine treated cells at 10, 30, 60 and 120 min. These blots were probed with cDNA probes specific for c-fos, c-jun and c-myc. Evaluation of NRK apoptosis was performed after treatment with morphine and subsequent staining with H-33342. The isolated DNA from control and morphine treated NRK cells was Iabeled with [^{32}P]dCTP and run on gel electrophoresis. Western blots were prepared from cell lysates of control and morphine treated cells and probed with anti-p53 antibody. Morphine enhanced ($P<0.001$) NRK proliferation and mRNA expression of c-fos and c-jun at lower concentrations in a dose and time dependent manner. Morphine at higher concentrations promoted apoptosis and synthesis of p53. Morphine treated cells showed Integer multiples of 180 base pair (ladder pattern) confirming apoptosis. These results indicate morphine may be directly contributing to renal interstitial scarring in patients with heroin-associated nephropathy.

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ANERGY AND IMMUNE SUPPRESSION IN INTRAVENOUS HEROIN ADDICTS WITH HEPATITIS C

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Intravenous heroin addicts who are HIV positive are known to have a high rate of anergy and immune suppression. Heroin addicts in California have a very low rate of HIV positivity but have a high rate of active, hepatitis C Infection. To determine if addicts with hepatitis C and who are HIV negative demonstrate anergy and susceptibility to AIDS, tuberculosis and other infections, 156 heroin addicts maintained with methadone at five different locations in the Los Angeles Basin were selected for study. AlI were HIV negative but had hepatitis C in varying stages. Ages ranged from 25 to 68 years and subjects had been addicted for periods ranging from 13 to 38 years. All were given intradermal skin tests with antigen for tuberculosis (PPD - intermediate), candida, mumps, and tetanus. Twenty-four (24;15.0%) showed no reactivity to any antigen as judged by 5mm or more of induration at 48 and 72 hours post-administration. Eight (8; 33.33%) of these cases demonstrated one or more low, lymphocyte indicators. Seventeen (17; 11.0%) demonstrated a positive PPD test, and nine of these cases had tested negative in the year prior to this test indicating that tuberculosis is spreading in the California addict population. This study also suggests that anergy and infectious disease susceptibility is present in some intravenous heroin addicts who have hepatitis C and are HIV negative. Identification and improvement of immune suppression in the methadone patient is warranted as a strategy to contain infectious disease.

HEPATITIS C VIRUS INFECTION IN COCAINE USERS--A SILENT EPIDEMIC

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About 250 cocaine users were solicited through advertisements for a study requiring otherwise healthy subjects. These subjects were screened by an extensive phone interview for the presence of other psychoactive drug dependence or any significant medical or psychiatric condition. Individuals were specifically asked about ever having hepatitis and their HIV status. Individuals who were dependent on other drugs of abuse, alcohol, or had a significant medical or psychiatric history were excluded. The remaining 95 volunteers were brought to our clinical research center and tested for hepatitis B, hepatitis C and HIV. Subsequently, of these 95 assumed healthy subjects, 36 (38%) tested positive with antibodies to the hepatitis C virus. Only 1 (1%) tested positive with hepatitis B and 2 (2%) with HIV. The Milwaukee Regional Blood Center has reported a 0.12% incidence hepatitis C viral (HCV) infection among blood donors in this area. The demographics of this cohort were 73% African-American, 75% male, 75% never married, 43% employed with a mean age of 36±8 years. The percentage of subjects reporting any lifetime intravenous drug use among the HCV(+) and the HCV(-) cohorts was 79% vs. 38%. While many vectors involved in HCV transmission are still unclear, others have reported a high prevalence of HCV infection in cocaine users both in those with and without a history of intravenous drug use. Other aspects of cocaine use, sharing paraphernalia for intranasal use, or lifestyle factors may play a role in HCV transmission. Since up to 40% of HCV infections may progress to cirrhosis, this is an epidemic among a population that is most often uninsured and receiving little medical care. These subjects also form a pool for the transmission of HCV to the community. This study, with the finding of a 38% HCV infection rate among well-screened cocaine users, highlights the need for new public health interventions.

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HEPATITIS B IN INJECTION HEROIN USERS: A FOLLOW-UP

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This study is an update of a study on Hepatitis B in injection heroin users presented here last year. We report findings on 34 subjects, 12 of whom were negative for Hepatitis B. We sought to examine the relationship between mood, fatigue and hepatitis status in light of our earlier findings that Hepatitis B negative patients demonstrated higher sexual risk behavior than Hepatitis B positive patients. No drug risk differences between groups was found. We hypothesized that patients who were positive for Hepatitis might have less energy and feel sicker than their negative cohort, which might explain their lower sexual risk behavior. All patients were male veterans in Methadone Maintenance Treatment at the SF-VAMC, who typically have a twenty year or more history of substance abuse. The mean age of this population was 48. Sixty-eight percent were Caucasian, and 29% were African-American. Thirty-two percent were married or living with a partner. Twelve percent reported combat history and 59% reported a history of cocaine use. Sixty-eight percent were living in a home or apartment. We administered The Profile of Mood States (POMS). the Pleasant Events Scale and three fatigue scales developed by Krupp. Kobashi, and Haylock to all but two of our original subjects, who were lost to follow-up, and eight new subjects. Contrary to our expectations. we found that patients who were negative for Hepatitis B reported significantly more fatigue than patients who were Hepatitis B positive. We tested several possibilities that use of clean needles or no sex might account for the differences we found, but they had no effect. While it is possible that current blood tests are not sensitive enough to pick up low levels of infection in those we found to be negative for Hepatitis, we believe that there may be an as yet undiscovered reason for the behavioral differences we found.

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NUTRITIONAL STATUS AND HEPATIC FUNCTION DURING DRUG USE AND ABSTINENCE

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While it is widely appreciated that active drug abusers are often undernourished, the epidemiology and clinical significance of this phenomenon have not been well-studied. In addition, malnutrition and refeeding may be associated with abnormal hepatic function, but such abnormalities have not been studied in drug abusers. We addressed these issues by retrospectively abstracting data from the rewards of 301 consecutive subjects admitted to the NIDA DIR research ward for the period 1994-1996. Data included sociodemographic characteristics, predominant drug of abuse, nutritional parameters (e.g., weight, weight change, serum cholesterol, albumin, total lymphocyte count), hepatic parameters (e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT), hepatitis B surface antigen); and HIV antibody status. The sample was predominantly male (76%), African-American (87%). and employed (70%); with an average age of 32.4 ± 5.4 years, and a body mass index (BMI: kg/m^2) of 23.8 ± 4.2. The predominant drugs of abuse were cocaine (51.5%) and heroin (42.5%). Upon admission, 12% of the sample were malnourished. The most prevalent diagnostic indicator of malnutrition was < 80% ideal body weight. Heroin abusers were more likely to be malnourished at admission (P = .016). There was no association between any other study variable and malnutrition. In analysis adjusted for length of stay (M = 22 ± 19 days), malnourished patients gained an average of 3 BMI units (2.9 ± 4.3 kg) over the course of the inpatient stay. Refeeding was associated with modest increases in AST (19%) and ALT (38%) among those not malnourished at admission. Among the malnourished, refeeding was negatively associated with AST levels. The magnitude of the associations suggests that, among the drug abusing population, refeeding does not significantly alter hepatic function.

SUPERVISED TUBERCULOSIS CHEMOPROPHYLAXIS FOR DRUG USERS ENROLLED IN A METHADONE PROGRAM

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Drug users (DU) are at high risk for Mycobacterium tuberculosis (TB) infection. Previous research revealed newly detected latent TB infection in 9% DU enrolled in methadone maintenance treatment program (MMTP) in New Haven, CT. Chemoprophylaxis (chemo) with isoniziad (INH) greatly reduce the risk of developing active disease. Medication compliance has been identified to be most difficult for DU. In this study, to enhance compliance with INH, DU enrolled in MMTP who were identified to be tuberculin skin test positive (PPD+) were offered supervised TB chemo (SC) with INH added to their daily methadone dose. From May 1966 to May 1997. 49 DU went evaluated. Forty patients were found eligible to initiate INH. of whom, 5% (2/40) refused treatment. Out of the 38 patients (mean age 40 +/- 8 yrs) who consented to INH chemo, 89% (34/38) consented to SC and 11% (4/38) accepted lNH without supervision (non-SC). So far, among the SC group 38% (13/34) have completed INH chemo, 41% (14/34) are in progress and 20% (7/34) have discontinued INH without completion. Among the non-SC group, by self report, 50% (2/4) have completed INH chemo and 50% (2/4) have discontinued. The reasons for incomplete chemo included 13% (5/38) were dicharged from MMTP, 5% (2/38) were incarcerated, 3% (1138) lost to follow-up although still in MMTP, and 3% (1/38) had elevated liver enzymes related to acute hepatitis B infection. Although all patients were recommended for monthly follow-up visits for symptom checks and liver function tests evaluation, only 45% (17/38) returned for one or more visits. There were no INH related toxicity observed. In summary, supervised TB chemo with INH added to methadone for DU in MMTP is a feasible method of enhancing INH compliance in DU. INH seemed to be well-tolerated by patients although medical follow-up to assess toxicity was poor. There were no observed INH related toxicity during this study period.

TUBERCULIN REACTIVITY AMONG DRUG USERS VARIES BY YEARS OF INJECTION BUT NOT BY SPECIFIC DRUG OR ROUTE OF USE

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Drug users are al high risk of tuberculous (JB) infection. Identifying subgroups of active drug users with a greater prevalence of TB infection may be valuable in guiding the development of TB services and in targeting interventions to disrupt transmission. Participants at a New York City syringe exchange and an inpatient detox program were offered PPD testing, and were interviewed. From 4/95-8/31/96, 984 completed PPD testing to date. Thirty-four % were female, 53% nonwhite, 86% US born, 28% homeless, 29% without health insurance. PPD reaction rates were 15% >=10 mm, 3% 5-9 mm, 69% PPD (-). 13% anergic, with a 0.3% rate of active TB. The proportion with PPD (+) (>= 10mm) increased with age and with years of drug use (both per 10 yr strata, both $p < 0.001$). PPD (+) rates were higher among older DUs with longer histories of drug use [<5 yrs DU, age œ 35 yr, 5% PPD (+); < 5 yr DU, age > 35 yr, 13% PPD (+); > 5 yr DU, age < 35 yr, 17% PPD (+); > 5yr DU age > 35 yr, 21% PPD (+)]. PPD (+) rates did not vary by specific drugs used (past 6 months or ever) or by routes of drug use (injection only-14% (+) PPD, inhalation only-18% (+) PPD, both-12% (+) PPD; $p = 0.16$). Rates of TB infection increase among older drug users and are augmented by years of injection drug use but are not markedly affected by the specific drug or route used, suggesting that the duration of time spent in drug using environments increases TB infection risk.

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TUBERCULOSIS DIRECTLY OBSERVED PREVENTIVE THERAPY FOR ACTIVE DRUG USERS IN TWO SETTINGS

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Efficient means of delivering TB preventive therapy to drug users (DUs) are needed. Syringe exchange programs (SEP) have the potentiaI to deliver health interventions to DUs. We conducted TB screening in DUs both at a New York City SEP and inpatient detox facility and administered DOPT at the SEP and in an HIV clinic. To date 46 eligible DUs have been recruited for DOPT (17 from SEP, 27 from detox, 2 from a female DU support group) with twice weekly INH. Incentives were provided weekly based on adherence (31 patients [pts]) only at the HIV clinic. The mean age was 40 yrs, 39% were female, 80% nonwhile, 47% homeless, 18% without health insurance, 33% HIV (+). Forty % injected heroin, 15% injected cocaine, 57% used crack, 38% drank alcohol to intoxication. To date, 10 pts (22%) have completed ≥ 6 months (mos) of INH with ≥ 80% adherence (# doses taken/# doses scheduled). Ten (22%) are still in therapy (median 91% adherence, range 28-100%; 60% were ≥ 80% adherent). Twelve (26%) were transferred to care elsewhere (6 to other provider settings, 4 to long term drug Rx. 2 incarcerated). In 1 (2%) INH was discontinued due to adverse reaction after 2 mos. Thirteen (28%) were lost to follow-up (4 never showed for DOPT despite initially agreeing: 9 lost after 1-6 mos (median, 3). DUs recruited for DOPT at the SEP ($p <0.002$) and DUs given DOPT at SEP ($p < .002$) were less frequently lost than those recruited from detox or medicated at the HIV clinic, despite the use of incentives only at the HIV clinic. While measures to improve adherence are needed, SEPs are valuable sites for screening active DUs for TB and may be useful sites to deliver DOPT to active DUs.

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HOW DOES INFORMATION ABOUT "BAD" HEROIN SPREAD AMONG INJECTION DRUG USERS?

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Revention research and intervention activities require an understanding of bow to effectively communicate with injection drug users and other marginalized communities al risk for HIV infection. This project aimed to determine how information is disseminated and interpreted within the injection drug user community. We studied how information about a batch of "bad" heroin that appeared "on the streets" of Philadelphia on May 9, 1996, flowed through a sample of drug users. Thirty qualitative interviews were conducted between June and September 1996, as part of Project LinCS, a CDC funded study to assess community attitudes toward government-sponsored HIV vaccine trials. Respondents were selected from a cohort of drug users enrolled in Philadelphia's HIVNET (HIV Network for Prevention Trials) project. Individuals were chosen from the cohort who represented a variety of ages. races, neighborhoods and years of heroin use. The data repaid suggest that an active information network exists within the Philadelphia injection drug user community. Despite their differences, almost all 30 respondents reported bearing about the "bad' heroin within one day. Most respondents first heard about the "bad" heroin from local television news. After first bearing about it, additional information was received from television news by 27 (90%) from the newspaper by 21 (70%). and from friends by 15 (50%) respondents. Twenty-four (80%) respondents told others about the "bad" heroin. Overall, the content of the messages conveyed among the respondents was protective and safety-oriented.

A LONGITUDINAL EVALUATION OF ANABOLIC/ANDROGENIC STEROID ABUSERS ACROSS ONE OR TWO CYCLES OF USE

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The illicit use of anabolic/androgenic steroids (AASs) has been mported for individuals seeking to improve their athletic performance or enhance their physical appearance. While serious adverse medical events seem to be rare, psychological and psychiatric morbidity may be more common. Still; however, the relationship between AAS use and changes in affect and behavior is far from clear. The present investigation assessed subjects for up to one year with a comprehensive behavioral and clinical battery. The study was conducted at the University of Pennsylvania Treatment Research Center between September 1994 and August 1996. Subjects were studied through one (n=5) or two (n=2) on/off cycles of AAS use. Drugs were obtained and self-administered by individuals through their usual mechanisms. Subjects returned to the research clinic at approximately 2-week intervals to complete the assessment battery. Few clinically relevant changes in physiological parameters or laboratory measures were noted. Although changes in various behaviorai rating scales (e.g., Beck Depression Inventory, Profile of Mood States questionnaire, and the Buss-Durkee Hostility Scale) were observed across time, these changes were not clearly related to periods of reported AAS use. Additional factors such as life events, subjects' other drug use. and the extended duration of activity of some of the AAS preparations probably influenced the results. "Off" cycles were associated with a greater percentage of subject-reported decreased testicular size, appetite frequency of sexual activity, and libido. The results provide the first reported evaluation of the effects of AASs across and between cycles of use, for periods of up to one year, when these drugs are administered in a naturalistic pattern of abuse. Overall, the data are not consistent with readily observable or predictable effects secondary to the use of multiple, high-dose AASs.

COCAINE AND THE HEART: MORPHOLOGICAL AND MOLECULAR CORRELATES

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Left ventricular hypertrophy and cardiomyopathy in the absence of coronary insufficiency have been reported in chronic cocaine consumers. The present experiments were designed to study the cardiac morphological and molecular correlates associated with chronic cocaine administration. Rats fitted with osmotic pumps implanted in the peritoneum were administered continuously cocaine (10 to 40 mg/kg/day) for 14 to 28 days. Control animals were aiministered saline. Weight gain and behavior were the same in both groups. Tolerance to the initial hypertensive effect of the drug was observed after 6 days. Cocaine treated animals presented cardiac morphological and cytogenetic changes. There was a significant ($p<0.01$) left ventricular hypertrophy associated with disseminated ultrastructural lesions of the myofibrils, elongation of the sarcomeres and abnormal mitochondria. Association of alcohol (20 g/kg in 10% glucose i.p.) for 7 days, resulted in disseminated areas of necrosis. Molecular alterations of the cardiomyocytes were also observed, with an induction of gene expression for ANF (atrial natriuretic factor) a shift in myosin heavy chain gene expression and activation of the genes encoding for type I and II collagen. Protooncogenes fos and MYC were not affected as they are in the neuronal cells of the nucleus acumbens indicating a possible cocaine tissue specificity. Chronic cocaine intoxication in the rat causes left ventricular hypertrophy, cardiac ultrastructural lesions and modifications of the cardiomyocyte phenotype. The mechanisms of the morphological and molecular cardiac aterations, induced by chronic cocaine and administration remain to be established. A direct intracellular toxicity of the alkaloid might be invoked since cocaine accumulates in tissues following chronic administration.

CARDIOVASCULAR EFFECTS OF COCAINE

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Using continuous non-invasive cardiovascular monitoring, eight healthy cocaine addicts receiving intravenous cocaine (0.325 mg/kg iv or 0.650 mg/kg iv) in a double-blind placebo-controlled experiment demonstrated significant increases in pulse and mean arterial pressure which peaked about 5 min. post injection and was sustained for a further 55 min. cocaine administration has no significant effect on oxygen saturation, and no abnormalities of rhythm or conduction were seen on the electrocardiogram. These doses and method of intravenous cocaine administration, and our procedures for cardiovascular monitoring, appear relatively safe for laboratory studies of healthy cocaine addicts with no preexisting cardiovascular disease.

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ACUTE AND CHRONIC TOLERANCE TO CARDIOVASCULAR EFFECTS OF SELF-ADMINISTERED COCAINE IN RATS

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Cardiovascular effects during chronic, limited access (2 hr/day) cocaine self-administration were studied in Sprague-Dawley rats implanted with telemetric devices. Following training to lever press for food, rats were tested for cocaine (1 mg/kg/infusion) self-administration for four weeks, followed by extinction with saline during week 5 and then re-testing of cocaine self-administration during week 6. Th first infusion of cocaine within a given session produced rapid (< 60 sec) increases in diastolic. systolic and mean pressures and in heart rate (HR). The subsequent cocaine infusions within the same session produced increases in pressures that were significantly smaller than that of the first infusion and failed to increase HR. There was an early (<40 min) overall within session reduction in HR as compared to pie-session base-line measures. These patterns of responses were seen on all days of testing, however, the mean increases in pressures and HR produced by the first infusions during the daily sessions of weeks 4 and 6 were significantly smaller as compared to the corresponding increases seen during the first week of testing. These data indicate that there are two kinds of tolerance to pressor and tachycardiac responses to cocaine. One is an acute tolerance, which occurs within each session following a single infusion of cocaine, while the other is a chronic tolerance which occurs over several weeks of cocaine self-administration.

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CHRONIC COCAINE USE ALTERS RESPIRATORY SINUS ARRHYTHMIA AND HEART RATE REACTIVITY TO POSTURE CHANGE

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While cocaine has prominent acute cardiovascular effects (tachycardia, increased blood pressure and reduced respiratory sinus arrhythmia [RSA]), little is known about chronic changes in the neural regulation of cardiovascular functioning as a result of cocaine dependence. We assessed cardiac functioning in 40 chronic cocaine users with cocaine dependence (DSM-IIIR) and 19 control subjects who reported no substance abuse other than tobacco. RSA, a component of heart rate variability reflecting vagal (parasympathetic) control of the heart, and heart rate were calculated from ECG recordings obtained during supine, sitting, and standing positions for 10 minutes each. We hypothesized that chronic cocaine use would alter normal cardiac reactivity to posture change via the baroreceptor reflex. In comparison to non-users, cocaine users bad larger decreases in RSA and increase heart rate when changing position from sitting to standing. Similar findings resulted when 24 outpatient cocaine users and 16 drug-free residential cocaine users were analyzed separately. Both cocaine using groups responded to the standing challenge with larger RSA decreases than nonusers. Outpatient cocaine users responded with greater bean rate increases than nonusers. These results suggest chronic alterations in the neural control of cardiac function in chronic cocaine users, even when drug-free.

ELECTROPHYSIOLOGICAL EVIDENCE OF COCAINE EFFECTS ON CARDIAC CONDUCTION IN HUMANS

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Cocaine is well known to produce acute serious cardiac consequences. Less well understood are cocaine's subclinical effects, including actions on cardiac electrical conduction. We evaluated this using 12-lead, signal-averaged (high resolution) electrocardiogram (ECG) Marquette MacVu) data obtained a mean [SD] of 7.7 [5.3] days into monitored abstinence on a closed research ward from 27 prescreened (medical history, physical examination, routine clinical laboratory tests, standard 12-lead ECG) healthy male IV/smoked cocaine users (19 Atrican-American, 8 white; age 33.9 [4.5] years; 11.4 [6.2] years of cocaine use, using 18.6 [6.3] days/month). The cocaine users had a longer filtered QRS duration (mean [SE] = 114.5 [9.5] msec) and shorter root-mean square voltage in the terminal 40 msec (32.2 [12.7]μV) compared to published values for sex-matched normal controls (Timmermans *et al.,* 1994), with the differences trending in the direction of threshold values used to diagnose a late ventricular potential. Six subjects subsequently received each of 3 IV cocaine doses (10, 25, 50 mg) at least 2 days apart with serial recording of standard 12-lead ECGs Cocaine administration was associated with significant dose-dependent increases in QTc interval, with no significant changes in PR interval or QRS duration. At the 50 mg dose, QTc interval increased from 396 [2] msec (mean [SE]) at baseline to 437 [7] msec 4 minutes after cocaine injection and 412 [4] msec after 41 minutes. While the clinical significance of these findings in otherwise healthy individuals is unknown, they suggest that cocaine may produce specific acute and subacute changes in cardiac electrical conduction.

REFERENCE: Timmermans C., *et al.,* Pacing and Clin Eletrophysiol 17(3 Pt 1):303-311, 1994.

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POTENTIALLY ADVERSE CARDIOVASCULAR CHANGES ASSOCIATED WITH EXPERIMENTAL COCAINE ADMINISTRATION

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We studied acute effects of cocaine administered IV at Img/sec in order to determine whether pretreatment with putative therapeutic medications alters subjective or physiologic effects of cocaine. Cocaine-dependent subjects were carefully screened to exclude those with preexisting medical disease or substance dependence other than cocaine. The laboratory is equipped as an ICU with crash cart, nurse and ACLS trained physician in attendance. After each saline or cocaine infusion, pulse, blood pressure, and EKG morphology are monitored on a beat by beat basis, and the results are confirmed using manual sphygmomanometry. To date, 102 cocaine administrations have been performed in 28 subjects (mean age 41, range 3147, including 26 unique subjects and 2 subjects who participated in two protocols). Of these 102 cocaine administrations, subjects in 9 developed changes in pulse or blood pressure which prompted us to drop the subject from the protocol; no subject developed an adverse reaction which produced morbidity. Because these 9 subjects were dropped from the protocol, 9 of 28 subjects were unable to complete the study. For example, one subject developed a diastolic blood pressure of 120 to 130 (mmHg); another had a rapid rise in systolic blood pressure to above 200 for about 1 minute. Two subjects developed excessive premature atrial contractions (PACs), both after the 20mg cocaine dose. One subject developed unexplaned EKG changes suggestive of right ventricular hypertrophy (or artifact). In all cases the vital signs returned to normal within an hour without morbidity. Age, amount or duration of cocaine or other drug use did not predict outcome. Our experience demonstrates that idiopathic and potentially adverse alterations in vital signs occur after approximately 9% of cocaine administrations, in about one third of subjects studied. Close monitoring and the availability of appropriate medical personnel are required even after relatively low doses.

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ERYTHROCYTHEMIA ("BLOOD DOPING") DUE TO SPLENIC CONTRACTION AFTER INTRAVENOUS COCAINE

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Cocaine is among the most dangerous drugs of abuse due to the risk for acute thrombotic events. Erythrocythemia ("blood doping") has been previously found in human subjects following intranasal cocaine administration. We therefore measured sequential hematologic parameters after a moderate dose of cocaine was administered to healthy human subjects by intravenous (i.v.) route. Fourteen healthy male volunteers with reported sporadic prior cocaine use Participated after informed consent. Vital signs and electrocardiographs were continuously monitored before and for 180 minutes after administration of iv. cocaine (0.40 mg/kg, n=7) or placebo (n=7). There was a significant increase in hematocrit, hemoglobin concentration, and red blood cell (RBC) mass 10 minutes after i.v. cocaine which persisted for 20 minutes ($p=0.001$). The white blood cell and platelet counts showed no increase after cocaine challenge. Splenic volume as assessed by magnetic resonance imaging decreased by $27.0 \pm 2.5\%$ (mean $\pm$ S.D.) 10 min. after cocaine administration, and returned to baseline within 40 min. Infusion of RBCs from splenic contraction into the general circulation may be the mechanism for the increase in RBC mass. These data demonstrate that acute erythrocythemia ("blood doping") occurs following a moderate dose of i.v. cocaine in healthy humans which may alter blood viscosity and contribute to medical risk for acute thrombotic events.

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A NOVEL PARADIGM TO INVESTIGATE TITRATION OF DRUG DOSE IN RATS REINFORCED BY INTRAVENOUS COCAINE OR HEROIN

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The purpose of the present experiment was to investigate dose-regulation in rats self-administering heroin or cocaine when both dose size and interdose interval were under the subjects' control. This paradigm allowed the subjects to increase and decrease their dose in discrete steps throughout the session. Twenty Wistar rats were assigned to one of two drug groups that were given access to either cocaine (n=10) or heroin (n=10) during daily 5 hr sessions. Drug dose was determined by altering the duration of the infusion from 0 to 25 sec. The duration of infusion depended on which lever was pressed. A response on the lever with a stimulus signaling an increase in dose size increased the infusion duration by 3 sec, and a response on lever with a stimulus signaling a decrease in dose size, decreased the infusion duration by 3 sec. At the beginning of each session, infusions durations started at 12 sec. When a maximum duration of 25 sec or a minimum duration of 0 sec was reached, that duration remained in effect until the other lever was pressed. Significant correlation coefficients were obtained for interdose interval (IDI) and infusion duration (dose) for both groups. Furthermore, daily and hourly drug intake for cocaine and heroin groups were relatively constant. These findings indicate that subjects regulated hourly and daily drug intake by adjusting magnitude of dose and interdose interval throughout drug self-administration sessions.

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SECOND-ORDER SCHEDULES OF ORAL COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

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Three rhesus monkeys were allowed access to cocaine under second-order, fixed-ratio, reinforcement schedules. Under this arrangement, stimulus lights which were either explicitly paired with reinforcer delivery or never paired with reinforcer delivery were presented at different frequencies during the overall ratio. The overall fixed-ratio value was varied from 64 to 256. The number of stimulus presentations during the ratio was varied from 0 to 256. All fixed-ratio and stimulus presentation frequency values were tested under reinforcer paired and reinforcer nonpaired stimulus conditions. Cocaine self-administration and cocaine intake were reduced as overall fixed-ratio value was increased. There were no systematic differences between the paired and nonpaired conditions. There were no systematic dilferences among stimulus presentation frequencies. The former finding is consistent with previous literature. The lack of any systematic effects of the pairing operation and stimulus presentation frequency may be due to the monkeys previous extended history of fixed-ratio cocaine-maintained responding.

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REINFORCED AND EXTINGUISHED BEHAVIOR USING TWO PROGRESSIVE-RATIO SCHEDULES OF COCAINE DELIVERY

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Ptogressive-ratio (PR) schedules of drug delivery have been used by an increasing number of investigators in the area of drug self-administration. These schedules are popular partly because subjects' performance is thought to reflect the reinforcing efficacy of the drug dose that maintains responding, and PR-maintained behavior has been used frequently as a baseline against which the effects of various pretreatments are assessed. Recent research has indicated that specific procedural variations may improve the quality and usefulness of the data collected: Woolverton (1995) and Rowlett *et al.* (1996) described innovative PR schedules of drug delivery in which the response requirements did not increase from one ratio to the next (as is typical), but instead increased across "blocks" of ratios within each session. The current studies were undertaken to further evaluate the similarities and differences between performances generated by conventional PR schedules (1-trial PR program) and one with blocks of ratios (5-trial PR program) in rhesus monkeys. Performance was examined across a range of unit doses of cocaine and also during extinction (i.e., saline substitution). In both procedures the average number of ratios completed increased across small to mid-sized unit doses, and often decreased at the largest unit doses tested. The peak of the unit-dose-effect function occurred at a lower dose (10 ug/kg/inj) for the 5-trial program than for the l-trial program (10-56 ug/kg/inj), and overall intake of drug during the 5-trial program was much greater than intake during the 1-trial program. Patterns of extinction were also different across the two PR schedules. Subjects whose behavior was relatively insensitive to extinction on the 1-trial program displayed more rapid and complete decreases in responding on the 5-trial program. In addition to improving our understanding of PR schedules of drug-maintained behavior, these data may offer suggestions for future research in the area of behavioral economics. REFERENCES: Available upon request.

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REINSTATEMENT OF COCAINE SELF-ADMINISTRATION BY STRESSORS FOLLOWWG CHRONIC EXTINCTION

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The ability of electric footshock (EFS) or a conditioned stimulus paired with the delivery of EFS to reinstate responding previously reinforced by cocaine was investigated following chronic extinction. Six adult male Wistar rats were trained to self-administer cocaine (0.5 mg/kg/inf) under a fixed-ratio 4 schedule of reinforcement with a 90-second limited-bold during daily 2-hour sessions. Once stable responding was observed, self-administration was extinguished by presenting no programmed consequences of lever-pressing. Following 2 or 4 weeks of extinction, the ability of EFS (0.6 mA, 0.5 msec duration. every 15 sec for 15 min), a pair of stimuli (10 sec tone and light) previously paired with the delivery of EFS (3 consecutive pulses. 0.5 msec duration, 0.6 mA intensity, 0.5 msec interval) under a random interval 5-min schedule during daily 1-hour sessions, or a neutral stimulus (tone and light not paired with EFS) to reinstate responding was investigated. After 4 weeks of extinction, no significant reinstatement was observed when EFS was presented for 15 min immediately prior to the subsequent extinction session. Likewise, the presentation of the conditioned stressors or neutral stimuli failed to reinstate responding when these stimuli were presented either immediately prior to or during (i.e., 60 min after the start of) extinction sessions. However, reinstatement was observed following 2 weeks of extinction when EFS (15 min) or the conditioned stressor were presented immediately prior to the next extinction session.

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ACTH AND CORTISOL IN COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

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There is a substantial body of work strongly suggesting positive relationships between plasma glucocorticoid levels and cocaine self-administration (SA) behavior in rats (eg., Piazza; Goeders). This study investigated whether cortisol feedback is important in a primate model of cocaine SA, as well as whether there would be any differences between the cortisol response evoked by contingently and non-contingently administered cocaine. Four male rhesus monkeys (Macaca mulatta), each with a surgically-implanted venous catheter, were used in this study. Cocaine (0.01, 0.03, 0.1 and 0.3 mg/kg/inj) or saline was available on a fixed-ratio 30 time-out 600-s (FR 30 TO 600) schedule. Non-contingent tests involved infusions automatically given in a pattern identical to the SA session from the previous day. Venous blood was sampled before, during and after a.m. 130 min SA sessions and plasma cortisol and ACTH levels were measured by RIA. A positive correlation was found between amount of cocaine taken and plasma cortisol levels, although under these conditions there was no difference in the cortisol response to behaviorally contingent and non-contingent cocaine administration. Etomidate (0.1, 0.3 and 1.0 mg/kg), an intravenous sedative-hypnotic previously shown to block cortisol responses to ACTH stimulation, was infused prior to the SA session. Etomidate was shown to block the increase in cortisol observed with 0.1 and 0.3 mg/kg/inj cocaine and produce an accumulation in ACTH, although the amount of cocaine injected during the session was not changed. Thus, although there is a positive correlation between cocaine intake and plasma cortisol, blocking cortisol production does not appear to reduce SA behavior.

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CORTICOTROPIN-RELEASING FACTOR RECEPTOR BLOCKADE ATTENUATES THE REWARDING PROPERTIES OF COCAINE IN RATS

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The behavioral profile of corticotropin-releasing factor (CRF) in mediating anxiogenic-like and aversive responses to stressors may be particularly relevant for dependence and withdrawal in drug-experienced organisms. Moreover, stressful aspects of drug exposure in the drug naive organism may also induce CRF system activation, In the present studies, the dependence of aversive properties of cocaine on activation of endogenous CRF systems has been evaluated in rats using taste conditioning and runway self-administration paradigms. Systemic cocaine administration (20 mg/kg i.p.) produced a conditioned saccharin aversion which was dose-dependently potentiated by central administration of the CRF receptor antagonist. D-phe CRF (12-41). In addition, acquisition of intravenous cocaine self-administration (0.75 mg/kg/inj i.v.) produced goal-box avoidance and conditioned place avoidance responses which were significantly accelerated by CRF antagonist treatment in self-administering, but nor cocaine-naive subjects. In contrast, CRF receptor stimulation using CRF itself abolished cocaine-induced increases in goal lafencies in the runway paradigm. This generalized involvement of CRF systems in cocaine-related motivational/associative states is consistent with the comprehensive role of CRF in mediating emotional responses to non-drug stressors and suggests the utility of CRF receptor antagonists in counteracting the acquisition of cocaine use.

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COCAINE PREEXPOSURE FAILS TO SENSITIZE TASTE AVERSION LEARNING

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Previously, we have reported that animals given massed or spaced preexposure co cocaine (either intraperitoneal or subcutaneous) did not display sensitized aversions to cocaine during subsequent conditioning (see Diamond and Riley, Soc. Neurosci. Abstr. 21:1953; 1995; Diamond and Riley, Soc. Neurosci. Abstr. 22:1583; 1996). In fact, preexposed subjects were retarded in the acquisition of cocaine-induced taste aversions. The present series of studies further investigated the effects of cocaine preexposure by examining such preexposure under conditions which typically produce sensitization to the motoric effects of cocaine, i.e., multiple intraperitoneal injections (10) of low doses (10 mg/kg) of cocaine or a single intraperitoneal injection of a high dose of cocaine (40 mg/kg). Following preexposure under these conditions, subjects were given a novel saccharin solution to drink followed by a subcutaneous injection of cocaine (32 mg/kg) to assess the effects of preexposure on aversion conditioning. Under all preexposure conditions, there was no evidence of sensitized aversions to cocaine (relative to subjects preexposed to vehicle and subsequently injected with cocaine during conditioning). As in our previous work (see above), cocaine preexposure (single or multiple injections) attenuated cocaine-induced taste aversions. These data suggest that preexposure to cocaine attenuates or weakens its aversive properties which in turn results in weakened cocaine-induced taste aversions. Such an attenuation may contribute to the sensitization of the rewarding effects of cocaine with chronic exposure.

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LiCL-INDUCED CONDITIONED TASTE AVERSIONS: A COMPARISON BETWEEN LEW/N AND F344/N RAT STRAINS

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Previously, we have reported that cocaine-induced taste aversions were differentially acquired by Lewis and Fischer rat strains (Glowa *et. al.,* Psychopharmacology 114:229-232; 1994). Specifically, doses of cocaine that had no effect in the Fischer strain produced robust aversions in the Lewis strain, suggesting that the two strains differ in their relative sensitivities to the aversive effects of cocaine. The present study extended this analysis by examining LiCl-induoed aversions in the two strains. Specifically, 24 Lewis and 24 Fischer rats were adapted to water restriction and then allowed limited access to a novel saccharin solution. Different groups within the two strains were then injected with various doses of the emetic LiCl (0.3, 0.6 and 1.2 mEq, 0.15 M) or with the LiCl vehicle. These pairings were repeated every fourth day for a total of four trials. For both strains, LiCl-induced aversions were dose-dependent with the higher doses of LiCl producing greater suppression of consumption. There were significant differences between the strains in their sensitivity to LiCl. Specifically, at the intermediate dose (0.6 mEq) Lewis rats acquired aversions at a faster rate and to a greater degree than Fischer rats. There were no differences between strains following injections of the vehicle or the highest dose of LiCl. Lewis and Fischer rats appear differentially sensitive to the aversive effects of LiCl, suggesting that differences between these strains occur for effects other than the reinforcing effects of drugs and for drugs other than drugs of abuse.

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ENHANCED EXTRACELLULAR ASPARTATE (ASP) RESPONSE TO COCAINE IN BEHAVIORALLY SENSITIZED RATS

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The effect of behavioral sensitization to cocaine was determined on ASP and glutamate (GLU) in male Sprague-Dawley rats. Seven days after guide cannula implantation, a concentric microdialysis probe was inserted into the nucleus accumbens (NAcc) core. After a 4 hr equilibration, samples were collected in 10-min fractions for 2 hr to establish baseline values in the awake rat. Cocaine (15 mg/kg) or saline was injected i.p. and fractions collected for 2 hr. Videotapes of the rats were scored by observers blind to treatment. Rats receiving cocaine for the first microdialysis procedure were divided into 2 groups receiving 5 additional daily cocaine or saline injections in home cages; rats receiving saline for the first microdialysis procedure were divided into 2 groups receiving 6 additional cocaine injections (the first on the day of microdialysis) or 5 additional daily saline injections in home cages. A second microdialysis procedure was performed in which rats were challenged with cocaine or saline 48 hrs after the last injection. To exclude an effect of repeated microdialysis on extracellular ASP or GLU, another group of rats was exposed to elevated K+ (70 mM) via the microdialysis probe, followed by a second exposure 1 week later. Kruskal-Wallis and Mann-Whitney U tests revealed behavioral sensitization of rats receiving 6 injections of cocaine ($Z=-2.107$, $p < 0.05$). Two-way repeated measures ANOVA of the areas under the curve revealed a significant interaction of treament and repeated measure such that rats receiving 6 injections of cocaine exhibited increased extracellular ASP when challenged with cocaine ($p < 0.05$). GLU was nof significantly increased. No difference was observed in the effect of high K+ on extracellular ASP and GLU between the first and second exposures.

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CONCURRENT-SCHEDULE PERFORMANCE UNDER LONG VI SCHEDULES OF COCAINE OR FOOD AVAILABILITY

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Concurrent schedule respouding maintained by cocaine urder short variable-interval (VI) schedules has been shown to conform to the generalized matching equation. That is, drug maintained behavior is apportioned in accordance with relative frequency of reinforcement. The purpose of the present experiment was to examine the ability of the generalized matching equation to account for choice under long VI schedule of cocaine or food presentation. One group of rhesus monkeys (N=4) was prepared with indwelling i.v. catheters and allowed to respond under concurrent VI schedules of cocaine delivery (0.025, 0.05 or 0.1 mg/kg/inj) with an average inter-reinforcer interval of 30 min. In a second group of monkeys (N=4), a comparable experiment was conducted with responding maintained by differing magnitudes of food (1, 2, or 4 banana-flavored pellets). For both groups, the same reinforcer followed responding on either lever, the only difference between the options being the schedule of reinforcement. Although results from the two groups were similar, the behavior of the cocaine group more closely fit the predictions of the generalized matching equation. Specifically, goodness of tit was better for the cocaine group (0.83 versus 0.78), them was a greater tendency toward under-matching in the food group (0.51 versus 0.70), and response bias was greater for the food group (0.79 versus 0.99). This finding suggests that under the conditions studied, the generalized matching equation predicted choice maintained by drug somewhat better than food-maintained choice The results expand the applicability of the generalized matching actuation to choice maintained by long VI schedules of drug injection.

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MOTIVATIONAL EFFECTS OF COMBINING STIMULI INDEPENDENTLY ASSOCIATED WITH FOOD AND COCAINE

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In previous experiments, the compounding of two discriminative stimuli associated with the same reinforcer increased rats' responding approximately three-fold, regardless of whether the reinforcer was food, water, cocaine, or shock-avoidance. Compounding a discriminative stimulus associated with food with one associated with water increased responding two-fold. Compounding an appetitive discriminative stimulus (associated with food) with an aversive one (associate with shock avoidance) did not increase responding. In the present experiment, compounding a discriminative stimulus associated with food with one associated with cocaine increased responding two-fold. These results support the hypothesis that 1) the motivational effects of stimuli associated with reinforcers from opposite classes (appetitive and aversive) are mutually inhibitory, 2) the effects of stimuli associated with reinforcers from within the same incentive class are mutually enhancing, and 3) the effects of combining stimuli associated with two different reinforcers from within the same class are not as strong as strong as those of combining two stimuli associated with the same reinforcer. These results also suggest that discriminative stimuli associated with a non-drug reinforcers may increase the motivation to self-administer cocaine when encountered in combination with drug-related stimuli.

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CONDITIONED SUPPRESSION OF OPERANT RESPONDING WITH COCAINE IN RATS

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In the current study, the conditioned suppression procedure was used to study drug conditioning. Conditioned suppression involves the pairing of a drug injection with a discrete, environmental stimulus. That stimulus-drug pairing is presented during ongoing operant performance and conditioning is measured as a disruption in that performance. Rats were trained to nose-poke on a food-reinforcement schedule. A 5-min tone-light compound stimulus was then presented 30 min into the session. Two min after the onset of the stimulus, either saline or cocaine (1.0 or 5.6 mg/kg, i.v.) were administered to separate groups of rats. For a fourth group, the stimulus was presented and the 5.6 mg/kg dose of cocaine was injected in an unpaired fashion. After four training days, a test was given where the tone-light stimulus was presented alone. No disruption of responding during the stimulus was observed for the saline and unpaired groups. When the stimulus was paired with 5.6 mg/kg cocaine. however, it produced a nearly 50% reduction in responding and even the stimulus paired with 1.0 mg/kg group produced some suppression of responding. In preliminary studies, the 5.6 mg/kg dose alone clearly disrupted responding, while the 1.0 mg/kg dose produced small increases in response rates. The conditioned suppression observed with the stimulus paired with 5.6 mg/kg cocaine extinguished over 5 days of stimulus alone presentations. Thus, the conditioned suppression procedure may be a useful model for studying the conditioned effects of drugs of abuse, even psychomotor stimulants, although it is unclear whether response-rate increases can be conditioned to discrete stimuli in this manner.

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NORADRENERGIC INVOLVEMENT IN THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE IN RATS

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Noradrenergic involvement in the cocaine-saline discrimination was assessed in rats (N=24) trained to discriminate cocaine (10 mg/kg) from saline using a two-lever, water-reinforced FR20 procedure. Results indicated that the alpha-2 agonist clonidine (0.01-0.06 mg/kg) and the beta-1,2 antagonist (-)-propranolol (4-16 mg/kg) produced a maximum 50-60% cocaine-lever responding, whereas the NE reuptake inhibitor nisoxetine (8 mg/kg), the alpha-1 antagonist prazosin (0.2 mg/kg) and the alpha-2 antagonist idazoxan (2-8 mg/kg) engendered primarily saline-lever responding. Coadministration of a ftxed dose of nisoxetine (8 mg/kg) or idazoxan (4 mg/kg) plus cocaine (0.625-5 mg/kg) produced a “supra-additive” enhancement of the cocaine dose-response curve, whereas (-)-propranolol (8 and 16 mg/kg) plus cocaine engendered a modest “additive” effect. Conversely, prazosin (0.03-1 mg/kg) or clonidine (0.06 mg/kg) resulted in a 70% reduction in cocaine-lever responding when combined with a dose of cocaine (5 mg/kg) that produced >80% drug-lever responding when given alone. These results support previous evidence demonstrating a role of NE systems in mediating the discriminative stimulus effects of cocaine.

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POTENTIATION OF THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE BY CYMSERINE

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Butyrylcholinesterase (BChE) is a primary cocaine metabolizing enzyme in both humans and animals. The present study examined the effect that cyrmserine, a BChE inhibitor, has on the discriminative stimulus properties of cocaine. Sprague Dawley rats (N = 9) were trained in a 2-lever drug discrimination paradigm to discriminate cocaine (10 mg/kg. i.p., given 10 min pre-session) from its vehicle (saline). Responding was maintains by a fixed-ratio 10 (FR 10) schedule of food reinforcement. The subjects were trained 5 days per week, 15' per day, using a double alternation schedule (2 days vehicle followed by 2 days cocaine). Once subjects met criteria (=>90% appropriate responding and less than 10 incorrect responses on the first trial) for 8 consecutive sessions they were switched to a single alternation schedule with a maximum of 2 test days per week. Before test sessions, during which both levers were active, the animals were created with saline or cocaine (0.3, 1, 3, 10, 20 mg/kg) alone or cymserine (30 mg/kg, i.p.) followed 40 min later by saline or cocaine (0.3. 1, 3, 10, 20 mg/kg, i.p.). A time course was also examined where cocaine 10 mg/kg was given 60, 90, 120, 150, and 180 min pre-session or 40 min following cymserine 10 mg/kg. Cymserine 30 mg/kg shifted the cocaine dose effect function to the left. Cymserine 10 mg/kg increased the duration of the cocaine discriminative stimulus properties.

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GENETIC ANALYSIS OF COCAINE-INDUCED PLACE PREFERENCE IN SMXA RI INBRED STRAINS OF MICE

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It is well known that genetic factors play an important role in drug responses. Genetic factors associated with drug responses can be determined using many inbred strains or recombinant inbred (RI) strains of mice. SMXA RI strains of mice were derived from two distinct inbred strains, A/J and SM/J strains. The SMXA Rl strains consist of 26 substrains: one of the greatest number of substrains among many RI strains of mice. The SDP of 158 markers in SMXA Rl strains of mice has been established. The present study was designed to determine the chromosomes and their loci associated with cocaine-induced place preference using conditioned place preference paradigm. First, cocaine (8 mg/kg, s.c.)-induced place preference was examined in genetically distinct A/J and SM/J strains of mice. In A/J mice, cocaine produced a significant place preference, but in SM/J mice, cocaine produced neither significant place preference nor place aversion. The strain difference observed here suggests that genetic factors may play an important role in modulating the cocaine-induced place preference. Secondly, the cocaine-induced place preference was determined in 26 SMXA Rl strains of mice. In SMXA RI mice, cocaine-induced place preference was found to be distributed unimodally. Quantitative trait loci analysis using these data indicated that 7 loci on 4 chromosomes, especially D9Mit16 located 61 cM on chromosome 9, are involved in the expression of rewarding effect of cocaine.

RATE OF RISE IN BRAIN CONCENTRATION DETERMINES REINFORCING STRENGTH OF COCAINE IN ONLY 63% OF TESTED RATS

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One of the central dogmas in addiction research maintains that the reinforcing strength and, thus, the abuse liability of a drug are determined by the rate of rise of the drug's brain concentration after administration (Jaffe 1990). In order to test this hypothesis, intravenous cocaine (0.083 - 2.25 mg/kg^{-1} $injection^{-1}$) was made available to Long-Evans rats in a self-administration paradigm (FR1 TO 150 s) at two injection speeds (injection interval 6 s or 150 s) that were tailored to yield the same peak brain cocaine concentrations but a 25-fold difference in the initial rate of rise in brain concentrations, using the pharmacokinetic data by Pan *et. al.,* (1991). Accordingly, *in vivo* microdialysis experiments showed that the peak nucleus accumbens dopamine overflow was essentially identical for both injection speeds. The lower initial rate of rise in the brain cocaine concentration resulted in a decreased reinforcing strength of cocaine in only 5 of 8 tested rats. In one of these 5 animals, response rates were decreased at the lower injection speed at both the peak and the ascending part of the cocaine dose-response curve. Three animals showed decreased rates of responding at the lower injection speed only at the lowest cocaine dose that maintained responding at the higher injection speed (i.e., the threshold dose). One animal showed decreased responding only for the cocaine dose, that maintained peak rates of responding at the higher injection speed. These data suggest that the initial rate of rise in the brain concentration of a drug of abuse controls behavior to a much lesser degree than previously thought.

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REPEATED DOSING WITH ORAL COCAINE IN HUMANS: PHARMACODYNAMIC AND PHARMACOKINETIC EFFECTS

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This inpatient study examined the effects of repeated oral cocaine dosing in human cocaine abusers. During each of a possible 16 sessions, five identical doses were given at 1 hr intervals; subjective. objective, and physiological measures, including plasma and urine, were collected before, during and for up to 24 hr after dosing. Doses were administered in ascending order over consecutive sessions, beginning at 100 mg/capsule and increasing by 25 mg/capsule/session for a maximum of 400 mg/capsule with intermittent placebo sessions. Preliminary results (n=4) indicated that the lowest doses (100-150 mg) were not reliably detected by all volunteers; ratings of magnitude of drug effect and euphoria ("high," "good effects") showed dose-related and sustained elevations at doses $\geq$ 175 mg. Similarly, heart rate and blood pressure were not appreciably altered by the lowest doses, while doses >150 mg reliably produced dose-related cardiovascular responses. In contrast, pupil diameter was increased by even the lowest doses of cocaine. Preliminary pharmacokinetic data indicated that clinically significant plasma concentrations of cocaine (i.e., 500-1000 ng/ml) proportional to dose were achieved by the oral route of administration and that plasma cocaine concentrations showed cumulative increases with successive hourly oral doses. These data indicate that orally administered cocaine produces effects qualitatively similar to those produced by other routes of administration. However, the onset of oral cocaine action is slower, and thus oral cocaine may be more safely tolerated in controlled studies of chronic cocaine exposure and withdrawal in humans compared to other routes of administration associated with faster cocaine delivery.

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HOW DEPENDABLE IS THE IP ROUTE? PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) EVIDENCE FOR COCAINE AND MIDAZOLAM

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Cocaine (coc) or midazolam (mid) by the IP route decreased the reinforcement rate (RR) of a differential reinforcement of low rate (DRL 45-s) performance in 3-h sessions. However, the effects of these Iwo drugs on RR as the PD measure were not always consistent for a given dose. Two groups of rats were used to investigate the dependability of the IP route: 10 and 20 mg/kg coc (N=8); 3 mg/kg mid (N=4). Each dose was given twice and separated by 3-5 days. Drug effects on RR were reproducible for the respective two injections except for 10 of the 40 injections, for which RR was variable or remained at baseline level. Furthermore, this diminished effect occurred randomly following either the fit or second injection. Hence, the differences could not be attributed to sensitization or tolerance. Inasmuch as PD often can be predicted from PK, parallel PK were conducted for coc (N=4) and mid (N=6) to study the relation between drug concentration-time profile (CTP) and performance. Within-subject variability of cot and mid CTPs for a given dose was as evident as those for the PD. One of the extreme occasions was that coc CTP was just at the detection limit following IP 20 mg/kg cocaine. These results confirmed that the retarded serum coc or mid CTP accounted for the diminished performance. However, the mechanism(s) involved in the undependable effect of the IP route on CTPs remains to be clarified, especially as no difficulty occurred for caffeine. A reproducible CTP is essential before other mechanisms accounting for the change can be inferred.

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CONCURRENT PHARMACOKINETICS OF COCAINE AND ADRENOCORTICOTROPIC HORMONE IN MEN

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Acute cocaine administration increases ACTH, and this may influence cocaine's reinforcing effects. The goal of this study was to quantify the covariance between plasma cocaine levels and ACTH. Eighteen healthy male occasional cocaine users participated in a double-blind study, intravenous cocaine (0.2 mg/kg, 0.4 mg/kg) or placebo was infused over 1 min. and samples for cocaine and ACTH analysis were collected at 2, 4, 8, 12, 16, 20, 30, 40, 60, 80, 120, 180, and 240 min. Peak cocaine plasma levels averaged 101.2 ± 14.6 ng/ml and 231.5 ± 20.1 ng/ml. ACTH increases were significantly correlated ($p<0.0001$) with increases in plasma cocaine levels ($r=.78$ $r^2=.62$, $r=.67$ $r^2=.44$). Pharmacokinetic analysis showed that the tmax for cocaine (8.0 ± 1.0 min.) and ACTH (8.7 ± 0.7 min.) were almost identical. Area under the curve was calculated using the trapezoidal rule, the area under the curve (AUC) for 0.2 mg/kg was 6463 ± 1070 ng•min/ml, AUC for 0.4 mg/kg was 15603 ± 1010 ng•min/ml. The AUC for ACTH after 0.2 mg/kg cocaine was 1873 ± 188.3 pmol•min/L and after 0.4 mg/kg cocaine was 1966 ± 101.3 pmol•min/L. The mean half-life (t 1/2) for cocaine was 46.7 ± 4.0 min and t 1/2 for ACTH was 37.2 ± 3.7 min. Cardiovascular and subjective effect measures were correlated with increases in plasma cocaine levels and ACTH.

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THE EFFECTS OF BUTYRYLCHOLINESTERASE ON PLASMA COCAINE CONCENTRATION

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Studies have shown that butyrylcholinesterase (BChE, E.C.3.1.1.8) is a major enzyme responsible for the metabolism of cocaine for humans. More recently, we have demonstrated that, when administered as a pretreatment, horse-serum derived BChE (HS-BChE) significantly reduces cocaine-induced locomotor activity in the rat. To determine whether or not this result may have been due to alterations in cocaine metabolism, an in vitro study was performed with rat plasma spiked with HS-BChE. Specifically, cocaine was added to rat plasma with and without exogenous HS-BChE and cocaine concentrations together with metabotites, were quantitated. To further elucidate and characterize the action of BChE on cocaine, the concentration-dependent action of HS-BChE on the time-dependent metabolism of cocaine *in vivo* was analyzed. Four groups of 6 rats were unplanted with arterial catheters for blood sampling and venous catheters for the administration of HS-BChE. HS-BChE was administered (i.v) 30-min prior to a cocaine (17.0 mg/kg i.p) challenge. Rats received one of the following: saline(i.v)+cocaine, HS-BChE (50 IU)=cocaine, HS-BChE (500 IU)=cocaine, and HS-BChE (5000 IU)+cocaine. Plasma cocaine concentrations were not affected by saline, 50 IU or 500 IU HS-BChE. Rats receiving 5000 IU of HS-BChE showed a marked increase in cocaine metabolism, while cocaine's disappearance dropped from 26.7-min in control animals to 13.2-min in animals receiving 5000 IU HS-BChE. When compared to controls, the highest dose of HS-BChE (5000 IU) produced a clear increase in EME production. Our data suggest the HS-BChE pretreatment alters the metabolism of cocaine in a way that further reduces cocaine's half-life in plasma and that HS-BChE also shifts the metabolic profile for cocaine towards more EME production.

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INHIBITION OF CYTOCHROME P450 2D6 MODIFIES CODEINE METABOLISM AND ABUSE LIABILITY

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Codeine is an opioid drug that is a widely abused drug worldwide. The genetically polymorphic human drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6) catalyzes the O-demethylation of codeine to morphine. Morphine and its metabolites are more active than codeine and contribute substantially to the analgesic effects of codeine. We conducted a study to determine the importance of O-demethylation to codeine's reinforcing properties. Twelve extensive metabolizers received 3 doses of codeine (60/120/180 mg) and placebo to determine the best liked dose (BLD). The BLD was repeated after quinidine (QD) placebo; QD 50 mg; and QD 50 mg q.i.d. for 4 days. QD is a potent CYP2D6 inhibitor *in vivo*. The mean urinary O-demelhylation metabolic ratios for codeine increased from 0.25 0.33 (placebo) to 0.82 0.36 (single QD) and 1.0 0.55 (chronic QD) ($p < 0.01$). After QD, mean peak plasma morphine levels decreased by 71% (single dose) and 91% (chronic) ($p < 0.001$) confirming inhibition of codeine O-demethylation by QD. The acute QD treatment, in particular, decreased the subjective and physiological effects of codeine on most measures. The results indicate that CYP2D6 activity contributes importantly to codeine abuse liability.

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PHARMACOKINETICS OF INTRAVENOUS HEROIN IN MORPHINE-MAINTAINED HUMANS

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The pharmacokinetics of intravenous heroin were evaluated in seven heroin-dependent individuals (six men, one woman), maintained on divided daily doses of oral morphine. The research volunteers were participating in a 2.5-week study of heroin self-administration in which they received a dose of intravenous heroin (pbo, 6.25, 12.5, 25, and 50 mg) in the morning. Blood (5-6 mL) was taken at times 0, 2, 4, 10, 20, 40, and 60 minutes through an indwelling intravenous catheter in the arm opposite the heroin administration arm. The blood was collected in vacuum tubes containing NaF and K oxalate and immediately placed on ice before centrifuging for isolation and subsequent freezing of plasma. Heroin (H), 6-monoacetyl morphine (MAM), and morphine (M) were measured in plasma using liquid/liquid extraction, derivitization of the MAM and M, followed by capillary GC-MS in the positive chemical ionization mode with simultaneous ion monitoring. Internal standards consisted of deuterated labeled H, MAM, and M. Plasma concentration-time curves were analyzed using a one-compartment model and AUC was determined by the trapezoidal method. For both H and MAM, AUC and Cpmax increased dose-dependently. The plasma half-life for H ranged from 10 to 14 minutes and for MAM from 24 to 31 minutes, for the dose levels studied. Tmax for H occurred between 2.0 and 3.3 minutes after injection and for MAM between 2.0 and 3.0 minutes after injection.

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SENSITIVE GC-MS METHOD FOR DETERMINATION OF BUPRENORPHINE AND NORBUPRENORPHINE IN RAT PLASMA

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A sensitive, specific, and robust capillary CC-MS method has been developed and validated for simultaneous determination of buprenorphine (BUP) and its active metabolite, norbuprenorphine (NBUP), in rat plasma by using levallorphan as the internal standard (IS). Sample preparation involved a clean-up procedure by a C_8 cartridge and a reaction with pentafluoropropionic anhydride, the derivatizing agent. Separation was carried out by an HP-I fused silica capillary column (12 m x 0.2 mm I.D.) using helium as the carrier gas. Oven temperature was 150 °C for 2.5 min initially, increased at 15 °C/min to 280 °C for 8 min. Injection temperature was 150 °C. Selected ion monitor mode was used in the electron impact mass detection set at 300 °C. The retention times for BUP (m/z=524), NBUP (m/z=648) and IS (m/z=403) were 15, 12 and 8 min, respectively, with baseline separation. No interference from blank plasma was observed. With a sample size of 0.1 ml rat plasma, excellent linearity was found between 0.5 to 30 ng/ml with limit of detection of 0.2 ng/ml and limit of quantitation of 0.5 ng/ml for both BUP and NBUP, respectively. Assay validation was performed at concentrations of about 1, 7 and 27 ng/ml, representing low, medium and high concentrations. Intra-day assay precisions were <11% for BUP and <12% for NBUP, and accuracies were within 10% for nominal concentrations. Inter-day assay precisions were <13% for BUP and <15% for NBUP, and accuracies were within 10% for nominal concentrations. The absolute recoveries for both entities were near-quantitative and no concentration-dependence was found. This method will be applied to the pharmacokinetic/pharmacodynamic studies of BUP and NBUP in rats and extended for the analysis of human plasma matrix.

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GENETICALLY DEFICIENT CYPZD6 METABOLISM PROVIDES PROTECTION AGAINST ORAL OPIATE DEPENDENCE

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Oral opiates (e.g. codeine, oxycodone, and hydrocodone) are metabolized by cytochrome CYP2D6 to metabolites of increased psychoactivity (e.g. morphine, oxymorphone, and hydromorphone). CYP2D6 is genetically polymorphic, 4-10% of Caucasians being homozygous for deficient alleles (poor metabolizers, PMs) with no CYP2D6 activity. We tested if the failure to activate oral opiates was a protection factor in opiate dependence, by genotyping (CYP2D6*3 and *4 defective mutant alleles) Caucasians (n = 452) who met or didn't meet DSM criteria for oral opiate dependence. In opiate (± smoking) dependent subjects (n = 89) we found no PMs. In contrast, the PM frequency in never- and multi-drug dependent controls were 4% and 6.5%, respectively. This under-representation of PMs (Fisher's, p = 0.05) in people dependent on oral opiates suggests that CYP2D6 defective genotype is a pharmacogenetic protection factor for oral opiate dependence (estimated odds ratio 7). This is the first demonstration of differences in geneticaily determined P450 metabolism influencing risk for substance dependents, suggesting that these differences may influence the risk for dependence of other substrate drugs, and may occur with other genetically variable P450s.

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κ OPIOID DISCRIMINATION IN FEMALE VS. MALE RATS

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Eight female and eight male rats were trained to discriminate the κ opioid (5α,7α,8β)-(-)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl] benzeneacetamide (U69,593,0.13 mg/kg s.c.) from vehicle. Female tats took significantly longer to acquire the discrimination than males did (66.9±27.1 vs. 44.1±17.9 sessions, respectively), and the ED50 for U69,593 substitution was significantly higher in females than in males (0.074 vs. 0.025 mg/kg). The time course of U69,593 substitution also differed between females and males: peak and offset occurred earlier in females than in males. Another κ opioid agonist, bremazocine, substituted for U69,593 but the ED50 for bremazocine substitution was significantly higher in females than in males (0.0039 vs. 0.0006 mg/kg). The κ/μ opioid agonist ethylketazocine substituted for U69,593 in all males and 5 of 7 females. The μ agonist morphine and the δ agonist BW373U86 did not substitute for U69,593 in either sex. U69,593 also produced significantly less mine output -- but equivalent antinociception -- in females compared to males (e.g., 5.92±1.71 vs. 14.83±2.05 ml urine/kg body weight in females vs. males, respectively, after 1.0 mg/kg U69,593). Sex differences in acquisition and time course of the U69,593 discrimination. and in the potency of U69,593 to produce discriminative stimulus and diuretic effects suggests differential U69,593 pharmacokinetics in female and male rats. However, the fact that no sex differences were observed for U69,593's response rate-decreasing or antinociceptive effects argues against a simple pharmacokinetic explanation.

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EFFICACY OF SWEAT PATCHES TO MONITOR COCAINE AND OPIATE USE DURING TREATMENT

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improved methods for monitoring illicit drug use are needed in clinical treatment trials. A new technique, sweat patch analysis. was used to determine cocaine and opiate use in methadone maintenance patients enrolled in a voucher-based contingency management trial. The results of thrice weekly urine drug tests (EMIT immunoassay cutoffs; 300 ng/mL) from 44 human subjects were compared to results of 355 sweat patches that were applied for 7 days. Sweat was analyzed for cocaine and heroin and metabolites by an ELISA immunoassay (cutoffs 10 ng/mL) and confirmed in a subset of samples by GC/MS (cutoffs 5 ng/mL). If any of three urine specimens were positive, drug use was assumed. if all three urine specimens were negative, drug abstinence was assumed. If either of two duplicate sweat patches worn by the subject was positive by the ELISA test, the sweat test result was judged to be positive. The sweat ELISA results for cocaine and opiates were 77.7 and 78.6% as accurate as compared to urine results. Sensitivities and specificities were 97.6 and 60.5% for sweat cocaine analysis and 68.8 and 86.1% for opiate analysis as compared to urine cocaine and opiate detection. In 75 cases (21.1%). the sweat was positive for cocaine or metabolites by the ELISA assay, but the three weekly urines at the 30 ng/mL cutoff were negative; however, in 36 of these 75 cases (48%) only one of the two patches applied to the patient was positive. GC/MS analysis of the sweat was available in 43 of these 75 cases and confirmed the presence of cocaine and analytes in 40 or 93% of the specimens. Additional controlled drug administration studies are needed to determine if the increased detection of cocaine by sweat analysis is due to greater sensitivity of sweat testing over urine analysis or to analytical variability or environmental contamination of the sweat patch. The accuracy, sensitivity and specificity of sweat ELISA results as compared to GC/MS results were 93.1. 93.5, and 90.5% for cocaine and 89.5, 96.7, 72.2% for opiates. Cocaine was detected in 99% of positive sweat patches with a mean GC/MS concentration of 990.6 ng/mL (range 0 to 26,490). In contrast, the mean benzoylecgonine and ecgonine methyl ester concentrations were 133.7 (range 0 to 2150) and 116 ng/mL (range 0 to 774), respectively. Fewer of the positive sweat patches were positive (≥ .5 ng/mL) for benzoylecgonine (78.2%) and ecgonine methyl ester (73.0%). Lower mean opiate concentrations were found in sweat: heroin 23.9 ng/mL (range 0 to 195) 6-acetyl-morphine (6AM) 21.2 ng/mL (range 0 to 181). morphine 20.8 ng/mL (range 0 to 112), and codeine 22.3 ng/mL (range 0 to 360). Heroin was detected in one fourth of all opiate positive sweat patches, while 6AM, morphine and codeine were detected in more than three fourths of all positives. Analysis of sweat patches may provide a more sensitive method for objectively monitoring drug use and provides an alternative method for evaluating behavioral interventions in drug treatment programs.

DETECTION OF FENFLURAMINE AND PHENTERMINE IN HAIR AND NAILS

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Fenfluramine and phentermine are widely prescribed in a combination known as fen/phen for use in weight loss. The determination of these drugs in human biological samples may be useful for medical reasons and for the insurance industry. Both hair and nails provide a longer historical record of drug use than either urine or blood, the more common samples tested for drug determination. An additional advantage to these specimens is the ease and non-invasiveness of collection. The determination of fenfluramine and phentermine in hair and nails taken from users of the fen/phen drug combination is described for the first time. The specimens were powdered in an amalgamator using stainless steel ball-bearings to provide milling action. The powdered substances were hydrolyzed overnight the drugs were extracted and analyzed using GC/MS in electron impact selected ion storage mode. The analytical method was linear over the range 0.05 - 5 ng/mg of hair. The limit of detection was 0.05 ng/mg of hair, sufficient for the determination of fenfluramine and phentermine in both hair and nails. The described procedure has applications in the medical and insurance fields.

NALTREXONE-DERIVED pA2 ANALYSIS OF THE ANTINOCICEPTIVE EFFECTS OF OPIOIDS IN RATS

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Effects of the μ-selective opioid antagonist naltrexone (NTX) were assessed alone and in combination with morphine, levorphanol and butorphanol in Sprague-Dawley rats using a warm water tail-withdrawal procedure. In this procedure, the lower 8 cm of each rats tail is placed in 40°, 52°, and 55° C water, and the latency to remove the tail from the water is measured. Morphine, levorphanol, and butorphanol (n=5) dose-dependently increased tail withdrawal latency from both 52° and 55° C water, when combined with morphine, NTX (0.03-0.3 mg/kg) produced dose-dependent rightward shifts in the morphine dose-effect curve. Similarly, when combined with levorphanol, NTX (0.03-0.3 mg/kg) produced dose-dependent rightward shifts in the levorphanol doze-effect curve. NIX (0.03-0.3 mg/kg) produced rightward shifts in the butorphanol dose-effect curve, however these shifts were not dose-dependent Apparent pA2 values for naltrexone as an antagonist of morphine and levorphanol were similar in both 52° C and 55° C water. Apparent pA2 values for naltrexone in combination with butorphanol could not be calculated however a pKB analysis showed butorphanol to be more sensitive to NTX antagonism than either morphine or levorphanol. These results indicate that both morphine and levorphanol's antinociceptive effects are mu mediated, whereas butorphanol's antinociceptive effects are not.

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ORPHANIN FQ BLOCKS THE ANTINOCICEPTION INDUCED BY OPIOID AGONISTS ON THE COLD-WATER TAIL-FLICK TEST

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Recent studies have shown that orphanin FQ (OFQ)/nociceptin, a 17-amino-acid peptide, is an endogenous agonist whose receptor is similar in sequence to mu, delta and kappa opioid receptors (-75% homology). It was reported that OFQ can block antinociceptive effects induced by opioid receptor agonists in the radiant beat tail-flick test and warm water tail-withdrawal test. The present studies were designed to see the effect of OFQ on antinociception induced by opioid receptor agonists In the cold water tail-flick (CWT) test. Adult male SD rats were used. OFQ was diluted with phosphate-buffered saline (vehicle). The results showed that intracerebroventricular (icv) injection of OFQ at doses of 50 fmol to 10 nmol did not induce a significant change in the CWT test. In rats given subcutaneous (sc) injections of saline or morphine (8 mg/kg), icv injection of OFQ (10 nmol) 15 min later produced a significant reversal of sc morphine antinociception ($p<0.01$, ANOVA followed by Duncan's test), compared to the corresponding saline control group. Vehicle (t=+15 min, icv) was totally ineffective against sc morphine antinociception ($p>0.01$), compared to the corresponding saline control group. When the kappa opioid receptor agonist spiradoline (80 mg/kg, sc) was used instead of morphine, similar results were observed. In another series of experiments, we found that intracerebroventricular (icv) injection of OFQ (10 nmol) reversed the antinociception induced by icv injection of the specific mu opioid agonist PL017 (2 μg). delta opioid agonist DPDPE (100 μg) and kappa opioid agonist dynorphin (10 nmol), respectively. These results indicate that OFQ may be an endogeneous anti-opioid peptide in the brain of rats.

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ORPHANIN FQ PEPTIDES *IN VITRO* BIOTRANSFORMATION IN HUMAN BLOOD

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Orphanin FQ (OFQ)/nociceptin is a newly isolated and sequenced non-opioid neuropeptide of 17 amino acid residues related in sequence to dynorphin A (1-17). *In vitro* biotransformation of this peptide in human (n=5) blood, incubated at 37°C, was studied. The major and several minor biotransformation products were detected and identified using matrix-assisted laser desorption/ionization mass spectrometry. Cleavage at peptide linkage Phe(1)-Gly(2) was the predominant biotransfomation pathway with OFQ (2-17) as the major product. Cleavages at basic amino acid residues, e.g. Arg(8)-Lys(9), Arg(12)-Lys(13), were observed, to form OFQ (1-8), OFQ (1-9), OFQ (1-11), OFQ (1-12) and OFQ (1-13), although these were not major biotransformation pathways under these *in vitro* experiment conditions. Other minor biotransformation products included OFQ (3-17), OFQ (4-17), OFQ (5-17), OFQ (1-10), OFQ (1-14), OFQ (2-8), OFQ (2-9), OFQ (3-10), OFQ (2-12) and OPQ (4-12). *In vitro* biotransformation of the major processed product OEQ (2-17), was also studied. Processing studies were carried out in freshly-drawn human (n=5) blood incubated at 37°C for various time periods. In these studies, no major biotransformation pathways were detected, although a variety of minor biotransformation products were detected and identified, e.g. OFQ (3-17), OFQ (4-17), OFQ (5-17), OFQ (2-8), OFQ (2-9), OFQ (2-12), OFQ (4-12), OFQ (7-12), and OFQ (8-12).

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PHARMACOLOGICAL CHARACTERIZATION OF THE MIXED OPIOID AGONIST-ANTAGONIST CYCLAZOCINE

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The affinity, selectivity and antinociceptive properties of cyclazocine for the multiple opioid receptors was characterized. In competition binding assays with bovine striatal membranes, cyclazocine showed little opioid selectivity, binding to all three receptors with a K_1 value of 1 nM or less. In behavioral analgesic assays, cyclazocine failed to produce maximal antinociception in the mouse 55°C warm-water tail-flick assay at i.c.v. doses up to 100 nmol. However, cyclazocine produced maximal antinociception in the mouse writhing assay, producing a 50% antinociceptive response with a dose (and 95% C.L.) of 4.2 (2.1-8.1) nmol when administered i.c.v., nearly five times more efficacious the kappa agonist U50,488, which had a D_{50} value of 20 (11-33) nmol. The antinociceptive effect lasted no more than 2 hr, and was significantly reduced by the administration of selective opioid antagonists for all three opioid receptors, although this reduction was most pronounced with the kappa antagonist, nor-BNI. An i.c.v. dose of 0.3-nmol cyclazocine significantly antagonized the antinociceptive effect of morphine in the tail-flick test. Doses of cyclazocine ten-fold higher produced antagonism of antinociception induced by the delta-selective agonist DPDPE and the kappa-selective agonist U50,488. Taken together, these data suggest that low doses of cyclazocine produced both agonist effects mediated by the kappa receptor and antagonistic effects to mu opioid-induced antinociception as previously demonstrated. However, at slightly higher doses, cyclazocine further demonstrated both agonist and antagonist activity at all three opioid receptors.

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BEHAVIORAL EFFECTS OF BUTORPHANOL AFTER CLOCINNAMOX ADMINISTRATION IN RHESUS MONKEYS

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Butorphanol has approximately equal affinity for mu and kappa, opioid receptor sites (Ki_{DAMGO}: 0.50 nM, Ki_{U69593}: 0.68 nM), yet its behavioral effects are consistent solely with a mu mechanism of action. Using food-reinforced drug discrimination and diuresis assays in rhesus monkeys, the present study investigated the effects of butorphanol alone, and in the presence of either me reversible opioid antagonist quadazocine or the mu receptor insurmountable antagonist clocinnamox. Alone, butorphanol (0.001 - 0.1 mg/kg s.c.) generalized to fentanyl, but not to ethylketocyclazocine (EKC) in fentanyl-and EKC-trained monkeys, respectively; butorphanol did not alter urine output. In the presence of quadazocine (0.1 and 1 mg/kg s.c.). butorphanol's discriminative stimulus, rate-suppressive, and diuretic effects wee unchanged, although its potency was decreased. After the administration of clocinnamox (0.1 mg/kg s.c.), butorphanol generalized to EKC, and produced a 300% increase in urine output. These kappa agonist-like effects were observed 24-72 hr after clocinnamox administration, and a return to mu agonist-like effects were observed 1-2 wk after clocinnamox administration. These results demonstrate butorphanol's *in vivo* agonist activity al mu and kappa opioid receptors; further, the use of irreversible antagonists such as clocinnamox may provide a novel technique in the study of mixed agonists such as butorphanol.

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EFFECTS OF CLOCINNAMOX IN COMBINATION WITH ETORPHINE IN A PRIMATE TITRATION PROCEDURE

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Effects of the irreversible, μ-selective opioid antagonist clocinnamox (C-CAM) were assessed alone and in combination with etorphine in squirrel monkeys responding under a shock-titration procedure. In this procedure, shock intensity increased every 15 s from 0.01 mA to 2.0 mA in 30 increments. Five lever presses during any given 15 s shock period produced a 15 s shock-free period after which shock resumed at the next lower intensity. When given alone, etorphine (n=3) dose-dependently increased the intensity below which the monkeys maintained shock 50% of the time (median shock level, MSL) and decreased response rates (RR). When combined with etorphine, C-CAM (0.03-0.1 mg/kg) produced dose-dependent rightward shifts in the etorphine dose-effect curves for MSL and RR as early as 4 hours after administration. Etorphine failed to produce maximal effects on MSL or RR in the presence of the highest dose of C-CAM tested (0.1 mg/kg). Etorphine's effects returned to within 1/4 log unit of control values 3 days after administration of 0.03 mg/kg C-CAM whereas etorphine's effects returned to within 1/4 log unit of control values 10 days after administration 0.1 mg/kg C-CAM. When compared to prior research on the effects of C-CAM on other opioids, these results indicate that etorphine is a higher efficacy μ-opioid agonist in this procedure.

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BIOTRANSFORMATION AND DURATION OF ACTION OF DYNORPHIN A(2-17) IN RHESUS MONKEYS

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The non-opioid peptide dynorphin A(2-17) [DYN A(2-17)] is active when administered systemically or centrally, in tests of antinociception, and in reducing the expression of morphine withdrawal signs in rodents. The mechanism of these effects is unknown at present. By using the technique of matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS), we have previously found that the endogenous opioid peptide DYN A(1-17) is biotransformed in rhesus monkey blood *in vitro* and *in vivo* into DYN A(2-17) (Yu et al., 1996; J Pharmacol Exp Ther 279:507-514). One aim of the present experiments was to study the biotransformation of DYN A(2-17) in rhesus monkey blood, using MALDI MS. Freshly drawn rhesus monkey blood (n=3) was incubated at 37°C. Dynorphin A(2-17) (0.59 mg/ml) was added to the blood and aliquots were removed at various times after addition (0-120 min). Two identifiable pathways of biotransformation were detected. Firstly, a sequential cleavage of the N-terminal glycine residues, to yield DYN A(3-17) and DYN A(4-17). The second pathway involved the cleavage between arginine residues in positions 6 and 7, which yielded DYN A(7-17). In all subjects, intact DYN A(2-17) was still detected afler 60 min incubation. Dynorphin A(1-17) and A(2-17) (0.32-3.2 mg/kg) were administered i.v. to rhesus monkeys (n=4) in the warm waler (50°C) tail withdrawal assay, a test of thermal antinociception. DYN A(1-17) was only slightly effective at the highest dose studied. In contrast, DYN A(2-17) produced dose-dependent antinociception with an apparently higher peak effect, up to 30 min after administration. These studies show that intravenously administered DYN A(2-17) produced thermal antinociception in primates.

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CHANGES IN CNS-DERIVED TNFα IN THE DEVELOPMENT OF A CENTRAL COMPONENT TO PERSISTENT PAIN

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Changes in CNS levels of proinflammatory cytokines such as TNFα have been associated with the development of certain types of persistent pain. Additionally, many persistent pain syndromes having a central component are believed to involve abnormal sympathetic activity. Changes in TNF levels are associated with modifications in adrenergic responsiveness, and TNF is an important endogenous modulator of CNS NE release. We have previously demonstrated an interactive relationship between TNF-α production and α_2 adrenergic regulation of NE release in the CNS. Thus, we hypothesize that TNF-α may exert its effects in the development of persistent pain by its actions at central α_2 adrenergic receptors. The present study examines pain-associated changes in central TNF production in a neuropathic pain model. Rats underwent unilateral ligature placement around the sciatic nerve, and at t=2,4,6 and 8 days post-surgery, paw-withdrawal latency was measured as an index of hyperalgesia. Additionally, several regions of the CNS were harvested and assayed for TNF content. The results demonstrate that alterations in TNFα expression occur in regions of the brain associated with adrenergic function during the induction of neurolpathic pain, and that increases in cylokine levels coincide with the period of peak hyperalgesia. Based on previous results from our laboratory, we speculate that persistent increases in TNF levels will shift α_2 adrenergic responsiveness from inhibition to facilitation. Elucidating the interaction between proinflammatory cytokines and adrenergic responses in the CNS in a model of centrally-miediated pain will contribute to our understanding of the mechanisms involved in me pathogenesis of such chronic pain syndromes.

Key words: TNF, Pain, Adrenergic, CNS.

HYPERALCESIA IN METHADONE-MAINTAINED PATIENTS

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It is increasingly evident that pain and opioid addiction a not urelated phenomena. Preclinical data indicate that rats made tolerant to the antinociceptive effects of opioids are also hyperalgesic to painful stimuli theorized to be due to NMDA receptor-mediated responses. Consistenl with this finding, we previously demonstrated that methadone-maintained heroin addicts evidence significantly less tolerance for cold-pressor pain than drug-free ex-addicts[1]. In this extension of that work, pain tolerance was compared between samples of methadone-maintained subjects (n=35) and normal controls (n = 42) matched on gender and race. Methadone-maintained subjects were on a stable dose. of methadone; pain tolerance was measured within two hours of being dosed. Mean pain tolerance (each sb underwent 3 cold-pressor trials separated by at least 48 hours) was significantly lower for the methadone-maintained group. Degree of hyperalgesia was unrelated to absolute methadone dose.

References:

[1]Compton M. Cold-pressor pain tolerance in opiate and cocaine abusers: Correlates of drug type and use status. J Pain Symptom Manage 1994; 9462-473.

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SUBJECTIVE, PSYCHOMOTOR, AND ANALGESIC EFFECTS OF CODEINE AND MORPHINE IN HEALTHY VOLUNTEERS

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Oral codeine and morphine are commonly prescribed for pain relief in medical settings. The abuse liability of these drugs and their effects on cognitive/psychomotor performance in nondrug-abusing volunteers have not been well characterized. The purpose of the present study was to characterize the effects of two oral doses of codeine and morphine on mood, psychomotor performance, physiological measures, and pain in healthy volunteers. A randomized, double-blind, placebo-controlled crossover design was conducted with twelve healthy, nondrug-abusing volunteers. Each session began with 15 minutes of baseline testing; then subjects ingested a solution that contained codeine 60 or 120 mg, morphine 20 or 40 mg, or placebo. Testing continued for 5.5 hours after drug ingestion, and dependent measures included subjective effects, cognitive/psychomotor performance, physiological measures, and ratings of pain intensity induced by a cold-pressor test (nondominant forearm in 2°C water for 90 seconds). Subjects reported weak to mild drug effects with codeine and morphine, including increased scores on the Pentobarbital-Chlorpromazine-Alcohol Group scale of the Addiction Research Center Inventory. Both drugs increased ratings of "dry mouth" on the Opiate Adjective Checklist and ratings of "coasting," "heavy/sluggish," and "nauseous" on a Visual Analog Scale. Neither drug impaired cognitive/psychomotor performance as measured by the Digit-Symbol Substitution Test and tests of logical reasoning. auditory reaction time, eye-hand coordination, and short- and long-term memory. Both drugs produced miosis, which was dose-related and analgesia which was dose-related for morphine but not for codeine. Some subjects liked the drug effects; others did not. These results suggest that codeine and morphine, at the doses tested, are effective analgesics that do not impair performance and produce mild subjective effects.

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EFFECTS OF SEVOFLURANE AND NITROUS OXIDE ON THE PAIN RESPONSE AND OTHER BEHAVIORS IN HEALTHY VOLUNTEERS

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The present study examined the effects of sevoflurane (S) and nitrous oxide (N), by themselves and in combination, on the pain response, psychomotor performance, and sedation in healthy volunteers. Isoflurane, a volatile inhaled general anesthetic, has been shown to antagonize the analgesic effect of N in rats (Goto et al., 1996). In addition, N has been shown to oppose the depression of isoflurane on the CNS (Yli-Hankala, et al, 1993). However, other effects of N, such as psychomotor impairment, are potentiated by isoflurane in humans (Zacny *et al.,* 1996). Based on these findings, we hypothesized that S, a volatile inhaled general anesthetic, would antagonize the analgesic effects of N and that N would antagonize the sedation caused by S. Finally, we predicted that N would potentiate the psychomotor impairment caused by S. Nine subjects (7 males, 2 females, mean age 25 years) participated in this IRB-approved, randomized, crossover experiment. Subjects, over the course of three sessions, inhaled 0, 0.2, or 0.4% end-tidal S for a 68 min inhalation period. Each inhalation was divided into four 17-min blocks. During either the second or fourth block, 30% end-tidal N was added. During these two blocks, psychomotor performance (as assessed by the Digit Symbol Substitution Test), pain responses (as assessed by use of a 2-min cold water test), and sedation (as assessed by subjects' visual analog scale ratings) were evaluated. N produced analgesia but S did not antagonize this effect. There was a main effect of S on subjects' ratings of sleepiness and these ratings either decreased or remained the same when N was added to S. Lastly, S potentiated the psychomotor-impairing effects of N. Since the drugs differed in their sedation profiles, the potentiatied psychomotor impairment of S by N suggests that the impairment induced by N and the impairment induced by volatile anesthetics are mediated by different neurochemical mechanisms of action.

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DEVELOPMENTAL PCP EXPOSURE PRODUCES LONG-LASTING DECREASED LOCOMOTOR RESPONSES TO PCP AND MK-801

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Previous studies from our laboratory have shown that subchronic developmental exposure to phencyclidine (PCP) on postnatal days (PND) 24-37 (but not PNDs 4-17) results in allerations in the behavioral response to a pharmacological challenge with PCP or the NMDA antagonist, MK-801, 10 and 20 days after cessation of treatment. The present studies were designed to determine the persistence of these effects. Rats were dosed with saline or 7.5 mg/kg PCP on PNDs 24-37. Ten and 20 days, and 61 and 68 days (PND 105) post-dosing, locomotor activity was measured for one hr following a challenge with either saline, 2.5 mg/kg PCP, or 0.1 mg/kg MK-801. Activity was measured via an automated system. PCP treatment resulted in decreased locomotor responses to both PCP and MK-801 challenges for up to 68 days post-dosing. The locomotor response to a saline challenge was not affected by pretreatment with PCP. These results suggest that subchronic exposure to PCP results in long-lasting decreases in the locomotor response to both PCP and MK-801. The mechanism(s) mediating this change in responsiveness are unclear but might involve alterations in NMDA systems or treatment-induced alterations in PCP metabolism during development.

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CHRONIC PHENCYCLIDINE ADMINISTRATION INDUCES APOPTOSIS IN THE RAT OLFACTORY TUBERCLE AND PIRIFORM CORTEX

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Acute or chronic low-dose administration of phencyclidine (PCP) and other NMDA receptor antagonists causes neurotoxicity evidenced by vacuolization, hsp70 induction, and increased GFAP in rat retrosplenial/cingulate cortex as well as in other corticolimbic brain regions. A variety of drugs, including both typical and atypical antipsychotics, have been shown to protect the affected brain regions from neurotoxicity produced by NMDA receptor antagonists. Although the vacuolization, hsp70 induction, and increased GFAP produced by NMDA receptor antagonists are believed to occur primarily via a necrotic mechanism, we wished to investigate the possibility that chronic PCP administration in rats induced apoptosis as well. We administered 20 mg/kg PCP i.p. once a day for 5 consecutive days to adult female Sprague Dawley rats, a pattern that closely resembles the binge pattern of administration by drug abusers. Seventy-two hours following the last PCP injection, the rats were administered 3.2 mg/kg PCP and locomotor activity was monitored for 90 min. Immediately afterwards, the rats were anesthetized and perfusion fixed for immunochemical assessment of terminal dUTP nick-end labeling (TUNEL) as a marker of apoptosis. Behavioral analysis revealed that chronic PCP treatment produced a robust sensitization to PCP challenge. Other experiments revealed that a 1 hr. Pretreatment with 10 mg/kg clozapine (an atypical antipsychotic) blocked the development of sensitization. A single 20 mg/kg injection of PCP produced no TUNEL staining of nuclei in any rat brain region observed including the retrosplenial/cingulate cortex. However, chronic PCP administration caused a regionally-specific, substantial increase in the number of positively TUNEL-stained nuclei in the olfactory tubercle and piriform cortex that was verified as apoptotic by electron microscopy. Clozapine prevented the PCP production of positively TUNEL-stained nuclei in the olfactory tubercle and piriform cortex.

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FACTORS AFFECTING ACQUISITION OF ORAL PCP SELF-ADMINISTRATION IN RHESUS MONKEYS

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The effects of drug dose and a nondrug alternative reinforcer on rates of acquisition of oral PCP self-administration in drug naive rhesus monkeys were examined. Acquisition was studied using 3 separate groups of 6-7 monkeys, One group received a low PCP dose (0.0375 mg/delivery) and the other two groups received a high PCP dose (0.15 mg/delivery). One of the high dose groups had concurrent access to a saccharin solution (0.03% wt/vol) and water during the intersession (17.5-hr) period. Food satiated monkeys were initially given access to water under a fixed-ratio (FR) 1 schedule during daily 3-hr sessions. Water was then replaced with PCP during the session. The monkeys were then reduced to 85% of their free-feeding body weight and were fed before the session, and the FR value was increased from 1 to 2.4 and 8. Food was then given post-session and water and PCP were available under concurrent FR 8 schedules. Acquisition was considered to occur if PCP intake exceeded water intake. Monkeys receiving the low PCP dose maintained higher response rates and lower drug intake per session than monkeys receiving the high PCP dose. Monkeys receiving the high PCP dose maintained higher response rates and drug intake than monkeys receiving the high PCP dose with saccharin during intersession. When all 3 groups were given concurrent access to PCP and water, PCP intake was greater than water intake although the magnitude of this effect was greater in the group of monkeys receiving the high PCP dose. PCP maintained higher response rates than water when saccharin was replaced by water during intersession in the high PCP dose group. Within-group data revealed that a higher percentage of monkeys acquired PCP reinforcement in the group given assess to the high PCP dose than the other two groups. These data suggest that drug dose and presence of alternative nondrug reinforcers affect acquisition of drug self-administration in nonhuman primates.

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MEDICATIONS DEVELOPMENT FOR DRUG ABUSE: A DRUG CLASS-SPECIFIC PHARMACOKINETIC ANTAGONIST FOR PHENCYCLIDINE

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Use of phencyclidine (PCP) and other arylcyclohexylamines in humans can result in severe toxicity or even death. We have developed an anti-PCP monoclonal antibody Fab fragment which acts as a pharmacokinetic antagonist to reverse these effects. The aim of this study was to determine if the anti-PCP Fab fragment was effective against structural analogs of PCP. To test our hypothesis we chose two analogs, 1-[1-(2-thienyl)-cyclohexyl]piperidine (TCP) and *N*-ethyl-1-phenylcyclobexylamine (PCE) because these drugs are more potent than PCP and they have also been reported to be drugs of abuse. For the studies, each male Sprague-Dawley rat received seven treatments in a repeated-measures, mixed-sequence design (n=4). The behavioral parameters 'distance traveled' and 'total movement were used to assess the ability of the Fab fragment to inhibit drug-induced effects in the animals. PCP, TCP, and PCE were each administered as i.v. 3 mg/kg doses. The Fab was given i.v. as a 1.0 mole equivalent dose 30 min after drug administration. The Fab was equally effective al antagonizing the locomotor effects of PCP, TCP, and PCE (RM ANOVA followed by Student-Newman-Keuls, $P < 0.05$). For example, the average distance traveled induced by PCP (417 m), TCP (541 m), and PCE (691 m) was decreased after Fab treatment to 76 m, 107 m, and 125 m, respectively. As a control, we determined that the Fab did not antagonize the locomotor effects of methamphetamine. We conclude that the anti-PCP Fab can antagonize several potent arylcyclohexylamines, and these data suggest that monoclonal antibodies can be developed for treating classes of drugs. as well as individual drugs.

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ANTIBODY-BASED MEDICATIONS DEVELOPMENT FOR PHENCYCLIDINE (PCP) ABUSE: OPTIMIZATION OF ANTI-PCP FAB RENAL CLEARANCE

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We have previously shown that a high-affinity monoclonal antibody fragment (Fab) against PCP is very effective in reversing PCP-induced behavioral effects and in rapidly redistributing PCP out of the CNS. The purpose of these studies was to optimize conditions for use of an antibody-based medication for PCP abuse. Although the Fab-PCP complex can be eliminated via the kidney, the details of this process are not well understood. To study the effect of fluid loading on anti-PCP Fab elimination, male Sprague-Dawley rats (n=4) received PCP (1 mg/kg i.v.) followed 10 min later by a 1 mol-eq anti-PCP Fab dose, with or without lactated ringer's (21 ml/kg i.v.). Urine output was higher following fluid loading over the First 3 hr ($P<.05$). however anti-PCP Fab elimination did not differ from controls at any time point. The total amount of anti-PCP Fab appearing in the urine was 55.7±6.1% of the anti-PCP Fab dose compared to 64.1±10.3% without fluid loading. To study the effect of urinary alkalinization on PCP and anti-PCP Fab co-elimination, rats (n=1) received $NaHCO_3$ at 8 min after PCP administration (8 mEq/kg + 2 mEq/kg every 45 min for 3 hr) followed 2 min later by 1 mol-eq anti-PCP Fab. Urine alkalinization did not affect the amount of Fab being excreted (69.1 4.1%) or the co-elimination of PCP (41.4±7.2%). To study the effect of Fab dose on anti-PCP Fab elimination, rats (n=3-4) received PCP (0.1, 0.3, 1.0 and 3.0 mg/kg) followed 10 min later by a mol-eq Fab dose (21-617 mg/kg). Elimination of Fab following the 21 mg/kg dose (50.0±4.1%) was statistically lower than that of the 62 mg/kg (65.4±10.3%) and 617 mg/kg (66.0±6.7%) doses ($P<.05$), but not the 206 mg/kg dose (57.4±5.12). In summary, anti-PCP Fab treatment significantly improves PCP excretion, presumably through elimination of an intact PCP-Fab complex which is unaffected by anti-PCP Fab dose, fluid loading and urinary alkalinization.

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REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF MEMANTINE, A LOW AFFINITY NMDA CHANNEL BLOCKER

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Memantine (MEM) is currently in use in Europe for the treatment of various neurological disorders. It is a low affinity channel blocker of NMDA receptors whose rapid binding kinetics are thought to limit its phencyclidine (PCP)-like side effects. MEM and its analog, amantadine (AMA), which has also been demonstrated to have some NMDA antagonist activity. were evaluated for PCP-like behavioral effects. The discriminative stimulus properties of MEM and AMA were tested in monkeys and rats trained to discriminate PCP from saline using a standard two-lever chug discrimination paradigm. In monkeys, MEM produced complete substitution. AMA occasioned little or no responding on the PCP-associated lever. In rats, MEM resulted in full substitution for PCP, but only at response rate suppressing doses. AMA was without PCP-like effects in rats. IV self-administration of MEM and AMA was tested under a fixed ratio schedule of reinforcement in monkeys trained to lever press for infusions of PCP. MEM served as a reinforcer in all subjects at one or more doses tested. Results with AMA were inconsistent. Overall, MEM was shown to produce PCP-like discriminative stimulus effects in rats and monkeys while AMA did not. MEM also served as a positive reinforcer in rhesus monkeys, while AMA served as a weak reinforcer in only some subjects. Both AMA and MEM are reported to serve as NMDA antagonists, yet clear differences exist in their behavioral effects with MEM acting more like a PCP-like antagonist. In addition, despite the rapid channel kinetics of MEM's NMDA receptor blockade it may have some PCP-like abuse potential in humans at doses above the normal therapeutic levels.

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NMDA RECEPTOR ANTAGONIST MEMANTINE DOES NOT ALTER "BINGE" COCAINE INDUCED ELEVATION OF DYNORPHIN mRNA

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The noncompetitive NMDA receptor antagonist MK 801 has been reported to attenuate the increase in striatal dynorphin peptide levels induced by repeated cocaine administrations. We have examined the effect of another noncompetitive NMDA receptor antagonist, memantine (1-amino-3,5-methyladamantane), which is clinically used for the treatment of dementia and Parkinson's disease, on preprodynorphin (Dyn) mRNA levels in the rat brain after one day "binge" pattern cocaine administration (three 15 mg/kg injections i.p. with 1h interval). To minimize the effects of stress, mate Fischer rats were injected with saline for 6 days prior to the test day. On the seventh day, all rats received injections of either saline (1mg/kg, i.p.) or memantine (10 or 20 mg/kg, i.p.) 30 min prior to start of the "binge" administration of cocaine or saline in four treatment groups: a) saline/saline; b) memantine/saline; c) saline/cocaine and d) memantine/cocaine. Rats were sacrificed 30 min after the final injection and the amount of Dyn mRNA were determined for selected brain regions by a solution hybridization RNase protection assay. Data were analyzed using analyses of variance with repeated measures followed by Newman-Keuls post hoc tests. Dyn mRNA levels were increased in the caudate putamen of rats following "binge" cocaine administration ($p<0.05$). Memantine, at 10 or 20 mg/kg. did not alter the cocaine-induced increase in Dyn mRNA levels in this brain region. There were no significant differences in the Dyn mRNA levels in the caudate putamen between memantine/saline and saline/saline rat groups, although memantine injections alone led to a dose dependent increase in circulating levels of corticosterone and a marked behavioral effect.

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EFFECTS OF TOLUENE ON RECOMBINANT NMDA RECEPTORS

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Toluene is a widely used industrial solvent and a drug of abuse. Previous studies have shown that toluene depresses neuronal activity and causes behavioral effects similar to those observed for ethanol. In this study the oocyte expression system was used to tesl the hypothesis that toluene, like ethanol, inhibits the function of NMDA receptors. Oocytes injected with mRNA for the NR1 subunit and that of various NR2 subunits were maintained in L-15 media for up to 7 days prior to recording. Drug solutions were prepared by mixing toluene with emulphor (ethoxylated castor oil) at a 1: 1 ratio (v: v) and diluting this mixture to the appropriate concentration with barium-containing Ringer solution (Ba-NFR). NMDA-induced currents were measured in BA-NFR at a holding potential of -80 mV using two-electrode voltage-clamp. Emulphor up to 0.1% had no significant effects on the resting membrane potential or on NMDA-induced currents. In contrast, toluene-containing solutions dose-dependently inhibited NMDA-induced currents in oocytes expressing the NR1/2A, NR1/2B or the NR1/2C subunit combinations. The inhibition was rapid, almost complete and reversible although some channel rundown occurred at higher concetrations. The NR1/2B combination was the most sensitive with an IC_{50} value of 0.17 ± 0.02 mM. The NR1/2A and NR1/2C receptors were 8 and 12-fold less sensitive with IC_{50} values of 1.4 ± 0.17 mM and 2.1 ± 0.27 mM, respectively. These results suggest that the effects of toluene on neuronal activity may be mediated in part by inhibition of NMDA receptors.

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TOLUENE ALTERS RAT VTA DOPAMINE (DA) AND NON-DA NEURONS THROUGH A DOSE-DEPENDENT MECHANISM

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Inhalant abuse is a prevalent form of substance abuse best categorized as the intentional inhalation of organic solvent containing products consumed for their psychotropic effects. The present study was designed to assess the effects of toluene on the activity of VTA DA and *non*-DA neurons, using extracellular recordings in ketamine anesthetized rats breathing acute concentrations of toluene (11,500 ppm) similar to those consumed by inhalant abusers (10,000-20,000 ppm). lnhalation elicited two dissimilar dose-dependent patterns of response in DA neurons. The first pattern (n=28) was a biphasic response consisting of a low dose stimulation (+221% ± 72% at 1-8 minutes) followed by high dose attenuation (-162% ± 6.3% at 8-17 minutes). The second pattern (n=28) was composed of an inhibition of firing (reaching -97% ± 2.9% in 1-17 minutes). In contrast, non-DA neurons (n=8) displayed only uniform inhibitions (reaching -80% at 1-8 min) during inhalation. Blood samples taken at the same time as recordings and analyzed by GC/FID indicated comparable blood toluene concentrations (4-79 µg/ml at 1-14 min) for both DA patterns of response. It was also determined that olfactory sensation did not play a role in the observed toluene induced changes in DA cell firing. Thus, toluene at concentration's relevant to those found in human abusers profoundly alters the activity of mesolimbic dopamine neurons. a system known to be involved in the reinforcing properties associated with drugs of abuse.

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PHENCYCLIDINE- AND DIAZEPAM-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF ABUSED INHALANTS IN MICE

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Previous research has found that the abused solvents, 1,1,1-trichloroethane (TCE) and toluene share pharmacological properties with CNS depressant drugs, including anxiolytic effects and ethanol-like discriminative stimulus effects. In the present studies, mice were trained to discriminate between diazepam (DZ; 2.5 mg/kg) and vehicle or between phencyclidine (PCP; 2.0 mg/kg) and saline. Stimulus generalization was examined after 20-min inhalation exposures to TCE (4.000-16,000 ppm), toluene (1,000-6,000 ppm), methoxyflurane (500-4,000 ppm) and flurothyl (300-900 ppm). In the DZ-trained mice, methoxyflurane fully substituted for DZ at 2,000 ppm and severely reduced responding at 4,000 ppm. TCE produced partial substitution. Flurothyl and toluene produced no appreciable DZ-lever responding at any concentration. Concentration-related increases in PCP-lever responding were observed for toluene with maximal levels of 70% PCP-lever responding occurring at 6,000 ppm. Methoxflurane and TCE did not substitute for PCP. Although DZ and PCP both produce CNS depressant effects, they do so by different mechanisms (GABA vs. NMDA). The present results suggest that the mechanisms of action through which TCE, methoxyflurane, and toluene produce their CNS depressant effects may also differ.

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NEUROTOXICITY PROFILE OF DEXTROMETHORPHAN AND THE 3-AMINO ANALOG AHN649: CORTICAL EEG AND BEHAVIORAL STUDIES IN THE RAT

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The [+]-methyl morphinan dextromethorphan (DM) exhibits a broad spectrum of CNS pharmacology relative to potential chical therapeutics, including antitussive, anticonvulsant and neuroprotective properties. While generally considered safe, a major concern exists regarding possible adverse effects of high doses of DM including the potential for drug abuse and the induction of toxic psychotic reactions. Since DM is rapidly metabolized to dextrorphan, a drug possessing PCP-like properties which, in part, likely contribute to its CNS toxicity, a series of DM analogs have been synthesized which are less likely to metabolize to dextrorphan (or do so at a reduced rate). One such analog is the anticonvulsant and neuroprotective 3-amino-17-methyl morphinan, AHN649. This study examined the potential neurotoxicity of DM and AHN649 in the rat. Male S.D. rats (300-350 g) implanted with cortical electrodes and a jugular vein cannula were injected i.v. (1 min infusion) with DM (12.5-37.5 mg/kg, n=25) or AHN649 (10-100 mg/kg, n=35). Low doses of DM (12.5-25 mg/kg) produced EEG seizures (ED_{50} = 19 [14-28] mg/kg). Typically, EEG seizure activity commenced immediately postinjection (within 1 min) and was accompanied by clonic behavior followed by postictal depression. Sedation was evident in non-seizing animals given DM (ED_{50} = 30 [13-66] mg/kg). DM-induced lethality was immediate, occurring within 30-60 sec of the start of the i.v. infusion (LD_{50} = 27 [24-31] mg/kg). In contrast, AHN649 failed to induce seizures or clonus at doses up to 100 mg/kg. However, a mild sedation accompanied by EEG slowing was evident at the 20-80 mg/kg dose range (ED_{50} = 25 [13-45] mg/kg). Higher doses (60-100 mg/kg) of AHN649 were also lethal (LD_{50} = 79 [62-100] mg/kg). For both drugs, lethality appeared to be cardiorespiratory and not related to CNS neurotoxicity. These results indicate that while i.v. DM may be predisposed to serious CNS neurotoxicity, AHN649-induced neurotoxicily may be minimal. Furthermore, based upon unpublished *"in vivo* neuroprotection" data, AHN649 appears relatively safe and may exhibit an improved therapeutic index over DM.

EFFECTS OF SIGMA LIGANDS ON COCAINE-INDUCED CONVULSIONS

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The ability of sigma ligands to alter cocaine-induced convulsions was tested in Swiss Webster mice. Mice were pretreated for 15 min with vehicle or a sigma ligand (up to 30 mg/kg, i.p.), then challenged with a convulsive dose of cocaine (60 mg/kg, i.p.). Convulsions were observed in 100% of mice preheated with vehicle (saline, 50% DMSO). The following sigma ligands which are thought to act, at least in part, as antagonists or partial agonists significantly attenuated cocaine-induced seizures (50% or better protection at the most effective dose): BD1008, BD1018, BD1047, BD1060, BD1061, BD1063, BD1067, LR132, LR172, LR176, haloperidol, reduced baloperidol. At the highest dose tested in this preliminary study, BMY14802 protected 40% of animals, while rimcazole was anticonvulsive in only 20% of mice. In contrast, the putative sigma receptor agonists, DTG and BD1052, worsened the severity of the cocaine-indured seizures, with DTG (30 mg/kg, i.p.) ultimately producing death in all animals tested. The pattern of results suggests the involvement of sigma-1 receptors in these effects. Further studies are underway to evaluate the effects of sigma ligands on other cocaine-induced behaviors.

THE NEUROTOXIC EFFECT OF IBOGA ALKALOIDS MAY BE MEDIATED BY SIGMA-Z RECEPTORS

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Ibogaine suppresses drug self-administration and is being investigated as a possible treatment for drug abuse. However, at high doses in rats, it produces neurotoxicity in the cerebellum (O'Hearn and Molliver 1993). We have shown that sigma-2 receptor ligands cause dose-dependent morphological changes and cell death upon chronic exposure in culture (Vilner *et al.* 1995). Ibogaine and some of its congeners have been demonstrated to have moderate sigma-2 affinity (Bowen *et al.* 1995; see Williams *et al.,* this volume). Thus, we investigated the cellular effects of iboga alkaloids *in vitro.* Human SK-N-SH neuroblastoma cells were cultured in the presence of 3 - 30 uM of the sigma-2-active iboga alkaloids ibogaine, (±)-ibogamine, and (±)-4-(2-methoxyethyl)-desethylibogamine. These compounds produced dose- and time-dependent morphological changes which were characterized by loss of processes, cell rounding, detachment and ultimately cell death. However, noribogaine (NI) and (±)-4-(2-methoxyethyl)-18-carbomethoxydesethylibogamine (MC), which are weak or inactive at sigma-2 sites, showed little or no toxicity at comparable times and doses. Similar results were observed with primary cultures of rat cerebellar granule cells using ibogaine vs. NI. These results are consistent with me reported lack of toxicity of NI and MC *in vivo* (Glick *et al.* 1996a,b). The sigma-2-active alkaloids produced a rise in [Ca++]i in SK-N-SH neuroblastoma cells, which may possibly be linked to me neurotoxicity, whereas the inactive compounds had no effect on [Ca++]i. Although sigma-inactive and lacking in effect on [Ca++]i, (±)-coronaridine did produce morphological changes and cell death. However, the morphological changes were distinct from those produced by the sigma-active iboga alkaloids (ie. appearance of abundant intracellular granules, which did not occur with the other ibogaine analogs), suggesting action via a mechanism unrelated to sigma receptors. In conclusion, sigma-2 sites may play a role in the neurotoxic and tremorigenic effects of iboga alkaloids, but are unlikely to be involved in their anti-addiction properties since both NI and MC are active at suppressing drug self-administration despite low sigma-2 affinity (Glick *et al.* 1996a,b). Reference list is available from senior author upon request.

COMPARATIVE *IN VIVO* NEUROBIOLOGICAL EFFECTS OF IBOGAINE AND MK-801 IN RATS

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Ibogaine (IBO) is a naturally-occurring indole alkaloid with putative anti-addictive properties. While IBO interacts with multiple targets in the brain, recent evidence suggests the drug acts as an NMDA antagonist similar to MK-801. The purpose of the present work was to compare neuroendocrine and neurochemical effects of IBO and MK-801 *in vivo*. Male rats (n=6-8) received either IBO (10 & 100 mg/kg, ip). MK-801 (0.1 & 1 mg/kg, ip). or saline. Groups of rats were decapitated 30 and 60 min after injection; trunk blood was collected for analysis of corticosterone and prolactin by RIA, whereas brains were harvested for analysis of DA, 5-HT and their metabolites by HPLC-EC. IBO and MK-801 caused comparable elevations in circulating corticosterone, but only IBO increased prolactin. IBO produced marked dose-dependent reductions in DA with concurrent increases in the metabolites, DOPAC and HVA. The prolile of IBO-induced effects on DA function was consistently observed in the cortex, striatum, and olfactory tubercle. MK-801, on the other hand, ten&d to increase DA and its metabolites. Neither drug consistently affected 5-HT systems. The present findings show that the effects of IBO on neuroendocrine secretion and DA neurotransmission are not mimicked by MK-801. Thus, the *in vivo* actions of IBO can not be explained simply on the basis of antagonism at NMDA receptors.

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STRUCTURE-ACTIVITY STUDIES FOR BINDING OF IBOGA ALKALOIDS TO SIGMA RECEPTORS

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We have previously shown that ibogaine and some of its natural congeners are selective ligands for sigma-2 receptors with moderate affinity, Ki = 137 - 201 nM (Bowen *et al.,* Eur J Pharmacol 279, R1-R3, 1995). Sigma-2 affinity was unaffected by the position of the aromatic methoxy group (ibogaine vs. tabemanthine) or the absence of an aromatic methoxy group altogether ((±)-ibogamine). However, neither a free phenolic hydroxyl moiety (noribogaine) nor an 18-carbomethoxy group ((±)-coronaridine) were tolerated. Here we investigate additional ibogaine analogs to further determine the effect of substitution on the aromatic ring and at the 18-position, and to assess the effect of substitution on the 4-ethyl side-chain. All novel analogs tested had low affinity for sigma-1 sites (Ki = 4.5 uM - 28.6 uM). A 12-O-tert butyl group was tolerated equally as well (Ki = 247 nM) at the sigma-2 site as the 12-methoxy group in ibogaine. (±)-4-(2-Hydroxyethyl)-desethylibogamine had sigma-2 Ki = 209 nM. (±)-4-(2-Methoxyethyl)-desethylibogamine ((±)-4-MDI) exhibited sigma-2 Ki = 42.8 nM. Thus, methoxy substitution of the 4-ethyl side chain enhances while hydroxylation slightly decreases sigma-2 affinity. (±)-4-(2-Methoxyethyl)-18-carbomethoxydesethylibogamine was practically inactive at sigma-2 sites (Ki = 7.5 uM). (±)-4-(2-Methoxyethyl)-18-hydroxymethyldesethylibogamine exhibited sigma-2 Ki = 1 .0 uM. These data confirm the detrimental effect of substitution at the 18-position. Optical resolution of (±)-4MDI revealed 22-fold enantioselectivity, with (-)-4-MDI being the most active isomer (Ki = 30.6 nM vs. 662 nM for (+)4MDI). (-)-4-MDI, with high affinity and 150-fold selectivity for sigma-2 sites over sigma-1 sites. may prove to be a useful tool for the study of sigma-2 receptor function. This study shows that sigma-2 binding affinity is quite sensitive to modifications of the indole ring, 4-ethyl side-chain, and 18 position on the saturated ring system.

IN VIVO IBOGAINE BLOCKADE AND *IN VITRO* PKC ACTION OF COCAINE

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Ibogaine may have anti-addiction potential against alcohol, psychostimulant and opiate abuse, but its mechanism its mechanism of action is incompletely understood. Protein kinase C (PKC) plays a key role in a number of cellular and neuronal functions. For the *in vivo* studies, we first determined the acute and subacute effects of ibogaine (1-5 mg/kg) in mice using the plus-maze test. Acutely, increasing doses of ibogaine produced a reduced aversion to the open arms. The sub-acute administration provoked a variable response which was characterized by fluctuation in aversive and anti-aversive behavior of the animals to the open arms of the plus-maze during the 14-day treatment period. A separate group of mice received 1.0 mg/kg cocaine for 14-days and upon abrupt cessation from cocaine treatment, ibogaine 2.5 mg/kg was administered to a subgroup of these mice. Ibogaine reversed the withdrawal aversions produced by the abrupt cessation from cocaine administration. For the *in vitro* studies. the expression and activity of PKC isoforms and Ca^{2+} levels were examined following incubation of PC12 cells with cocaine. We report that cocaine disrupts signal transduction in PC12 cells by altering the expression and activity of PKC isoforms and Ca^{2+} levels. The data obtained suggest 1) that the PC12 cells may be useful in studying the neurobiology of abused drugs like cocaine *in vitro*. 2) that if anxiety is a factor in drug-dependency, then the anti-addictive property of ibogaine *in vivo* may be associated with modifying the CNS neurotransmission that may be involved in anxiety and 3) cocaine differentially altered the expression of PKC isoforms accompanied by increased levels of Ca^{2+} total PKC activity. It remains to be de&mined if ibogaine will block the effects of cocaine on the expression of PKC isozymes and activity.

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BEHAVIORAL PROFILE OF CONSTITUENTS IN AYAHUASCA, AN AMAZONIAN PSYCHOACTIVE PLANT MIXTURE

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Ayahuasca is a psychoactive plant mixture originating in the Peruvian upper Amazon, typically composed of a combination of the banisteriopsis vine and the hallucinogenic plant *psychotria viridis.* Ayahuasca has long been used by aboriginal populations for its putative spiritual and medicinal benefits, but more recently it has become the basis of religious ceremonies in urban South America and elsewhere. Although the presumed primary chemical constituents of ayahuasca have been identified, little is known about their basic pharmacology and potential synergistic effects in the central nervous system. Two major constituents of ayahuasca, harmine and dimethyltryptamine (DMT), were selected for detailed study in mice using the functional observational battery (FOB), a standard neurobehavioral test battery, and the acoustic startle response. The data from these studies was used as reference data for studies involving the interaction of DMT and banisteriopsis extract preparation. In the FOB, DMT (5-32 mg/kg) altered posture, increased ease of removal, increased gait score, decreased mobility, and decreased arousal. Harmine (5-32 mg/kg) dose-dependentIy decreased arousal levels, impaired mobility and gait, increased ease of removal, reactivity to being handIed and gait score, and induced clonic and tonic involuntary movements. In the acoustic startIe procedure, harmine produced decrease in startIe amplitude but had no effect on prepulse inhibition, a measure of sensorimotor gating. DMT had no effect in either startle measure. In the FOB a harmine (5-32 mg/kg)/DMT (32 mg/kg) combination exacerbated the effects of harmine alone. The effects of the banisteriopsis extract preparation were consistent with the effects of harmine alone. The combination of extract and DMT (32 mg/kg) increased the effects of the extract alone. In PPI the extract decreased startle amplitudes whereas the combination increased amplitudes. These data will form the basis for a better understanding of the acute psychoactive effects of ayahuasca in man, and assist in elucidating the cellular basis for its claimed medicinal benefits, as well as its potential hazards.

GENES ENCODING MARIJUANA RECEPTORS

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There has been some controversy about the medicinal use of marijuana. Cannabinoids are the constituents of the marijuana plant (*cannabis sativa*). Recent advances include the cloning of the cDNA encoding the rat, human, mouse and fish CNS (CB1, CB1A) and the peripheral (CB2) cannabinoid receptors (*Cnrs*). Putative endogenous cannabis-like ligands in the brain, including anadamide and an antagonist, SR141716, that hinds the *Cnrs* have been identified. We cloned, sequenced, constructed the helical structure and localized the murine CB1 *Cnr* gene to chromosome 4. There is extensive nucleotide and protein sequence homology between the mammalian *Cnr,* CB1 that are distinct from *Cnr* CB2. The chromosomal location of the human and mouse CB1 genes adds a new marker to the region of the human 6q genes of mouse-human homology. The Northern blot analysis data using the CB1 cDNA probe indicate that the CB1 gene is not only differentially expressed in the naïve mouse strains but also following anandamide administration. The neurobehavioralchanges following the administration of anandamide or Δ^9-THC to the mouse strains may be associated to the differential expression of the brain *Cnrs*. The identity of the differentially expressed genes using the differential display polymerase chain reaction (DDPCR) in the brain following treatment of mice with anandamide remains to be determined. We concluded that it is unlikely that the CB1 *Cnr* mediates all the cannabimimetic actions of cannabinoid or after smoking marijuana. An understanding of the *in vivo* role of cannabinoids and their receptors may require the careful analysis of targeted gene mutations in mice.

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SYNTHESIS AND EVALUATION OF ARACHIDONYLPHOSPHONATES AS CANNABINOID RECEPTOR LIGANDS

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Analogs based on the endogenous cannabinoid ligand arachidonylethanotamide (anandamide) are a new class of compounds that can serve as probes of the cannabinoid receptors (CB) and the neurochemical system it represents as well as the enzymes responsible for the synthesis and breakdown of anandamide. Deutsch and coworkers have shown that methyl arachidonylfluorophosphonate (MAFP) inhibits anandamide amidase/synthase with an IC_{50} in the nM range and binds to the CB1 receptor more strongly than anandamide. This binding precludes subsequent binding of the highly active non-classical cannabinoid CP 55,940. We have found MAFP itself to exhibit no effect on the twitch response yet it behaves as an irreversible antagonist of cannabinoid-induced inhibition of electrically-evoked contractions of the myenteric plexus-longitudinal muscle preparation of the guinea-pig small intestine (GPI) at a concentration of 1 μM. While blocking the inhibitory effects of the cannabinoid agonists CP55,940, WIN55,212-2, delta-9-THC, nabilone and R-(+)-methandamide, the twitch inhibition of nor-morphine and clonidine and the ability of acetylcholine to induce contractions were not affected, demonstrating a level of cannabinoid specificity. We have also found that substituting the pentyl terminus of anandamide with the 1,1-dimethylheptyl (DMH) group enhances binding to the rat brain receptor preparation by two orders of magnitude, suggesting that combining the DMH-arachidonyl structure with the methyl fiuorophosphonate moiety could result in a high affinity, cannabinoid selective, irreversible antagonist for the CB1 receptor the current work presents a previously unpublished synthesis of MAFP and its application towards the synthesis of methyl 1,1-DMH-arachidonylfluorophosphonate.

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EFFECTS OF SR141716A ON DIAZEPAM SUBSTITUTION FOR Δ^9-THC IN RAT DRUG DISCRIMINATION

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Diazepam (DZP) produces consistent partial substitution for Δ^9-tertahydrocannabinol (THC) in rats trained to discriminate this cannabinoid from vehicle. In order to determine whether this effect might be related to DZP action at cannabinoid receptors, we examined the effects of SR141716A, an antagonist of brain cannabinoid (CB1) receptors, on DZP substitution for itself or for THC. Rats were trained to discriminate either THC (n=7) or DZP (n=7) from vehicle in a two-lever drug discrimination procedure for food reinforcement. As in previous studies, DZP partially substituted for THC. In contrast, THC did not substitute for DZP in any rats. Hence, cross-generalization of these two drugs was asymmetrical. When tested in combination with DZP, SR141716A did not block the partial substitution of DZP for THC nor did it antagonize the discriminative stimulus effects of DZP in DZP-trained rats. These results suggest that the partial overlap in the discriminative stimulus effects of THC and DZP is not mediated by DZP action at CB1 receptors, However, the fact that DZP produced partial substitution for THC is consistent with a GAB Aergic component to cannabinoid drug discrimination.

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ABSTINENCE SYMPTOMS FOLLOWING ORAL THC ADMINISTRATION IN MEN AND WOMEN

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Tolerance and withdrawal after the frequent administration of high doses (210 mg/day) of Δ^9-tetrahydrocannabinol (THC) have been reported (Jones and Benowitz, 1976), yet little is known about the effects of lower THC doses, which are more relevant to the effects of chronic marijuana use. In this 20-day residential study, we measured a range of behaviors (food intake, performance tasks, subjective effects, social interaction) in male and female marijuana smokers both during THC administration (20, 30 mg qid) and for 4 days after THC administration. Each day, daily marijuana smokers (4M, 4F) worked on 5 psychomotor tasks during the day (1000 - 1700), and in the evening engaged in private or social recreational activities (1700 - 2330); visual analog, subjective-effects measures were completed 10 times/day. Food and beverages were available ad libitum. Placebo THC (qid) was administered on days 2-3, 8-11, and 16-19. THC was administered on days 4-7 (20 mg qid) and on days 12-15 (30 mg qid). Capsules were given at 1000, 1400,1800, and 2200. THC increased ratings of "High." "Good Drug Effect," "Willingness to Take Dose Again" and "Trouble Sleeping" compared to baseline (days 2-3). THC also increased food intake by 35-45%, and decreased social interaction compared to baseline; these effects tended to be dose-dependent in men but not in women. Tolerance developed to the effects of THC on mood but not on food intake or social behavior. Abstinence from THC increased ratings of "Anxious," and "Restless," decreased food intake by 20-30%, and increased social interaction compared to baseline. Mood changes were most pronounced during abstinence from the higher THC dose. Thus tolerance and dependence develop following exposure to lower THC doses and less chronic dosing than have been previously utilized. These data suggest tolerance and dependence to THC may play a role in maintaining chronic marijuana use.

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EFFECT OF A BRIEF MOTIVATIONAL GROUP THERAPY ON READINESS TO CHANGE SCORES IN SUBSTANCE ABUSERS

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The motivation of a client to change behavior is an important determinant of engagement and retention in substance abuse treatment. Our goal was to study the readiness for change in alcohol and other drug abusers evaluated for substance abuse at an outpatient clinic. Clients participated in a 3 session Self Assessment Treatment Group that gave them a chance to explore their substance use behaviors in an educational and supportive manner while allowing them to "self assess" their behaviors and desires to change over the 3 week period. 43 clients completed the SOCRATES, an alcohol and drug specific readiness to change questionnaire, at treatment entry and at the end of the 3 group sessions. Findings indicated that marijuana abusers, as compared to those clients abusing alcohol, showed the most significant change across the 3 sessions in their readiness to address substance abuse problems. Clients did not differ in stages of change scores al treatment entry, but marijuana abusers showed significantly higher scores on the action and maintenance subscales of the SOCRATES at the end of treatment which reflected readiness to address their drug use behavior. These findings suggest that a brief motivational and educational self-assessment group can be an effective intervention to engage and retain marijuana abusers in outpatient treatment.

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TEST-RETEST RELIABILITY OF THE ALCOHOL AND DRUG SECTIONS OF SCHEDULES FOR CLINICAL ASSESSMENT IN NEUROPSYCHIATRY (SCAN)*

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This report presents the results of a test-retest reliability study of the alcohol and drug sections of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), investigating the diagnosis of alcohol and drug dependence and abuse, disorders via a within-site design. Reliability for the past 12 months, prior to past 12 months, and lifetime back were evaluated across ICD-10, SMI-III-R and DSM-IV diagnostic at sites located in both Ankara Turkey and Farmington. Connecticut, USA. The study also tested the diagnostic concordance in a relatively heterogeneous group of treatment and community subjects in both countries. The subjects were recruited from the general population, special treatment settings and from general medical settings. A total of 287 subjects were recruited. The two sites were comparable across most demographic variables and inpatient treatment status. The test-retest administration of the interview were separated by intervals ranging from 3 to 20 days for the Farmington site with an average of 7.25, and by intervals ranging from 3 to 10 days for the Ankara site with an average of 5.95 days. In the study, kappa a measure of agreement corrected for chance was used as a measure of reliability. The results show that the alcohol and drug sections of SCAN version 1.0 reliably identifies patterns of dysfunctional use, abuse and dependent for alcohol and other drugs during the past 12 months, prior to past 12 months and the individual's lifetime. Although there were some methodological limitations, the present report supports the usefulness of semi-structured interviews in attaining diagnoses of abuse and dependence when administered by clinicians from different mental health disciplines and diverse cultural origins.

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POSTER SESSION III

ROLE OF OPIOID SYSTEM IN ETHANOL-INDUCED PLACE PREFERENCE UNDER CONDITIONED FEAR

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Psychological stress (PS) is considered an important motivating factor in the continued ethanol (ET) intake, and may be related to the rewarding effect of ET. It has hitherto been suggested that both PS and ET modulate endogenous opioid system. The present study attempted to establish ET-induced place preference using conditioned fear stress (CFS) as PS, and to clarify the role of endogenous opioid system in rewarding effect of ET using the conditioned place preference paradigm. Male Sprague-Dawley rats were subjected to CFS (at 24 hours after electric foot shock exposure), and then ET (300 mg/kg) or saline was injected i.p. For conditioning, animals were immediately confined to one compartment after ET injection and to the other compartment after saline injection. This conditioning session was repeated twice (for 8 days). After the conditioning, test session was Performed on day 9. ET treatment with CFS, but not without CFS, significanlly induced a place preference. In addition, the development of ET-induced place preference in ET-treated rats that were subjected to another CFS immediately before the test session was clearly enhanced. Pretreatment with nonselective opioid receptor antagonist naloxone (3 mg/kg, s.c.) or selective delta opioid receptor antagonist NTI (3 mg/kg, s.c.) significantly antagonized the ET-induced place preference. These results indicate that PS may play an important role in the development of rewarding effect of ET and that the rewarding effect of ET under PS may be partially mediated by endogenous opioid system.

THE EFFECTS OF NALTREXONE NALTRINDOLE AND BETA-FUNALTREXAMINE ON ALCOHOL CONSUMPTION IN THE RAT

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There is considerable evidence from both preclinicai and clinical investigations suggesting a link between endogenous opioids and the motivation to consume alcohol. While both naltrexone (ntx), a nonselective opioid antagonist, and naltrindole (nti), aδ selective antagonist, have been demonstrated to reduce ethanol consumption. the contribution of specific opioid receptor subtype remains unclear. These experiments were designed to compare the effects of ntx, nti and beta-funaltrexamine β-fna), a μ selective antagonist, on alcohol consumption in nondeprived Wistar tats provided with daily 1 hour access to a 6% alcohol solution. In Experiment 1, ntx at doses of 0.1, 0.25, 0.5, 1.0, 3.0 and 10.0 mg/kg significantly reduced alcohol consumption compared to saline control. At higher doses, e.g. 10.0 mg/kg, ntx antagonizes δ as well as μ receptors. However, between doses of 0.5 and 10.0 mg/kg the dose response curve for ntx was flat suggesting that ntx may reduce ethanol consumption by antagonizing only μ receptors. In Experiment 2, nti at doses of 5.0 and 20.0 mg/kg did nor alter ethanol consumption. In Experimenl 3, a single dose of β-fna. 20.0 mg/kg, significantly reduced ethanol consumption for two days, while a dose of 5.0 mg/kg did not. These data suggest that alcohol consumption may be primarily modulated by μ receptors. The failure to replicate the reduction in alcohol consumption following administration of α δ antagonist may be due to the use of alcohol preferring rats in those experiments compared to the use of genetically heterogeneous Wistar rats in the present experiments.

NALTREXONE DOES NOT BLOCK THE ACUTE BEHAVIORAL EFFECTS OF PENTOBARBITAL IN HUMANS

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Naltrexone, an opioid antagonist is used as an adjunct in the management of alcohol abuse and dependence. The mechanism by which naltrexone exerts its clinical effect is unknown, but it has been shown to block some of alcohol's acute "pleasurable" subject-rated drug effects. The aim of the present study was to determine if this effect is specific to alcohol, or whether naltrexone also blocks the acute "pleasurable" subject-rated drug effects of other commonly abused sedatives. To accomplish this aim, 8 volunteers (5 females, 3 males) received pentobarbital (0, 150 and 300 mg), alone and in combination with naltrexone (0, 50 and 100 mg). Pentobarbital, a barbiturate hypnotic, was chosen because it is a commonly abused sedative that produces "pleasurable" subject-rated drug effects. Subjects received one of 9 possible dose combinations under double-blind conditions during each of 9 experimental sessions. Order of drug administration was mixed, and at least 48 hours separated all sessions. Subjects ingested naltrexone 60 minutes after pentobarbital. The timing of pentobarbital and naltrexone administration was arranged to have the peak behavioral effects of pentobarbital occur across peak plasma levels of naltrexone. Drug effecrs were assessed before drug administration and periodically afterwards for 5 hours using a battery of subject-rated drug-effect questionnaires and performance measures previously shown to be sensitive to the acute effects of sedative drugs. Pentobarbital alone (*i.e.,* in combination with placebo naltrexone) produced prototypical sedative-like subject-rated drug effects (*e.g.,* increased ratings of "Drug Effect", "Like Drug". "Good Effects", "Drunk", "High" and Sedation) and impaired performance as a function of dose. Naltrexone alone (*i.e.,* in combination with placebo pentobarbital) did not affect these measures. Naltrexone generally did not alter the subject-rated or performance- impairing effects of pentobarbital to a statistically significant degree. These findings suggest naltrexone's ability to attenuate "pleasurable" sedative-induced subject-rated drug effects may be specific to alcohol. Supported by a gram from the Alcoholic Beverage Medical Research Foundation.

EFFECTS OF PIMOZIDE ON SUBJECTIVE RESPONSES TO ETHANOL IN HUMANS

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Evidence from studies with laboratory animals suggests that dopamine is involved in the reinforcing and stimulant-like effects of several drugs of abuse, including low doses of ethanol (Imperato and Di Chiara, 1986). Because reinforcing effects of drugs are often closely associated with their subjective effects, it might be expected that dopamine may also be involved in the subjective feelings of euphoria that humans report with drugs of abuse and alcohol. Surprisingly, few studies have explored the neurochemical mechanisms underlying the euphorigenic effects of drugs or alcohol in humans. In the present study, 14 normal healthy volunteers consumed a beverage containing a low dose of ethanol (0.25 g/kg) or placebo, 4 hours after raking a capsule containing the dopamine antagonist pimozide (4 mg) or placebo. Subjective ratings of drug effects were measured for 4 hours after ethanol administration. Subjects reported feeling the effects of this low dose of ethanol and reported significant increases in ratings of drug "liking". Pimozide administered alone decreased ratings of liking and increased ratings of feeling "down," indicating that the dose was centrally active. However, when the two drugs were given in combination pimozide did not attenuate the effects of ethanol. These results do not support the idea that dopamine mediates the euphorigenic effects of a low dose of ethanol in healthy volunteers.

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EVALUATION OF GENDER EFFECTS ON SCHEDULE-INDUCED ALCOHOL CONSUMPTION IN CYNOMOLCUS MONKEYS

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Schedule-induced pulydipsia (SIP) has been used to induce excessive drinking in laboratory animals and has been suggested as a possible factor in human excessive alcohol consumption. In an initial investigation of gender influences on susceptibility to schedule-induced ethanol consumption, several parameters of drinking were studied in 6 cynomolgus monkeys (2 males and 4 females). The monkeys had daily sessions under a fixed-time (FT) 180 s schedule of food (1 g pellets) presentation with 4% (w/v) ethanol available from a drinking apparatus that contained an in-line flow meter interfaced to a computer system. Sessions ended after 1.0 g/kg ethanol intakes were reached. A gender difference was found in mean session volume ingested (males =146±6ml, females =72±3ml), but this difference was nullified when body weight was factored in the measure. Gender differences were also found in mean number of drinking bouts (males =16±1, females =14±1) and mean volume ingested per bout which remained significant when body weight was factored in the measure (males=1.32±0.04 ml/bout/kg, females = 2.03±0.2 ml/bout/kg). There was no ditference in the pattern of drinking during the FT (IOC values: males and females = -0.24) or the mean length of the session (males and females= 48 min). In addition, 3 monkeys (1 male, 2 females) were tested under FT values of 120, 180, 240 and 300 s. Number of bouts and volume ingested was bitonic in relation to schedule, with peak values found under FT 180-240 s. These preliminary results indicate that male and female cynomolgus monkeys show similar adjunctive behavior with a difference in the microstructure of consumption and that SIP is useful for inducing equivalent alcohol consumption across genders.

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CHARACTERISATION OF CHANGES IN MOOD DURING ACUTE AND PROTRACTED ALCOHOL WITHDRAWAL

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The alcohol withdrawal syndrome in humans includes mood and psychiatric disturbances, especially anxiety and depression. Symptoms are reported to be most severe in the first five days following the last drink but have also been reported to persist for weeks and months following cessation of drinking. Most reports on the intensity ad time course of these withdrawal symptoms are primarily cross-sectional in nature, employ non-standardised methods of assessment and have a narrow symptom focus. There is a need to characterise the intensity and duration of these symptoms since persistent mental health disturbances may result in relapse drinking. This study employed three standardized questionnaires: the Beck Depression Inventory (BDI), the State Trait Anxiety Inventory (STAT) and the Profile Of Mood States (POMS). Questionnaires were administered to 25 subjects presenting to an in-patient unit for treatment of alcohol withdrawal. Subjects experiencing withdrawal received standard clinical treatment. including monitoring of withdrawal severity using the CIWA-Ar with diazepam dosing when scores were greater than 10. Questionnaire administration occurred on days 2 and 5 (acute withdrawal phase) and days 14, 42 and 70 (protracted withdrawal phase) following cessation of drinking. Subjects' scores were compared with questionnaire norms, and data were analysed using a mixed model analysis of variance. Withdrawal subjects experienced significant anxiety and depression during the acute phase, which persisted for at least two weeks following the last drink. Data from days 42 and 70 indicated that some subjects still exprienced anxiety and depression. although means were not significantly different from normal scores. Fatigue-inertia and confusion-bewilderment were also most severe during the acute phase, and persisted for at least two weeks following the last drink. Further research will examine the relationship between withdrawal severity and relapse to alcohol use.

EFFECTS OF ALCOHOL ON MOOD, EQUILIBRIUM, AND SIMULATED DRIVING

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This study compared the effects of alcohol on simple versus complex behavior in 18 adult humans. Subjects received doses of 0.0, 0.5, and 0.8 g/kg ethanol in a randomized double-blind design. Forty minutes after finishing drinking, subjects completed a 60-minute battery of tests including 1) a sensory organization test of posturography (EquiTest), 2) latency to apply brake following appearance of a barrier in a driving simulator (brake reaction time), 3) visual analog subjective effects scales (VAS), 4) the Profile of Mood States (POMS), 5) critical flicker fusion (CFF), and 6) choice reaction time (CRT). Alcohol reduced composite equilibrium scores in a dose-related fashion (0.0 g/kg=78, 0.5 g/kg=72, 0.8 g/kg=60; $p<.0001$). Following the high dose but not the low dose. subjects' EquiTest vestibular and somatosensory scores were lower and visual preference scores were higher than scores with the placebo ($p<.001$). indicating increased reliance on visual information rather than on input from the vestibular or somatosensory system to maintain balance. Brake reaction time increased with increasing alcohol doses (0.0 g/kg=.59 sec, 0.5 g/kg=.63 sec, 0.8 g/kg=.71 sec; $p<.0001$). Alcohol increased VAS "dizzy", "high", and "drug effect" ratings in a dose-related fashion. VAS "drowsy" scores increased comparably with both doses. POMS, CFF, and CRT scores with alcohol did not differ significantly from scores with the placebo beverage. These data suggest that ethanol doses that neither influence certain mood states nor impair simple psychomotor tasks nonetheless do impair equilibrium and complex psychomotor tasks (e.g., driving).

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PROSPECTIVE ASSESSEMENT OF DSM-IV ALCOHOL DISORDERS AMONG 14-17 YR OLDS IN MUNICH GERMANY

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Background: General population surveys of substance and psychiatric disoders among adults show that alcohol disorders are among the most prevalent in the community. In addition, these studies indicate the prevalence of alcohol abuse and dependence is highest among the youngest age groups and that the peak incidence of first onset occurs in the late teens. Despite these findings, relatively little information is available on the distribution, determinants and development of DSM-defined alcohol disorders among adolescents. The objective of this work is to compare follow-up with baseline information to examine patterns of disorder incidence, persistence and remission in a population of 14-17 year old adolescents. **Methods:** Baseline cross-sectional interviews assessing DSM-IV substance disorders were conducted during the spring of 1995 in a random sample of 14-24 year olds from Munich, Germany. Follow-up interviews were conducted among all 14-17 year olds approximately 20 months later (response rate=91%, n=1220). Baseline and follow-up assessments were made using a version of the WHO-CIDI modified for DSM-IV. **Results:** At baseline, DSM-IV alcohol abuse (men: 15.1%, women: 4.5%) was considerably more prevalent than dependence (men: 10.0%; women: 2.5%) with few cases among respondents younger than 16 years of age and peak first onset at 16-17 years of age. Exploratory analysis of retrospectively assessed diagnostic stability show: a temporal progression to abuse and then dependence, that nearly half of past abuse diagnoses are in remission, that abuse remission is more common than progression to dependence, and that dependence is highly persistent, especially among women. Follow-up of the 14-17 year old sub-sample found similar results although diagnostic remission was more frequent in this young age group. **Conclusions:** Alcohol disorders are frequent in adolescents and young adults being characterized by transient abuse and less prevalent but persistent dependence syndromes. These findings are discussed with regards to the clinical validity of DSM-IV criteria in adolescents and young adults.

A COMPARISON OF A SELF-ADMINISTERED ASI WITH THE STANDARD ASI INTERVIEW

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The present investigation examined the concurrent validity of a self-administered version of the Addiction Severity Index (SA-ASI). One hundred and five men (75% black, 25% white; 44 ± 7 years old) were recruited for participation upon admission to outpatient treatment for opiate dependence (methadone maintenance, n=51) or alcohol/cocaine dependence (abstinence oriented rehabilitation, n=54) at the Philadelphia VA Medical Center. Participants completed either a standard ASI interview or SA-ASI, and 1 to 5 days later completed the alternate version of the ASI. Results indicated that the SA-ASI and standard ASI Composite Scores were significantly and highly correlated; Medical .41, Employment .95, Alcohol .76, Drug .77, Legal .65, Family/Social .93 Psychiatric .71. In general, more clearly specified and operationalized behaviors and experiences bad higher levels of agreement whereas agreement for items more open to subjective interpretation was not as good. This was true for both current and lifetime information, Much of me information collected during a standard ASI interview can bc validly obtained in a self-administered formal. Further work is needed to refine items and to determine under what circumstances and with what populations a SA-ASI can yield valid data.

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AGE AT ONSET IN ALCOHOLISM: INFLUENCE OF GENES ENVIRONMENT AND SIBLING COMPETITION

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Background: Age at onset has been important to understanding disease throughout medicine. Contrasting early versus late. age at onset has also played a prominent role in the study of alcoholism: early onset indicating a more genetically influenced case or subtype. However, genetic influence on milestones in me development of alcoholism has not been examined other than first drink. This study investigated the relative genetic and environmental influence on age at first intoxication and first alcohol problem. Also examined was the genetic influence shared between age at onset and alcohol dependence. **Methods:** The sample consisted of 118 male twin pairs ascertained through 16 public and private alcohol and drug abuse treatment programs in Minnesota from 1982-88. Distributions of age at onset for this sample and heritability of alcohol dependence were shown to be comparable to general population estimates. StructuraI equation modeling was used to identify the types of influence (genetic, environmentaI, and gene-environment interactions) necessary to explain variation in age at onset and estimate the level of influence attributable to those factors. **Results:** Distinct etiologies for age at first intoxication and age at first problem were found. First intoxication was influenced equally by common and unique environment. First problem was predominantly additive genetic in origin, although moderate sibling competition was also evidenced. Contrary to expectations, genetic influence on age at first problem appeared consistent across me range of onset ages. Also, age at first problem and alcohol dependence shared only a small amount of genetic variance and no environmental variance. Conclusions: These findings highlight the complex etiology of alcoholism. Not only is the disorder likely to be multifactorial in origin, hut it may be that distinct sets of genes and environmental factors influence different aspects of alcoholism's development.

SIBLING RISK FOR SUBSTANCE USE AND DEPENDENCE: COMPARISON OF ILLICIT DRUGS, TOBACCO AND ALCOHOL

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Sibling risk for drug use and dependence was estimated in a population based sample of multiple household respondents to the 1991, 1992, and 1993 National Household Survey on Drug Abuse. From a total of 87.915 respondents, 835 pairs of individuals from the same household were identified as being likely sibs (same sex, age difference < 10 years, both indicating a sib living in the household both reporting living with same biological parent). The sample included 438 male and 397 female pairs: mean age older sib 21.1 years, younger sib 16.4 years. Risk to younger sib was estimated from older sib drug status after controlling for group differences in race, sex, and younger sib age. Comparisons were made for ever used, problem use, and DSM-IIIR dependence on alcohol, tobacco (cigarettes), marijuana, and all illicit drugs except marijuana. Significant sibling influences were seen with all drugs ($p<.0006$). Younger sib was more likely to be affected when the older sib used drugs, had drug problems, or was drug dependent than when the older sib did not. Sibling risk was lowest for tobacco use (Odds Ratio (OR)=3.9) and any illicit drug use (OR = 3.2), and higher for alcohol use (OR=4.4) and marijuana use (OR=8.1). Sibling risk for tobacco and alcohol showed little increase as severity of problem increased from use to problem use to dependence (for tobacco, 3.9, 2.5, and 3.4; and alcohol, 4.4, 3.1, and 4.4, respectively). However, sibling risk for marijuana and any illicit drug except marijuana increased with increases in problem severity (far marijuana, 8.1, 9.6 and 112.4; for any illicit drug except marijuana, 3.2, 20.6, and dependence not calculated due to small N, respectively). The results suggest the sibling risk of drug use may be greater for illicit man for licit drugs and increase more with severity of drug problem.

INTERGENERATIONAL TRANSMISSION OF DRUG USE PATTERNS AND NORMS

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The purpose of this study was to assess the association between parents' licit and illicit drug use patterns and attitudes and their offspring's use both in adolescence (Time 1) and in adulthood (Time 4). Parental behaviors and attitudes were assessed from parent self-reports as well as offspring perceptions. We used data from the Rutgers Health and Human Development Project, a four-wave, prospective study of substance use behaviors in a nontreatment sample (N=1201). Correlational analyses indicated that offspring perceptions of mothers' and fathers' use of alcohol and, especially, cigarettes were consistent with parent self-reports. Thus. these results suggest that adolescent perceptions of their parents use can be used with relative confidence in lieu of parent self-reports. Regression analyses indicated that higher levels of parent drinking, cigarette smoking, and marijuana use predicted higher levels of offspring use in adolescence and adulthood and that parent drug use as compared to attitudes was a better predictor of offspring use in adolescence and especially in adulthood. Overall, parental modeling of licit and illicit drug use behaviors did not strongly influence offsprings' use. Hence, we will need to consider other aspects of the parent-child relationship in future research on the intergenerational transmission of drug use.

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DIRECT AND INDIRECT EFFECTS OF TEMPERAMENT ON SUBSTANCE USE IN ADOLESCENT CHILDREN OF DRUG ABUSERS

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Children of drug abusers (CDA's) are at risk for substance abuse. This study examined the relationships among temperament, coping behavior and early substance use in 99 adolescent children of opiate dependent parents. Based on prior research, it was hypothesized that 1) difficult affective temperament, and the temperament dimensions of high activity, low positive mood and rigidity (measured by the DOTS-R) would be associated with more frequent substance use in adolescent children of opiate addicts; 2) that difficult affective temperament, high activity, low positive mood and rigidity would be associated with maladaptive coping styles (avoidant coping, aggressive coping, and helplessness/ behavioral disengagement) in CDAs; and 3) that maladaptive coping would mediate the relationship between temperament and substance use. Data based on self-report, were analyzed using simple and multiple regression. As predicted, the temperament dimension of high activity was significantly related to anger/aggression coping and overall avoidant coping, as well as to alcohol use. Rigidity was related to overall avoidant coping, alcohol use and overall substance use (cigarettes, alcohol and marijuana). Anger coping and overall avoidant coping were related to overall substance use. The findings provide evidence that anger coping mediates the relationship between high activity and overall substance use in this population.

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EFFECTS OF DRUG ABUSE ON THE FAMILY: FAMILY MEMBERS, THE PROBLEMS, AND TREATMENT OUTCOMES

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Little research has examined the effects of drug abuse on the family and significant others (FSOs) of drug users. We recruited 52 FSOs through an advertisement offering help for people worried about the drug use of a family member or close friend. All subjects completed two social adjustment scales (SAS); one for themselves and one for the drug abuser. They also completed a Significant Others Needs Survey (SONS) which identified problems experienced due to the drug abuser. Thirty of these individuals also met inclusion criteria for an intervention phase of the study. (They had regular contact with a drug user who was not in treatment.) These subjects were randomly assigned to either a unilateral behavioral or 12-step intervention. They additionally completed a Profile of Mood States (POMS) at intake, and repeated all measures at 10 weeks after treatment intake. We found that most FSOs report problems with money, the relationship with the drug user, social/emotional issues, and health. Physical abuse was reported in 33% of the cases. FSOs report social adjustment that is significantly different from a community sample in some areas, with partners of drug abusers appearing more affected than parents, and drug abusers themselves with the poorest adjustment The behavioral intervention resulted in significantly better treatment attendance and completion by the FSOs and in more drug abusers entering treatment. Significant improvements in mood and social functioning were seen for both groups at follow-up. Reductions in the number of problems reported on the SONS at follow-up was also noted by both intervention groups. Data from this small sample suggest that FSOs have significant problems due to involvement with a drug user and that they can benefit from unilateral interventions.

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THE IMPACT OF A SUBSTANCE ABUSE PREVENTION PROGRAM ON PARENTAL SELF-ESTEEM, COPING, CHILDREARING SKILLS AND SATISFACTION

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Research has consistently shown certain parental attitudes and behaviors increase risk of child drug abuse while other behaviors tend to inhibit the involvement in drugs. However, there have been limited prevention programs aimed at parents of preschool school children. The data presented are from an evaluation of a patent-focused substance abuse prevention program for Head Start (preschool parents). Pre and post test data were collected on 480 comparison and experimental group parents. Locus of control, self-esteem and parenting skills were significantly associated with drug use of parents ($p<.05$). Results revealed significant treatment effects for coping skills ($p<.05$). There were no significant treatment effects for, locus of control, opinions about drug. parenting satisfaction, and parenting skiffs. These findings have implications for targeting prevention efforts toward empowerment and self-efficacy rather than on specific behaviors such as childrearing and attitudes towards drugs.

USE OF INHALANT DRUGS BY 12-17 YEAR OLDS: DATA FROM THE NATIONAL HOUSEHOLD SURVEY ON DRUG ABUSE

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Estimated risk of starting to use inhalant drugs has jumped sharply in recent years for 12-17 year old American youths, with a more modest upswing for 18-25 year olds. Shedding new light on these recent trends, our paper offers evidence from analyses of epidemiological data collected for the 1990-1995 National Household Surveys on Drug Abuse (NHSDA). **Methods:** Each year of operation, NHSDA draws a large probability sample of youths and adults (e.g., $n > 2000$ 12-17 year olds). Participants are assessed via confidential self-report interviews and questionnaires. Variance estimation and significance testing accounted for sampling weights and complex sampling designs. **Results:** Our estimation of age-specific risk for inhalant drug use shows that the recent acceleration is not randomly distributed in the population; it differs for sub-types of inhalant drugs. Risk of inhalants use is just as large for 13 yr olds as for 17 yr olds. There is a recent decrease in inhalants use among "Blacks," but there is no consistent male-female difference. Nearly half of recent inhalant users had used inhalants for at least two years; among inhalants users, multiple occasions of use and use of multiple inhalants are common. **Discussion:** Inhalant drug use, often is dismissed as a transitory behavior with trivial public health significance. Recent epidemiological data challenge this perspective, and invite more detailed investigations.

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ACCULTURATION, SUBSTANCE USE AND MEXICAN-AMERICAN YOUTH

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Mexican-Americans comprise one of the largest, youngest and fastest growing groups in the U.S., with large numbers of relatively recent immigrants. Because of these circumstances, it is important to examine the relationship between acculturation and substance use patterns. Acculturation and substance use among Mexican-American children and adolescents was assessed for 231 Mexican-American youths of ages 9 to 17 years. Acculturation to the predominantly European-American majority in the U.S. was conceptualized as a function of the primary language spoken at home. 1) parent(s) who speak Spanish only; 2) at least one patent who is bilingual; and 3) parent(s) who speak English only. Because this study investigated illegal behaviors, it was felt that the best information could be obtained by seeking youth at high risk for substance use at places less identified with the "official" world, e.g. schools. Ethnographic methods were thus used to recruit subjects off the streets primarily at youth centers, in contiguous communities of Los Angeles. Consenting youths were interviewed using standardized, structured interview protocols. Patterns of use were examined for cigarettes, alcohol, marijuana/hashish and other drugs. Findings indicated no significant differences between groups by level of acculturation (p: chi-square tests). Relatively few of the youths reported smoking cigarettes, and 38.1% reported drinking the past month. Use of illicit substances was not common among this youth, and marijuana/hashish was the drug of choice (91.2%) among "users". Degree of acculturation seemed to bear influence on how often, when and where youth used substances. The present findings do not support U.S. public stereotypes that less acculturated youth are at higher risk for substance use.

STAGES OF DRUG USE AMONG AMERICAN INDIAN ADOLESCENTS

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Objective: To determine if the predominant pattern of the progression of substance use among a large sample of American Indian (AI) adolescents matches the pattern identified by Kandel and colleagues among non-Indian adolescents *[i.e., 1) alcohol; 2) marijuana; 3) other drugs, and 4) cocaine]*. **Method:** Data came from surveys completed by 1.194 Al high school students. Pairwise comparisons of age of first use for alcohol, marijuana, inhalants, cocaine, and other illicit drugs were examined. Loglinear modeling was used to describe the sequence of substance use beyond the pairwise comparisons. **Results:** Only 35% of these AI youth who used both alcohol and marijuana reported using alcohol first; 58% tit the previously described progression of substance use. An alternative model, which fit 92.7% of these Al youth, allowed for the initiation with alcohol, marijuana, or inhalants and movement from the use of one of these substances directly to the use of other drugs. **Conclusions:** The early stages of substance use for these AI youth differ from those described by Kandel and colleagues. The previously described stages of substance use are not a universal phenomenon, and may show further variation across other cultural groups.

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SUBSTANCE ABUSE AND VIOLENCE AMONG ADOLESCENTS LIVING IN A RURAL ENVIRONMENT

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Substance abuse and violence among America's youth has emerged as a significant problem, for which no effect prevention has been developed. This study examined the relationship between substance abuse, violent behavior, locus of control, and depression. The sample size consisted of 150 adolescents attending a rural high school in Southeast Texas. Four instruments were administered, the Reynolds Adolescent Depression Scale, Nowicki-Strickland Locus of Control Instrument, Coopersmith Self-Esteem Instrument, and a questionnaire developed by the researchers. Analyzes was performed separately for each racial subgroup. Preliminary findings of the subjects self report usage of alcohol. marijuana, and other illegal drugs indicate a significant correlation to their engagement in violent or delinquent behavior. Results also indicated a high correlation between depression and violent behavior. A total of 90% of the respondents scared high on external locus of control. Multiple regression analysis indicated a difference among the ethnic groups.

LONGITUDINAL TRAJECTORIES OF DRUG USE AND DEVIANT BEHAVIOR AMONG ADOLESCENTS AND YOUNG ADULTS

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This study tested the hypothesis that longitudinal trajectories of deviant behavior are differentially associated with longitudinal trajectories of alcohol or other drug use problems throughout adolescence and young adulthood. Data were obtained from a random, non-clinical, sample of 1200 subjects who were originally tested in 1979-81 at the ages of 12, 15 or 18. Subjects returned 3, 6 and 13 years later to provide longitudinal information up to the age of 31. Trajectories of both deviant behavior and drug use problems were constructed. Results of analyses conducted by age and gender found that subjects who either reported no previous history or limited deviant behavior exhibited few substance use related problems. In addition, 22% of the habitual alcohol abusers and 46% of the habitual marijuana abusers were chronic delinquents. Late onset of problem marijuana use was found to be highly associated with both late onset and chronic deviant behavior, while late onset alcohol abusers tended to exhibit lower levels of delinquent behavior. At T4, DSM-IV categories of antisocial behavior were examined. Chronic marijuana and alcohol abusing males of all ages out paced chronic alcohol-only abusing males (and all females) in aggressive and reckless behavior but 31 year old alcohol abusing males were highest in failed obligations, lying, deceit and lack of remorse. Other DSM-IV categories varied by age cohort and gender. Results suggest that in this sample of middle and working class subjects, chronic alcohol abuse is much less associated with chronic levels of deviant behavior than is the persistent problem use of marijuana and alcohol combined, especially among males, aged 25-28.

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ONE-YEAR OUTCOME OF ADOLESCENT GIRLS REFERRED FOR CONDUCT DISORDER AND SUBSTANCE ABUSE/DEPENDENCE

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Do psychiatric disorders. delinquency, and substance use improve in adolescent females who were previously referred to day treatment for their comorbid conduct and substance use disorders? What variables are associated with outcome? **Methods:** We re-evaluated 46 conduct-disordered (CD), substance-using adolescent females an average of one year after discharge (range 6-21 months) using the same structured assessment used at intake. Treatment length averaged 16 weeks (0-57 weeks). **Hypothesis:** At follow-up, these females will improve their: (1) CD, (2) psychiatric comorbidity. (3) substance use. **Results:** Follow-up assessments revealed significant improvement in (1) criminality and CD, and (2) attention-deficit hyperactivity disorder (ADHD). However, substance involvement or depression did not improve, regardless of success in or length of treatment. ADHD and depression were significantly related to drug and other comorbidity outcome at follow-up, but CD, self-concept, age, or employment were not related to drug or comorbidity outcomes. **Conclusions:** Although substance use tends to worsen over time and depression does not change, females' delinquency and ADHD symptoms appear to improve at follow-up. ADHD, depression, IQ, and poor peer relationships may be important variables related to outcome in females.

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ADHD AND DEPRESSION IN SUBSTANCE USING DELINQUENTS: RELATIONSHIP TO NICOTINE DEPENDENCE

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Major Depression (MDD) and attention deficit hyperactivity disorder (ADHD) are prevalent in adolescents with conduct disorder (CD) and substance use disorders (SUD). ADHD and CD may be associated with cigarette smoking, which is generally thought to be an early stage in the developmental sequence leading to further SUD. MDD is also associated with more smoking in adolescents and adults. **Hypotheses:** Onset of smoking and severity of tobacco dependence will correlate with (1) MDD and ADHD severity and (2) the combination of CD, MDD, ADHD, with onset of smoking or tobacco dependence will jointly explain other SUD, but each variable's differential importance may vary by gender. **Methods:** Structured interviews provided diagnostic and severity information on 285 male and 82 female adolescents (ages 13-19) referred to treatment for comorbid CD and SUD. **Results:** (1) CD, ADHD, and MDD severity correlated with more tobacco dependence as well as more severe non-tobacco SUD in males and females; ADHD and CD correlated with younger smoking in males only. In multiple regressions adjusting for age, severity of ADHD, CD, MDD, and tobacco dependence jointly significantly associated with more non-tobacco SUD (R=.33) in males, whereas only severity of tobacco dependence and depression significantly associated with other SUD in females (R^2= .20). For males ADHD, CD, and MDD in combination with younger smoking also significantly associated with other SUD (R^2=.27). **Conclusions:** In these CD/SUD adolescents, tobacco dependence appears to correlate with ADHD, MDD, CD, and other SUD; for males only, younger onset of smoking demonstrates the same association with other comorbidity and non-tobacco SUD. Clinical implications are discussed.

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AN OPEN TRIAL OF BUPROPION FOR ADHD IN ADOLESCENTS WITH CONDUCT DISORDER AND SUBSTANCE USE DISORDER

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Adolescents with conduct disorder (CD) and substance use disorder (SUD) have higher rates of comorbid attention deficit hyperactivity disorder (ADHD) than those without CD and SDD. Comorbid ADHD may contribute to more severe SUD. Treatment of ADHD may enhance effective treatment of substance abuse and behavior problems, yet there are few data regarding pharmacologic treatment of ADHD in this population. Pilot data are presented from an ongoing study on 7 adolescent boys in a residential treatment program focusing on substance and behavioral treatments. All bad diagnoses of CD, SUD, and ADHD. Patients were titrated to a maximum dose of bupropion, 100 mgs TID. Conners' Hyperactivity Index (HI) and Daydream-Attention (DA) scores, along with Clinical Global Ipression (CGI) severity of illness scores were obtained at baseline and at the 5 week post assessment. Mean Conners' HI scores declined from 76.3 to 60.7 ($p<.03$, Wilcoxon Signed-Ranks Test) (20% decline). Mean DA scores declined from 59.7 to 52.1 ($p<.02$, Wilcoxon Signed-Ranks Test) (13% decline). The CGI severity of illness declined from 4.9 to 2.9 ($p<.02$, Wilcoxon Signed-Ranks Test) (41% decline). These preliminary data suggest that bupropion may be a useful treatment for ADHD in adolescents with CD and SUD, calling for a controlled trial of bupropion in such youths.

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MEASURING TREATMENT PROCESS: GROUP PSYCHOTHERAPIES FOR ADOLESCENT SUBSTANCE ABUSERS

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The group Session Rating Scale (GSRS) a group therapy process measure was studied to determine 1) its appropriateness for adolescents, 2) its inter-rater reliability, 3) its internal consistency, and 4) its ability to discriminate the active ingredients of cognitive-behavioral therapy (CBT) from interactional therapy (IT). Trained raters independently assessed ten videotaped sessions of group psychotherapy employing the two modalities involving 32 adolescents diagnosed with substance use disorders in an outpatient setting. Interrater reliabilities were moderate to high, with those for CBT being higher than those for IT. Internal consistency of CBT items was moderate, while those of IT were moderately high. Discriminability between the two treatment modalities was high. The frequency of active ingredients was therapy-specific: high for the relevant and low for the non-relevant therapeutic modality items. The GSRS was found to be effective in the measurement of treatment process for adolescents with substance use disorders. It may serve as a useful tool for the training of therapists in providing manual guided CBT and IT group therapies in clinical and research settings.

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A COMPREHENSIVE TREATMENT MODEL FOR COURT ASSIGNED, ADJUDICATED ADOLESCENT DRUG ABUSERS

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We have developed the Comprehensive Treatment model as one condition in a random assignment experimental evaluation of interventions for drug abusing adolescents adjudicated by the Family Court of Philadelphia and placed on probation. The model is designed to bring together a series of interventions that have been demonstrated by previous research to contribute effectively to improved outcomes in substance abuse treatment. Comprehensive Treatment includes 3 months of intensive day treatment followed by 6 months of after-school outpatient treatment. Day treatment includes individual cognitive-behavioral therapy, pragmatically focused family therapy, intensive case management, group training in interpersonal problem-solving skills, daily community meetings, and 3 hours daily of school in a classroom of 9 or fewer students. In outpatient treatment, clients continue to receive the individual therapy, family therapy, and case management. The interpersonal skills training is focused on relapse prevention. Self-Help groups are instituted, and a community service project is scheduled as a culminating experience. The Comprehensive Treatment design is grounded in the theoretical expectation that each intervention component will prove effective to a limited degree, but that a number of intervention components should be addictive in efficacy. In practice. however, the components must be delivered in a carefully coordinated manner to prevent their interfering with one another. For example, family therapy and individual therapy or case management and individual therapy may complement and strengthen one another or may conflict with one another and weaken intervention. The Comprehensive Treatment model includes frequent team meetings to enable staff to coordinate the components of treatment and manage transitions from day treatment to outpatient treatment smoothly.

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RELAPSE PREVENTION GROUP THERAPY FOR PATIENTS WITH COEXISTING SUBSTANCE USE DISORDER AND BIPOLAR DISORDER

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Although bipolar disorder is the Axis I psychiatric illness that places individuals at greatest risk for coexisting substance use disorder, there has been litlle research on the treatment of this population of dually diagnosed patients. As part of a NIDA Stage 1 Behavioral Therapies Development project, we have therefore been developing an integrated relapse prevention group therapy for this patient population. Patients with current bipolar disorder and substance use disorder were eligible for the project, consisting of a 12-week long therapy group. Each hour-long group consisted of a check-in period, followed by discussion of a topic that was relevant to both disorders (e.g., denial vs. acceptance of one's illness, dealing with family members, getting a good nights sleep). Outcome measures included substance use, medication adherence, and psychiatric symptoms. Patients were compared with a cohort of patients with the same diagnostic profile who received "treatment as usual." i.e., the therapeutic regimen prescribed by their treatment team, but without the group therapy. The group therapy was an "add-on" treatment, not a "stand-alone" treatment. Preliminary results indicate promise for the group therapy, particularly in the area of drug use and medication adherence.

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COMPARING TREATMENTS FOR DUAL DIAGNOSIS

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This research evaluated the effectiveness of two treatment models adapted for adults with a dual diagnosis: 12-Step and Rational Emotive Behavioral Therapy. The aims of the proposed research are to determine (1) to what extent these two treatment approaches are effective with this challenging population, and (2) whether subject characteristics will contribute to differential effectiveness of the two approaches. Subjects are randomly assigned to one of the two treatment modalities. These intensive day treatment programs created for the study meet five days a week, five hours a day, for six months. Number and types of groups are equivalent for the two programs. Thus far, data collection is in process for 105 clients. Preliminary results reveal the following subject characteristics: a) over 1/3 have a chronic medical problem, b) half are socially isolated, c) 113 are on probation, d) 96% have used substances an average of 10 years, e) 3/4 were rated as having moderate to extreme need for alcohol or drug treatment, and f) need for psychological counseling was rated moderate to extreme for all clients. The most frequent psychiatric disorder at intake is schizoaffective disorder followed by major depression and paranoid scizophrenia. However, proportionately more clients with paranoid schizophrenia graduate; clients with primary mood or thought disorder are most likely to graduate. No one with a primary personality disorder has yet graduated.

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COMPARISON OF OPIOID ABUSERS WITH INDEPENDENT VERSUS SUBSTANCE-INDUCED MAJOR DEPRESSION

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Depressive disorder is one of the more common psychiatric syndromes found among opioid abusers. A substantial proportion of the cases appear to be substance-induced conditions. This study compares the demographic and clinical characteristics and treatment outcome of 82 opioid abusers with a lifetime diagnosis of major depression. Patients were newly enrolled in opioid substitution therapy. Cases of major depression were first rated as either substance-induced (SI) or independent (LD) forms. Diagnoses were made using the Structured Clinical Interview for DSM-HI-R administered 3 to 4 weeks after admission. Major depression subgroups were compared on demographic and clinical characteristics and on several measures of treatment outcome. Six month treatment outcome measures include the ASI (baseline, months 3 and 6), random mine toxicology, and treatment retention. More patients were classified as having SI versus ID major depression (77% vs. 23%, $p<.001$), and the ID group contained a greater percentage of females (89% vs. 62%, $p=0.02$). The ID group also had a higher lifetime rate of anxiety disorder than the SI group (37% vs. 13%, respectively, odds ratio 0.345 (0.144-0.827)). Treatment retention over six months was greater in the ID versus SI group (95% vs. 76%, $p=0.017$). There were no significant differences between the two groups' overall rates of continued drug use during treatment, as determined by self-report and urine toxicology. These data suggest potentially important differences in characteristics and treatment retention, as well as some notable similarities in the characteristics and early treatment response among opioid abusers with lifetime substance-induced versus independent forms of major depression.

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VENLAFAXINE IN THE TREATMENT OF A POPULATION WITH MAJOR DEPRESSION AND COCAINE DEPENDENCE

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The link between depression and cocaine abuse is complex and has not yet been fully elucidated. We studied 13 patients who have both cocaine dependence and major depression. All patients were part of another larger double-blind trial using desipramine and had either not responded, or could not tolerate the side effects to desipramine. Thirteen patients were enrolled, 10 men and 3 women. The mean age was 37.5 ±7.3, all patients had a Hamilton Depression rating greater than 14 at baseline, and all patients had used at least $20 worth of cocaine per week in the four weeks before beginning the study. All patients received weekly relapse prevention therapy. Two patients dropped out one because of a side effect after a single dose, and one who despite significant improvement in his depression, elected to enter in patient treatment because of continued cocaine use. The remaining 11 patients had a significant reduction in mood symptoms with treatment. Hamilton score at baseline was 18 ± 3, Hamilton Score at week 6 was reduced to 1.6 ±1.4. Nine of 11 bad this response in the first week of treatment. Five patients achieved total abstinence, and the. rest had a greater than 75% reduction in cocaine use by self report as compared to baseline. The Clinical Global Improvement (CGI) scores were significantly improved at week 3, and this response was maintained through the remainder of the study. The median effective dose of venlafaxine for depression response was 150mg per day, and no serious side effects were reported. These results indicate that venlafaxine may be a safe, well tolerated, rapidly acting, and effective treatment for patients with depression and cocaine dependence

EFFECT OF IBOGAINE ON ETHANOL (ETOH) INTAKE A1ND MOTIVATED RESPONDING IN MALE WISTAR RATS

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Ibogaine has been shown to reduce morphine, heroin and cocaine self-administration in rats. To determine the effect of ibogaine on ETCH intake, male Wistar rats (n=8) trained on an FR4 schedule of ETOH reinforcement received injections of ibogaine (10, 20 and 40 mg/kg ip) 30 mins prior to the test session. Ibogaine produced a decrease in the number of ETOH reinforcers obtained ($F(7.21)=4.48$, $p=0.014$) and response rate ($F(7,19)=0.69$, $p=0.003$), while increasing the latency to obtain the first reinforcer ($F(7,21)=4.35$, $p=0.016$). An increase in ETOH motivated responding on the day following ibogaine treatment ($F(7,21)=3.56$, $p=0.032$) was noted. In 8 rats trained on an FR4 schedule of reinforcement for a 0.9% saline solution, a comparable profile of responding to that seen in the ETOH reinforced rats was obtained, and this was similarly affected by ibogaine i.e. decreased number of reinforcers obtained ($F(7,21)=15.1$, $p=0.001$) and response rate ($F(7.19)=26.9$, $p=0.001$), and increased latency to obtain the first reinforcer ($F(7,21)=8.0$, $p=0.001$). However, there was no effect on saline responding on the day following ibogaine treatment ($F(7,21)=0.5$, NS). These results demonstrate a pronounced ability of ibogaine to suppress ETOH self-administration. However, as similar effects were observed in saline reinforced tats, the effects of ibogaine on ETOH consumption may not be wholly related to modification of reinforcement processes, but may reflect a secondary effect due to motoric impairments.

SKILLS TRAINING FOR SUBSTANCE ABUSING SCHIZOPHRENIC PATIENTS

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Mast schizophrenic substance abusers either do not tolerate or are not helped by standard treatments for substance abuse. We adapted cognitive-behavioral drug relapse prevention strategies originally developed for non-mentally ill substance abusers by using a skills training method originally developed to teach social and independent living shills to schizophrenics. The intervention consists of three components: 1) Basic Training (eight psycho-educational sessions); 2) Skills Training (24 sessions to teach nine relapse prevention skills) and 3) practice Sessions (32 sessions paired with the other two kinds of groups during which patients apply newly learned knowledge and skills to real-life situations). Thirty-four patients with DSM-IV schizophrenia or schizoaffective disorder and co-occurring substance dependence completed a feasibility study. On a test of drug relapse prevention knowledge and shills (assessed through role-play), patients scored poorly before the intervention (X=40.9, sd=11.78), but made large and significant improvements by treatment completion (X=102.0, sd=12.63; F(33)=601.14, p<.0001). This improvement was maintained at three-month follow-up (X=99.6, sd=11.11). Days using cocaine, alcohol and marijuana in the prior month fell significantly and remained low at 3 month follow-up.

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SUBSTANCE USE, PTSD, AND ANGER MANAGEMENT TREATMENT

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High levels of anger are associated with posttraumatic stress disorder (PTSD). Reilly *et al.* (1995) reported that PTSD was associated with higher levels of anger in a sample of alcohol and drug users. Despite these higher levels of anger in patients with PTSD, reductions in anger across a 12-week cognitive-behavioral anger management treatment (AMT) were comparable to the reduction achieved in a group of drug and alcohol patients without PTSD. We are now examine the extent reductions in anger are correlated with abstinence from drugs and alcohol. A sample of 23 patients with PTSD were administered an AMT; patients bad a diagnosis of alcohol dependence and/or cocaine dependence. Levels of trait-anger and anger-expression were measured at baseline and at weeks 6 and 12 (n=11). Trait-anger and anger expression decreased significantly between baseline and the end-of-treatment ($p < .5$). Patients who completed AMT were more likely to remain abstinent during the 30 days post-AMT compared to patients who did not complete AMT (43% versus 63%). although this finding requires replication ($p = .13$). These findings suggest that reductions in anger may contribute to abstinence, and that further studies should be conducted to examine the causal role of anger in substance abuse patients.

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THE ROLE OF WEIGHT CONTROL AS A MOTIVATION FOR COCAINE ABUSE

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Heavy use of cocaine and alcohol in female cocaine abusers with eating disorders has been reported, but the prevalence and motivation for concurrent substance abuse has not been well investigated. To study this question, 40 males and 37 females between 18 and 48 years old who endorsed cocaine as their primary substance of abuse were administered the SCID for DSM-111-R the Eating Disorder Inventory (EDI), and the Diagnostic Survey for Eating Disorders-Revised (DSED-R). Items addressing weight control drugs were added to the DSED as were questions inquiring about reasons for beginning or maintaining cocaine use. The results showed that 49% of the 37 women used cocaine as a weight control measure while 13% of the males did the same. Thirteen of the 18 women endorsing weight related use of cocaine had a current diagnosis of an eating disorder. Only 2 males (5)% bad a past history of an eating disorder. Eleven (85%) of those women with a current eating disorder endorsed using alcohol as an appetite suppressant. Females were significantly more likely than males to endorse beginning use of cocaine for decreasing appetite (χ^2=5.39, p 0.02) and losing weight (χ^2=11.94, p 0.0005); females were also significantly more likely than males to continue using cocaine use for decreasing appetite (χ^2=5.65, p 0.01) and for losing weight (χ^2=10.53, p 0.001.) Significant difference also existed between males and females on the Drive for Thinness subscale of the EDI (F=5.8±6.14, M=1.6±2.1: p 0.0008.) These findings support the need to evaluate weight control in cocaine users and provide specific treatment aimed at addressing the interaction between the eating disorder and the substance abuse problem.

PSYCHOLOGICAL CORRELATES OF JOB-SEEKING BEHAVIOR

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Current welfare reform initiatives, which have eliminated economic benefits for many able-bodied individuals, have increased the competition for a limited number of jobs. At the same time, there remains an interest in examining factors that positively influence and promote job-seeking attitudes and behavior in both those who lose a job, as well as those who are chronically unemployed. Learned helplessness has been identified as one factor that might contribute to chronic unemployment. For example, Goldsmith et al. (1995) have suggested that low expectancy for a successful work search can contribute to a cycle of negative ideation leading eventually to a withdrawal from the work force altogether. The present study was conducted to see if we could identify factors associated with job-seeking behaviors in a substance dependent population. Subjects were a cohort of 120 unemployed males seeking admission to a 12-week, outpatient cocaine treatment program. Complete nine-month follow-up data was successfully obtained on 84 (70%) of these individuals. Twenty-nine (34.5%) were employed either part or full-time at the time of follow-up. Interestingly, time in treatment was not related to changes in job status. Discriminant function analysis, employing personality and demographic variables collected nine months earlier at admission, correctly differentiated those obtaining employment from those not in 75% of the cases, χ^2 = 28.52, p<.0001. Variables associated with failing to obtain a job included lower scores on the Generalized Expectancy for Success Scale, poorer abstract thinking as measured by the Shipley-Hartford Institute for Living Scale, a poor employment history, difficulties with alcohol, and being older.

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LONG TERM RESULTS OF PSYCHOSURGERY IN COCAINE-SMOKING DEPENDENCE

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Psychosurgery (PS) involves surgical modification of the brain with the goal of reducing the symptoms of the most severely ill psychiatric patients who have not responded adequately to less radical treatment. Currently, PS is indicated in some chronic obsessive-compulsive and/or depressive disorders. PS had been used to control addictive diseases and alcohol but never for cocaine dependence treatment. Medical records of 28 volunteers. 27 males, 1 women, cocaine(coca paste)-smoking-abuse patients (DSM-III criteria), mean age 23.6 years, 17 singles, with avg 4.7 times they have been hospitalized, avg 6.754 years of smoke cocaine(coca paste mixed with tobacco), avg 23.2 coca paste cigarettes per binge(contained avg of 95 mg of cocaine plus 4 mg of nicotine per cigarette), avg 4.6 relapses per week, avg 5 days of longest abstinence in the last year, with delinquential history (89.2%), submmited to PS(anterior cingulotomy, involving bilateral removal of about 3-4 cm of tissue in Brodmann's Area 24), during 1981-83, were reviewed. In 1983, subjects with avg 14.5±12.5 (27-2) months after PS showed 67.8% of recovery, relapse avg dropped to 1.6 per week ($p<.001$), avg of longest abstinence increase to 289±169 days ($p<.001$), and delinquential behavior fell to 37%. In the last review (1995-96). 42.8% (11 m, 1 w), maintains their abstinence, 10 showed no successful (4 were killed in delinquential acts, 2 are in prison), and 6 we did not have any information, Medical evaluation (included neurological) reveal no deficit or side-effects nor deaths imputed to PS. About the control group (11 coca paste addicted patients who did not accept to be submitted to PS), 2 subjects killed their father, 1 was killed by his father, 2 improved with standard treatments and 6 were unsuccessful. This is the first report about PS results after more than 15 years of follow-up. When we initiated PS treatment, there was not an agreement that the use of cocaine produced dependence, and because crack was not even consumed, it raised several medical controversies.

PSYCHIATRIC COMORBIDITY OF CRACK COCAINE USERS IN NON TREATMENT-RELATED STUDIES

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Few studies have systematically examined the psychiatric profiles of crack cocaine users who respond to advertisements for participation in non treatment-related research studies. This study analyzed data collected over 4 consecutive months from 121 respondents (55% mates) to the following advertisement: *Paid Volunteers. Healthy men and women. ages 21-35, for cocaine/hormone related studies. Blood sampling involved.* Only 37 of the 123 respondents to a telephone questionnaire admitted to using crack cocaine. Eighteen of these were not included in this study for a variety of reasons including head trauma, failure to report to lab and suicide ideation. Of the remaining 21 crack users, 67% were male and 53% were minorities. These subjects were given the SCID (DSM-IV version) by two doctorate level clinicians and detailed questionnaires regarding drug use, antisocial personality disorder, health status and demographic data. Of those who received a SCID, 61.9% had a lifetime diagnosis of polysubstance dependence, 42.8% mood disorder, 9.5% anxiety disorder, and 61.9% antisocial personality disorder. There data suggest substantial psychiatric comorbidity may occur in crack users participating in non treatment-related research studies and highlights the need for thorough screening by appropriately trained individuals.

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SCHEMA-FOCUSED COGNITIVE THERAPY FOR PERSONALITY DISORDERED SUBSTANCE ABUSERS

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The presence of an untreated personality disorder may lead to worse compliance and outcome in substance abuse treatment. Therapeutic attention to the symptoms of personality disorder may reduce the severity of substance abuse and other Axis I symptoms which potentially contribute to relapse. Specific behavioral treatment for antisocial and borderline personality disordered drug abusers are being tested, but there have been no systematic evaluations of integrated treatments of a more diverse range of personality disorders commonly seen in substance abusers. This 3-year NIDA-funded Stage I behavioral therapies development program study provides 24 weeks of individual cognitive therapy which integrates relapse prevention with work on early maladaptive cognitive schemas (enduring negative beliefs about oneself, others, and events). Ten pilot subjects in methadone maintenance have been enrolled, doctoral-level psychotherapists have been trained. treatment manuals and adherence/competence rating scales have been developed and the randomized clinical trial (comparing Schema-Focused Therapy versus 12 Step Drug Counseling in 30 participants) has begun. Four case studies (from different DSM-IV Axis II Clusters) illustrate diagnostic differences in psychopathology, personality, and interpersonal functioning, the experience of early maladaptive schemas, coping styles, and substance abuse and psychiatric outcome.

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PERSONALITY DISORDERS AND CRIMINAL ACTIVITY AMONG COCAINE ABUSERS

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The association between personality pathology and criminal activity is well documented. It is often assumed, however, that substance abuse modifies this relationship. That is, personality-disordered individuals commonly abuse drugs and alcohol which, in turn. might increase the probability of their engaging in violence and other crimes. This study investigated the independent contribution of personality disorder diagnoses and symptoms to criminal activity among crack cocaine abusers when controlling for the severity of drug and alcohol abuse. Categorical diagnoses of personality disorders were generated from the SCID-II which was administered within two weeks of intake. Subjects with no Axis II diagnosis served as controls and were compared to subjects diagnosed with any personality disorder, any Cluster B disorder, and Antisocial, Borderline, Paranoid, or Narcissistic personality disorder. Axis II data were also analyzed dimensionally using numbers of symptoms within various diagnostic categories. Results revealed that, holding severity of substance abuse constant, subjects diagnosed with Cluster B, Antisocial, Narcissistic, and Paranoid Personality disorders reported committing significantly more violent crimes, and those with Narcissistic personality disorder had greater ASI Legal Composite scores. Regression analyses revealed that Axis II symptoms accounted for substantial incremental variance in legal history above that accounted for by substance abuse. These data suggest that substance abuse does not explain most of the variance in aggressive and criminal behavior among cocaine abusers, and that ASPD is not the only Axis Il syndrome related to violence.

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PATHOLOGICAL GAMBLING IN COCAINE-DEPENDENT OUTPATIENTS

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Substance abusers have higher rates of pathologic gambling than the general population. Relatively little is known of the characteristics of co-morbid pathological gambling among cocaine abusers, with most prior studies done among alcoholics and polydrug abusers. We assessed the prevalence and characteristics of pathologic gambling among 313 cocaine-dependent (DSM-IIIR) outpatients (200 also opiate-dependent; no other current substance dependence except nicotine) who entered clinical trials of medication treatment for their cocaine dependence. Twenty-five (8%) subjects met DSM-IIIR criteria for current pathologic gambling (based on Diagnostic Interview Schedule), a higher prevalence than in the general population. Subject characteristics included mean age 35.6 years, 80% African-American, 24% female, 82% unemployed. 16% currently married, mean 11.5 years of education, mean age of onset of pathologic gambling 22.0 years and of cocaine dependence 25.1 years. Compared to the 288 other subjects, the 25 pathologic gamblers were significantly more likely to be unemployed (82% vs 49 %, but did not differ in other sociodemographic characteristics, age of onset of cocaine dependence (25.7 vs 25.1 years), length of stay in treatment, or proportion of cocaine-positive urine samples given during treatment, The 18 pathologic gamblers with concurrent opiate dependence had significantly longer duration of cocaine dependence than the 7 without opiate dependance (12.4 vs 6.6 years) and a higher proportion of cocaine-positive urine samples, but otherwise did not differ significantly. These findings suggest that pathologic gambling usually precedes development of cocaine dependence in outpatients with both disorders, but does not significantly influence treatment response, while concurrent opiate dependence may be associated with a poorer treatment response.
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INFLUENCE OF LIFETIME PROBLEM GAMBLING ON METHADONE TREATMENT OUTCOME

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Pathological gambling (PG) affects 1-346 of the general population but affects 8-15% of those with substance use disorders. Both substance use disorders and pathological gambling share similar behavioral characteristics and DSM-IV criteria. The relationship of PG on recovery from substance abuse is unknown. It was hypothesized that persons with lifetime PG (SOGS>3) would not do as well in treatment as those without PG. Patients (n=370) admitted to a outpatient methadone treatment program were evaluated using a comprehensive assesment battery at admission which included the SCID-P, SCID-II, ASI, South Oaks Gambling Screen (SOGS). All patients were then assigned one of four outcome ratings based on psychosocial functioning and weekly random urine drug screen analysis at discharge or nine months post admission. Patients rated "Highly Succesful" had significantly lower SOGS score ($F_{3,329}=3.02$, $p<.03$) than patients rated in the other three categories. Analysis of other contributing factors such as co-morbid psychiatric conditions are presented as well as the implications of this preliminary study such as the importance of screening methadone patients for PG and the possibility of a common underlying etiology such as an impulse control disorder.

DRUGS AND CRIME: COMMON AND DISTINCT ETIOLOGIES

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The overall aim of this research project is to examine the pathways from childhood through adolescence and young adulthood to drug use, crime, other problem behaviors and pathways to successful transitions. The Woodlawn prospective, developmental study of children provides an opportunity to examine how first grade social adaptational status, adolescent drug use and assault, social bonds, poverty, and other family circumstances influence the life course into adulthood. In 1963, Woodlawn was one of the poorest communities in Chicago; most residents were African American. All first grade children attending Woodlawn's nine public and three parochial schools were assessed (N=1242). They were followed as adolescents and most recently as young adults (N=953). Our analytic strategy used information gathered in the adult follow-up at ages 31-33 to construct homogeneous subgroups of individuals who had similar socioeconomic, behavioral, and psychological profiles. Using a standard agglomerative clustering procedure, the males and females were grouped separately in to seven clusters. We examine the childhood and adolescent family, social, and behavioral antecedents to these clusters. The clusters varied by problem behaviors and poverty. One cluster showed the overlap of substance use and interpersonal aggression, but other clusters showed high levels of one but not the other. Clusters with problem behaviors tended to be higher on poverty. However, not all poor clusters had high drug use/intetpersonal aggression. Continuity existed between drug use in adolescence and young adulthood. Early family origins were predictive of later poverty, however, there were important exceptions. First grade teacher ratings of aggression and shy-aggression distinguished mate clusters high on drug use and/or interpersonal aggression. Social bonds during adolescence were protective.

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ADULT DRUG ARRESTS AS AN INDICATOR OF JUVENILE DRUG ARRESTS: THE IMPLICATIONS FOR TREATMENT

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The purpose of this study is to evaluate patterns of drug arrests by the Federal Bureau of Investigation for the years 1979 through 1993 to determine if an increase in adult arrests results in a change in juvenile arrests. The 1,422,910 juvenile arrests and 11,807,894 adult arrests are categorized by either sale and manufacture (346,771 juvenile, 3,256,191 adult) or by possession (1,076,139 juvenile, 8,551,703 adult) of drug. Drugs are then categorized by 4 different classifications: 1.opiates, cocaine and derivatives; 2. marijuana; 3. synthetic narcotics; and 4. dangerous non-narcotics. Tie series regression analysis was used to include the influence of time. Increases in adult arrests are followed by a statistically significant increase ($p \leq .0001$) in juvenile arrests for sate and manufacture in Croups 1 and 4. The same pattern of adult and juvenile arrests is seen for sate and manufacture in Croup 3; however, the statistically significant relationship is not as strong. Only Group 1 shows a statistically significant relationship ($p \leq .0001$) of increasing adult arrests to increasing juvenile arrests for drug possession. Sale and manufacture of drugs is considered a more serious crime than possession. This results in greater efforts by the legal and law enforcement systems to punish these crimes. This is reflected in the time series regression model developed here. The model predicts arrests of adults and juveniles more often than for possession offenses. The model predicts juvenile arrests from adult arrests for possession of opiates, cocaine, and derivatives, the drug classification containing drugs often considered the most serious. In the U.S., society often feels that adults draw juveniles to crime. In all cases, this time series model indicates that juvenile arrests increase after adult arrests increase. An explanation is that the criminal justice systems focus first on adults for either sate and manufacture or possession arrests in any drug classification group. Since many individuals arrested on drug charges are also users who are required by the legal system to enter treatment, the arrest patterns may serve as reasonable indicators of age groups of persons and the change in classes of drugs for which arrested individuals will need treatment over time.

DRUG USE AND HIV RISK BEHAVIORS AMONG ADOLESCENTS DETAINED IN THE JUVENILE JUSTICE SYSTEM

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Data from 668 adolescents in juvenile facilities in 13 counties in California were analyzed as part of the California Juvenile Drug Use Forecasting Program. Analysis of the data show: (1) females made up 11.8% (n=79) and males made up 88.2% (n=589) of the sample, (2) the mean age was 16.1 years, and (3) the ethnic make-up was 24.4% African American (n=163), 25.4% White (n=170), 35.8% Hispanic (n=239). and 14.4% Other (n=96). Forty-one percent (n=262) tested positive for a single drug, and 9.9% (n=66) were positive for two or more drugs including marijuana (34.6%, n=231), amphetamines or methamphetamines (5.5%, n=37), cocaine (5.2%, n=35), PCP (1.6%, n= 11), and opiates (1.2%, n=g). Eighty-two percent (n=536) reported being sexually active with 64.5% (n=431) reporting having more than one sexual partner in the past year, 45.8% (n=306) were not using condoms regularly, and 47% (n=314) were usually high while having sex, three percent (n=20) had a history of injection of drug use, and 0.4% (n=3) reported a history of needle sharing. Urine testing indicated that nine males and no females were HIV-1 Antibody positive. Adolescents detained in the juvenile justice system are an important sub-group of at-risk youth in need *of* prevention and early intervention services for drug use and HIV infection among other problems. Stronger links between the correctional health and public health systems and comprehensive case management services in the community could improve access to substance abuse treatment programs, HIV education, and health and mental health services for these young people.

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FACTORS ASSOCIATED WITH CRIMINAL RECIDIVISM AMONG SUBSTANCE DEPENDENT INMATES

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Convictions related to drug and alcohol abuse have contributed greatly to the problem of prison overcrowding throughout the United States. Many of these inmates represent substance dependent individuals who are young, non-violent, and who pose a minimal threat to society. For these individuals, treatment may represent a better alternative than incarceration, for both them and for society. Moreover, substance abuse treatment may reduce one of the major frustrations in dealing with an addicted, criminal population -- recidivism. To this end, criminal recidivism data are presented for a group of approximately 500 substance dependent inmates who served the remainder of their prison term in community based treatment rather than in prison. Logistic regression analyses will be used to identify those factors most likely to be associated with rearrested for non-technical violations.

INCREASING EMPLOYMENT OF OPIOID DEPENDENT OUTPATIENTS: A NOVEL BEHAVIORAL INTERVENTION

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The present study assessed the impact of a new, mandatory employment requirement in a community-based methadone treatment program. Patients who had been treated on our methadone program for at least one year but who were not currently employed (n = 36) were required to enhance their treatment with 20 hr of employment (paid or volunteer). Patients with significant psychiatric or medical disabilities were excluded from the requirement Patients were informed by counseling staff that they had two months to secure employment. Those who did not comply within this time period were transferred to higher intensity treatment (i.e., more required treatment groups) for 10 weeks focusing on resistance to this intervention and were eventually started on a 21-day methadone detoxification until employment was verified. Seventy-five percent of the patients secured employment ad maintained the position for at least one month. Positions were found in an average of 60 days. Most patients (78%) continued working throughout the 6 month follow-up. Those who failed to find work or maintain employment engaged in more illicit drug use. These results demonstrate that behavioral contingencies can motivate many methadone maintenance patients to obtain verified employment in the community.

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HEALTH STATUS OF EMPLOYED PATIENTS AND PRE-EMPLOYMENT TRAINING PARTICIPANTS/NON-PARTICIPANTS IN METHADONE CLINICS

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Clinical observation of pre-employment training groups at methadone clinics indicated that a large proportion of the participants appeared to suffer from major illness, thus possible interfering with the ability to find and maintain work after completing this training. The literature suggested that clinical populations recruited from "street addicts" often have many serious health problems, but we were not aware of any studies that examined rates of physical health-related impairments that may limit the success of rehabilitation efforts. To begin to address this shortcoming, we examined the medical charts of 153 patients enrolled in two methadone maintenance facilities: 58 employed 50 unemployed who attended preemployment training, and 45 unemployed who declined to attend. The results of annual physicals were evaluated for systems impairment and overall ability to hold a job (pan-time, full-time, physical, non-physical) by a physician not employed by the clinics who was blind to the individuals' work status. There was little difference among the groups in individual system impairment. Surprisingly, when overall ability to hold a job was evaluated, those who were employed were almost universally found to be less able to do so than those who were unemployed. Those who were employed were found to be equally able to hold full-time work, but less able to hold part-time work (χ^2= 3.55, p = .06) and less likely to be able to hold non-physical work (χ^2 = 6.02, p<.05) while being no more likely to be able to do physical labor. Those who were employed when compared against those who were unemployed, were also found to be less able to hold any type of work at all (χ^2 = 4.67, p<.05). These results suggest that motivation to work is more important than physical health.

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COCAINE LEGALIZATION? DESIGNING EXPERIMENTS

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Cocaine legalization (CL) aims to make inexpensive cocaine available legally to drive out illegal dealers. With no experimental data popular-press articles promote CL (Buckley 1996). Drug-abuse scientists, wanting experimental data, largely avoid this debate. We explore methodoligic and ethical issues in CL studies. Non-Medical CL might change laws to increase cocaine availability to the level of OTC drugs, alcohol, or tobacco, aiming at crime reduction for society generally; increase harm to users themselves would be expected. However, our review suggest that this experiment would unacceptably increase the general prevalence of cocaine use, morbidity, and mortality. Another approach proposes non-treatment cocaine use-stations with free, unlimited cocaine for onsite use by certified addicts. Our review does not predict that this experiment would generally increase unacceptable morbidity and mortality in the stations. Medical CL would aim to benefit individual addicts by providing controlled doses as treatment in methadone-like clinics. This would not increase the prevalence of cocaine use. However, we review evidence that methadone doses induce opioid satiety, while cocaine may induce the cocaine craving; thus, clinic doses of cocaine might stimulate (rather than reduce) the demand for street cocaine. Moreover, to compete with street dealers cocaine clinics would need to provide higher doses at lower cost, raising the probability of significant medical and behavioral toxicity in these outpatients. Thus, the risk/benefit ratio precludes this experiment. We conclude that the probability of adverse effects properly blocks experiments on cocaine legalization.

PREVALENCE OF DRUG ABUSE AMONG DEAF PERSONS: SURVEY METHODS AND PRELIMINARY RESULTS

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Hypothesis: It has been hypothesized that deaf individuals use illicit drugs at higher rates than the general hearing population. To date, this subject has not been investigated. **Method:** A computerized video survey in which questions are available in two sign language modalities, speechreading, and English captions was developed in order to facilitate understanding and clarity for deaf persons. Respondents answered questions directly, input by computer touchscreen. Thus, the system has the desirable features of having standardized questions delivered by a person (the signer or speechreader on screen) as well as the anonymity of a self-administered questionnaire. **Interim results:** three hundred sixty-Iwo deaf subjects were recruited via targeted sampling techniques, primarily in New York State. Self report of lifetime use of marijuana was 39%, cocaine, 13%, heroin, 2%, hallucinogens 6%, for all ages and gender groups combined. Further analyses by subgroup and comparisons between deaf and hearing populations on recent and lifetime use of each drug will be presented.

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A META-ANALYSIS OF DRUG ABUSE TREATMENT EFFECTIVENESS: PRELIMINARY RESULTS

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The effectiveness of drug abuse treatment is a question that continues to be raised in policy discussions of public funding for treatment and within the context of health care reform and managed care. The current study uses meta-analytic techniques 10 code and analyze treatment effectiveness studies conducted in the United States and Canada since 1965 that meet specified eligibility criteria. The overall objectives of the project are to describe the history and current state of research on drug treatment effectiveness, to cumulate effect sizes across studies ("What is the magnitude of the effect of treatment on specific outcomes?"), and to identify factors associated with treatment effectiveness ("What seems to work, with whom, under what conditions?"). In this preliminary analysis of 102 studies (out of an estimated 380 to be coded), estimated weighted average effect sixes are reported for selected outcome measures by treatment type. The results are further divided into single-group designs and treatment-control group designs. For me stronger treatment-control group designs, average effect sizes ranged from .22 to .49 for substance abuse outcome measures, from -0.13 to .41 for crime measures, and from .16 to .40 for employment and education measures. The fact that the homogeneity test (Q) was rejected for most of the effect sizes indicates that additional categorical or multivariate analyses are needed to identify variables that account for the variation in effect size. Analysis of the full dataset will result in more precise and reliable effect size estimates and in the identification of moderator variables that might be useful in program design or policy decisions.

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A META-ANALYSIS OF DRUG ABUSE TREATMENT EFFECTIVENESS: STUDY CHARACTERISTICS AND METHODOLOGY--PRELIMINARY RESULTS

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The effectiveness of drug abuse treatment is an issue that continues to be raised in debate over public funding for treatment services, health care reform, and managed care. This study reports partial and preliminary findings of a meta-analysis of studies of treatment effectiveness that were conducted in the United States and Canada since 1965 and which satisfy certain eligibility criteria. The results are based on the first 102 studies to be coded out of an estimated 380. The overall objectives of the project are to describe the history and current state of research on drug abuse. treatment effectiveness, to calculate the magnitude of treatment effects on specific outcomes (i.e., the effect size), and to identify factors associated with effective treatment.

Based on an analysis of the first 102 cases, this study found that studies varied in the amount of information they reported. All studies provided sufficient information to determine their basic methodology, but they did not always report data on the demographics of the sample (e.g., age, ethnicity, gender) or describe the treatment being evaluated in detail. It also found that the studies were heterogeneous. The evaluations were evenly split between those with a pre-experimentai design and those with a true experimental or quasi-experimental design. Studies also covered a wide range of treatment modalities and techniques. Other preliminary findings include: most samples were primarily male; Hispanics were represented less than Whites or Blacks; studies were concentrated in just 19 states; and heroin was the primary drug problem in most studies.

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ON METHODS FOR THE ANALYSIS OF LONGITUDINAL DATA FROM CLINICAL TRIALS

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A variety of statistical approaches for the analysis of 2-group longitudinal designs are available to the investigator. We used derived calculations and computer simulations to compare the statistical power of six analytic methods; Student's t-test and Mann-Whitney-Wilcoxon rank test on mean least-squares regression slopes estimated for each subject, and on pre-post differences, multivariate repeated measures analysis of variance (MANOVA) and mixed-model analysis of variance. Comparisons were made under conditions of sample size, number of assessments, and dropout rates common to substance abuse research. Factors included effect size, attrition pattern, sample size, and visit-to-visit correlation levels. Results indicated that simple method often show the best power for detection of simple (i.e., linear) effects. The use of slope estimates as summary statistics were surprisingly poor under intent-to-treat. The MANOVA performed poorly (relatively) due to 'wasting' of degrees-of-freedom. Levels of assessment-to-assessment correlations mattered little but effects MANOVA and the use of slope estimates under MT.

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EFFECTS OF SYMMETRY VIOLATIONS AND MISSING DATA: TYPE I ERROR FOR MAXIMUM LIKELIHOOD AND LEAST SQUARES ANALYSES

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Missing data occur in nearly every longitudinal study carried out to evaluate the effectiveness of proposed treatments for substance abuse. Two major problems associated with analyzing longitudinal data using a traditional Repeated Measures ANOVA approach are missing data and violations of the sphericity (or compound symmetry) assumptions. Maximum likelihood procedures for analyzing longitudinal designs with missing data are becoming more prevalent. These programs (e.g., BMDP 5V) allow the user to specify the covariance structure to be modeled However, in some packages, compound symmetry is the default. Unless the researcher has prior knowledge, an incorrect covariance model may be used or the data must be analyzed using several covariance models and the best fitting model chosen. As part of an ongoing series of Monte Carlo analyses, two patterns of non-symmetry are used to assess Type I (alpha) error associated with Repeated Measures ANOVA/ANCOVA and Maximum Likelihood analysis strategies. The pattern and degree of missing observations, the pattern of the covariance structure, and the sample size have been assessed for their effects on Type I error rate, in a two-group, five repeated measures design. Type I error data will be presented for two linear dropout rates (20% and 60%), two missing data rates (10% and 33%), and two sample sizes (n=15, 45 per group), under symmetry and two patterns of non-symmetric covariance matrices. Type I Error for Maximum Likelihood results are inflated over nominal alpha levels under conditions where compound symmetry is not met.

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CAN MATCHING THEORY DISTINGUISH THE MOTIVATIONAL AND THE MOTORIC EFFECTS OF DRUGS?

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Matching theory states that response rate increases hyperbolically with increases in reinforcement rate. An interpretation of the equation that describes this function requires that one estimated parameter, *k,* reflects the total amount of behavior possible in a given environmental context. and another parameter, r_1, reflects the motivational level of the organism. The use of matching theory to distinguish the motoric and the motivational effects of drugs is premised on this interpretation. This interpretation, referred to as the response strength interpretation, requires that any variation in the value of the reinforcer should leave the value of *k* unchanged. Therefore, the key to falsifying the response strength interpretation of matching theory is to show that *k* varies with reinforcer value. The present experiment varied reinforcer value by manipulating deprivation level (Experiment 1) and the concentration of sucrose in water (Experiment 2). Rats responded on a series of VI schedules at each level of reinforcer value. The hyperbola was fitted to the response and reinforcement rates produced at each level of reinforcer value, and the parameter *k* was determined. Results show that *k* varied across reinforcer value. The study suggests that the current response strength understanding of matching theory is not accurate, and it calls into question the ability of matching theory to distinguish the motivational from the motoric effects of drugs.

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NEUROPSYCHOLOGICAL ASSESSMENT OF DRUG ABUSE: RESEARCH ISSUES

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Research findings suggest illicit drug abuse may alter the neurobiology and neuropsychological processes of addicted human beings. This paper will review research on the residual effects of drug abuse and discuss the research studies that are needed to elucidate the neuropsychological correlates of the effects of abused drugs. Suggestions will be made regarding scientific issues involved in designing studies to assess the specific drugs of abuse. In addition, conceptual issues regarding neuropsychological assessment will be discussed. Also. issues regarding identification of concurrent comorbid psychiatric conditions in drug addicts will be clarified. Recommendations for specific batteries of neuropsychological tests to be used in clinical research studies will be provided.

Key Words: neuropsychology, drug abuse, residual effects, cognition

KNOCKOUT TRANSGENIC MICE: MU OPIOID RECEPTOR, DOPAMINE AND SYNAPTIC VESICULAR TRANSPORTERS

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The dopamine and synaptic vesicular monoamine transporters (DAT and VMAT2) accumulate dopamine and serve as targets for cocaine and amphetamine actions. The mu opioid receptor (MOR) is linked with morphine analgesia and reward. To further investigate the roles of these proteins in drug actions, we isolated murine 129 genomic clones for each and produced transgenic mice deleted in 1 (all viable) or 2 gene copies (DAT and MOR viable) that each revealed modest adaptive changes in other neurochemical systems. Drug responses in these animals reveal dramatic dependence of morphine analgesia and conditioned place preference reward on MOR expression, dependence of cocaine reward on DAT expression, and requirement for full DAT and VMAT2 expression for full amphetamine reward. Heterozygous mice revealed interesting consequences of reducing expression levels to half of wildtype values. These mice add significantly to our understanding of molecular sites for behaviorally-significant drug actions in the brain, and suggest substantial consequences of genetic differences in expression of these drug target sites.

COMT, DRD3 AND DRD4 GENE MARKER FREQUENCIES IN POLYSUBSTANCE ABUSERS AND CONTROLS

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Allelic variants at the dopaminergic gene loci are candidates to contribute to genetic components of interindividual differences in vulnerability to substance abuse. COMT (catechol-O-methyltransferase) degrades dopamine while D3 and D4 G-linked receptors recognize it. COMT alleles encode enzymes whose activities vary 3-4-fold. DRD4 alleles encode receptors that may differ in G-protein coupling efficacies. Comparisons of allele frequencies in nonusing control research volunteers to those in volunteers reporting substantial polysubstance use revealed that users displayed significantly more homozygotes for the high activity COMT allele, a trend toward more long-repeat DRW variants, and no difference in DRD3 markers. Dopaminergic gene variants are candidates for contributions to interindividual differences in vulnerability to substance abuse.

CART PEPTIDE IMMUNOHISTOCHEMISTRY IN THE RAT

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CART mRNA is a novel transcript that is increased after psychostimulant administration in brain, The predicted CART peptide contains a leader sequence and several pairs of basic amino acids suggesting that it is processed and released. We have made polyclonal antisera against several peptide fragments that span the parent polypeptide (we acknowledge Drs E. DeSouza and N. Ling for some peptide synthesis). Using immunostaining, we found CART peptide immunoreactivity in the same cell groups that contain CART mRNA which indicates that the mRNA is translated. These immunoreactive cells were found throughout the brain and in the pituitary and adrenal medulla. Antisera raised against several peptide fragments showed somewhat different staining patterns, suggesting that the full length CART peptide is processed into smaller peptides. These data suggest that CART peptides ate putative neurotransmitter/cotransmitters involved in several physiologic processes including feeding, drug reward, autonomic control, sensory function and stress responses.

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RAT STRAIN DIFFERENCES IN SENSITIVITY TO THE ANTINOCICEPTIVE EFFECTS OF MU OPIOIDS

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The antinociceptive effects of the mu opioids levorphanol, morphine, buprenorphine, butorphanol and nalbuphine were assessed in rat strains using a hot water tail-withdrawal procedure. These drugs were chosen to cover the range of intrinsic efficacy at the mu receptor, from relatively high (e.g. levorphanol and morphine) to relatively low intrinsic efficacy (e.g. butorphanol and nalbuphine). Sensitivity to the antinociceptive effects of higher efficacy opioids did not differ across rat strains. In contrast. sensitivity to the effects of lower efficacy opioids varied greatly across the four strains of rats. For example, in 50 degree water, butorphanol and nalbuphine produced maximal or near maximal effects in Fischer 344 and Sprague-Dawley rats. In Long-Evans rats, butorphanol and nalbuphine produced half-maximal effects. Whereas in Lewis rats, no antinociception was observed when tested with butorphanol or nalbuphine. The pattern of results was similar when tested in 52 degree water; however, the absolute level of antinociception was consistently lower. These results indicate that the level of antinociception produced by mu opioids depend not only on the intrinsic efficacy of the drug and the water temperature, but also on the strain of tat employed.

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NOVEL CART PEPTIDES - A PSYCHOSTIMULANT-LIKE BEHAVIORAL PROFILE

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CART is a novel, interesting mRNA that is increased by acute psychostimulant drug administration. Immunolocalization has identified CART peptides in specific brain regions associated with the control of locomotion and feeding such as the nucleus accumbens, paraventricular nucleus of the hypothalamus and the amygdala. An endogenous role(s) for CART peptides has yet to be identified and the aim of this study was to examine the effect of CART peptide fragments (ICV) and central immunoneutralisation of endogenous CART peptides on food intake (FI) and locomotor activity (LA). Mate Sprague-Dawley rats were cannulated ICV and divided into groups (n=4-12). Each of four groups received one of three peptide fragments (Frag 1, 1a or 1b) or saline ICV just prior to lights out and FI (g) in the first 2 hours of the dark phase was measured. The dosing was repeated but following ICV injection food was withdrawn and LA (m) in the first 2 hours of the dark phase was recorded. CART Frag 1 decreased FI (3.2±0.2g*) and increased LA (387±118m*) compared to injection of saline (4.1±0.3g; 160±30m). However, Frag 1 specifically increased LA (464m*) with no effect on FI (4.5±0.4), whereas Frag 1b specifically decreased FI (2.6±.0.3g*) with no effect on LA (153±36). * indicates significant difference from saline $p<0.05$. Interestingly, ICV injection of polyclonai antibodies raised against CART peptide fragments significantly increased FI and attenuated cocaine-induced locomotor activity compared to injection of pre-immune serum. By dividing the larger peptide (Frag 1) into two smaller fragments (Frag 1a and 1b), at a possible *in vivo* cleavage site, peptides were isolated with selective effects on either activity or food intake. lmmunoneutralisation studies suggest a role for CART peptides in the mechanism of action of cocaine-induced locomotor activity and in the central control of food intake. This is the first evidence for centrally-mediated effects of CART peptides.

INCREASED BREAK-POINTS ON PR SCHEDULE REINFORCED BY IV COCAINE IN 5-HT1B RECEPTOR KNOCKOUT MICE

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The present experiment tested the hypothesis that serotonin 5-HT1B receptors are implicated in the reinforcing efficacy of cocaine. For this purpose, 129/Sv-ter mate mice lacking 5-HT1B receptors (knockout mice; n=12) and the wild-type (n=7) were tested in cocaine IV self-administration in a progressive ratio (PR) schedule. Subjects were initially trained to press a lever for fond as a reinforcer, and subsequently implanted with a permanent indwelling jugular catheter. Two days after surgery, mice started cocaine (2.0 mg/kg/inj) self-administration acquisition under a fixed ratio 1 (FR1) schedule. Once acquisition criteria (75% of active lever pressings and at least 16/20 injections within 3-b for three consecutive days) was obtained, mice were switched to the PR schedule, and allowed to self-administer cocaine for 3-h, upon completion of each ratio, in an exponential sequence from 2 to 603. Once stability under the PR schedule (number of reinforcers per session not differing by more than 2, for three consecutive days) was obtained, mice were tested with different doses of cocaine (0.5-4.0 mg/kg/inj); one dose per day, over three consecutive days. Knockout mice obtained a significant higher number of reinforcers than the wild-type at all doses tested. An univariate analysis (ANOVA) confirmed a significant effect between genotypes ($F(1,8)=7.21$; $p<0.05$). These results suggest that 5-HT, through activation of 5-HT1B receptors, plays an inhibitory role in the reinforcing efficacy of cocaine.

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EFFECT OF CHRONIC 'BINGE' PATTERN COCAINE ON THE 5-HT2A AND 5-HT1A RECEPTORS IN THE RAT BRAIN

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The effect of chronic cocaine exposure on the central serotonergic system in the rat was investigated using ketanscrin, a selective 5-HT2A receptor antagonist, and 8-OH-DPAT, a selective 5-HT1A receptor agonist, as tritiated ligands in a quantitative autoradiography study. The regions analyzed include frontal, parietal, agranular insular and piriform cortex, caudate-putamen, olfactory tubercle, nucleus accumbens, thalamus, hypothalamus, hippocampus, dentate gyrus, dorsal raphe, septohippocampal nucleus and claustrurn No signficant difference in the binding of ketanserin was found in any brain region but a significant decrease of the binding of 8-OH-DPAT was found in the ventromedial hypothalamus (t-test: $p<0.001$) and the dorsal dentate gyrus (t-test: $p<0.05$) in the rats administered with cocaine in a "binge" pattern (14 days, 15mg/kg/injection) as compared with rats administered with saline. It is known that 5-HT1A receptors modulate HPA axis activity and are probably involved in depression and anxiety. These data suggest that the 5-HT1A receptors may be involved in the change of the HPA activity and may participate in the psychiatric manifestation following chronic cocaine administration.

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DOSES OF GBR12909 WHICH SUPPRESS COCAINE SELF-ADMINISTRATION IN NONHUMAN PRIMATES SUBSTANTIALLY OCCUPY DA TRANSPORTERS

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GBR12909 (GBR) is a high affinity, selective and long-acting inhibitor of DA uptake which has been proposed as a potential treatment agent. GBR produces a persistent and noncompetitive blockade of DA transporters and substantially reduces cocaine-induced increases in extracellular DA. Slow i.v. infusion of GBR to Rhesus monkeys selectively reduced (1 mg/kg) and eliminated (3 mg/kg) cocaine self-administration. This study tested the hypothesis that doses of GBR which reduce cocaine self-administration in nonhuman primates produce significant occupation of DA transporters. DA transporters were quantitated in two baboons using [11C]WIN35,428 and PET. The baboons underwent four PET scans (performed on two separate study days, 3-4 weeks apart). Blood pressure, temperature, heart rate and oxygen saturation were monitored throughout each study. On the first scan of the first study day the baboon received saline (3 ml/kg) 90 min before the injection of the radiotracer. GBR (1 mg/kg i.v.) was infused 90 min before the second [11C]WIN 35,428 study. The second study (34 weeks from the first study day) was conducted identically to the first study, except that the dose of GBR was 3 mg/kg. Doses of 1 (n=1) and 3 mg/kg (n=2) produced % reductions of binding potential of 18 and 53%, respectively. GBR was welI tolerated in all baboons. One baboon showed transient bradycardia (that lasted less than 5 min) immediately after the injection of 1 mg of GBR. No changes in blood pressure or oxygen saturation were observed in any of the baboons. These results demonstrate that doses of GBR which suppress cocaine self-administration in nonhuman primates also produce high occupancy of the DA transporter. Viewed collectively with other work, these data strongly suggest that occupancy for the DA transporter by GBR explains its ability to attenuate cocaine-induced increases in extracellular DA and to suppress cocaine self-administration. Moreover, these data suggest that clinical trials (planned) of orally administered GBR should use doses which produce at least 50% occupancy of the DA transporter.

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REDUCTIONS IN DOPAMINE TRANSPORTER AND D_1 RECEPTOR BINDING AFTER CHRONIC GBR 12909

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Chronic continuous infusion of cocaine produces partial behavioral tolerance to cocaine and tolerance to the inhibition of dopamine uptake. by cocaine, without changing dopamine transporter binding. The selective dopamine uptake inhibitors GBR 12909 and RTI-117 also produce partial behavioral tolerance, but their chronic effects on the dopamine system are unknown. GBR 12909 (25.8 mg/kg/day), RTI-117 (3.62 mg/kg/day), cocaine (50 mg/kg/day), or vehicle were continuously infused into male Sprague-Dawley tats via osmotic minipump. The pumps were removed after seven days of infusion, and 24 hours later, [^{125}I]RTI-121 and [^{3}H]SCH 23390 binding were assessed using autoradiography for dopamine transporters and dopamine D_1 receptors, respectively. [^{125}I]RTI-121 binding was decreased in both caudate putamen and nucleus accumbens of GBR 12909-treated rats, while cocaine and RTI-117 slightly inreased [^{125}I]RTI-121 binding. Similarly, only GBR 12909 significantly reduced [^{3}H]SCH 23390 binding in both brain regions, despite continuous dopamine uptake blockade by all the drugs. Thus, the combination of a decrease in the number of transporters, along with blockade of uptake leads to a large excess of synaptic dopamine, which in turn appears to down-regulate dopamine receptors. These findings suggest that GBR 12909 interacts with the dopamine transporter in a qualitatively different manner from that of cocaine and its analogs.

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IRREVERSIBLE LIGANDS BASED ON RIMCAZOLE AS PROBES FOR THE DOPAMINE TRANSPORTER

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Dopamine transporter (DAT) heterogeneity is demonstrated by high and low affinity components of binding and dopamine uptake, by cocaine and cocaine analogs. Previous studies have suggested that these different components play distinct functional roles in the behavioral effects of cocaine. Studies indicate that the high affinity component is related to the psychomotor stimulant actions of cocaine. Rimcazole is a sigma ligand that is not a psychomotor stimulant, and indeed attenuates the locomotor stimulant actions of cocaine. Rimcazole binds to the DAT monophasically and it has been hypothesized that it may be interacting exclusively at a low affinity component of the DAT. We have prepared irreversible ligands based on the rimcazole structure in which the alkylating moiety (iothiccyanate, NCS) is attached to the distal nitrogen of the piperazine ring via alkyl chains of varying lengths, or directly attached to one of the aromatic groups. Importantly, the analog with the highest affinity for the DAT binds in a monophasic and irreversible manner, as evidenced by the greatly diminished binding of [^{3}H]WIN 35,428 in tissue that had been pre-incubated with the ligand and then thoroughly washed using centrifugation. We dose dependent reduction in B_{max} occurred without change in the K_d, which is indicative of irreversible binding. In conclusion, these ligands may prove to be important tools with which to study the significance of the low affinity site on the DAT. Because rimcazole does not share the behavioral profile of cocaine, and in fact appears to play a modulatory role, these compounds may provide leads for a novel cocaine-abuse treatment.

SYNTHESIS AND MOLECULAR MODELING OF NOVEL AROMATIC SUBSTITUTED 3α-DIPHENYLMETHOXYTROPANE ANALOGS

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A previously prepared series of *para* and *meta* substituted-α-diphenylmethoxy-lα H,5α-H-tropane analogs has been shown to contain compounds that are selective, high affinity probes for the dopamine transporter. Inspection of the structure-activity relationships (SAR) within this series of compounds via molecular modeling has indicated that these aromatic substituents play an important role in the potency and selectivity of these compounds. A cross-validated CoMFA model of the binding domain on the dopamine transporter was constructed using this series of compounds (predictive r^2=0.722). To further explore the optimal structural requirements for potent and selective dopamine transporter binding, and thus further enhance the model of this binding site, additional compounds containing particular aromatic substitution patterns were synthesized The compounds were evaluated for inhibition of [^{3}H]WIN 35.428 binding at the dopamine transporter and [^{3}H]dopamine uptake in rat caudate putamen. ln general, most of the newly prepared compounds were more potent in inhibiting WIN 35,428 binding (range=23-187 nM) and dopamine uptake (range=139-795 nM) than either cocaine or benztropine. Based on this model, it appears that relatively large, electron withdrawing groups are not favored at this binding site. The experimentally determined binding and uptake results of these compounds agreed well with predicted values from the CoMFA model. Overall, it can be seen that substitution of a small halogen on one or both phenyl rings results in compounds with highest potency at the dopamine transporter. These findings provide additional SAR at the dopamine transporter and may provide leads toward the development of novel cocaine therapeutics.

SYNTHESIS AND TRANSPORTER BINDLNG PROPERTIES OF 3α-(SUBSTITUTED PHENYL)TROPANE-2β-CARBOXYLIC ACID ESTERS

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Several 3α-(4-substituted phenyl)tropane-2β-carboxylic acid esters (**1**) were synthesized, and their transporter binding properties compared with analogous 3β-(4-substitued phenyl)tropane-2β-carboxylic acid esters (**2**), most analalogs of 1 show a marked increase in selectivity for the dopamine transporter (DAT) relative to the 5-HT transporter with only a modest drop in potency at the DAT. These results were unexpected as allococaine (**3**) is 60-fold less potent than cocaine (**4**) at the DAT. NMR studies suggest that the These results were unexpected as NMR studies suggest that the 2α,3β-compound 1 exists predominantly in the boat conformation. Molecular modeling studies will be presented to assist in the interpretation of the binding data.

FUNCTIONAL SELECTIVITY AT THE D_2 DOPAMINE RECEPTOR: DEPENDENCE ON MINOR AGONIST STRUCTURAL CHANGES

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It is widely accepted that a major factor in the reinforcing effects of cocaine and some amphetamine-like drugs is their facilitation of dopamine neurotransmission (e.g., increasing synaptic concentrations of dopamine). Thus, the ability to activate pre- and postsynaptic dopamine receptors selectively could be a useful tool in the treatment of individuals abusing these drugs. The present study is an extension of previous work utilizing the D_2 agonist dihydrexidine (DHX) and several of its analogs, compounds that have unusual D_2-like functional profiles. In rat brain preparations, DHX ($K_{0.5}$ = 100 nM in rat striatum) has agonist properties at functions mediated by "postsynaptic" D_2 receptors (e.g., inhibition of striatal adenylyl cyclase), but no agonist effects in D2-mediated "presynaptic" functions (e.g., inhibition of nigral cell firing, or inhibition of dopamine synthesis or release), despite the fact that DHX binds with similar affinity to both pre- and postsynaptic receptors. Previous studies using D_2-transfected MN9D cells, a clonal mesencephalon-derived line that can synthesize and release dopamine (making it a model of dopamine neurons), showed similar "functional selectivity" of DHX and its analogs in this cell line transfected with a single dopamine receptor isoform. In MN9D cells, DHX and its analogs inhibited adenylyl cyclase to the same extent as other full D_2 agonists, but not only failed to inhibit depolarization-induced [^{3}H]dopamine release, but actually antagonized the activity of other agonists. Conversely, dinapsoline, a compound structurally similar to DHX, does not exhibit this functional selectivity. acting as an agonist at both of these measures. Dinapsoline is strikingly similar to DHX in terms of the key 3-D pharmacophoric elements believed to be. responsible for binding to dopamine receptors, differing only in subtle changes to the drug backbone. These data suggest that minor structural changes that do not affect binding to the receptor can have significant effects on the functional consequences of drug-receptor interaction, and may determine whether a compound interacting with a single receptor isoform causes agonist or antagonist functional effects.

[^{3}H]COCAINE BINDING TO HUMAN HIPPOCAMPUS AND AMYCDALA: DISSOCIATION FROM TRANSPORTERS

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Brain regions rich in dopamine are principal targets of cocaine after i.v. administration. Nevertheless, high levels of cocaine also accumulate in the amygdala and hippocampus (Madras and Kaufman, 1994). We profiled these sites in human brain, using a high specific activity form of [^{3}H]cocaine. Although technically difficult, radioreceptor assays revealed saturable and moderately high affinity [^{3}H]cocaine binding sites in the amygdala and hippocampus. As in striatum, [^{3}H]cocaine binding was inhibited in the nanomolar range by cocaine congeners that block dopamine transport (WIN 35,428, dichloropane, RTI-55, norcocaine). However, other dopamine, serotonin or norepinephrine transport inhibitors, including mazindol, GBR12909, difluoropine, citalopram, talsupram were weak inhibitors of [^{3}H]cocaine binding, as were dopamine, serotonin, and norepinephrine. The data indicate that the majority of cocaine binding sites in the hippocampus and amygdala are not associated with monoamine transporters. Although the nature of these tropane recognition sites is not known, the rank order of potency of the compounds wig facilitate evaluation of their pharmacological relevance.

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COCAINE INTERACTIONS WITH LUTEINIZING HORMONE

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Although cocaine is known to affect basal levels of anterior pituitary hormones, there has been relatively little attention to the possible effects of the hormonal milieu on the acute effects of cocaine. It is generally acknowledged that cocaine's reinforcing effects reflect its activities on the dopaminergic system. Cocaine acts as an indirect dopamine agonist and binds to the dopamine transporter to block dopamine reuptake. There has been considerable interest in using dopamine receptor selective agonists and antagonists to antagonize or to substitute for cocaine's effects, characterization of the dopamine transporter by Kuhar and co-workers indicates that it is a glycoprotein of which approximately 20 percent is carbohydrate. The anterior pituitary hormone, luteinizing hormone (LH) is also a glycoprotein, and it's carbohydrate side chains that are very similar to those found on the dopamine transporter. This structural similarity suggested that LH might bind to cocaine in blood. We now report that stimulation of LH release by administration of synthetic luteinizing-hormone-releasng-hormone (LHRH) to four male rhesus monkeys resulted in a LHRH dose-dependent decrease in peak plasma cocaine levels. After intravenous administration of placebo-LHRH and 0.8 mg/kg of cocaine, peak cocaine plasma levels averaged 479 (±135) ng/ml. Whereas after administration of 15 and 30 mcg/kg/iv of active LHRH, peak cocaine plasma levels averaged 278 (±90) and 183 (±56) ng/ml. There was a significant ($P<(0.01)$ negative correlation between plasma cocaine and LH levels. These studies are in progress.

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REPEATED ADMINISTRATION OF A SELECTIVE KAPPA-OPIOID RECEPTOR AGONIST DECREASES DOPAMLNE TRANSPORTER NUMBER IN THE NUCLEUS ACCUMBENS OF THE RAT

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It has previously been shown that the selective κ-opioid receptor agonist U69593 prevents long-term alterations in behavior which occur following repeated administration of cocaine, Recent data have shown that it also attenuates alterations in dopamine uptake and release which occur during abstinence from cocaine. The site and mechanism by which κ-agonists modulate the actions of cocaine; however, remains unclear. Accordingly, the present study evaluated the influence of U69593 upon dopamine transporters. Male Sprague-Dawley rats received once daily injections of U69593 (0.04-0.32 mg/kg) for five days, after which binding of [^{3}H]WIN 35,428 to the dopamine transporter was measured in the caudate putamen and nucleus accumbens. Saturation curves using increasing concentrations of labeled ligand were constructed and analyzed via Scatchard transformation so that K_D and B_{max} values could be determined. The number of dopamine transporters was dose-dependently reduced in the nucleus accumbens 3 days following the cessation of U69593, with no change in affinity for [^{3}H]WIN 35,428. In contrast, U69593 treatment failed to modify transporter binding in the caudate putamen. These data demonstrate that the repeated administration of a selective κ-opioid receptor agonist produces alterations in dopamine transporters within the nucleus accumbens and that this effect is regionally specific. They further suggest that the interaction of k-opioid receptor agonists with cocaine is mediated presynaptically, at the level of the dopamine transporter.

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EFFECTS OF U69593, A K-OPIOID AGONIST, ON D2 AGONIST-INDUCED INHIBITION OF DOPAMINE DYNAMICS IN THE DORSAL STRIATUM

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the acute and sensitized locomotor stimulant effects of cocaine in rats can be blocked by repeated prior administration of the selective κ-opioid receptor agonist, U69593. Although the mechanism by which U69593 interacts with effects of cocaine is unknown. there is accumulating evidence that K-agonist treatment reduces mesolimbic dopamine concentrations and that chronic treatment downregulates dopamine receptors in mesolimbic regions. The present studies were undertaken to further explore the effects of a 3-day, once daily U69593 treatment on acute responses to the D2/D3 dopamine receptor agonist, quinpirole, using *in vivo* microdialysis and locomotor activity measures. Following implantation of microdialysis cannula in the dorsal striatum, each rat was allowed 5-7 days of recovery and was then treated with 0, 0.10 or 0.32 mg/kg/day U69593 on experimental days 1-3. On day 5, basal dialysate samples were taken for 1.5 hours, followed by an acute challenge with 0.05 mg/kg quinpirole SC. Dialysate samples were then taken every 20 minutes for 2 hours. frozen on dry ice, and later analyzed using HPLC with electrochemical detection. For an additional group of rats, quantitative microdialysis techniques were used to determine the influence of U69593 treatment on dopamine uptake and extracellular concentration. In a third group, an acute locomotor challenge with cumulative doses of 0.3-3.0 quinpirole on day 5 followed the same 3-day U69593 treatment. Results suggested that repeated prior U69593 treatment dose-dependently reduced the acute effects of quinpirole on diatysate dopamine concentration in the dorsal striatum, and reduced the locomotor stimulant effects of quinpirole. There was no effect of U69593 treatment on basal extracellular dopamine concentration or on dopamine uptake, as estimated by quantitative microdialysis techniques. Taken together, these data suggest that repeated administration of a K-agonist can attenuate D2/D3 -mediated effects in the striatum, and these results ate consistent with findings that chronic K-agonist treatment downregulates striatal D2 receptors. These effects may contribute to the ability of K-agonists to block acute and sensitized behavioral effects of cocaine.

DYNORPHIN$_{2\text{-}17}$ ALTERS STRIATAL DOPAMINE DIALYSATE LEVELS AND COCAINE-INDUCED BEHAVIORAL SENSITIZATION

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Kappa-opioid receptor agonists prevent sensitization to the locomotor stimulant effects of cocaine (Heidbreder, *et al.,* 19%), reduce cocaine-induced alterations in dopamine dynamics (Thompson *et al.,* 1996), and decrease dopamine in then, accumbens and striatum (Spanagel *et al.,* 1990, Maisonneuve, *et al.,* 1994). Similar findings have been shown for prodynorphin-derived peptides that bind to the kappa-opioid receptor (Claye, *et al.,* 1996;. Reid *et al.,* 1990). The present studies were conducted to determine if the non-opioid dynorphin fragment, dynorphin$_{2\text{-}17}$ (DYN$_{2\text{-}17}$), produces similar behavioral and neurochemical effects. First, the effect of DYN$_{2\text{-}17}$ (0.5 mg/kg, iv) or vehicle on the acute locomotor stimulant effect of cocaine (20mg/kg, ip) was assessed. No differences in locomotor activity were observed. Second, the effect of DYN$_{2\text{-}17}$ on behavioral sensitization to the stimulant effect of cocaine was assessed Rats were treated with cocaine (10mg/kg, ip) or vehicle once daily for 7 days. On the first 5 days, rats also received DYN$_{2\text{-}17}$ (0.5mg/kg iv) or vehicle 15 min prior to the cocaine injection. Locomotor activity in response to a cocaine challenge (0, 5, 10 or 20 mg/kg, ip) was assessed 48 hr after the last cocaine pretreatment. The locomotor stimulant effect of cocaine (10 and 20 mg/kg) was significantly enhanced by prior exposure to cocaine and DYN$_{2\text{-}17}$ blocked the enhanced response. This effect of DYN$_{2\text{-}17}$ was dose-related and unchanged in rats treated with nor-BNI, a selective kappa-opioid receptor antagonist. Third, the effect of DYN$_{2\text{-}17}$ on dopamine in the dorsal striatum was assessed by microdiatysis. DYN$_{2\text{-}17}$, perfused through the microdialysis probe, dose dependently increased dialysate dopamine concentration. These data suggest that DYN$_{2\text{-}17}$ like kappa-opioid receptor agonists, prevents the development of behavioral sensitization to cocaine. However, unlike kappa agonists and other opioid active dynorphin fragments, DYN$_{2\text{-}17}$ does not increase dopamine in dialysate from the striatum. References available upon request from ACT.

EFFECTS OF KAPPA OPIOID AGONISTS ON COCAINE SELF-ADMINISTRATION BY RHESUS MONKEYS

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Cocaine and kappa selective opioid agonists have opposing effects on brain dopamine levels and kappa agonists attenuate cocaine's behavioral effects under some conditions. For example, kappa agonists attenuate cocaine-related behavioral and reinforcing effects in rats and antagonize cocaine's discriminative stimulus effects in squirrel monkeys. In this study, we examined the effects of kappa opioid agonists on cocaine and food self-administration in cocaine-experienced rhesus monkeys. Cocaine (0.01 and 0.032 mg/kg/inj/i.v.) and food (1 gm banana pellets) were available in 4 daily sessions on a second-order FR4 (VR16:S) schedule of reinforcement. A series of benzomorphan and arytacetamide kappa agonists were administered by continuous i.v. infusion. At least two doses of each kappa agonist were administered chronically for 10 days to groups of 4 monkeys. After each treatment condition, monkeys were given saline treatment for at least 4 days or until cocaine and food-maintained responding returned to baseline levels, Our studies with ethylketocyclazocine and U50,488 suggested that kappa opioid agonists modulate the reinforcing effects of cocaine. Tolerance to adverse side-effects [emesis, sedation] developed within 1 or 2 days after treatment began. Further studies to analyze the interactions between cocaine and enadoline. (-) spiradoline, PD117302, bremazocine and Mr2033 are now ongoing. Data obtained will indicate the conditions under which kappa agonists may influence cocaine's reinforcing effects and suggest their potential usefulness as treatment medications.

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IN VIVO MICRODIALYSIS OF THE VENTRAL PALLIDUM DURING COCAINE SELF. ADMINISTRATION

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Work with drug reinforcers has focused on the importance of the nucleus accumbens. Recent research (e.g., turnover studies, in preparation) suggests a major role for other structures. The present study utilized *in vivo* microdialysis of the ventral pallidum during cocaine self-administration (SA) to assess levels of extracellular dopamine (DA) and serotonin (5-HT). Seven catheterized rats were allowed access to 3 doses (0.17, 0.33 and 0.67 mg/inf) of cocaine during each session. Doses occurred in ascending order during 1 hr components separated by 10 min blackouts. Two responses were required to initiate infusions. Infusions/component was a decreasing function of dose. Four rats served as "yoked controls." Sessions for these subjects were conducted in operant chambers wired to chambers in which rats self-administered cocaine. Saline was infused whenever the SA rats produced an infusion. Microdialysis probes (1.5 mm) were inserted through previously implanted guide cannulae and artificial CSF was perfused at a rate of 0.5 µl/min. Samples were collected every 10 min. One microliter of the dialysate was injected into a microbore HFLC system and electrochemical detection used to assess DA and 5-HT. A 0.5 µl atiquot was used to determine the amount of cocaine. Baseline concentrations of DA and 5-HT averaged, respectively, 2.0 nM and 0.6 nM. At the beginning of cocaine SA, DA increased by 200-300% while 5-HT was increased about 200%. Increasing doses of cocaine resulted in increases in the concentration of DA, but not 5-HT. The concentration of cocaine averaged 2.0 VM during the SA of all cocaine doses. Levels of cocaine, DA, and 5-HT were not increased in the yoked rats. These data suggest that ventral pallidum dopaminergic innervation may have a significant role in cocaine SA.

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PHARMACOTHERAPY OF COCAINE ABUSE WITH RTI-113

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Phenylttopancs are reasonable candidates as medications for cocaine abuse. Ideally, such compounds would be potent, selective for the dopamine transporter, long-acting to facilitate dosing and enter the brain slowly. Many of the RTI compounds have such properties. We selected RTI-113 a potential prototypic substitute agonist because of its high potency and selectivity for the dopamine transporter. In rat locomotor activity studies, RTI-113 increased activity and was potent and long-lasting. ln studies with nonhuman primates, it increased dopamine efflux in the nucleus accumbens and it had significant stimulant effects on schedule-controlled behavior that were slow in onset and long in duration; compared to cocaine, RTI-113 was approximately 10 times more potent. In drug self-administration studies, RTI-113, when administered to rats just prior to the self-administration session, caused a dose-related reduction in cocaine self-administration. Thus, RTI-113 is a potential medication for treating cocaine abuse in humans.

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OLANZAPINE ATTENUATES THE DISCRIMINATIVE STIMULUS AND REINFORCING EFFECTS OF COCAINE

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This study investigated the ability of olanzapine, a newly marketed "atypical" antipsychotic with affinity for 5-HT_2, D_1, D_2, and muscarinic receptors, to block the discriminative stimulus and reinforcing properties of cocaine in male Sprague-Dawley rats. Subjects were trained to discriminate intraperitoneally (i.p.) administered cocaine (5 mg/kg) from vehicle using a 2 lever, food-reinforced (FR 10) discrimination procedure. Pre-treatment with i.p. clozapine (6 - 18 mg/kg) or olanzapine (1.5 - 6 mg/kg) 45 min prior to cocaine administration produced a significant close-dependent decrease in discriminative performance and an increase in the time to FR 10 selection. The ability of i.p. olanzapine to block the reinforcing effects of cocaine was further investigated by using the conditioned place preference paradigm and the iv drug self-administration procedure. Pre-treatment with olanzapine (1.5 - 4.5 mg/kg) significantly attenuated the ability of cocaine to produce conditioned place preference. Olanzapine (1.5 - 6 mg/kg) also dose-dependently attenuated cocaine self-administration (0.33 mg/infusion) on a FR 2 schedule of reinforcement. These results indicated that olanzapine can block the discriminative stimulus and reinforcing properties of cocaine.

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EFFECTS OF 7-NITROINDAZOLE, A SPECIFIC BRAIN NOS INHIBITOR, ON COCAINE DISCRIMINATION IN RATS

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Pretreatment with the brain and endothelial nitric oxide synthase (NOS) inhibitor NC-nitro-L-arginine methyl ester (L-NAME) has previously been shown to produce a 3-fold decrease in the ED_{50} for cocaine in rats trained to discriminate 10 mg/kg cocaine. Given alone, L-NAME did not substitute for cocaine. In addition, the D_1 receptor antagonist SCH 23390 and the D_2 receptor antagonist haloperidol blocked the enhancing influence of L-NAME on the discriminative stimulus (DS) effects of cocaine (Edwards and Kantak, 1995). Since L-NAME non-selectively inhibits NOS, it is not clear if its interactions with cocaine were related to brain and/or endothelial NOS inhibition. The present study examined the effects of the specific brain NOS inhibitor 7-nitroindazole (7-NI) in eight tats trained to discriminate 10 mg/kg cocaine. Like L-NAME, 7-NI (3.0-17.8 mg/kg) did not substitute for cocaine, but produced a dose-dependent leftward shift in the cocaine dose-response curve. Pretreatment with 10 mg/kg 7-NI produced a 3-fold decrease in the ED_{50} for cocaine (3.6 my/kg vs.1.1 mg/kg). Enhancement of the DS effects of cocaine by 7-NI was blocked by a low dose of SCH 23390 (0.003 mg/kg) that did not alter the DS effects of cocaine atone. The ED_{50} values were similar for SCH 23390 + 7-NI + cocaine (2.7 mg/kg) and cocaine alone (3.6 mg/kg) treatments. The present results support the importance of dopamine receptors for mediating the influence of 7-NI on the DS effects of cocaine, and also suggest that the enhancing effects of NOS inhibitors on cocaine are specific to brain NOS.

EFFECTS OF D2, D3 OR D4 DOPAMINE RECEPTOR BLOCKADE ON SELF-ADMINISTRATION OF COCAINE AND QUINELORANE IN RATS

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Novel dopamine receptor antagonists were used to investigate the relative roles of D2, D3 and D4 receptors in the reinforcing effects of cocaine. Eight male rats self-administering 0.25 mg cocaine i.v. under a FR 5 TO 20s schedule were pretreated (0.1-10 mg/kg i.p.) with the D2 preferential antagonist L-741,626 or the D3 preferential antagonist L-745,829. The D2 antagonist was significantly more potent (3%-fold) than the D3 antagonist in increasing self-administration, and produced a greater than 60% increase above baseline at a dose of 3.0 mg/kg. In contrast. the D3/D2 agonist quinelorane (0.25 μg i.v., n=5) given in combination with cocaine dacreasol self-administration rates by greater than 50%. The D2 antagonist (1.0-3.0 mg/kg), but not the D3 antagonist, reversed the effects of quinelorane on self-administration. *In vitro* studies revealed 20-fold and 40-fold selectivities, and nanomolar affinities, for these D2 and D3 antagonists at their preferred receptors, respectively. Moreover *ex vivo* studies showed rat brain concentrations approached 10 μM after administration of 10 mg/kg i.p. of either compound. Finally, pretreatments with the highly selective D4 antagonist L-745,870 (0.3-32.0 mg/kg i.p., n=5) failed to produce effects consistent with antagonism of the reinforcing effects of cocaine Despite much indirect evidence that dopamine agonists modulate the behavioral effects of cocaine through D3 receptors, studies with these particular antagonists fail to support the hypothesis that the reinforcing effects of cocaine are dependent upon, or modulated through, D3 or D4 receptors in the rat.

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BEHAVIORAL EFFECTS OF DOPAMINE D2/D3 AGONISTS IN RHESUS MONKEYS: INTERACTION WITH COCAINE

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The behavioral effects of cocaine have been shown to be mediated in part by dopamine D_2 and D_3 receptors. In order to further investigate the receptor mechanisms involved in cocaine's effects, the D_2/D_3 agonists quinpirole (D_2 binding affinity: 6.4 nM; D_3: 1.7 nM), (±)-7-OH-DPAT (D_2: 2.6; D_3: 0.4) and R-(+)-7-OH-DPAT (D_2: 56; D_3: 0.57) were examined in two animal models of cocaine abuse. In i.v. self-administration studies (n=3), responding was maintained under a fixed-interval 5-min schedule of cocaine presentation. When substituted for the baseline dose of cocaine (0.03 mg/kg/inj), quinpirole (0.001-0.01 mg/kg/inj) maintained rates of responding above saline rams. indicating mat it was functioning as a reinforcer. Two cocaine-naive animals did not acquire quinpirole self-administration. suggesting that cocaine modified the D_2/D_3 receptor system. In animals (n=4) trained to discriminate cocaine (0.1-0.3 mg/kg, i.m., 10-min pretrearment) from saline, quinpirole (0.001-0.56 mg/kg) fully substituted for cocaine (>80%) in three of four monkeys. Neither (±)-7-OH-DPAT nor R-(+)-7-OH-DPAT fully substituted for cocaine up to doses that had significant rate-decreasing effects (n=2); consistent with a D_3-mediated effect, R-(+)-7-OH-DPAT was more potent. When me rate-decreasing effects were attenuated by increasing me pretreatment time, (±)-7-OH-DPAT fully substituted for cocaine. These results indicate that quinpirole and (±)-7-OH-DPAT have cocaine-like discriminative stimulus effects. These data provide further support that the behavioral effects of cocaine may be mediated through dopamine D_3 receptors.

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THE GABA TRANSAMINASE INHIBITOR γ-VINYL GABA ATTENUATES COCAINE SELF-ADMINISTRATION IN RATS

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Previous work in our laboratory has demonstrated that the irreversible GABA transaminase inhibitor γ-vinyl GABA (GVG) raises brain stimulation reward (BSR) thresholds and attenuates the threshold-lowering effects of cocaine. To further test the hypothesis that increased levels of GABA have an inhibitory effect on dopamine-mediated reward systems, the effects of GVG on i.v. self-administration of cocaine in four male Wistar rats were examined. Rats were trained to self-administer cocaine (0.3 mg/kg/infusion) on an FR5 schedule. Once stable responding had been established, rats were injected (ip) with GVG (100, 200, or 300 mg/kg) or saline three hours prior to the start of the self-administration session. Preliminary results indicate that GVG dose-dependently decreased cocaine intake: pretreatment with saline reduced responding to 96% of baseline (n=3), 100 mg/kg GVG to 90% of baseline (n=2), 200 mg/kg GVG to 60% of baseline (n=4), and 300 mg/kg GVG to 6% of baseline. These results support those found previously in our BSR studies and provide further evidence to suggest that increases in GABAergic activity have an inhibitory influence on dopamine-mediated reward.

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EFFECTS OF A SLOW-ONSET, LONG-ACTING DOPAMINE REUPTAKE BLOCKER ON BRAIN REWARD MECHANISMS

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Cocaine's abuse potential has been linked to its *rapid* blockade of presynaptic dopamine (DA) reuptake in brain reward loci. Also, persons with vulnerability to cocaine abuse may have hypofunction in these brain reward systems. Thus, development of slow-onset long-acting DA reuptake blockers for cocaine substitution therapy seems logical. Using rational drug design and a pharmacophore model, a series of such compounds were synthesized. The lead compound, CDTP-30,640, was tested *in vivo* in lab rats in brain reward-related paradigms. It dose-dependently augmented electrical brain-stimulation reward (BSR) as potently as cocaine, but with a slow-onset long-acting profile. Its effect on BSR was additive with cocaine, but only when cocaine was given many hours after it, to coincide with CDTP-30,640's slow-onset peak effect. When co-administered to rats self-administering cocaine i.v., it dose-dependently reduced cocaine self-administration, When substituted for cocaine in experienced self-administering rats, it maintained self- administration behavior at slightly above saline levels. Thus, CDTP-30,640's action on brain reward mechanisms is cocaine-like, but with a slow-onset long-acting profile, suggesting possible therapeutic utility.

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THE EFFECTS OF CHRONIC DOPAMINE ANTAGONISTS ON COCAINE SELF-ADMINISTRATION IN RATS

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These experiments tested the hypothesis that chronic administration of the dopamine (DA) antagonists flupenthixol (FLU), SCH23390 (SCH) and eticlopride (ETI) would produce sensitization to the reinforcing effects of cocaine. Rats (N=18) were trained to self-administer cocaine (i.v.) under a fixed-ratio 2 (FR2) schedule of reinforcement. After baseline dose-response curves were obtained, rats were treated chronically with either FLU (3.2 mg/kg/12 hr/5 days; SC), SCH (0.25 mg/kg/12 hr/7 days; SC), or ETI (0.25 mg/kg/12 hr/7 days; SC). Either 24 (SCH and ETI) or 72 (FLU) hours following the last chronic injection, dose-response curves for cocaine self-administration were obtained. Chronic administration with the D1 (SCH) or the mixed dopamine antagonist (FLU) shifted the dose-response curve for cocaine self-administration to the left, indicating sensitization to the reinforcing effects of cocaine. In contrast chronic treatment with the D2 antagonist ETI shifted the dose-response curve for cocaine self-administration to the right, indicating tolerance to the reinforcing effects of cocaine. This suggests that both the D1 and the D2 receptor subtypes are involved in mediating the reinforcing effects of cocaine; but they differ functionally.

BEHAVIORAL EFFECTS OF DOPAMINE D_1 LOW-EFFICACY AGONISTS IN MONKEYS

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The effects of dopamine D_1 agonists with low to moderate agonist efficacy in studies of adenylate cyclase stimulation or in radioligand binding experiments to evaluate the effects of GTP on binding affinity (e.g., SKF 77434, SKP 38393, and SKP 75670) have effects that overlap those of dopamine receptor blockers. For example, they may produce catalepsy-associated behavior in observational studies, decrease leverpress response rates, and antagonize discriminative-stimulus or reinforcing effects of psychomotor stimulants such as cocaine or methamphetamine. The present experiments were designed to further evaluate the relationship between D_1 agonist efficacy and behavioral effects by studying the observable and stimulant-antagonist effects of SKF 83959, a D_1 agonist that has been reported to produce ameliorative effects in MPTP-treated monkeys, yet to have no agonist effects in biochemical studies of D_1 efficacy. In ongoing observational studies and in experiments in squirrel monkeys trained to discriminate injections of methamphetamine from vehicle, SKF 83959 (0.3-10.0 mg/kg, i.m.) does not appear to produce catalepsy-associated behavior, does not consistently reduce leverpress-response rates, and is not distinguished as methamphetamine. Yet, pretreatment with 3.0 mg/kg SKF 83959 displaces the dose-effect function for the methamphetamine-like S^D effects of the D_1 agonist R-6-BrAPB at least 3-fold rightward in all subjects. These findings suggest, tentatively, that the direct and stimulant-antagonist effects of D_1 low-efficacy agonists may be separable and that *in vitro* efficacy estimates may not directly correspond to the functional efficacy of D1 agonists in primates.

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RAPID ASSESSMENT OF COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

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Recently, self-administration techniques have been developed to allow the assessment of the effects of several doses of drug in the same session, speeding the evaluation of the compounds reinforcing effects (Winger *et al.,* 1989 Drug AIcohol Depend. 24: 135-142). In the present study similar techniques were used to train rhesus monkeys (n-4) to self-administer different doses of cocaine under a fixed-ratio (FR) schedule of reinforcement. After initial training in single component sessions, experiments were modified to comprise multiple 20-min components, each separated by a 20-min time-out (TO). During each component monkeys could lever press to obtain up to 10 injections of a given concentration of cocaine. Each injection condition was signaled by a different visual stimulus; for example, blue light was associated with no injection, white light with vehicle, green light with 0.01 mg/kg/inj, red light with 0.1 mg/kg/inj and so on. Doses were presented in ascending order and overlapping dose-ranges were studied on separated days. Finally, the effects of cocaine were determined at different FR values (FR 10-FR560). Results show that, with comparable schedule parameters, dose effect functions for cocaine self-administration using conventional and the rapid assessment procedure (RAP) overlap considerably. Using the RAP. dose-effect functions wee reproducible over many months, and the effects of individual doses were similar regardless of their order of presentation within the session. Dose-effect functions were shifted rightward by the D_1 dopamine receptor blocker SCH 39166, and the effectiveness and Potency of the antagonist varied under different FR values. These results show that rapid assessment procedures can be used to evaluate potential medications for cocaine addiction, and their effectiveness under different environment conditions.

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REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR IN A NONHUMAN PRIMATE MODEL OF RELAPSE: EFFECTS OF PREFERENTIAL DOPAMINE D_1 AND D_3 AGONISTS

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The present study investigated the effects of priming with dopamine D_1 and D_3 agonists on the reinstatement extinguished cocaine-seeking behavior. Using a nonhuman primate model of relapse, squirrel monkeys were trained to self-administer cocaine under a second-order schedule of *i.v.* injection. Completion of every tenth response (FR 10) during a 10-min fixed interval (FI 10-min) produced a brief (1 sec) visual stimulus, The first FR 10 completed after the 10-min FI elapsed produced both the brief stimulus and an injection of cocaine. High rates of responding (0.8-2.0 resp/sec) were maintained under these conditions by 0.1 or 0.3 mg/kg/injection cocaine. Responding was subsequently reduced or eliminated during a series of extinction sessions in which saline was substituted for cocaine and the brief stimulus was omitted. Following extinction, responding could be reinstated by administering a priming (noncontingent) injection of cocaine before the session. Cocaine-induced reinstatement was dose-dependent and could be mimicked by priming with methamphetamine. Neither the D_1 agonists SKF 81297 and SKF 82958 nor the D_3 agonist PD 128907 reinstated cocaine-seeking behavior at doses that have been found to mimic the discriminative stimulus effects of cocaine. In drug combination tests, pretreatment with either SW 81297 or SKF 82958 suppressed cocaine-induced reinstatement of drug-seeking, usually at doses that also suppress schedule-controlled behavior maintained by non-drug reinforcers. Pretreatment with PD 128907 did not attenuate cocaine-induced reinstatement at any dose tested. The results suggest that pharmacothetapics for cocaine addiction that target D_1 or D_3 receptors may be devoid of cocaine-like priming effects. The capacity of D_1 agonists to attenuate cocaine-induced reinstatement of drug-seeking warrants further investigation.

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INTRAVENOUS SELF-ADMINISTRATION OF BENZTROPINE ANALOGS BY RHESUS MONKEYS

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Chloro-substituted analogs (3'-Cl, 4'-Cl) of benztropine (B) bind to the dopamine transporter (DAD and inhibit dopamine uptake. 3'-Cl has locomotor and discriminative stimulus (DS) effects similar to cocaine (C), whereas 4'-Cl weakly stimulates locomotion and only partially reproduces the DS effects of C. Based on this profile, 3'-CI may have reinforcing effects, whereas 4'-Cl may lack reinforcing effects despite binding to the DAT. To assess this Possibility, four rhesus monkeys were trained to self-administer i.v. C (0.03 mg/kg/inj, FR 10, 1 hr/day). When inj/hr were stable (±15% variation for 3 sessions, no upward or downward trend), saline (S) was made available until responding declined to low levels and was stable. Responding was re-established with C, and doses of C, B, 3'-Cl and 4'-Cl were available for at least the same number of sessions as S, and until responding was stable. C (0.003-0.1 mg/kg/inj) maintained responding above S levels, whereas B (0.003-1.0 mg/kg/inj) did not. Both 3'-Cl (0.001-0.3 mg/kg/mj) and 4'-Cl (0.001-1.0 mg/kg/inj) also maintained responding above S levels. Responding at some 3'- and 4'-Cl doses was more variable and took more sessions to reach stability than C. These data indicate that although B blocks dopamine uptake, it was not a reinforcer. Although 4'-Cl has diminished C-like locomotor and DS effects compared to 3'-Cl, both analogs had reinforcing effects. Variable responding maintained by the analogs may be due to relatively weak effects and/or long durations of action.

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FURTHER EVALUATION OF THE BEHAVIORAL EFFECTS OF 2-ß-PROPANOYL-3ß-(4-TOLYL)-TROPANE (PTT) IN MONKEYS

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2-ß-propanoyl-3ß-(4-tolyl)-tropane (PTT) is a cocaine analog that binds with high affinity and selectivity to me dopamine transporter. Previous studies indicated that PTT has a unique behavioral profile in monkeys, having cocaine-like discriminatlve stimulus effects, but not functioning as a reinforcer when substituted for cocaine. The purpose of this study was to further evaluate the behavioral effects of PTT in rhesus monkeys. In Exp. 1, monkeys (N=2) responded under a multiple food-drug-food fixed-ratio (FR) 30 schedule. Food components (1g pellets) lasted 30 min and the drug component (cocaine 0.03 mg/kg/inj, i.v.) was 60 min. Presession administration of (+)PTT (0.003-0.056 mg/kg, i.v.) and cocaine (0.01-3.0 mg/kg, i.v.) produced nonspecific rate decreasing effects on food- and cocaine-maintained responding. In Exp. 2, saline was self-administered and the ability of (+)PTT and cocaine to reinstate responding was evaluated (N=3). Both PTT (0.003-0.056 mg/kg, i.v.) and cocaine (0.03-3.0 mg/kg, i.v.) resulted in increases in total saline injections. PTT administration resulted in more saline injections compared to the maximal effects observed following cocaine pretreatments. PTT was at least 1.0-log unit more potent man cocaine in reinstating responding. These results provide evidence that a drug that does not function as a reinforcer, but does have discriminative stimulus effects similar to cocaine, can reinstate cocaine-seeking behavior. It is, at present. not clear whether such an outcome indicates that PTT can induce relapse in cocaine abstinent drug abusers.

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INDEPENDENT INTERACTION OF ALPRAZOLAM AND CAFFEINE UNDER CHRONIC DOSE REGIMENS ON DRL 45-S PERFORMANCE

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In previous research, we found an independent interaction of alprazolam and caffeine in rats under acute dose regimens using two measures (reinforcement rate and shorter-response rate) of a differential reinforcement of low rate performance (DRL 45-s) in 3-h sessions. Applying the same behavioral endpoints, the present study investigated the alprazolam-caffeine interaction under chronic dose regimens. Both drugs were administered by me oral route. Acute alprazoIam and caffeine dose-response curves (DRCs) were characterized and were then used to determine the maintenance dose for the respective chronic dose regimens. Both drugs decreased the reinforcement rate and increased the shorter-response rate in a dose-related fashion. An alprazolam DRC also was determined during chronic-caffeine, chronic-alprazolam, and concurrent chronic-caffeine-alprazolam dose regimens. Complete tolerance to caffeine induced rate changes was observed on the second day. Incomplete tolerance occurred only at higher alprazolam doses (7-12.5 mg/kg). Cross tolerance was not found between alprazolam and caffeine. Upon discontinuation of both drugs, performance progressively returned to baseline. The four alprazolam DRCs as well as the effect-time profiles demonstrated that caffeine altered neither the magnitudes nor the patterns of alprazolam effects on the two rates under chronic dose regimens. The Pöch DRC method further confirmed the independent interaction of alprazolam and caffeine. Thus, the independence of the interaction held for both the acute and chronic dose regimens despite the development of tolerance in the latter regimens.

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EPHEDRINE AND CAFFEINE ARE CAPABLE OF POTENTIATING EACH OTHERS AMPHETAMINE-LIKE STIMULUS EFFECTS

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Tests of stimulus generalization were conducted using male S-D rats (n=7) trained to discriminate (+)amphetamine (AMPH; i.p., 15-min psii; ED50=0.3 mg/kg) from 0.9% saline vehicle using a Vl 15-s schedule of reinforcement. Substitution occurred with (-)ephedrine and caffeine (ED50 doses = 4.5 and 13.0 mg/kg, respectively); (+)ephedrine produced a maximum of 50% AMPH-appropriate responding at 12 mg/kg and disruption of behavior at higher doses. This apparently represents the first time an AMPH stimulus has been demonstrated to fully generalize to caffeine. A fixed dose of caffeine (3 mg/kg; which, by itself, elicited only 1% AMPH-appropriate responding) puduced a two-fold leftward shift of the (-)-ephedrine dose-response curve (ED50 = 2.8 mg/kg). In a separate experiment, this caffeine dose plus the ED50 dose of (-)-ephedrine resulted in the animals making >90% of their responses on the AMPH-appropriate lever. A fixed dose of (-)-ephedrine (2 mg/kg; which, by itself, elicited 0% AMPH-appropriate responding) produced a two-fold leftward shift of the caffeine dose-response curve (ED50=5.2 mg/kg). These results suggest that (i) ephedrine and caffeine can produce AMPH-like stimulus effects, that (ii) the AMPH-like stimulus character of ephedrine is associated primarily with the (-)-isomer, and that (iii) (-)-ephedrine and caffeine are capable of potentiating each others AMPH-like stimulus properties.

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COMPARISON OF INTRAVENOUS CAFFEINE AND NICOTINE IN COCAINE ABUSERS

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The present study compared the effects of intravenously administered caffeine and nicotine in cocaine abusers who were also cigarette smokers. Subjecls (N=9) resided as inpatients on a residential behavioral pharmacology research unit. Cigarette smoking was permitted. However, cigarette smoking was restricted at least 8 hours before each session. For consistency with the nicotine intake, subjects were administered caffeine (150 mg/70 kg, b.i.d.) in capsules, with the last dose given at least 8 hours before each session. In each session, physiological and subjective data were collected before and repeatedly after an intravenous injection of placebo, caffeine (100, 200, 400 mg/70 kg) or nicotine (0.75, 1.5, 3.0 mg/70 kg) over a 10-second period. Both caffeine and nicotine produced dose-related increases in subjective ratings of “drug effect”, “good effects”, “drug liking”, “stimulated” and “high” which peaked approximately two minutes after injection. Nicotine generally produced greater effects than caffeine on these measures. On a drug identification questionnaire, the highest dose of nicotine was identified as a stimulant (like amphetamine, cocaine) by significantly more subjects than the other nicotine or caffeine doses. The majority of subjects also identified the highest dose of nicotine as cocaine. Overall, both caffeine and nicotine produced positive subjective effects. However at the doses studied, nicotine produced greater effects and was more likely to be identified as cocaine than caffeine.

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EFFECTS OF AN ALTERNATIVE REINFORCER AND CAFFEINE ON HUMAN COCAINE SELF-ADMINISTRATION

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In this ongoing study we am examining the influence of alternative monetary reinforcement and caffeine pretrearment on the probability of cocaine use in humans under double-blind laboratory conditions. The experiment consists of two phases. First, participants choose between cocaine hydrochloride and active placebo, both of which are administered intranasally in 10 mg unit doses. Those who select cocaine over placebo proceed to the second phase. During the second phase participants are pretreated with several caffeine doses (0, 150, 300mg/70kg) and then allowed to choose between cocaine and varying amounts of money. To date 12 participants have completed the first phase of the study, of which, 11 selected cocaine over placebo. Seven participants have completed the second phase of the study. In 6 of these 7 participants, choice of cocaine decreased as the amount of money available for me monetary choice increased, demonstrating that the behavioral control exerted by cocaine was dependent on the magnitude of the alternative reinforcer available. Results suggest that caffeine pretreatment has no effect on the choice of cocaine versus money. These results demonstrate further the relationship between the availability of alternative reinforcers and cocaine use, and suggest that caffeine does not alter this relationship.

CHARACTERISTICS OF PATIENTS WITH CHRONIC USE OF OTC ANALGESICS CONTAINING CAFFEINE

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For some patients, chronic use of over-the-counter analgesics (OTCAs) containing caffeine may be related to caffeine-dependence and/or caffeine withdrawal The purpose of this study was to compare daily users of OTCAs containing caffeine to daily users of OTCAs not containing caffeine. Chronic OTCA users (N=162) were recruited through newspaper advertisements and participated in a structured telephone interview that characterized the pattern, type and amount of their OTCA use, as well as the reasons for their initial and continued use of OTCAs. Thirty of the 162 participants (18.5%) reported daily use of OTCAs containing caffeine. Their average daily caffeine use from analgesics was 274 mg (range 48-780 mg). Compared to patients who used chronic OTCAs that did not contain caffeine, there was no significant difference in their daily non-analgesic related dietary caffeine consumption. However, users of caffeine-containing OTCAs were significantly more likely to report having headache (a frequent feature of caffeine withdrawal) as their current, primary, and only pain. In addition, they were significantly more likely to have gone to special lengths to obtain their OTCA, to have had friends or family members complain about their OTCA use, and to have tried to quit using OTCAs. These results suggest one component of continued use of caffeine-containing OTCAs for some patients may be related to the caffeine content of these medications.

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CO-MORBID PSYCHIATRIC DIAGNOSIS AND PERSONALITY DIMENSIONS IN PATIENTS ENROLLED IN A METHADONE MAINTENANCE TREATMENT PROGRAM

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Co-morbid psychiatric disorders among methadone maintenance (MM) patients are clinically challenging and present difficulties in preventing relapse. Among NM patients, co-morbid diagnoses frequently include unipolar depression antisocial personality, alcoholism and anxiety disorders. The comorbid psychiatric disorders and personality dimensions in patients enrolled in an MM program have not been studied extensively. The goal of the present work is to elucidate co-morbid diagnoses and to describe the personality dimensions in a population of patients in MM treatment. The results obtained may help establish a relationship between personality dimensions and treatment response in this population. Each patient was interviewed using the Structured Clinical Interview for DSM-IV for Axis-I Disorders (SCID-I) and asked to complete the Tridimensional Personality Questionnaire (TPQ). The TPQ (Cloninger, 1993) yields measures of temperament and character across three dimensions: novelty seeking, harm avoidance, and reward dependence. Also a structured questionnaire was used to obtain parental psychiatric and substance abuse history. Adoption studies have indicated that vulnerability to substance abuse may be a partially inherited condition with strong influences from environmental factors as well. All patients (N =34) currently included in the study developed opioid dependency (OD) before age 20 with Addiction Severity Index (ASI) score at least 7 on the drug severity profile and total ASI score of 25 or more. Individuals with epilepsy, schizophrenia, schizooffective disorder, bipolar illness, or mental retardation were excluded. All patients (19 y/o- 59 y/o) had a history of relapse after multiple inpatient and outpatient treatment for substance dependence, and at the time of interview they met criteria for Opioid Dependency (100%). Sedative-Hypnotic Dependency (23.5%). Major Depressive Disorder (17.6%) and Substance Induced Anxiety Disorder (14.7%). We observed a significant relationship between alcohol/drug abuse co-morbidity in first degree relatives (mother or father) and substance abuse in their sibling (62% vs 37%; p=0.013), in comparison with the patients with no co-morbid family history. Only 11 patients (37%) had parents with negative history of Alcohol or Drug Abuse. This is compatible with substantial heritability of risk for substance abuse/dependence in first degree relatives of these patients. In the personality dimensions our patients scored high in novelty seeking and harm avoidance but low on reward dependence. Our results show the high prevalence of psychiatric and substance abuse disorders in this population as observed previously by Brooner R.K. *et al.,* 1997 and Rounsavibe B.J. *et al.* 1982, 1986. This population is engaged in frequent exploratory activities, impwsive decision making with poor social attachment and low sentimentality. This study has the goal of coil data in =200 probands and controls in order to assess more completely co-morbid diagnoses and personality characteristics in this population.

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POSTER SESSION IV

REVERSIBLE AND RAPID EFFECTS OF METHAMPHETAMINE ON DOPAMINE TRANSPORTERS

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High-dose methamphetamine (METH) administration causes reactive oxygen species formation *in vivo.* Because of this finding, and the observation that reactive oxygen species decrease dopamine transporter (DAT) activity *in vitro,* effects of METH administration on DAT activity in rat striatum were investigated. A single METH injection causes a dose-dependent (0-15 mg/kg) decrease in [^{3}H]dopamine uptake into striatal synaptosomes prepared 1 h after METH administration; an effect attributable to a decreased Vmax of [^{3}H]dopamine uptake. Similarly, multiple high-dose administrations of METH (10 mg/kg/dose; 4 injections at 2-h intervals) rapidly decreased DAT function. The decreases in DAT activity after either a single or multiple METH administrations were reversed 24 h after treatment. Taken together, these data suggest that METH selectively decreases DAT activity, perhaps through a reactive oxygen species-mediated mechanism. These findings may have important implications regarding the role of oxidative events in the physiological regulation of monoaminergic systems.

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THE AMPHETAMINE-INDUCED INCREASE IN EXTRACELLULAR DOPAMINE IS IMPULSE-DEPENDENT AS WELL AS IMPULSE-INDEPENDENT

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The specific opioid receptor antagonist naloxone attenuates the effects of amphetamine in a wide variety of behavioral paradigms. Naloxone also attenuates the amphetamine-induced increases in extracellular dopamine in both the striatum (STR) and nucleus accumbens (NACC) of rats. Therefore, it has become of interest to better elucidate why an opioid receptor antagonist attenuates the effects of amphetamine. One possible explanation for these observations is that amphetamine, which is known to cause the release of other neurotransmitters, may cause the release of endogenous opioids which, in turn, cause a disinhibition of central dopamine neurons. In this case, there would actually be two components to the increase in extracellular dopamine seen after amphetamine administration: (1) direct release of dopamine by amphetamine acting at the dopamine terminal (i.e. an impulse-independent action), and (2) indirect release of dopamine by amphetamine promoting the release of endogenous opioids (i.e. an impulse-dependent action). Therefore, this research was designed to determine whether there is both an impulse-dependenl as well as an impulse-independent component to the increase in extracellular dopamine seen after amphetamine administration. Microdialysis was performed on adult male rats that had surgically implanted guide cannula aimed at the dorsal surface of the STR. After the collection of baseline samples, 1μM of the sodium channel blocker tetrodotoxin (TTX) or vehicle was added to the perfusate of the probe. Thirty minutes following the initiation of TTX, cumulative doses of SC *d*-amphetamine (0.0, 0.1, 0.4, 1.6, 6.4 mg/kg) were administered at 30 min intervals. The data indicate that 1μM TTX attenuates the amphetamine-induced increase in extracellular dopamine by approximately 30%. This observation suggests that the amphetamine-induced increase in extracellular dopamine does have an impulse-dependent component.

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THE *DELTA* OPIOID DADLE ATTENUATED METHAHPHETAMINE NEUROTOXICITY VIA OPIOID AND NONOPIOID MECHANISMS

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The *delta* opioid peptide DADLE ([D-ala^2,D-Ieu^5]enkephalin) can prolong organ survival time in an organ preservation preparation (Chien *et al.,* 1994). As the survival of organ might involve oxidative mechanisms, this study examined if DADLE might protect against dopaminergic (DA) terminal loss induced by methamphetamine (METH). Male CD 1 mice received *i.p.* injections of 5 or 10 rng/kg of METH four times in a day given 2 hrs apart. DADLE, when given, was injected *(i.p.)* 30 min before each METH injection. Two weeks later, animals were sacrificed and brains removed and processed for autoradiographic examination using a DA transporter rnarker [^{125}I]RTI-121. METH caused 40% (5 mg/kg) and 65% (10 mg/kg) decreases in striatal (ST) DA transporter. The nucleus accumbens (NA) was less affected by both doses of METH. DADLE at 4 mg/kg completely blocked the DA terminal loss in all areas induced by 5 mg/kg of METH. In mice receiving 10 mg/kg METH, DADLE (4 mg/kg) completely blocked the DA terminal loss in the medial ST and in the NA. However, a partial blockade was observed in the lateral ST. Naltrexone was used to lest the involvement of opioid receptors in this action of DADLE using mice receiving 10 mg/kg of METH. Naltrexone (0.1 mg/kg) reversed the neuroprotective effects of DADLE in the ST but not in the NA. Thus, DADLE blocks METH-induced DA terminal loss *via* opioid and nonopioid mechanisms. DADLE may therefore provide some utility in the treatment of METH neurotoxicity or abuse and, by extension, of the progressive course of Parkinsonism.

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OPPOSITE EFFECTS OF 7-OH-DPAT ON AMPHETAMINE-INDUCED STEREOTYPIES AND CONDITIONED PLACE PREFERENCE

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Low doses of 7-OH-DPAT (0.01-0.1 mg/kg) produce a decrease in locomotion and sniffing, but do not produce conditioned place preference (CPP). In the first experiment, the effects of these doses of 7-OH-DPAT on motor behaviors and CPP produced by amphetamine (1 mg/kg) were examined. In the second experiment. the effect of 0.1 mg/kg 7-OH-DPAT on amphetamine (0-10 mg/kg) dose-response curves for the same behaviors were examined, For both experiments, three two-day conditioning trials were conducted On one day, animals received an injection of their assigned dose of 7-OH-DPAT co-administered with amphetamine and were placed into a distinct comment for 40 min. On the other day, animals received an injection of saline and were placed into a different compartment for 40 min. Locomotion and headbobbing were measured following acute and repealed drug administration. CPP was assessed the day following the last conditioning trial. In me first experiment. amphetamine-induced locomotion was dose-dependently decreased by 7-OH-DPAT following repeated administration which was likely due to the emergence of headbobbing, a behavior not observed with amphetamine alone. Amphetamine-CPP was not altered by co-administration of 0-0.03 mg/kg 7-OH-DPAT, but was attenuated by co-administration of 0.1 mg/kg 7-OH-DPAT. In the second experiment, 0.1 mg/kg 7-OH-DPAT produced a decrease in amphetamine-induced locomotion al lower doses of amphetamine (0-0.5 mg/kg). However, 7-OH-DPAT produced increase in headbobbing and no changes in locomotion at the higher doses of amphetamine (0.5-10 mg/kg). Amphetamine-CPP was attenuated by co-administration of 7-OH-DPAT. These findings suggest that 0.1 mg/kg of 7-OH-DPAT attenuates the reinforcing properties of amphetamine despite enhancing stereotypic behaviors.

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LM-39, A TETRAHYDROISOQUINOLINE RELATIVE OF THE DESIGNER DRUG MDMA, AS A TRAINING DRUG IN RATS

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Structurally, LM-39 is related to a putative metabolite of methylenedioxyphenylalkylamines, such as the designer drug MDMA. We reported the synthesis of LM-39 and that it lacks amphetamine-like locomotor activity in mice (Med Chem Res 1996, 6, 412); LM-39 also fails to substitute for (+)amphetamine in 1 mg/kg (+)amphetamine-trained rats (7% appropriate responding at 5 mg/kg). But we reported that LM-39 (5 mg/kg) produces 75% MDMA-appropriate responding in rats trained to discriminate MDMA from vehicle; this suggests that LM-39 possesses some MDMA-like characler. To further characterize this agent, we trained 5 male S-D rats to discriminate LM-39 (5 mg/kg; ip) from vehicle using a VI 15-s schedule of reinforcement (ED50=0.9 mg/kg). Administration of MDMA resulted in a maximum of 76% LM-39-appropriate responding at 1 mg/kg; higher doses resulted in disruption of behavior. Interestingly. the LM-39 stimulus generalized to a positional isomer (LM-40; ED50=2.7 mg/kg) although LM-40 had been previously shown to lack MDMA-like stimulus properties (i.e., 16% MDMA-appropriate responding). LM-39 may represent the first member of a structural class of agents with a novel behavioral profile.

PHARMACOLOGICAL EFFECTS OF MDMA IN HUMANS: A DOSE-FINDING PILOT STUDY

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3,4-Methylenedioxymethamphetamine (MDMA) is a synthetic amphetamine derivative. Although MDMA is an increasingly popular recreational drug among american and european young people, there are only few experimental data of its pharmacological properties in humans. This study was designed to assess the acute pharmacological effects of MDMA, and to determine the dose to be used in future investigations. Six healthy male recreational users of MDMA participated in different experimental sessions (4-8). They received single oral doses of MDMA (50, 75, 100, 125 and 150 mg), amphetamine sulphate (AMP 20, 30, 35, 40 mg) or placebo. Drugs were administered double-blind and randomized (lower doses were allocated before higher doses for safety reasons). Study variables included: vital signs (blood pressure, heart rate, temperature, pupil diameter), psychomotor performance (reaction time, DSST, Maddox-wing), and subjective effects (visual analog scales, ARCI-49 item short form and POMS questionnaires). MDMA and AMP produced a dose-related increase in blood pressure, heart rate (different time profile for both drugs) and pupil size (only MDMA). No significative changes were found on psychomotor tasks, although AMP produced an sligth improvement. MDMA produced higher scores on subjective effects and drug-induced euphoria ("high", "liking", ARCI-MBG) than AMP. A dose-response relationship was found for MDMA effects. Only MDMA poduced slight changes in visual and body perceptions. The results seems to indicate that MDMA could have a high abuse potential.

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THE DISCRIMINATIVE STIMULUS EFFECTS OF AMINEPTINE IN RATS

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Amineptine hydrochloride is an antidepressant with general properties supposed to be similar to those of amitriptyline. Amineptine is used as an antidepressant in France, in Spain and in Italy. Amineptine which is mainly dopamine reuptake pump blocker, has been subject to and withdrawal has beenprolonged and difficult. Eleven Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg i.p.) from saline. The discriminative stimulus effects of amineptine (1 ; 2.5; 5 ; 10; 15; 20 mg/kg i.p.) and (+)-amphetamine (0.3; 0.6; 1.25; 2; 2.5; 5 mg/kg i.p.) were studied after administration. The complete generalization was obtained at 15 mg/kg for amineptine, and 2 mg/kg for (+) amphetamine. Generalization from cocaine stimulus to amineptine or (+)-amphetamine was an increasing function of dose. Amineptine, a dopamine reuptake pump blocker used as an antidepressant, is abused in France by drug addicts. We showed, in rats trained to discriminate cocaine from saline, amineptine substituted for cocaine as a discriminative stimulus. In rats trained to discriminate (+)-amphetamine from saline, amineptine substituted for (+)-amphetamine as a discriminative stimulus. Drug discrimination procedure, in which amineptine showed cocaine-like activity, confirms *a posteriori,* the abuse potential of amineptine.

COMPARATIVE PHARMACOLOGY OF METHAMPHETAMINE AND COCAINE: DRUG DISCRIMINATION AND PHYSIOLOGIC EFFECTS

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Because both cocaine and methamphetamine are psychostimulant sympathomimetics which block synaptic monoamine reuptake, we compared pharmacologic effects of methamphetamine and cocaine in 12 subjects. Blood pressure (SBP and DBP), heart rate (HR), rate pressure product (RPP), and subjective drug effects were compared after double-blind, placebo-controlled, 1 min intravenous infusions of 0.6 mg/kg cocaine or 15 mg methamphetamine. Data was analyzed by ANOVA. Both drugs raised SBP and RPP. Cocaine increased HR by 25±15 compared with a small decrease after methamphetamine of 3±9 bpm. A greater increase in DBP occurred after methamphetamine than cocaine (14 vs 10 mmHg). The increased RPP after methamphetamine was due to increased SBP but not HR. In contrast, cocaine increased RPP primarily by increasing HR. Peak intoxication was higher with cocaine than methamphetamine (58±34 vs 18±23), probably due to the relatively low methampheramine dose. Subjects correctly distinguished cocaine from methamphetamine within 3 minutes or less by qualitative subjective differences in drug experience. We conclude from this preliminary experiment that cocaine and methamphetamine have physiologic and subjective differences which may mediate risks of drug toxicity or dependence.

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REVERSAL OF ETHANOL-INDUCED BODY SWAY BY METHAMPHETAMINE IN STANDING HUMANS

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Stimulant drugs are known to affect motor system behaviors. However, since young, healthy adults perform so well in measurements of motor behaviors, it is difficult to show a performance improvement. In this double-blind study, ethanol was used to impair stance stability, allowing the effects of methamphetamine to be examined in 8 healthy nondependent methatnphetamine-experienced volunteers (7 male, 1 female). Ethanol (1.0 g/kg administered orally in divided doses over 30 minutes) or placebo was followed, 60 minutes after ethanol administration began, by (S)-(+)-methamphetamine HCl (30 mg intravenously over 1 minute) or placebo. Stance stability, in both eyes open and closed conditions, was measured before and at 35, 120, 220, 320, 520, and 620 minutes following ethanol using a stable platform which quantified components of body sway (path length, average distance from median, and Romberg ratios). Methamphetamine alone had no effect on body sway. Ethanol produced an increase in eyes open path length and eyes closed average distance from median. The ethanol-induced increase in body sway was antagonized by the subsequent administration of methamphetamine. Subjective ethanol intoxication was attenuated, but not eliminated. by methamphetamine. Methamphetamine's ability to antagonize ethanol-impaired stance stability suggests that motor behavior tasks may be insufficient for assessing ethanol intoxication in individuals who may be stimulant users.

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EFFECTS OF D-AMPHETAMINE IN WOMEN DURING THE FOLLICULAR AND LUTEAL PHASE OF THE MENSTRUAL CYCLE

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Little is known about the interactions between ovarian hormones and responses to psychoactive drugs in humans. Studies with laboratory animals indicate that hormones may have direct or indirect actions in the central nervous system, which may influence responses to psychoactive drugs. For example, estrogen may have direct actions on dopaminergic neurons, and dopamine is also thought to mediate the behavioral effects of stimulant drugs. In the present study, 12 healthy, regularly-cycling women received d-amphetamine (AMPH; 15 mg, oral) and placebo at two hormonally distinct phases of the menstrual cycle, the follicular phase, and the luteal phase. The follicular phase is characterized by low levels of estrogen and progesterone, whereas the luteal phase is characterized by higher levels of estrogen and progesterone. Subjective, behavioral and physiological effects were assessed for 4 hours after drug administration. It was hypothesized that the effects of AMPH would be greater during the luteal phase due to higher levels of estrogen. Results of preliminary analyses indicate that regardless of phase, AMPH produced its prototypic effects of increasing stimulation, elation, and heart rate. Interestingly, there was some support for a phase by drug interaction on measures of stimulant-like effects and heart rate. Contrary to our hypothesis, AMPH appeared to have a greater effect during the follicular phase than the luteal phase. Positive correlations were observed between plasma estradiol levels and these effects within the follicular phase, but not within the luteal phase. It is possible that the high levels of progesterone present during the luteal phase are in some way masking potential estrogen and dopamine interactions.

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IS NOVELTY-SEEKING BEHAVIOR RELATED TO DRUG-INDUCED LOCOMOTOR ACTIVITY IN INBRED RAT STRAINS?

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In humans, the propensity to use drugs is related to "novelty-seeking." Rats prefer novel places and acquisition of amphetamine (AMP) self-administration and AMP-induced activity correlates with locomotor activity in a "novel" environment and with corticosterone (CORT) levels. Yet, locomotor activity does not measure novelty-seeking because rats cannot escape from the apparatus. Rather, it may be a stress response. This study examines the relationship between novelty-seeking behaviors, CORT responses, and AMP-induced locomotor activity by assessing these in inbred rat strains (Lewis and Fischer 344) known to differ in behavioral responses to drugs and in CORT levels. Novelty responses were assessed in a place conditioning apparatus, a playground maze, and during the first exposure to a locomotor apparatus. Following these first exposures. CORT was assayed and fecal boli measured. The latter measures were assessed after restraint stress, too. These measures were compared to locomotor activity induced by AMP (2 mg/kg SC). Fist, novelly responses differed across procedures. Lewis rats preferred a novel environment (place conditioning) but showed the lowest locomotor counts during the first locomotor apparatus exposure and the fewest novel object contacts (playground maze). F344 rats avoided the novel environment but showed greater locomotor counts and novel object contacts. Second, the novelty apparatus exposures caused less stress than restraint; CORT levels were lower for Lewis and SD rats and fecal boli were lower for F344 and SD rats under these conditions. Third AMP-induced activation was related to different novelty measures across strains, Finally, these results provide some support for the notion that AMP responses are related to inherent locomotor activity in a novel environment and to CORT levels. Compared to F344 rats. Lewis rats have lower CORT levels and lower locomotor activity in a novel environment and after AMP. Yet, these factors did not consistently predict AMP-induced activity. Further, Lewis rats more readily acquire cocaine self-administration.

EFFECTS OF PRIOR EXPOSURE TO AND PRIMING WITH AMPHETAMINE ON THE SELF-ADMINISTRATION OF A LOW DOSE OF THE DRUG

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Prior exposure to amphetamine is known to result in both sensitized locomotor responding to and an increased propensity to self-administer the drug. However, the relationship between sensitized locomotor responding and enhanced self-administration remains unclear. The present experiment further examined this relationship. Rats were administered 10 preexposure injections of either amphetamine (AMPH-PRE: 1.5 mg/kg IP) or saline (SAL-PRE: 1.0 ml/kg IP) and, following catheterization, were given the opportunity to self-administer amphetamine. During the self-administration sessions, an ACTIVE (10 µg/kg amphetamine per infusion, IV) and an INACTIVE lever were inserted into the test chamber. Prior to the first eight daily self-administration sessions, animals were given a priming injection of amphetamine (1.0 mg/kg IP), followed by 3 sessions with no priming and concluding with 2 final sessions with priming. On the first session with priming, the AMPH-PRE animals showed sensitized locomotor activity relative to the SAL-PRE rats. Both groups self-admininstered amphetamine, however, when priming injections were discontinued, the AMPH-PRE animals continued to lever press and the SAL-PRE animals ceased responding. When the priming injections were restored the SAL-PRE animals resumed sell-administering amphetamine at levels equivalent to their AMPH-PRE counterparts. Temporal measures of ACTIVE lever responding revealed that early in acquisition AMPH-PRE rats increased responding during the time-out period (TORs). Both increased TORs and locomotor activity levels later characterized the AMPH-PRE rats when drug priming was discontinued. These data show that prior exposure to amphetamine indeed produces enhanced levels of locomotion and self-administration, but also reveal a complex relationship between these two responses to and for amphetamine.

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OPIOIDS MODIFY THE DISCRIMINATIVE STIMULUS EFFECTS OF d-AMPHETAMINE IN SQUIRREL MONKEYS

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Five monkeys were trained to discriminate 0.3 mg/kg of d-amphetamine (i.m.) from saline using a discrete trial termination/avoidance task. Dose-effect curves were determined for d-amphetamine and cocaine, the kappa opioid agonists, Cl-977 and U69,593, and the mu opioid agonist, morphine. The dose-effect curve of d-amphetamine was redetermined in the presence of various doses of all three opioids and the dose-effect curve of cocaine was redetermined in the presence of morphine. d-Amphetamine and cocaine substituted dose-dependently in all monkeys. In four of the five monkeys, U69,593 substituted partially or completely for the d-amphetamine discriminative slimulus (DS). CI 977 substituted completely in two monkeys, but not at all in the other three monkeys, Morphine engendered no substitution in four monkeys and complete substitution in one monkey. The d-amphetamine dose-effect curve was shifted by U69,593, CI 977, and morphine, but these effects were highly variable across monkeys. The dose-effect curve of cocaine was not altered by morphine in the three monkeys tested thusfar. These data suggest that both kappa and mu opioids can modulate the DS effects of d-amphetamine in squirrel monkeys; however, they do so with a high degree of variability. The DS effects of cocaine do not appear to be altered by morphine.

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d-AMPHETAMINE DISCRIMINATION IN HUMANS: EFFECTS OF TRAINING DOSE AND RELATION TO SUBJECT-RATED DRUG EFFECTS

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Preclinical laboratory studies suggest training dose is an important determinant of subsequent discrimination performance. The present experiment assessed the discriminative-stimulus and subject-rated effects of *d*-amphetamine in separate groups (N=4/group) of human volunteers trained to discriminate between placebo and either 10 mg (low dose) or 20 mg (high dose) *d*-amphetamine. d-Amphetamine (1.25, 2.5, 5, 10, and 20 mg) increased drug-appropriate responding as a function of dose and produced clear dose-related stimulant-like effects (e.g., "Like Drug," "Stimulated," 'TaIkative") in the low-dose group. The dose-response functions for discrimination performance and subject-ratings were virtually identical. further supporting the notion that the discriminative-stimulus and subject-rated effects of drugs covary. In the high-dose group, *d*-amphetamine also generally increased drug-appropriate responding and subject-rated effects as a function of dose. However, the dose-response functions for discrimination performance and subject-ratings were somewhat dissimilar. These findings suggest that the discriminative-stimulus and subject-rated effects of commonly abused drugs are not isomorphic, and that discrimination performance in humans is not based solely on "subjective" drug effects. These findings are also concordant with preclinical research and extend the findings regarding the effects of training dose in humans to another pharmacological class. Future research should focus on the relation among these effects and their relevance to the assessment of the abuse potential of drugs.

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A COMPARISON OF THE PRECLINICAL PHARMACOLOGY OF MODAFINIL AND AMPHETAMINE-LIKE DRUGS

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Modafinil is a chemically and pharmacologically unique compound that reduces excessive daytime sleepiness (EDS) in narcoleptics in two phase III clinical trials. Like amphetamine, modafinil increases wakefulness in a variety of preclinical models. However, the wakefulness produced by modafinil differs from amphetamines in that modafinil-induced wakefulness does not result in a surge in NREM rebound sleep and does not increase locomotor activity when normalized to wakefulness. Some of the effects of modafinil are attenuated by prazosin, but modafinil does not affect cataplexy, a behavior that is attenuated by a_1-adrenergic agonists, or modify the actions of a-adrenergic agonists *in vitro.* Thus, modafinil is not a direst or indirect a-adrenagic agonist, but may require an intact a_1-adrenergic system in order to demonstrate an increase in wakefulness. Modafinil does not bind potently to the dopamine uptake site (K_i=2 μM) and its *in vivo* effects are not modified by dopamine antagonists. Modafinil is inactive in behavioral, electrophysiological and neurochemical paradigms of dopamine activation. Modafinil, unlike amphetamine or cocaine, does not induce ipsilateral rotations in rats with unilateral 6-OHDA lesions. Thus, activation of dopaminergic pathways does not underlie the *in vivo* actions of modafinil and suggests minimal abuse potential. In summary, modafinil selectively increases wakefulness by a mechanism that is different from that of amphetamine-like agents. Thus, modafinil provides an alternate approach to treating EDS.

SENSITIZATION TO APOMORPHINE IS MANIFEST WITHIN HOURS, CONDITIONING IS MANIFEST ONLY WEEKS LATER

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Rats were lesioned in one substantia nigra with 6-hydroxydopamine. Two to three weeks later they were tested for circling in response to 0.05 mg/kg apomorphine. Animals which made fewer than 60 turns/20 min were tested with apomorphine again 2. 4 and 16 hours later (group 1) or 4. 8 and 12 hours later (group 2). Some rats not responsive to the first dose circled actively in response to the second; a majority circled by the fourth dose (12-16 hr after the first) with mean rotations increasing - 10-fold (Fig.1). Sensitized rats remained sensitized for months. Rats that did not sensitize to apomorphine within 4 injections were ultimately found to have less extensive striatal dopamine depletions than those that did. The pharmacokinetics of apomorphine argue that the sensitized behavior cannot be atributed to drug accumulation. Most rats that became sensitized also ultimately became conditioned to circle contralaterally in response to being placed, unrugged, into the rotation environment, but this conditioned behavior was not seen until weeks after initial treatment.

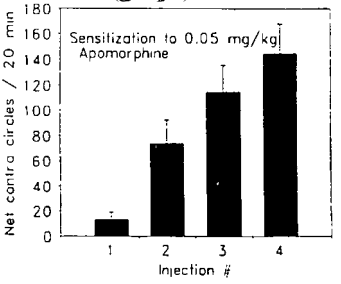

Fig. 1. Sensitization to apomorphine develops within hours.

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RESPONSIVENESS TO SEROTONERCIC DRUG CHALLENGE AFTER HIGH-DOSE FENFLURAMINE TREATMENT

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IT is well established that fenfluramine (FEN) can deplete brain serotonin (5-HT) in animals, but functional impairments associated with such 5-HT depletion have been difficult to identify. In the present work, we examined neumendwine responsiveness to 5-HT agonists in rats exposed to repeated high-dose FEN treatment. Mate rats fitted with indwelling catheters received FEN (20 mg/kg, sc. bid) or saline for 4 days. At 1 and 2 weeks after treatment, rats were challenged with iv FEN (3 mg/kg), MCPP (a 5-HT receptor agonist, 3 mg/kg), or saline. Repeated blood samples were withdrawn and plasma was assayed for prolactin and corticosterone by RlA. Both FEN and MCPP increased circulating prolactin and corticosterone in all rats. However, FEN-induced corticosterone secretion was blunted in FEN-treated rats. In addition. prior exposure to FEN significantly attenuated the prolactin response evoked by either FEN or MCPP. The repeated FEN regimen dramatically reduced (> 50%) 5-HT and 5-HIAA levels in the ventromedial hypothalamus, basolateral amygdala, and hippocampus. These data suggest that depletion of 5-HT after high-dose FEN is accompanied by functional alterations in 5-HT systems mediating neroendocrine transduction. Whether changes in responsiveness to FEN and MCPP are indicative of true 5-HT neurotoxicity remains to be determined.

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ANORECTIC AMPHETAMINES DIFFERENTIALLY AFFECT MONOAMINE TRANSMISSION IN RAT BRAIN

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A number of amphetamine derivatives are prescribed as appetite suppressants. but few studies have examined the neurochemical actions of these drugs *in vivo*. We evaluated the effects of several amphetamine analogs on extracellular DA and 5-HT in rat nucleus accumbens using *in vivo* microdialysis. Microdialysis probes were inserted into previously implanted guide cannulae and perfused with Ringers' solution overnight. On the following morning, phentermine, phendimetrazine, diethylpropion, or fenfluramine was infused locally through the probe (10 and 100 μM), and dialysates were assayed for DA and 5-HT by HPLC-EC. Phentermine was the only analog to significantly elevate DA after a 10 μM dose (300%, $P<0.01$). At 100 μM, phentermine increased DA 15-fold while the other drugs caused only modest increases. Fenfluramine was the only analog to significantly elevate 5-HT at 10 μM (600%, $P<0.001$). At 100 μM fenfluramine produced a 15-fold rise in 5-HT whereas the other drugs elicited small variable increases. Our findings show that phenylethylamines with similar anorectic potency display differential effects on DA and 5-HT neurons. The results with phendimetrazine and diethylpropion are especially noteworthy; these drugs stimulate locomotor activity and maintain self-administration behavior yet fail to appreciably affect extracellular DA in the nucleus accumbens. Thus, the psychostimulant properties of some amphetamine analogs may involve non-DA mechanisms.

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ABUSE LIABILITY ASSESSMENT OF SIBUTRAMINE

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Sibutramine is a serotonin and norepinephrine reuptake inhibitor under investigation as an anorectic agent. This study examined acute subjective, reinforcing, and physiological effects with the primary goal of assessing the abuse liability of sibutramine. Cole (unpublished data) demonstrated low abuse potential for 20 and 30 mg sibutramine (doses within the therapeutic range for weight loss); however no data existed on the abuse potential of supratherapeutic doses. This study, therefore examined higher doses (25 and 75 mg) of sibutramine and compared its effects to placebo and d-amphetamine (20 mg) as a standard positive control. Twelve polydrug abusers with no history of dependence on any drug served as subjects in this six-week, double-blind, placebo-controlled, inpatient/outpatient study. Subjects participated in four drug sessions, in which they completed subjective effects scales including the Profile of Mood Stales (POMS). Visual Analog Scales (VAS), and the Addiction Research Center Inventory (ARCI). The Multiple Choice Procedure (MCP; Griffiths *et al.,* 993) was used to evaluate reinforcing efficacy. In this procedure, volunteers made choices between receiving increasing monetary amounts or another drug dose. Sibutramine 25 mg produced subjective effects that were indisringuishable from placebo. Sibutramine 75 mg produced significant unpleasant effects, and volunteers would give up an average of $4.04 from their study pay rather than receive the drug again, d-Amphetamine 20 mg served as an adequate positive control. It therefore appears that sibutramine lacks abuse liability in acute dose testing.

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FLUOXETINE TREATMENT OF SMOKABLE AMPHETAMINE DEPENDENCE IN THE NORTHERN MARIANAS ISLANDS

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We performed an open trial of Fluoxetine as pharmacotherapy for amphetamine dependence in a rural pacific island setting. Twenty-two subjects who met DSM-IV criteria for amphetamine dependence were entered into the study, which lasted 8 weeks. Mean dose of Fluoxetine was 35mg. The medication was well tolerated and 19 of the 22 (86%) completed the study. The study population was ethnically diverse, consisting primarily of native pacific islanders. Study participants were evaluated on intake for co-morbid psychiatric disorders with 33% meeting criteria for Major Depression. 24% Anxiety Disorder, 14% Psycholic disorder, and 4% Eating disorder. Study participants were screened weekly for self report drug use and drug craving and bi-weekly for drug urine testing. Improvement was demonstrated for all outcome measures in this open trial with reduction in amphetamine positive drug urine tests from 63% at intake to 15% at week 8. Mean self reported amphetamine use dropped from 1.9 times per week at intake to 0.2 times per week at week 8. **Conclusions:** Fluoxetine was well tolerated and accepted as pharmacotherapy in this rural pacific island population and may be associated with improved treatment outcome. Additional study in a double blind trial is needed to further evaluate the use of this medication in the treatment of amphetamine dependence.

A COMPARISON OF CURRENT AND FORMER STIMULANT ABUSER'S SCORES ON THE WENDER UTAH RATING SCALE

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A recurring problem in the diagnosis of attention deficit hyperactivity disorder (ADHD) in adults is the retrospective diagnosis of childhood ADHD. The Wender Utah Rating Scale 25 item form has been found to have good reliability (Rossini & O'Connor, 1995) and to correctly identify 86% of adults with ADHD (Ward *et al.,* 1993). The prevalence of ADHD in populations of individuals abusing stimulants is higher than expected. This raises the question of whether the retrospective diagnosis of childhood attention deficit hyperactivity disorder in substance abusers is affected by their current drug use. To address this question we used scores on 25 questions from the Wender Utah Rating Scale. We compared a cohort of 28 subjects who are presently abusing methamphetamine with scores acquired as follow-up data from 47 former stimulant abusers treated for stimulant abuse in a Matrix clinic. All participants reside in the same area of San Bernardino County, California. There is a significant difference (1=2.27 df,73 p=.026) between the mean scores of the two groups. The mean score of the current abusers is 12 points higher than that of the former abusers. In addition the range is offset by about the same amount. The current abusers scores run from 9 to 93. while the scores of the former abusers run from 0 to 89. The variances of the two groups are equal. However, although 42% of the current abusers scored above the cutoff of 46 for ADHD and only 25% of the former abusers scored above 46, this difference was non significant. These results are consistenl with about a 10 point effect of current methamphetamine abuse on the Wender Utah Rating Scale. Thus stimulant use may affect a subject's perception of his or her childhood, and the number of abusers identified with adult ADHD may be over estimated.

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CHARACTERISTICS OF STIMULANT ABUSERS AND THEIR RESPONSE TO TREATMENT

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Stimulant abuse continues to present a significant public health concern. Characteristics of and the responses to treatment for 500 methamphetamine (MA) and 224 cocaine (COC) users seen at the Matrix Institute from 1988-95 are presented. The treatment provided was structured, cognitive/behavioral approach that included early recovery skills, family education, and relapse prevention groups. Results indicate intranasal use is preferred by MA users (55%) although the popularity of smoking is on the increase. MA users started using at a younger age (21.4 yrs. vs. 23.7 yrs.) and used heavily for a longer period prior to entering treatment (41.2 mos. vs. 39.7 mos.) compared to COC users. Intravenous MA use has a more severe impact on the user than other routes of administration, characterized by heavier use, greater criminal justice involvement, and more psychiatric complications. The two groups responded equally to the Matrix model of treatment in terms of participation, retention, and percent negative urine toxicology screens. These data support this treatment approach as one that can be effective for stimulant users, but the data also highlight the need for additional effective prevention and treatment strategies.

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LONG-TERM OUTCOMES FROM METHAMPHETAMINE ABUSE

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Methamphetamine abuse is spreading rapidly, with little information available regarding the persistent effects of chronic use. We present the results of a CSAT funded follow-up of 100 cocaine and 100 methamphetamine abusers one to five years after treatment admission to the Matrix Institute on Addictions. The follow-up included measures of current medical and psychiatric status (Brief Symptom Inventory), current drug/alcohol use and related effects (Addiction Severity Inventory), and recent service utilization including health care, legal, and public service access. A description of the sample of methamphetamine users across all these measures will be presented, as well as a description of bow these two groups differ at the time of follow-up.

COMPARISON OF BASAL MOTOR ACTIVITY, COCAINE-STIMULATION AND BRAIN COCAINE LEVELS IN MICE

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Genetically related differences in motor activity are considered to reflect differences in exploratory drive, reactivity to novelty and general level of arousal. Within and between session habituation and cocaine-induced motor stimulation were examined in 4 inbred strains (Balb/cByJ, DBA/2J, C57BL/6J and SJL/J), an F1 Hybrid (C57BL/6J x SJL/J) and an outbred strain (CD1). Strain differences were observed in total amount of locomotion during the first 2h exposure to the test apparatus with Balb mice exhibiting the highest, C57, Hybrid and CD1 mice intermediate, and SJL and DBA the lowest levels. All strains exhibited within session habituation, although only the Hybrid, CD1 and SJL mice showed a reduction in activity from the first to the second habituation session. All mice exhibited cocaine (30 mg/kg) induced increases in zone entries and 5 of the 6 strains exhibited increased rearings compared to saline. Rearings were not changed or decreased by cocaine only in the Balb mice. Locomotor sensitization following a second administration of cocaine (30 mg/kg) was observed in DBA and CD1 mice. Measurement of cocaine and its metabolites in brain tissue by HPLC following a single cocaine 30 mg/kg injection revealed that C57 had the highest brain cocaine concentrations compared to all other strains. Norcocaine was highest in DBA, CD1 and SJL compared to Hybrid and C57 mice. Benzoylecgonine was lowest in C57, SJL and Hybrid compared to Balb and DBA mice. These data illustrate genetic differences in cocaine-induced motor stimulation that cannot be solely attributed to differences in motor reactivity to novelty or cocaine pharmacokinetics and contribute to a comparative database for cocaine-sensitive behaviors in various strains of mice.

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LOCOMOTOR RESPONSE OF THE C57BL/6J MOUSE TO CHRONIC "BINGE" PATTERN COCAINE: DEVELOPMENT OF TOLERANCE

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Behavioral, and concomitant neuroendocrine and molecular changes in the brain of rats in response to cocaine administered in a "binge" pattern designed to mimic the way cocaine is taken by humans, have been studied in several laboratories. In order to exploit the genetic information of different strains of inbred mice and to serve as a background for studies in recently developed transgenic mice, we have extended me study of the effects of chronic "binge" pattern cocaine administration (BPCA) to the well studied C57BU6J mouse. Method: Six individually caged adult makes received three daily injections of cocaine (15/mg/kg ip) at hourly intervals starting half an hour into the light portion of the 12-12 hr light-dark cycle, and six received saline on the same schedule for 14 days, Spontaneous locomotor activity of each mouse was monitored in its home cage. Results: Cocaine-treated mice showed significantly higher levels of locomotor activity across the hour following each injection than did saline controls, $F(1, 10)= 13.61$, $p<0.01$, in agreement with our earlier study in Fischer rats (Unterwald *et al.,* 1994). But, in contrast to our finding of behavioral sensitization in the rat in that study, the locomotor response of C57 mice to BPCA was less pronounced (Newman Keuls *post hoc* test, $p< 0.05$). and shorter in duration, after chronic BPCA; that is, tolerance to the locomotor stimulating effect of cocaine was found. Also, in contrast to the still elevated plasma corticosterone levels found after 14 days BPCA in the rat (Zhou *et al.,* 1996), corticosterone levels after 14 days BPCA in the C57 mice were not significantly elevated. Conclusion: This study demonstrates differences between the rat and the mouse in response to binge cocaine administration. Further studies with inbred strains and transgenic mice, as well as between species, should help to elucidate the varied effects of cocaine. References available from authors.

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EFFECTS OF "BINGE" PATTERN COCAINE ON LOCOMOTOR ACTIVITY AND STEREOTYPY IN MALE C57BL16J and 129/J MICE: A DOSE RESPONSE STUDY

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With the expanding use of genetically engineered animals in addiction research it has become increasingly important to characterize the response to drugs of abuse in mouse strains commonly utilized as host strains for transgenic and knockout mice such as the C57BL/6J and 129/J strains. Therefore. the psychomotor stimulating effects of 4 doses of cocaine, administered in a "binge" pattern (3 equal injections at hourly intervals) were examined in adult mate C57BL/6J and 129/J mice. Mice were injected with either saline or cocaine (2.5 mg/kg/injection - 15 mg/kg/injection) in a "binge" pattern for 3 days. Spontaneous locomotor activity was monitored 24 hours daily in the home cage. Behavioral stereotypy was measured in the home cage at 15, 30, and 45 min following each injection. Behavioral stereotypy was observed following injections of 10 or 15 mg/kg of cocaine in C57BL/6J (Dose main effect: $F_{(4,31)} + 34.6$; $p < 0. 0001$) and 129/J mice (Dose main effect: $F_{(4,25)} = 28.9$; $p < 0.0001$). Lower doses of cocaine did not produce a consistent expression of behavioral stereotypy in either strain. Interestingly, the magnitude of stereotypy was significantly lower in 129/J mice compared to C57BL/6J mice at identical doses of cocaine. C57BL/6J mice also demonstrated a dose dependent cocaine-induced stimulation of spontaneous locomotor activity following administration of 10 or 15 mg/kg of cocaine (Dose main effect $F_{(4,31)} = 15.1$ $p < 0.0005$; Newman-Keuls post hoc tests: $p < 0.005$). 129/J mice did not exhibit increased locomotor activity in response to any dose of cocaine tested in the present study. These results extend earlier reported dose response findings in the mouse and provide a direct comparison of the psychomotor stimulating effects of cocaine in two strains of mice frequently utilized as host strains for transgenic animals. These data help establish a baseline for behavioral analysis of transgenic mice.

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GENDER DIFFERENCES IN COCAINE RESPONSIVITY IN RATS

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The purpose of the present study was to explore gender differences in the behavioral response to cocaine in rats alter a single dose, and after repeated cocaine treatment Male and female rats were treated for 3 or 14 days with saline or cocaine (15 mg/kg, ip, bid). Twenty four hours after the last dose, a dose response curve for cocaine-induced locomotor activation was determined by administering saline, 10.20 or 40 mg/kg of cocaine to animals from both chronic treatment groups. Locomotion was assessed using an Opto Varimax system and a manual rating scale derived from that of Ellinwood. Acute cocaine administration caused a significantly greater stimulation of locomotor activity in females than in males. After 3 days of cocaine treatment, automated locomotion scores for both males and females were enhanced relative to animals treated repeatedly with saline but there was no gender difference in sensitization. After 14 days of treatment, both chronic cocaine-treated males and females showed increases in cocaine-stimulated behavior with both behavioral measures relative to chronic saline-treated animals. Females showed markedly enhanced stereotypies at higher cocaine doses, although there was no global gender difference in sensitization. These results suggest that females show substantially greater responses than males to the first cocaine dose. 'the enhanced production of stereotyped behaviors after longer chronic treatment might not reflect greater sensitization, but the higher starting point from the large response to the acute dose.

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THE LOCOMOTOR STIMULANT AND DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE: ASSESSMENT OF THE 5-$HT_{1B/1D}$ ANTAGONIST CR127935

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Stimulation of 5-HT_{1B} receptors appears to mediate the locomotor hyperactivity induced by the 5-$HT_{1B/1A}$ agonist RU 24969 and (+)-3,4-methylenedioxymethamphetamine (MDMA) and RU 24969 enhances the discriminative stimulus effects of cocaine (COC). In the present study, we assessed the ability of the 5-$HT_{1B/1D}$ antagonist GR127935 (GR) to alter the hyperactivity induced by COC, RU 24969, and MDMA in locomotor activity monitors which measured peripheral, central and rearing activity. CR (5 mg/kg sc) significantly attenuated peripheral (-29%) and rearing activity (-53%) induced by COC (15 mg/kg, N=B/group), but 2.5 and 10 mg/kg of GR was without significant effect. Likewise, the peripheral activity induced by RU 24969 (2 mg/kg, ip) and MDMA (3 mg/kg, ip) was attenuated by GR (2.5 mg/kg, sc). The ability of GR to alter the stimulus effects of COC was also assessed in rats trained to discriminate COC (10 mg/kg) from saline in a two-lever, water-reinforced FR 20 paradigm (N=8). The stimulus effects of COC (10 mg/kg, ip) were not altered by pretreatment with GR (1-8 mg/kg, ip) and a fixed dose (2 mg/kg, ip) failed to shift the COC dose-response curve (0.625-10 mg/kg, ip). Although the antagonism of r5-$HT_{1B/1D}$ receptors may attenuate the hyperlocomotor effects of RU 24969 and MDMA, the discriminative stimulus and hyperlocomotor effects of COC appear to be resistant to GR. This questions the role of r5-$HT_{1B/1D}$ in the COC cue and suggests a minor role for this receptor subtype in the modulation of the locomotor effects of COC.

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EFFECTS OF INJECTION OF SCH 23390 INTO THE VENTRAL TEGMENTAL AREA ON COCAINE-INDUCED SENSITIZATION

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The mesolimbic dopamine system has been reported to play an important role in the development of behavioral sensitization to psychostimulant drugs. Previous studies have shown that intra-ventral tegmental area (VTA) injections of the dopamine D1 antagonist SCH 23390 blocked the development of the sensitized motor-stimulant response to amphetamine (Vezina, J. Neurosci. 16: 2411, 1996) and the acute motor-stimulant response to cocaine (Steketee and Braswell, Behav. Pharmacol., In Press). This study tested whether intra-VTA SCH 23390 could block the development of cocaine-induced sensitization. Male Sprague-Dawley rats received bilateral cannulae implants 1 mm above the A10 region for microinjections and 3 mm above the nucleus accumbens for *in vivo* microdialysis 1 week before the start of an experiment. On day 1, rats received intra-VTA injection of saline (0.5 µl/side) or SCH 23390 (15 nmol/side) 5 min before systemic injections of saline (1.0 ml/kg) or cocaine (15 mg/kg). The rats received the same injection regimen on days 2-4 in their home cage. On day 11, all rats received cocaine (15 mg/kg) injections. On days 1 and 11, motor activity and dopamine concentrations in the nucleus accumbens were monitored following injection. Intra-VTA SCH 23390 attenuated the acute response but did not alter the development of the sensitized behavioral response to cocaine. However, SCH 23390 did block the acute and development of the sensitized neurochemical responses to cocaine. These data suggest that dopamine D1 receptors in the VTA may be partially involved in the development of sensitization to cocaine.

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SEROTONIN-4 RECEPTOR ANTAGONIST AND COCAINE-INDUCED MOTORIC ACTIVITY

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Over the years, there have been many srudies that indicate that serotonin (5-HT) is able to modulate the activity of central dopamine (DA) neurons in the mammalian brain. DA-mediated behaviors such as stereotypy, hyperactivity and catalepsy are modified by alterations in central 5-HT transmission. Cocaine injections in rodents have been shown to induce some of these behaviors in rodents. Recently 5-HT4 receptors have been implicated in morphine condition place preference. The aim of this study was to examine the effect of 5-HT4 receptor antagonist on cocaine induced locomotor activity and stereotypy. We examined mice pretreated with GR125487D (0.001, 0.01, 0.1 mg/kg icv) prior to ip administration of 3, 10, 30 mg/kg of cocaine. Results indicate that GR125487D produced a dose-dependent suppression of locomotor activity: $F(Dose)=7.95$ $df=4.38$; $P<0.01$. At 0.001 mg/kg, GR125487D produced no significant degree of locomotor depression and maximal locomotor depression at 0.01 mg/kg. The maximally depressant dose of GR125487 significantly depressed saline and cocaine-induced locomotor activity. $F(pretreatment)=45.7$; $df=7.30$; $p<.01$. These data indicate that GR125487D does not selectively decrease cocaine-indeced motoric activity.

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BEHAVIORAL AND NEUROCHEMICAL EFFECTS OF LOCAL AND SYSTEMIC 4-CHLOROBENZTROPINE IN THE RAT

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The current studies compared the novel tropane analog 4-chlorotenztropine (4-Cl-BZT) and cocaine for their abilities to stimulate locomotor activity and to elevate extracellular dopamine in the nucleus accumbens as measured by *in vivo* microdialysis. Peripherally administered cocaine was found to be approximately twice as efficacious as a locomotor stimulant than 4-Cl-BZT. and was behaviorally active at lower doses than 4-Cl-BZT. At 10 mg/kg i.p., only cocaine elevated nucleus accumbens dopamine and induced locomotor activity. Unlike the rapid onset and short duration of action of cocaine, the locomotor stimulant effect of i.p. 4-Cl-BZT remained modest and sustained (to 2 hours) for all behaviorally active doses tested. When perfused locally through the microdialysis probe, both cocaine and 4-Cl-BZT dose-dependently elevated extracellular dopamine in the nucleus accumbens, with both drugs effective at 10-1000 μM and maximally effective at doses≥ 100 μM. However, 4-Cl-BZT elevated extracellular dopamine to a much greater extent than cocaine when infused directly into the nucleus accumbens (approximately 2500% of baseline maximally versus 500 % of baseline for cocaine). Furthermore. the duration of action of 4-Cl-BZT was significantly longer than that of cocaine. Whereas the effect of cocaine on exlracellular dopamine levels persisted for less than one hour, dopamine levels remain elevated above basal levels 4-5 hours after termination of 4-Cl-BZT infusion. Despite the pronounced effects of locally perfused 4-Cl-BZT on extracellular dopamine, bilateral microinjection of 4-Cl-BZT (30-300 nmol/side) directly into the nucleus accumbens induced only a modest sustained locomotor stimulation relative to the marked and rapid locomotor response to intra-accumbens cocaine (30-300 nmol/side). These results indicate that cocaine and 4-Cl-BZT differ in their behavioral efficacy after either peripheral or local administration, despite the ability of both drugs to elevate extracellular dopamine in the nucleus accumbens *in vivo*.

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NOVEL NMDA/GLYCINE SITE ANTAGONISTS BLOCK COCAINE-INDUCED LOCOMOTOR SENSITIZATION AND BEHAVIORAL TOXICITY

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The effectiveness of two novel NMDA/glycine site antagonists, ACEA- and ACEA-1328, were characterized against cocaine-induced convulsions, lethality, and locomotor sensitization. Pretreatment of Swiss Webster mice with these antagonists dose-dependently attenuated cocaine-induced convulsions and lethality; these effects were pharmacologically antagonized with D-cycloserine. Most importantly, following a lethal dose of cocaine, ACEA-1021 was effective in preventing death in 57-8646 of animals when they were post-treated either immediate prior to or after the occurrence of a seizure. In addition, at doses that did not alter spontaneous locomotion, the antagonists eliminated the development of locomotor sensitization to chronic cocaine, and abolished its acute stimulatory effects. The NMDA/glycine site partial agonist [R]-HA-966 also attenuated cocaine-induced convulsions, but the AMPA-selective antagonists, NBQX, failed to provide protection. These novel NMDA/glycine site antagonists are well tolerated *in vivo* and are not associated with the unfavorable side effects seen with previously tested non-competitive antagonists. These compounds are the first of their kind in showing protective effects against cocaine-induced convulsions, lethality, and locomotor sensitization and suggest that NMDA-receptor mediated excitatory mechanisms play important role in cocaine abuse and toxicity.

δ-OPIOID RECEPTOR AGONISTS POTENTIATE THE MOTOR EFFECTS OF COCAINE IN THE RAT

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Endogenous opioids modulate the brain dopamine systems and the effects of drugs that act via those systems, such as cocaine. To examine the possible role of δ-opioid receptors in these modulatory effects, the selective δ-opioid receptor agonists [D-Pen^2-DPen^5]enkephalin (DPDPE) and [D-Ala^2-D-Leu^5]enkephalin (DADLE) were tested in combination with cocaine for effects upon motor activity in rats. DPDPE (0, 10, 100 μg/10μl) or DADLE (0, 1.0, 3.0, 10μg/10μl) was given intracisternally as a 20 min pretreatment followed by cocaine (0, 5.6, 10, 17.5 mg/kg) given intraperitoneally as a 5 min pretreatment. Activity was recorded for 1 hr (n=8 all groups). DPDPE and DADLE both dose dependently increased the distance traveled and stereotypy counts following cocaine administration ($p<0.05$). For example, 10μg DPDPE and 10μg DADLE increased the distance traveled following 5.6 mg/kg cocaine from 2263±1120 cm to 12610±4364 cm and 11227±2174 cm respectively. These results suggest that activation of central δ-opioid receptors potentiates the motor stimulatory effects of cocaine.

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MORPHINE-INDUCED MOTOR ACTIVITY IS ENHANCED IN RATS TRAINED TO DISCRIMINATE COCAINE, BUT NOT AMPHETAMINE

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We evaluated the effects of morphine (0.56, 2.0, 3.0, 5.6, 15 mg/kg, s.c.) on the motor response of male Sprague-Dawley rats that had been trained to discriminate either 10 mg/kg cocaine or 1.0 mg/kg d-amphetamine from saline, and had been in an ongoing study over a period of 11.8 (4.4-19.1) or 10.5 (5.8-15.2) months, respectively. These groups of rats were also tested for sensitization and cross-sensitization to both of the training drugs. As compared to the drug-naive controls, the cocaine-trained rats showed significantly higher horizontal activity counts, more ambulation, and more stereotypy in response to morphine, whereas the amphetamine-trained group of rats did not. Cross-sensitization to morphine occurred independently of whether or not there was sensitization to the motor-stimulant effects of me training drug itself. The difference between the groups in responsiveness to the motor-stimulating effects of morphine must be due to the difference in the training drugs. Both groups were closely matched with respect to age and history of experimental testing. Moreover, the doses of the training drugs were equivalent in terms of discriminability and in motor-activating effects in the naive rats. Thus, long-term intermittent exposure to cocaine has effects on the neuronal substrates that mediate the motor response to morphine that are different from those of long-term intermittent exposure to amphetamine.

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EFFECTS OF COCAINE ABSTINENCE ON HUMAN MOTOR ACTIVITY

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Much behavioral work with cocaine in animals has used motor activity as the dependent variable, but there is little systematic data on human motor activity involving cocaine We studied the motor activity of 12 cocaine-dependent (DSM-IIIR) research volunteers, [10 African-American (8 males, 2 female), 2 Caucasian males] during 90 days of monitored cocaine abstinence on the closed DIR research ward. Mean age was 32.8 years; range 26-39 years. Subjects' motor activity was recorded over 24-hour periods by wrist-watch sized activity monitors (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) worn on their dominant wrist. These monitors record intensity of motor activity using a accelerometer generating a signal strength proportional to motion regardless of its plane or smoothness. Because of missing data, activity was analyzed separately over 3 intervals: Days 7-14 (N=9), Days 14-50 (N=10), Days 50-86 (N=6). Typical circadian activity variation was evident with lower activity between 11p.m.- 6 a.m. and higher activity between 7 a.m. - 11 p.m. There was a decrease in activity during mid-day (noon - 4 p.m.) only on day 10. These findings suggest that middle and late cocaine abstinence was not associated with substantial motor activity changes.

DAYTIME AND NIGHTTIME SLEEP PATTERNS DURING COCAINE ABSTINENCE

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Early stimulant withdrawal is associated clinically with increased sleep and dreaming. This has been confirmed by two prior sleep laboratory (polysomnography) studies of cocaine withdrawal lasting 3 days (n=3) and 3 weeks (n=9). We evaluated both nighttime and daytime sleep parameters in 12 chronic (mean [SD] 6.7 [3.7] years of regular cocaine use), heavy (23.1 [4.2] days used in past 30) cocaine users during 90 days of monitored (by random urine testing) abstinence on the closed DIR research ward, beginning 1.0 [0.5] days (range 0.5-2) after last cocaine use. Motor activity was recorded continuously by wrist-watch sized activity monitors (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) worn on the dominant wrist. Sleep parameters (duration, sleep efficiency [% time asleep], sleep latency [time to first sleep episode]) were generated using the scoring algorithm of Cole *et al.* (1992) (Action-W computer program, Activity Research Services, San Diego, CA), which is based on 6-min weighted sums of activity counts (shown to correlate 0.9 with polysomnography in normal subjects). Sleep parameters were analyzed separately for out-of-bed (daytime) and in-bed (nighttime) phases defined by subjects' written activity logs. Data were analyzed for 24-hr periods about weekly, beginning day 3 of admission, with n=7-11 because of missing data. There were few robust or significant changes in sleep parameters over time. There were trends towards decreasing nighttime sleep duration and efficiency and increasing sleep latency as cocaine abstinence continued. These findings are limited by the small and varying sample size, the absence of data from the first 2-3 days of abstinence. (when most change may be occurring), and the indirect nature of the sleep data (sleep scoring method never directly validated in cocaine users).

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AN OPEN-LABEL PILOT SAFETY STUDY OF LOFEXIDINE FOR THE TREATMENT OF OPIATE WITHDRAWAL

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Preliminary data have indicated that lofexidine, an alpha-2 adrenergic receptor agonist, may be effective for the clinical management of the opiate withdrawal syndrome while producing less hypotension than clonidine. The present 20-day, ongoing, inpatient study is being conducted to assess the relative safety of lofexidine and to obtain information related to its potential efticacy. Twenty-five to 30 subjects (total) will be studied at three plateau doses of lofexidine (1.6, 2.4, and 4.0 mg/day). Opiate-dependent individuals are stabilized on morphine subcutaneously (25 mg four times daily) for 8 days. On day 9, morphine is discontinued and lofexidine is administered daily through day 18. No medication is administered on days 19 and 20. The 1.6 and 2.4 mg/day groups have been completed. Nine subjects have taken lofexidine in the 1.6 mg/day dosage group and no serious adverse medical events have teen observed. Three of these subjects have completed the protocol; live dropped out secondary to opiate withdrawal symptoms and one for personal reasons. Nine subjects have taken lofexidine in the 2.4 mg/day group; again, no serious adverse medical events have been observed. Five of these subjects have completed the protocol and four dropped out secondary to opiate withdrawal symptoms. Five subjects in this group exhibited orthostatic hypotension. Of these live. four also reported vertigo that quickly resolved upon sitting. None of the subjects at either dose level experienced syncope, symptomatic bradycardia or persistent hypotension. Recruitment has just begin for the 4.0 mg/day dose group.

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SAFETY AND EFFICACY OF LOFEXIDINE ASSISTED METHADONE WITHDRAWAL

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Background: The α2 agonist lofexidine, is now widely used in the UK, to attenuate the signs and symptoms of opiate withdrawal. The side effect profile of lofexidine is less severe than that of clonidine and therefore it should offer a safer. more acceptable treatment. We hypothesised that "rapid induction" onto lofexidine on discontinuation from opioid (where the dose was increased to peak levels over 2 days, typically 1.6mg/day), could be managed safely and would be acceptable to patients and that such induction would attenuate symptoms of opioid withdrawal sufficiently to retain the patients in treatment. Procedures: Twenty-five opioid dependent patients underwent a 10-14 day lofexidine-assisted methadone withdrawal on an in-patient psychiatric unit. The Opiate Treatment Index (OTI) was performed on admission, and BP. pulse, Gossop Opiate Withdrawal Scale, and Profile of Mood States were performed daily. Results: The OTI showed the sample to be long-term opioid addicts (3-21 years), aged 20-50 years, dependent on 20-60mg methadone. No acute adverse reactions to lofexidine were observed but adjustment of dosing on a day to day basis was necessary in nearly 50% due to reduction in blood pressure. Opiate withdrawal symptoms typically peaked within 48-72 hours after cessation of methadone. Seventy-five % of the sample completed detoxification, and noncompletion was associated with a failure to reach the peak dose of lofexidine.

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OBJECTIVE ACTIGRAPHIC MEASUREMENT OF THE EFFECT OF HYPNOTICS DURING LOFEXIDINE ASSISTED METHADONE WITHDRAWAL

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Background: Sleep has never been measured objectively during the first 6 weeks of methadone withdrawal. This is surprising as methadone withdrawal has now been used for about 50 years, sleep is severely disrupted during acute withdrawal, it takes 3-6 months to return to normal following withdrawal, and is implicated in relapse. There is no good evidence that hypnotics are effective during acute withdrawal. We hypothesised that both drugs would increase total sleep time (TST), reduce the number/frequency of arousals and sleep latency during acute withdrawal. **Procedures:** Thirty long term opioid dependent (3-21 years) humans underwent a 10-14 day lofexidine assisted methadone withdrawal (15-60mg) on an inpatient psychiatric unit, while wearing the Actigraph activity monitoring system (Cambridge Neurotechnology Ltd, UK). Actigraph measures are known to correlate highly with sleep EEG measures. Subjects were their own controls. We compared the night of the hypnotic with the night before and night after on days 0-10 off methadone, for either 25-50mg promethazine or 7.5-15mg Zopiclone on alternate nights. Results: Zopiclone caused a significant decrease in night waking, the length of the wakings, in the number of sleep/wake shifts, and an increase in the length of the sleep bouts. TST was non-significantly increased by about 15 minutes. The amount of sleep obtained varied widely (SD=2 hours). Surprisingly there were no changes in sleep latency, and no changes with promethazine (which was also being used to treat anxiety in both groups). These findings demonstrate the potential of actigraphy and that zopiclone assists sleep during acute opioid withdrawal.

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CLINICAL STUDY OF SCOPOLAMINE DETOXIFICATION FOR THE TREATMENT OF HEROIN ADDICTS

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Preclinical study has shown that scopolamine could not only reverse morphine antinociceptive tolerance, but also block the naloxone precipitated withdrawal symptoms in morphine dependent rat and monkey and facilitate the morphine excretion. A study on evaluating the efficacy of treatment of heroin addicts (n=100) by scopolamine detoxification was undertaken, methadone (10 days program) group (n=50) and clonidine treated group served as controls. The results showed that the scores of abstinence syndrome in scopolamine detoxification group was lower than that those in clonidine treated group in the first three days of protocol, but this difference disappeared in the late stage of treatment, while the scopolamine detoxification was effective as methadone detoxification in the control of abstinence syndrome during the first live days of treatment but the difference in the scores of abstinence syndrome between scopolamine and methadone group was observed during the late five days of protocol. Treatment results were evaluated after a 6-month follow-up, there was a lower percentage of morphine catabolites in urine in the group of patients treated with scopolamine than that in methadone or clonidine treated group. The side-effects produced by scopolamine in general were dry mouth, somnolence, tachycardia blurred Eaton and so on, which relieved gradually or disappeared with the decreasing of its dose. In conclusion, scopolamine does not result in potential dependence and has definite curative effect in the treatment of heroin addiction.

EFFECTS OF BUTORPHANOL, HYDROMORPHONE, AND NALOXONE IN OPIOID-WITHDRAWN VOLUNTEERS

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This study sought to determine whether the opioid mixed agonist-antagonist butorphanol alters withdrawal symptom severity in hydromorphone-maintained volunteers exhibiting signs of spontaneous opioid withdrawal. Butorphanol was compared to naloxone (an opioid antagonist), hydromorphone (an opioid mu agonist), and saline in opioid-withdrawn volunteers, participants were 12 opioid-dependent volunteers who resided on a clinical research ward and were maintained on hydromorphone, orally administered daily in four 10 mg doses (40 mg/day total). prior to pharmacologic challenges, subjects were not administered maintenance doses of hydromorphone for 23 hrs such that challenge sessions took place while subjects exhibited signs of opioid withdrawal. Challenges were administered two times per week and consisted of a double-blind intramuscular injection of: butorphanol (0.375, 0.75, 1.5, 3 and 6 mg), naloxone (0.1 and 0.2 mg), hydromorphone (5 and 10 mg), or saline placebo. Physiologic measures and subject- and observer-rated behavioral responses were measured before dosing and for 2.5 hr after drug administration. Five of the 12 subjects who completed the protocol scored a mean of at least 2 on the Himmelsbach observer-rated withdrawal scale (possible range: 0 - 7); data analyses were based on these 5 subjects. Butorphanol and hydromorphone decreased withdrawal severity and increased scores on adjective scales and visual analog scales measuring opioid agonist effects. Naloxone slightly increased scores on opioid antagonist adjective scales and a subject-rated visual analog scale measuring "bad drug effects". These data indicate that butorphanol may be administered to volunteers maintained on short-acting opioids to alleviate withdrawal symptoms without precipitating withdrawal.

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THE EFFECT OF CYCLOSERINE ON NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

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NMDA antagonists attenuate opiate withdrawal in pre-clinical studies. The antimicrobial Cycloserine (CYC) is a partial agonist at the strychnine-insensitive glycine binding site *in vitro* and attenuates opiate withdrawal *in vivo*. The effect of CYC pretreatment on precipitated opiate withdrawal was studied in hospitalized heroin-dependent subjects stabilized on Levorphanol 6mg po tid. After an acclimatization challenge, 3 double-blind challenges were done with balanced, randomized pretreatment with placebo, CYC 375mg, or 750mg/70kg. pretreatment was in a single oral dose 6 hours before i.v. Naloxone 0.4mg/70kg. Opiate withdrawal measures were summarized as AUC-change and analyzed in a one-factor repeated measures ANOVA with planned comparisons of each active CYC dose to placebo. Six subjects completed all challenges. a seventh did not complete the 375mg CYC, and an eighth did not complete the 750mg CYC, prior to naloxone, CYC trended (p <.06) to lower total recall scores on the Buschke Selective Reminding Test (means of 109 after placebo, 105 after 375mg, and 99 after 750mg), and had no significant side effects. Within subject, withdrawal severity was relatively consistent across challenges. There were no trends towards attenuation of any withdrawal symptoms by CYC. Cycloserine, at the doses tested, showed no promise as a treatment of opiate withdrawal.

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ACUTE IBOGAINE AND COCAINE: ACTIONS AND INTERACTIONS IN RHESUS MONKEYS

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Ibogaine, an alkaloid from the shrub Tabernanthe iboga, is said to be useful in the pharmacotherapy of stimulant abuse (H. Lotsof, patent #4,587,243). It was tested in a cocaine hyperarousal model (Rausch) designed to investigate a stage of dependence most likely associated with compulsive abuse and other psychopathological changes (Aceto and Bowman, Arzniemittel-Forschung 43, 1993). Three or 4 monkeys (M. mulatta) per treatment regimen were pretreated s.c. with ibogaine (2 or 8 mg/kg) or vehicle (veh) and 20 min later received sterile saline (sal) or cocaine (1 mg/kg) i.v. Each animal was individually tested and observed by a trained "blind" evaluator who scored each monkey for the following signs: checking, escape attempts, restlessness, tremors and oral dyskinesias (chewing and tongue movements). The high-dose ibogaine-sal-treated monkeys displayed significantly more total signs than veh-sal treated monkeys and significantly fewer signs than the veh-cocaine group. When ibogaine and cocaine were given together, an increased incidence of tremors occurred, In addition, 2 monkeys receiving the high-dose ibogaine-cocaine dose regimen convulsed. It is concluded that ibogaine did not attenuate cocaine-induced hyperarousal; instead, it increased the incident of tremors and convulsions and perhaps stereotyped behavior in combination with cocaine. The results suggest that treatment of compulsive cocaine abusers with ibogaine (acutely) may have adverse consequences.

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AN OPEN-LABEL STUDY OF A FUNCTIONAL OPIOID KAPPA ANTAGONIST IN THE TREATMENT OF OPIOID DEPENDENCE

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Several lines of evidence, including the well-established observation that kappa opiate agonists produce dysphoria and psychotomimetic effects in humans, suggest that dysfunction of the endogenous kappa opioid system may contribute to opioid and cocaine addiction. The objective of this open-label study was to determine the effectiveness of a functional kappa antagonist as a treatment for opioid dependence. Fifteen treatment-seeking heroin dependent (DSM-IV) men (41±7 yrs old; 19±8 years heroin use) who were eligible for methadone maintenance but did not want it enrolled in the study. After inpatient detoxification at the VA and a naloxone-challenge test to verify that they were not physically dependent on opioids, subjects received naltrexone (50 mg po per day) to block mu opioid receptors. On the fourth day, patients received liquid buprenorphine (4 mg sl), a partial mu agonist and a kappa antagonist, in addition to naltrexone. All patients received medication at the clinic six days per week and a full program of psychosocial treatment. Outcome variables included pupillary diameter, urine toxicology, self-reported drug use, the SCL-90, ASI and the Beck Depression Inventory. Five patients (33%) completed the three-month study. Four were abstinent from opioids and cocaine for the entire study, and one was abstinent from opioids and cocaine for the last nine weeks. Six subjects dropped out due to either minor side effects or disliking the sensation of sublingual buprenorphine. Initial analysis of the data shows no changes in pupillary diameter. The positive response to treatment exceeds that ordinarily expected from naltrexone alone (90% dropout). These promising results suggest that controlled studies of this medication combination should be conducted.

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BUPRENORPHINE AND NALOXONE INTERACTIONS IN OPIATE-DEPENDENT PATIENTS STABILIZED ON BUPRENORPHINE

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Buprenorphine and naloxone combinations should have a lower abuse liability than buprenorphine atone for the treatment of opiate dependence. To assess the tolerability, comparative pharmacology, and absolute bioavailability of sublingual buprenorphine and naloxone, 9 opiate-dependent (8 men, 1 woman) volunteers were stabilized on 8 mg sublingual buprenorphine for 12 days. On days 9-11, subjects were given, in a doubleblind, 3x3 Latin square, within-subjects design, sublingual buprenorphine 8 mg alone or combined with naloxone 4 mg or 8 mg. A 30 min infusion of buprenorphine 4 mg and naloxone 4 mg on day 12 was used to determine absolute bioavailability. Plasma buprenorphine and naloxone were measured by LC/MS/MS. Results show daily administration of sublingual buprenorphine attenuates opiate withdrawal. No differences in opiate agonist or antagonist effects were seen between the sublingual buprenorphine and naloxone combinations and buprenorphine alone. Slowly administered intravenous buprenorphine and naloxone had only minimal withdrawal effects. Buprenorphine bioavailability, atone or in combination with naloxone,was -42%. Bioavailability of naloxone 4 mg and 8 mg was 9 and 7%, respectively, when combined with buprenorphine. Buprenorphine and naloxone combinations appear to be well tolerated.

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TESTING THRICE-WEEKLY ADMINISTRATION OF BUPRENORPHINE: PLASMA CONCENTRATION AND THERAPEUTIC EFFECTIVENESS

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Ten opiate dependent volunteers were maintained on three thrice-weekly dose schedules (A, B, and C) presented in a random order for two three week periods, and on a daily schedule (D) for one week at the end of the trial. Plasma samples were obtained 24.48, and 72 hours following administration of a three-day dose (A=32, B=40, and C=44 mg/70kg). and 24 and 48 hours following administration of a two-day dose (A=16, B=24, and C=34 mg/70kg). Three plasma samples were collected 24 hours following daily administration of buprenorphine 16 mg/70kg. Urine samples were collected three times per week, as well as daily information about withdrawal symptoms and use. of heroin. cocaine, alcohol, and other drugs. **Results:** All doses of buprenorphine were tolerated well by all subjects. The rate of withdrawal symptoms was low and did not differ across dosing schedules. Plasma buprenorphine showed a wide range of variability between subjects, and individual plasma levels did not stay consistently low or high across different dosing schedules for the same subject. Higher doses of buprenorphine resulted in higher plasma concentrations at each time point and plasma concentration decreased with time. The plasma buprenorphine at 72 hours following the administration of the three-day dose and at 48 hours after the two-day dose remained comparable to plasma concentrations at 24 hours following daily administration of 16 mg/70kg of buprenorphine. The differences in proportions of opiate positive urine toxicology results across dosing schedules did not reach the level of statistical significance. The average, self-reported amount of heroin was not statistically different across the dosing schedules. The highest reported rate of heroin use occurred 48 to 72 hours following administration of the three-day dose, when buprenorphine plasma levels were lowest. The lowest reported rate of heroin use occurred 0 to 24 hours following administration of either the two- or three-day doses of buprenorphine, when the plasma levels were highest.

SEXTUPLE THE DAILY BUPRENORPHINE DOSE DOES NOT SUPPRESS SUBJECTIVE WITHDRAWAL BEYOND 96 HOURS

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In previous research, quintuple (QN) the daily maintenance (M) dose of buprenorphine (BUP) administered every 120 hours did not suppress subjective complaints of withdrawal beyond 96 hours in opioid-dependent outpatients. This study compares QN dosing and SX dosing (sextuple M dose administered every 120 hours) to assess the effects of increasing the BUP dose in abating opioid withdrawal. Ten of 21 randomized subjects receiving BUP (sublingual M doses: 4 mg/ 70 kg, n=4; 8 mg/ 70 kg, n=6) completed the double-blind, placebo-controlled, 2-treatment, cross-over trial. Participation was contingent upon opioid abstinence and daily attendance. Eleven subjects were discharged due to noncompliance, 7 were under QN conditions and 4 were under SX conditions. Prior to randomization. subjects were exposed to six times their M dose under observation, and ratings of agonist effects were minimal in all subjects. Following baseline M dosing, subjects received each treatment (QN and SX), in a random order, for 4 repetitions. Subjects received placebo on interposed days. Measures of opioid agonist and withdrawal effects were assessed daily. Although observer-ratings of withdrawal increased across time since the last active dose under both conditions, the differences between the mean ratings and baseline measures were not statistically significant. Subjective ratings of withdrawal were significantly greater than baseline (M) ratings beyond 96-hrs post dosing under both the QN and SX conditions. There was no evidence, however, that subjective ratings of withdrawal differed between the two conditions. Thus, these preliminary results suggest that sextuple BUP doses do not abate withdrawal complaints for 5 days in opioid-dependent outpatients.

CRAVING DESPITE HIGH BUPRENORPHINE MAINTENANCE DOSAGES IN OPIATE DEPENDENCE

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Buprenorphine is reported to be agonist at μ-opioid receptor and antagonist at κ-receptor. It appeared as a potent analgesic available as sublingual tablet. For the treatment of opioid dependence, its specific pharmacological properties were studied on clinical trial comparing methadone and buprenorphine maintenance treatment. Initially frequency of use and low- high-dose were discussed, and recently higher dosages were suggested (8 mg/d). Nevertheless, such studies remain discussed in term of clinical eflicacy. In our clinical experience, we had to cope with patients who require more than 8 mg/d (up to 48 mg/d). In our sample (N = 150), we assessed therefore clinical status in patients who claimed the need of higher daily buprenorphine dose and who complained of craving symptoms. Addiction Severity Index, MADRS, Hamilton Anxiety, and SCL-90 were quoted. DSM III-R diagnosis for psychiatric comorbidity and personality disorders were explored. Buprenorphine route of administration and individual social status were examined. We compared patients receiving less and more than 8 mg/d (Mann-Whitney and χ^2 tests). Our study consist in preliminary results which confirm clinical heterogeneity in dose-response pattern for maintenance treatment and raise questions about adequacy in daily dosage suggested or reached. Our data suggest that patients with co-dependence, more psychological distress, and worst social conditions may require higher dosages than 8 mg/d. Buprenorphine efficacy on specific psychopathological dimensions may need future studies.

BUPRENORPHINE/NALOXONE: HIGHER DOSES CORRELATE WITH NEGATIVE URINE TOXICOLOGY RESULTS

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In the first clinical trial of its kind, twenty-five subjects were admitted to a six-week study using a buprenorphine / naloxone combination tablet. Twelve elected to continue receiving medication after the conclusion of the pilot study, at 4,8,16, and 20 mg doses, in order to evaluate the effect of longer treatment with the combination tablet. Dosing adjustments made during the continuation period were based upon urine toxicology results, objective ratings, and subjective reports of over- or under-medicating. Of those who received at least one dose increase, 59% showed increases in percent negative urine toxicology results with concurrent increases in dose. Fifty-two percent (52%) of the original twenty-five subjects never showed a treatment response based on urine toxicology. The subjects in this trial bad a relatively short period of daily use prior to entering treatment and, coupled with the high percentage of those who failed to respond at any dose, we report that these doses of opiate substitution are insufficient for severely dependent opiate users but may be useful for treatment of moderate opiate dependence.

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COMPUTERIZED QUALITY OF LIFE ASSESSMENT IN A CLINICAL TRIAL OF BUPRENORPHINE FOR OPIATE DEPENDENCE

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Opiate dependent patients enrolled in a study comparing liquid and tablet formulations of buprenorphine completed the Short Form 36 (SF-36) health status survey. Patients completed the SF-36 independently each month during the four month study. Patients used a free-standing computer to complete the survey. This allowed data to be entered directly into the data base and, since patients were prompted for all questions, helped to assure complete data collection. During the trial patients also completed the survey by pencil and paper. Thus, reliability of the computerized version could be evaluated. Finally, the patient's satisfaction with the computerized health status survey was assessed during the study and upon termination. A preliminary analysis was conducted using data from 72 patients, with 55 having completed the survey twice, 44 three times, 30 four times, and 17 all five times. The summated, transposed scores of each health dimension upon enrollment were as follows: physical function 77.3, role physical 73.7, bodily pain 63.2, general health 66.2. vitality 50.8, social function 68.1, role emotional 77.2, and mental health 59.8. Among the 44 patients having completed the survey twice, the dimensions of general health, mental health, vitality, and bodily pain improved significantly in the second month of the study ($p<.05$, paired t-test). These preliminary results suggest that the SF-36 health status survey is sensitive to improvements in quality of life associated with opiate treatment.

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EVOLUTION OF THE QUALITY OF LIFE OF PATIENTS UNDER SUBSTITUTION TREATMENTS: PRELIMINARY RESULTS

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FoIIow-up of 100 patients, 30 under sulfate of morphia 40 under methadone and 30 under subutex. It's a qualitative method consisting in semi-directive interviews organized around four points: access to medical care and prevention, socio-demographic situation, relational and psychological system and consumption of drugs. Our datas show a general improvement of the quality of life of the patients under sulfate of morphia. The treatment helped those 30 patients to build up a new project in their life. Concerning the follow-up of 100 patients : 1 patienl is dead of HIV. 1 patient is in hospital, 1 patient is incarcerated, we have lost sights of 2 patients. 2 patients have slopped their treatment in accord with their practitioner, 8 patients have gone through a relay a doctor in town. Among the 100 patients, 85 still get their prescription in the Clinique Liberté.

COMPARISON BUPRENORPHINE AND METHADONE MAINTENANCE IN OPIATE ADDICTS

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Methadone maintenance therapy is broadly established in Europe. Since 1987, methadone maintenance in opiate addicts is available in Austria, where presently 2500 subjects have been enrolled (8 million inhabitants). In 1993, we started to maintain subjects in an oral slow-release morphine maintenance program, where 1000 opiate dependent subjects with a mean daily dosage of 540mg have been enrolled. In USA, buprenorphine has been studied for many years in opiate addicts, no controlled studies have been performed in Europe so far. In 1996, buprenorphine was registered in France for maintenance therapy in opiate addicts. In the drug addiction out-patient clinic in Vienna a study with an open, controlled study design in comparing methadone and buprenorphine has been performed in opiate dependent subjects (DSM-IV 304.0). Twenty subjects on methadone were investigated over a study period of 6 months. The mean age in the study population (35 male and 5 female subjects) was 25,5 years, the mean duration of opiate dependence was 7,5 years. prior to tie study, all subjects were abusing heroin. The subjects were seen twice a week and received band-outs for the days between, supervised urine samples for toxicology were taken at each visit. The mean daily dosage of buprenorphine was 8mg, the mean oral dosage of methadone was 75mg. Preliminary results demonstrate that in regard to consumption of illegal drugs both groups were comparable.

LAAM IS NOT LESS POTENT THAN METHADONE: A RELATIVE POTENCY COMPARISON OF ACUTE AGONIST EFFECTS

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Prior reports suggest that levo-alpha acetyhnethadol (LAAM) is less potent than methadone, with a relative potency ratio of 0.8:1.0. However, This ratio appears to be based upon clinical trials that did not test multiple LAAM doses as is typically done in studies of relative potency. This study examined the relative potency of the acute agonist effects of LAAM and methadone using a within-subject, double-blind, double-dummy design. Nondependent, opioid-experienced, male volunteers (N = 5) received single doses of LAAM and methadone (15, 30, and 60 mg/70 kg, p.o.) and placebo. Test doses were administered once weekly according ma Latin-square design. Seven subjects were, scheduled to participate, but when 3 subjects failed to complete the study due to clinically significant respiratory depression after 60 mg/70 kg LAAM, the study was terminated for safety reasons. Physiological, subjective-report, and observer-rated measures were collected regularly for 12 hours to assess the magnitude and duration of drug effects. Data from all three domains indicate that LAAM is not less potent than methadone under acute dosing conditions. In fact, non-significant trends on many measures suggest that LAAM is more potent than methadone. An accurate LAAM methadone relative potency estimate may aid determination of adequate doses for daily methadone maintenance patients who choose to switch to more convenient thrice-weekly LAAM maintenance.

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OPIOID CROSS-TOLERANCE AND WITHDRAWAL DURING LAAM MAINTENANCE: A DOSE RESPONSE STUDY

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Levo-alpha-acetylmethadohadol (LAAM) is currently approved as an opiate maintenance treatment. This double-blind study was designed to characterize withdrawal suppression and opioid blockade produced by two different LAAM maintenance doses. Outpatient opioid-dependent volunteers were stabilized (5-7 weeks) on 25 (n=8) or 75 mg (n=8) LAAM administered every-other-day with placebo administered on intervening days. Following stabilization. four inpatient randomly-ordered experimental sessions were conducted at 24, 48, 72, and 96 hr after LAAM dosing; these intervals are consistent with those that occur during regular thrice-weekly treatment and following a missed dose. During each session, ascending doses of hydromorphone (0, 6, and 12 mg i.m.) were administered 45 min apart; physiological, subjective and objective effects were recorded throughout the session. Physiological and subjective indices of opioid withdrawal measured at baseline increased with time since last LAAM dose, but were not dependent on the maintenance dose. Withdrawal symptoms were mild in both groups, even at 96 hrs after LAAM dosing. Hydromorphone produced dose-related opioid agonist effects at all intervals in the 25 mg LAAM group; these effects were substantially attenuated in the 75 mg LAAM group. The since last LAAM dose had little influence on bydromorphone effects in either group. Thus, LAAM 75 mg provides opioid blockade and withdrawal suppression for up to 96 hr, whereas LAAM 25 mg is relalively ineffective at producing significant opioid blockade.

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LAAM: WHAT ABOUT BLOOD LEVELS?

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As the clinical use of LAAM is increasing, many clinicians who have come to appreciate the clinical utility of methadone blood levels. have begun to wonder if LAAM blood levels are readily available and if they would also be useful clinically. This type of information is virtually non-existent in the literature. The metabolism of LAAM is, however, more complex than that of methadone. LAAM, which has opiate effects of its own, has two active metabolites, nor-LAAM and dinor-LAAM, with the former being 7- to 10-fold more active than the parent compound. Because the Los Angeles Addiction Treatment Research consortium has been conducting clinical studies with LAAM, we decided to take advantage of the availability of a group of patients maintained on steady LAAM doses. In this ongoing effort, we have obtained blood levels of the two active metabolites of LAAM from nearly 50 patients.

OPIATE TREATMENT OPTIONS: PATIENTS PREFER LAAM

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To date there has been little documentation on individual preferences for opiate treatment. We evaluated treatment preferences for 93 subjects enrolled in one of two ongoing LAAM studies. Opiate treatment preferences were measured using a survey of attitudes and by noting treatment choices al the completion of the study. Surveys were administered at study completion/termination and the results to date (n=44) indicate strong preferences for LAAM over methadone on 13 of 16 treatment characteristics. Patients behavior also indicate clear preference for LAAM; only 9 to 93 subjects enrolled have elected for early termination of treatment with LAAM. In addition, 80% of subjects (n=25) chose to continue LAAM treatment at the conclusion of the study protocol. Patient characteristics including conclusion of the study protocol. Patient characteristics including SCID derived psychiatric diagnoses and ASI subscale scores will be evaluated as predictors of patient retention and other treatment effects with LAAM. Subjects' preferences for LAAM at the conclusion of the trial provides some of the best evidence of its acceptance.

A PILOT STUDY ON THE ADJUNCTIVE USE OF CIMETIDINE WITH LAAM FOR MAINTENANCE PHARMACOTHERAPY IN OPIATE DEPENDENT PATIENTS

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LAAM maintenance on a thrice weekly basis has been shown to be as effective as daily methadone maintenance. However, it has been clinically observed that patients on LAAM maintenance report higher levels of opiate withdrawal symptoms on Mondays as compared to Wednesdays and Fridays. Administering a higher dose of LAAM will not change the pharmacokinetics of the drug. It would result in a higher peak plasma level of LAAM without significantly prolonging it's half-life. We hypothesized that Cimetidine may prolong the duration of action of LAAM through competitive inhibition of the cytochrome P-450 enzyme system in the liver resulting in more continuous prevention of opiate withdrawal symptoms, leading to increased treatment compliance and reduced illicit opioid use. Sixteen opiate dependent subjects were inducted onto LAAM maintenance during week 1 (Dose: 30 mg on Mon, Wed and 39 mg on Fri), randomized to Cimetidine or placebo for weeks 2-5 and crossed over for weeks 6-9. Cimetidine/ placebo was discontinued at the end of week 9. During week 10 subjects were either detoxed from LAAM or transferred to the clinical program. There was no difference between the subjects use of illicit opioids while they were on LAAM-Cimetidine [52% (SD=50)]versus LAAM-ptacebo[60% (SD=49)]. Subjects did not use less illicit opioids on the week-end (measured by U.Tox screens) on Mondays as compared to the rest of the week while they were on LAAM-Cimetidine. While on LAAM-Cimetidine, 33% (SD=47) of the urine toxicology screens were positive for cocaine compared to 53% (SD=50) when on LAAM-Placebo. We plan to do further analysis comparing the blood levels of LAAM while subjects were on Cimetidine versus placebo and correlating it to their scores on the opiate withdrawal rating scale.

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DIFFERENCES AMONG INTRAVENOUS AND INTRANASAL OPIATE ABUSERS

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This study examines differences between intravenous (IV) opiate abusers and those who exclusively used intranasally (IN). Matched on age (X=31.7), race (83% African American, 17% Caucasian), and gender (57% Male), 27 IN users and 27 IV users were recruited from a three day inpatient detoxification unit. Subjects were compared based upon self-reports of drug use from the Addiction Severity Index (ASI), administered during the detoxification treatment. Subjects were interviewed again at 1 and 3 months following their discharge to assess drug use and treatment utilization. Although no significant differences were found in subjects' reported heroin use at intake (28 of the previous 30 days for both IV and IN), it was found that intravenous users had more days in the past 30 of alcohol use to the point of the effects being fell, and multiple drug use (i.e., more than 1 drug used per day). Despite age matching, IV users also reported more lifetime months of regular cocaine and multidrug use, as well as a more extensive history of alcohol use, with both an earlier onset and a longer history of drinking to the point of the effects being felt. Furthermore, while none of the IN users overdosed on drugs at all in their lifetime, the group of IV users averaged more than one overdose. One and three month results indicated few differences, although drug usage for both groups declined. The results show that intravenous users represent a group of opiate abusers who have both a more severe drug abuse pattern and a more extensive history of other drug use than intranasal drug abusers. These observations may have implications for treatment intervention and prognosis.

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OUTCOMES FOR HEROIN ABUSERS FOLLOWING 3-DAY INPATIENT DETOXIFICATION

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Inpatient detoxification services are popular with drug abusers. and may have therapeutic utility particularly if followed by longer-term aftercaretreatment. This study examined 6-month outcomes for i.v. opioid abusers (n=118) following enrollment in a 3-day inpatient Chemical Dependence Unit. Addiction Severity Index interview was administered at 1, 3 and 6 months post-detox. The followup sample was 67% male, 77% African-American and 38 years old on average and includes 94.4% of all patients who received initial interviews on thedetox unit. Relapse was common; 20% relapsed to first heroin use on day of discharge, 50% by end of week 1 and 80% by one month post-discharge. However, average days of heroin use afer detox declined 10 50% of predetox levels (10-15 days versus 28-30 days in the last 30). Money spent on all drugs declined to 25% of amount spent in 30 days pre-detox. At each followup point, 15-20% reported (urine verified) heroin abstinence; 20-30% reported regular use (21-30 days in past 30), while the remainder reported occasional use (1-20 days in past 30). In the fist post-detox month, 60% sought treatment (formal or self-help); 33% attended some form of treatment for more than one week. The study showed considerable individual variability in outcome after a brief inpatient detox. Although relapse is common, average levels of drug use are much lower after than before detox. Motivation for change appears to be high in this population, as evidenced by the number who seek and enter aftercare treatment. Targeted efforts to transition detox patients into aftercare could be a cost-effective way to delay relapse and improve longer-term outcomes.

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OPIOID CRAVING AND ATTITUDINAL CHANGES IN OPIOID ADDICTS TREATED IN A M-DAY AMBULATORY DETOXIFICATION PROGRAM

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The decreasing availability of inpatient substance abuse units has resulted in the shift of treatment from an inpatient to outpatient setting. For many opioid addicts, detoxification treatment with alpha-adrenergic drugs has not been successful. This study was designed 10 determine the efficacy of a 30 day ambulatory detoxification program utilizing gradual dose reductions of methadone and thrice weekly educational groups. Patients were assessed via a detailed drug use history, completion of a visual analog craving scale for heroin, presence of withdrawal symptoms, and urine toxicology samples at baseline and weekly thereafter. In order to assess patients' perceived ability to cope effectively without drugs, the Drug-Taking Confidence Questionnaire (DTCQ) was obtained at baseline and at completion of program. Fifty-six patients were included in the study Mean age was 43 years and mean use of heroin was 18 years. Fifty-one percent of sample completed the ambulatory detoxification program. there were no significant differences in completers (C) versus noncompleters (NC) in respect to length of heroin use or history of previous methadone treatment. Average length of treatment for C group was 27 days compared to 13 days. There were no significant differences between groups in regards to baseline ratings in DTCQ or cravings for heroin. Completers did have a significant difference ($p<.05$) in baseline vs termination craving scores. Eighty-two percent of completers continued with aftercare treatment compared to 7% of noncompleters. In summary, an ambulatory detoxification program can be considered a viable treatment option for heroin dependent patients.

WEEK-2 PERFORMANCE PREDICTS 6-MONTH TREATMENT RESPONSE AMONG METHADONE MAINTENANCE PATIENTS

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We examined urinalysis (UA) results and counseling attendance during the first 2 weeks of treatment to determine whether the early performance of 59 methadone maintenance patients could predict subsequent treatment response. Patients were dichotomized into outcome groups based on treatment retention and month-6 UA results. Poor outcome was defined by dropping out of treatment or submitting 50% or more cocaine or opiate-positive month-6 urine specimens. Good outcome was defined by remaining in treatment and submitting less than 50% cocaine or opiate-positive urines. Logistic regression analyses indicated that week-2 UA results and counseling attendance made independent and additive contributions to the prediction of 6-month outcome, though patient background factors (including pre-treatment drug use and psychosocial problem severity) did not. Strikingly, there were no good 6-month outcomes among the 20 patients who submitted one or more opiate-positive week-2 mines and failed to attend 2 scheduled counseling sessions in weeks 1-2. Among patients attending 2 counseling sessions and submitting 2 week-2 opiate-negative urines, 60% had good outcomes. These results were supported by secondary analyses using self-reported cocaine and heroin use in month 6 as outcome measures. Thus, 6-month outcomes were well predicted by early treatment performance. It remains a question whether these week-2 performance variables are indicators of patient motivation, or whether interventions that increased the likelihood of their occurrence would also improve subsequent treatment response. Generalizability is limited by the small sample size and specific treatment characteristics (e.g., twice weekly UAs and scheduled weekly counseling). Nonetheless, the results suggest that it may be possible, very early, to identify methadone patients unlikely to respond well to treatment as usual.

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NEW SELF-REPORT INSTRUMENTS FOR MEASURING ENVIRONMENTS OF METHADONE AND LAAM MAINTENANCE PATIENTS: PRELIMINARY FINDINGS

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The goals of this ongoing project are to develop self-report measures of the environments of methadone and LAAM maintenance patients and to test hypotheses relating environmental variables to treatment progress. Environmental domains studied include general level of reinforcement, stress (including daily stressors, chronic strains, and major life events), social influences on drug use and abstinence, perceived drug availability, and perceived risks of drug use. The project has three stages. In Stage 1, "Item Development and Pretesting" (now completed), we created initial versions of each measure and administered them to a pretest sample. Following modifications, we began Stage 2, "Psychometric Development," now in progress. Stage 2 (n=240) focuses on the psychometric adequacy of the measures. Interim data from 100 Stage 2 participants suggest adequate internal consistency and one-week test-retest reliability. Future psychometric work in this stage will include extensive item analysis using exploratory and confirmatory factor analysis. In Stage 3, "Validation" (n = 120), we will examine validity using other self-report instruments and objective data on patients' environments. The new measures, when completed, should contribute to scientific understanding of patients environments and clarify environmental correlates of treatment progress. Final versions of the measures and extensive reliability and validity data will be available upon study completion.

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PATIENT SATISFACTION SURVEY CONDUCTED BY CONTINUOUS QUALITY IMPROVEMENT COMMITTEE AT METHADONE MAINTENANCE TREATMENT PROGRAM IN NEW YORK CITY

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In the era of managed care, substance abuse treatment, like other areas of health care, has been subject to reviews of how to improve its delivery and effectiveness. Continuous Quality Improvement (CQI) programs have been one way to assess the delivery of substance abuse services. A major component of any CQI program is patient satisfaction. During 1995, the first year of a patient satisfaction survey at a large methadone maintenance program (N = 2,300) in New York City, a 30% random sample of patients was surveyed using a standardized instrument. The survey was administered by the patient Advisory Committee Members offering assistance to their peers. At the time of the survey, the mean length of stay of the respondents was 45 months with a median of 36 months. Over 75% patients responded that the care was satisfactory to excellent. Patients enrolled for less than 36 months responded more favorably than those. in treatment for more than 36 months regarding their satisfaction with the staff and the availability of medical services. This information suggests that patients with longer lengths of drug abuse treatment may have different expectations of substance abuse care than those patients who are enrolled more recently.

PROGRAM QUALITY EFFECTS ON PATIENT DRUG USE DURING METHADONE MAINTENANCE

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This study 1) measured the program quality variables found in Ball and Ross (1991) to be related to patient drug use, 2) identified how clinic differences in methadone program variables affect heroin and cocaine use, and 3) attempted to replicate the seminal Ball and Ross (1991) results with a larger sample of 17 methadone clinics. Principal components analysis reduced 22 treatment domain variables to eight program factors. Program quality variables were importanl factors in lower heroin use during the first year of treatment; patients' pre-treatment variables were generally more related to cocaine use than heroin use. Methadone dose was unrelated to heroin use, but was associated with higher cocaine use in the second and third years of treatment. Two counselor characteristics: being in recovery. and being tough-minded about addiction (i.e., more disapproving of drug use) were related to higher heroin use in the third year of treatment. Compared with Ball and Ross, this study found different numbers of program factors to be associated with patient drug use, probably due to studying 17 clinics instead of just six. However, both the Ball and Ross and current studies identified similar program factors, namely counseling contacts, director involvement and director experience to be associated with lower drug use by patients. The two studies also found that longer length of stay in treatment was associated with less patient drug use.

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PSYCHOSOCIAL TREATMENT FOR METHADONE PATIENTS: IS MORE BETTER?

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Two intensities of manual-guided psychosocial treatments for unemployed inner-city, methadone-maintained patients were compared in a randomized clinical trial. Outcomes included retention in treatment and illicit drug use. Of the 308 patients who were eligible for the study, 291 began their assigned treatment; 237 (81%) completed the 12-week study -- 82% completed the high intensity, 25-hour per week, Day Treatment Program; 81% completed the lower intensity, 2-hour per week skills training group. Contrary to hypothesis, there were no significant differences in illicit drug use between patients assigned to the two treatment intensities, as assessed by twice weekly mine toxicology screens for opiates and cocaine. Drug use decreased significantly for patients receiving either treatment intensity. Exploratory data analyses suggested that patients with high psychiatric severity scores on the ASI and patients in "bad standing" in their methadone program may benefit from more intensive treatment, and that patients new to methadone without these problems may more appropriately be referred to psychosocial interventions of lower intensity.

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UNRELIABILITY AND REASONS FOR UNRELIABILITY IN REPORTS OF CONSEQUENCES OF SUBSTANCE USE

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As part of a NIDA-funded study on the nosology of DSM substance use disorders, the one week test-retest reliability of the criteria for DSM-IV substance use disorders was tested, as measured by the WHO/NIH Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM). In this study of 344 substance users, we test the hypotheses that a) women are more reliable reporters than men, b) community subjects are less reliable in their reporting of drug use symptoms than subjects in drug treatment; and c) persons meeting criteria for a DSM-IV dependence disorder are more reliable than persons with subthreshold impairment. In addition to assessing the one-week test-retest reliability, our study assesses the self-reported reasons for discrepancies from one interview to the next. The CIDI-SAM is highly reliable for assessing DSM-IV dependence on opiates, cocaine, and alcohol. Cannabis dependence is less reliably reported, suggesting further evaluation is needed in both criteria and assessment. Men and women and community and treatment subjects were equally reliable. Tolerance, withdrawal, physical/psychological problems, and persistent desire to cut down need improvements. The common reasons for not reliably reporting symptoms include: misunderstanding the question, not remembering the answer, and not paying attention.

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DIFFERENCES ACROSS ETHNICITY IN RELIARILITY OF DIAGNOSING DSM-IV SUBSTANCE USE DISORDERS

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Cross cultural research on substance use disorders (SUD) demands diagnostic measures and criteria that apply equally well to persons of different ethnic backgrounds. To evaluate the acceptability and reliability of SUD in different ethnic groups, comparisons were made of the one week test/retest agreement on DSM-IV substance dependence disorders for 214 African American (AA) and 130 Caucasian (C) respondents using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM). Overall we found excellent reliability, using *kappa* (*k*) statistics, in diagnosing both AA and C respondents with alcohol dependence (AA *k*=.76; C *k*=.82) and opiate dependence (AA *k*=.79; C *k*=.76, excellent reliability for diagnosing AA respondents with cocaine dependence (*k*=.85), good reliability for diagnosing C respondents with cocaine dependence (*k* =.70), fair to good reliability for both AA and C respondents with cannabis dependence (AA *k*=.51; C *k*=.68). Reliability of the dependence/abuse criteria was consistent with the overall diagnostic reliability but some variation was noted. No significant differences in the *kappas* were found between the two ethnic groups for any of the substance dependence diagnoses and only one dependence or abuse criterion ("continued use of cocaine despite physical/psychological problems") differed significantly between AA and C respondents. These initial results indicate that DSM-IV dependence diagnoses as measured by the CIDI-SAM apply equally well to AA and C respondents.

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PREDICTIVE VALIDITY OF SUBSTANCE DEPENDENCE DIAGNOSES

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The present study examined the predictive validity of DSM-III R SCID-based substance dependence diagnoses (i.e., cocaine, sedative, and alcohol) for 518 opioid dependent outpatients entering methadone maintenance. Patients were followed for one year of treatment, which involved daily methadone substitution supplemented by individual and group counseling. Urine specimens were tested randomly one IO four times per month. Cocaine dependence was the most prevalent current disorder (31%), followed by alcohol (21%) and sedative (16%) dependence. Patients diagnosed with current cocaine, sedative, or alcohol dependence were more likely to use these drugs than were patients with past only or no dependence syndrome. Current cocaine dependence, but not sedative or alcohol dependence, predicted early treatment drop-out. The results demonstrate the predictive validity of several substance dependence diagnoses common among patients in substance abuse or other psychiatric treatment settings.

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CONCURRENT VALIDITY OF SUBTYPING ACCORDING TO LEVEL OF SOCIOPATHY AMONG ANTISOCIAL SUBSTANCE ABUSERS

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Research in the concurrent and predictive validity of the DSM diagnosis of Antisocial Personality Disorder (APD) has found that this diagnostic category, which focuses exclusively on behavioral criteria may be less clinically useful in the assessment and treatment of antisocial substance abusers than subtyping according to the character trait of sociopathy. Among substance abusers with APD. those with lower sociopathy seem to have less severe pre-treatment psychiatric and substance abuse severity than their counterparts with higher sociopathy. This study of 370 inpatient and outpatient alcohol, cocaine, and opiate abusers uses MANOVAs and planned comparisons to contrast non-APDs to APDs with low vs high sociopathy, as determined by a median-split of scores on the California Personality Inventory - Socialization Scale (CPI-So), on pre-treatment measures of substance abuse and psychiatric severity. PreIiminary analyzes indicate that those APDs with high sociopathy score significantly higher than APDs with low sociopathy on drug use severity (ASI) and on several measures of psychiatric severity (depression, anxiety, hostility, psychoticism, somatization). These findings both support the validity of this subtyping and suggest that attention be directed to the assessment of sociopathy in the clinical management of APD substance abusers. Additional analyses will evaluate 12 month follow-up measures.

SUBSTANCE ABUSE TREATMENT OUTCOMES AND PROGRAM DURATION

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The new managed cam environment requires behavioral health care providers to furnish better care for more people at a lower cost. Payors and patients alike want to see treatment outcome data demonstrating clinical efticacy and cost efficiency. This study examined the efficacy of a substance abuse treatment program delivered in three different durations at a privately-funded Southern California treatment center. Subjects entered either a two-, four-, or six-month program consisting of weekly relapse prevention and psycho-education groups, urine testing, and blood alcohol testing. Treatment outcomes such as addiction severity and level of functioning were examined with regard to length of stay. Seventeen (17) subjects from the two-month program and 45 subjects from the four-month program completed three interviews, one each at baseline, discharge, and six-month follow-up. Twenty-six (26) subjects from the six-month program completed interviews as baseline and discharge only. Instruments included the Addiction Severity Index, the Basis 32, and measures of overall satisfaction. Self-repotted relapse data were also Included. All programs produced Improvement in drug and alcohol use and in levels-of-functioning, and all were rated highly by patients. Additionally, the different treatment durations produced comparable outcomes on all measures.

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SEXUAL AND PHYSICAL ABUSE: DO THEY COMPROMISE DRUG TREATMENT OUTCOMES?

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Histories of sexual and physical abuse are frequently reported by individuals participating in substance abuse treatment. These experiences may be associated with psychopathology and poor drug treatment outcomes. This paper presents the findings from a longitudinal study of 330 subjects participating in 26 outpatient treatment programs. Sexual abuse among women was associated with higher levels of depression, anxiety, suicidal ideation, suicide attempts, and PTSD, while physical abuse was associated with fewer psychological disturbances. For men, sexual abuse was associated only with anxiety. Physical abuse was associated with depression, anxiety, suicidal ideation, and PTSD. However, no significant association was found between sexual and physical abuse, and lower levels of treatment engagemenl or drug use at follow-up. These findings indicate that mere is a complex connection between abuse, psychopathology, treatment engagement and relapse. Clinical and research implications of these findings are discussed.

PSYCHOLOGICAL IMPAIRMENT, TREATMENT SELECTION, AND ACCESS

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Individuals accessing substance abuse treatment and selecting particular modes of treatment exhibit impairments across multiple domains of functioning. particularly in the area of psychological functioning. Different treatment modalities serve different clientele due to factors related to treatment program designs and client self-selection elements. Early research has shown that level and type of impairment tend to vary by treatment type. Data from the Drug Abuse Treatment Outcome Study (DATOS) were analyzed to determine the sub-types, patterns, and rates of psychological impairment and other key behaviors among clients selecting and accessing long-term residential, outpatient drug-free, and short-term inpatient treatment modalities. Subjects were 10,010 clients interviewed at admission to programs participating in DATOS; 66% were male, 47% African American, 13% Hispanic, with an average age of 32.6 years. Stepwise logistic regression analyses were used to examine factors related to admission to the three modalities. Findings included significant determinants of treatment access in community-based treatment programs. Access to treatment in these programs can be explained in part by client factors such as psychological impairment, substance dependencies, need for services, health insurance, criminal justice referrals and status, and transportation barriers.

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DOES CENTRALIZED INTAKE AFFECT CLIENT OUTCOMES?

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As part of the national Target Cities Demonstration Project, San Francisco implemented centralized intake in its publicly-funded drug abuse treatment system. A key hypothesis driving the Target Cities project was that standardized clinical assessment and referral procedures along with systematic efforts to assign clients to the most appropriate treatment would yield improved outcomes. To test this hypothesis, clients who entered 6 treatment programs through the centralized intake unit (CIU group, n=267) were compared to clients who entered the same programs through usual routes (non-CIU group, n=200). Participants were interviewed al the time of admission, and at 1 month and 12 month follow-up. Outcome measures included the seven composite severity scores from the Addiction Severity Index (ASI). the Beck Depression Inventory, the Brief Symptom Index, and a measure of social support. Preliminary findings reported here concern outcomes al 1 month follow-up only. At baseline, the CIU group had greater severity of employment (t=-2.61. $p < .01$) legal (t=-2.01, $p < .05$) and psychological problems (t=-2.37, $p < .05$). more psychiatric symptoms (t=-2.72, $p < .01$), and less social support (t=4.53. $p < .001$). The CIU attracted and served a more severely disordered client population. At 1 month follow-up, both groups showed significant improvement on ASI measures of legal, alcohol, and drug problems, and on measures of depression, psychiatric symptoms, and social support. ANCOVA analyses controlling for baseline differences between groups showed that level of improvemenl did not differ by group. This effort at systemic change may have resulted in better access to treatment for the more severe client population, but did not result in better short-term (one month) client outcomes.

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COERCION, MOTIVATION, AND CHANGE IN DRUG ABUSE TREATMENT

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This study evaluated perceptions of coercive and noncoercive pressures to enter drug abuse treatment among 186 patients and their primary therapists in dual diagnosis inpatient (N = 61, 33%) intensive outpatient (N = 61, 33%) methadone maintenance (N = 33, 18%), and detoxification (N = 31, 17%) programs. Interview responses were tabulated according to a reliable coding procedure (Marlowe, *et al.,* 1996). Results indicate that perceptions of treatment-entry pressures differ significantly across settings ($p < .0001$); however, contrary to expectations, outpatients reported significantly more coercive influences and there were no differences by gender or race. Therapists' and patients' perceptions were highly discrepant ($p < .0001$) and patients' perceptions were impressive predictors of tenure, compliance, and outcome in treatment as well as readiness for change as measured by the URICA. These data suggest that "coercion" should not be equated with residential treatment and that assessment of treatment-entry pressures may have substantial prognostic value.

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FAILURE OF A FINANCIAL INCENTIVE TO REDUCE DRUG USE IN A METHADONE MAINTENANCE PROGRAM

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Patients enrolled in the Substance Abuse Treatment Clinic, a methadone maintenance clinic at the University of Arkansas for Medical Sciences, paid a weekly treatment fee of $17 to $62, depending on personal income. All patients were screened each week on a day selected at random for the presence of abused drugs (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methaqualone, opiates, phencyclidine, propoxyphene and methadone) in the mine. All patients were given a $5 reduction in their weekly treatment fee for any week that only methadone was detected in their urine sample. They were also offered one week of treatment at no cost if they could complete 25 consecutive weeks with detection of only methadone in their urine samples. Although many patients received the fee reductions ($24,103 was the cost of the program during a 15-month period), there was no reduction in the detection of these abused drugs in the urine. Generally, patients who were compliant remained compliant and those who were not compliant remained not compliant. Subsequent interviews with patients who were not compliant, suggested that $5/week was not sufficient to change their drug-taking behavior.

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INCENTIVE PROGRAM FOR BENZODIAZEPINE-DEPENDENT METHADONE PATIENTS SUSTAINS POST-DETOX ABSTINENCE

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This study examined whether incentives sustain abstinence following benzodiazepine inpatient detoxification. Benzodiazepine-dependent patients maintained on 60-100 mg methadone first completed a 7-day inpatient benzodiazepine detox. Patients then continued with outpatient methadone treatment, submitted urine samples 3 times weekly (M/W/F), and were randomized to either the Incentives (INC+) or No Incentives (INC-) condition. INC+ patients chose either a methadone take-home or a $25 voucher for each drug-free (i.e., for opiate, cocaine, and benzodiazepines) urine sample submitted. Following any drug-positive sample, patients were required to submit 3 consecutive drug-free mines to resume earnings. Drug use had no consequences for INC- patients. Fourteen patients participated and were evaluated for 12 weeks post-detox. During the 4 weeks prior to detox, INC+ (N=7) and INC- (N=7) patients submitled 91% and 86% drug-positive urines, respectively. Following detox, INC+ and INC- patients submitted 10% and 77% overall drug-positive urines, respectively ($p<.01$). Furthermore, all INC+ patients (N=7) showed at least 4 weeks of sustained abstinence, with four showing greater than 8 weeks of sustained abstinence during the 12-week evaluation (mean=8 wks). In contrast, almost all patients in the INC- group sustained one week or less of continuous abstinence, whereas one INC- patient sustained at least 3 weeks of abstinence (mean=1 wk; $p<.01$). These results demonstrate that providing incentives for drug-free urines are a useful relapse prevention technique and dramatically sustain post-detox abstinence with benzodiazepine-dependent methadone patients. Future studies are needed to determine whether inpatient treatment is an essential component for the success of this program.

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REWARDING CANNABIS ABSTINENCE IN METHADONE TREATMENT

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Most methadone maintenance clinics do not routinely test urine specimens for cannabis, or have consequences associated with its use. Two recent studies have indicated cannabis use is not associated with greater use of other dsugs of abuse by methadone clients. Clinic staff may feel that such tolerance policies give the message that cannabis use is sanctioned. Our clinic dealt with this dilemma by adding a requirement to the take home dose policy that clients provide cannabis free urinalyses (UAs) to achieve twice a week pick up status (2x/wk). Prior to the policy change the requirements for 2x/wk were: two years in treatment; six months negative UAs (except cannabis) and involvement in constructive activity. The clinic announced the policy change 4/1/95 with an 11/1/95 implementation date. The policy change was evaluated by monitoring the UA records and take home sfatus of all clients in treatment for the six months prior to implementation and one year after. At implementation 23 of the 120 clients (19%) had 2x/wk based on the previous criteria. Eleven of these- clients (47.8%) remained on 2x/wk throughout the study. Of these 8 (72.7%) provided no cannabis positive UAs. Three (27.3%) had cannabis positive UAs in the pre-implementation period, but none after. Five of 23 clients (21.7%) were inreased to three times a week status during the implementation month due to cannabis positive UAs. One of these clients has subsequently returned to 2x/wk by providing cannabis free UAs. No client who lost 2x/wk due to cannabis use provided a UA positive for other drugs of abuse. Seven (30.4%) of the 23 were cannabis negative throughout the study period, but lost their 2x/wk due to positive UAs for other drugs. Five of these subsequently regained 2x/wk. In summary, 4 of 8 clients (50%) on 2x/wk status who were using cannabis were able to discontinue their cannabis use in order to maintain or regain 2x/wk.

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INFLUENCE OF ALCOHOL USE M COCAINE ABUSE TREATMENT

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Studies have reported high comorbidity of alcohol abuse in individuals with cocaine abuse or dependence, however it has not been clarified whether alcohol use influences clinical and treatment response characteristics of cocaine abuse or dependence disorders. This study addresses this question in 128 cocaine abusing adults who participated in a randomized trial of cognitive behavioral vs. 12-step treatment. Subjects were assessed at baseline and weeks 4, 8, 12 and 26 on biologically-verified cocaine abstinence and a battery of psychometric measures. All subjects were crack cocaine smokers; most were male (99%). African American (80%), unemployed (84%). and homeless or marginally housed. Subjects were divided into three levels of alcohol use based on their self-reported frequency of drinking at intake. Nondrinkers (17 % of subjects) denied any alcohol use in the thirty days prior to intake. Less than Daily drinkers (48% of subjects) reported drinking at least once a week and as often as 2-6 times per week. Daily of More drinkers (35% of subjects) reported drinking at least daily and as often as 4 or more limes per day. We hypothesized that greater alcohol use in cocaine abusers would correlate with an increased alcohol, drug and psychiatric severity at baseline; increased success with 12-step treatment, and overall worse outcome as measured by abstinence at 12 and 26 weeks. Preliminary results suggest that cocaine abusers who have greater levels of alcohol use have greater alcohol and drug addiction severity at baseline. Level of alcohol use, did not interact with treatment condition or significantly predict ability to achieve cocaine abstinence suggesting that alcohol drinking status is not a critical prognostic factor in cocaine treatment outcome.

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EFFECTS OF PERSONALITY ON TREATMENT COMPLIANCE AND DRUG USE IN METHADONE PATIENTS

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This study evaluated the relationship between personality traits and treatment outcome in opiate abusers. New admissions to methadone maintenance (n = 111) completed the NEO Personality Inventory Revised (NEO-PI R; Costa and McCrae, 1985). Patients were randomly assigned to contingent (n = 58) or non contingent (n = 53) treatment. Patients in both conditions were referred to escalating intensities of counseling based on recent drug use and counseling attendance. In the contingent condition, continued methadone maintenance was linked to counseling compliance and drug use, while in the control condition continued methadone maintenance was independent of counseling and drug use. Weekly urinalysis results and counseling compliance were assessed over the first 90 days of randomized treatment. Personality traits were associated with drug use but not counseling Neuroticism correlated with both opioid ($r = -.21$, $p < .05$) and benzodiazapine ($r = .27$. $p < .01$) use, while +conscientiousness was associated with benzodiazepine use ($r = -.26$, $p < .01$) use. No condition and personality traits interactions were observed. Regression analyses showed that these variables did not significantly add to the total chug use variance after controlling for baseline drug use. NEO-PI R personality traits appear to be modestly related to drug use during treatment but do not add signiticantly to the predictive power of baseline drug use.

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VOUCHER-BASED REINFORCEMENT OF BRIEF COCAINE ABSTINENCE IN METHADONE PATIENTS

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Although voucher-based reinforcement has been effective in sustaining cocaine abstinence in methadone patients, not all patients have initiated abstinence when offered voucher reinforcers. This ongoing study evaluates a procedure that reinforces a brief period of abstinence (2 days) with one high-magnitude voucher to determine its effectiveness in initiating cocaine abstinence in methadone patients. Study patients are told on Monday of the test week that they will receive a $100 voucher if their urine on Wednesday indicates that they had abstained from cocaine. Patients were considered cocaine abstinent if their urine benzoylecgonine concentration decreased by 50% from Monday to Wednesday or if their Wednesday's mine benzoylecgonine concentration was $\leq$300 ng/ml, the standard cutoff for qualitative urine testing. Data from the test week were compared to equivalent periods in the weeks before and after the test week. Thus far, 38 cocaine abusing methadone patients have completed the study. Significantly($p < 0.001$) more patients met the cocaine abstinence criterion during the week in which the abstinence reinforcement contingency was in effect (87%) compared to the week before. (37%) and the week after (42%). Furthermore, almost all patients (95%) decreased their benzoylecgonine concentration from Monday to Wednesday of the test week; in contrast, only about half of the patients decreased from Monday to Wednesday of the weeks before (55%) and after (52%) the test week. Analyses based on the standard qualitative test of cocaine abstinence ($\leq$300 ng/ml) showed that more patients were cocaine abstinent during the test week compared to the other two weeks, however, the differences were not statistically significant. In conclusion, a high magnitude reinforcement ($100 voucher) contingent on a brief period of abstinence (2 days) as assessed by changes in urine benzoylecgonine concentrations appears to be an effective means of initiating abstinence in the vast majority of cocaine abusing methadone patients. This procedure might be useful in increasing the proportion of patients who respond to subsequent long-term interventions.

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METHADONE DOSE RESPONSE IN OPIATE DEPENDENT PATIENTS WITH COMORBID COCAINE DEPENDENCE

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A previous study comparing increasing and decreasing methadone (METH) dose contingency protocols indicated that high dose (100mg or 120mg) may be effective in decreasing cocaine use in refractory patients (Stine *et al.* 1992). That protocol had significant limitations (open study, few patients, behavioral contingency). Other studies described cocaine induced opiate withdrawal-like symptoms in comorbid patients (Stine *et al.* 1992) and reported higher correlation of withdrawal and cocaine use in patients on higher doses of both METH and buprenorphine suggesting these symptoms may participate in reduced use at higher doses (Stine *et al.* 1994). The current study is a randomized double-blind clinical trial comparing the effect of 40, 80, 120mg on opiate and cocaine use during 6 wks of maintenance after 6 wks of stabilization and dose adjustment. Subjects were METH treatment failures (refractory cocaine abuse) and entered on 40 mg METH. Of 59 subjects enrolled, 3 in progress, results from 48 are repotted. All 8 subjects not analyzed dropped out before beginning treatment. Mean age was 37±5.5, 66% males, 34% females, 57% Caucasian, 34% African American, 8% Hispanic. The primary outcome measures were cocaine and opiate urine toxicologies. Other outcome measures were times and dollars cocaine used, cocaine craving, high, other cocaine symptoms, opiate withdrawal and Beck Depression Inventory. Results from baseline through wk 13 were analyzed by repeated measures analysis of variance (RMANOVA). Cocaine use did not change significantly with treatment. Opiate use did show a significant decrease with dose by time: F=1.80 df=13.46 p=0.039. Opiate withdrawal symptoms also decreased: dose x time: F=2.140 df=13,46 p=0.010. Quality of cocaine high decreased (dose x time: F=1.736 df=13.46 p=0.050) but no other cocaine measures changed significantly. We conclude comorbid opiate and cocaine dependent patients may require higher doses of METH to decrease opiate use and withdrawal symptoms, and these doses may also decrease cocaine high.

DIFFERENTIAL RESPONSE TO IV CARFENTANIL IN CHRONIC COCAINE USERS, DEPRESSED PATIENTS, AND CONTROLS

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There is little human experimental data on the influence of chronic cocaine exposure on the acute response to opiates. Some animal data suggest cross-sensitization between cocaine and opiates. We evaluated this by comparing the side-effects experienced in response to an IV bolus of "C-carfentanil (CFN), a potent, specific synthetic mu-opioid agonist administered for positron emission tomography (PET) scanning to 14 chronic heavy cocaine users (COC) (12 men, mean [SD] age 32.1 [3.8] years), 18 depressed patients (DEP) (8 men, age 38.6 [8.3] years), and 12 healthy controls (CTR) (8 men, age 46.8 [14.6] years). DEP and CTR groups had no self-reported history of illegal drug use. The COC group had no opiate use within the prior 3 months. Potential opiate agonist effects (nausea, vomiting, dizziness, itching, headache) were scored as present (1) or absent (0) during the scan itself (90 min) and the following 90 min (possible total symptom count [SX CT] = 0-10). The COC group had a significantly lower SX CT (0.6 [1.4]) than the DEP (1.9 [1.8]) or CTR (2.6 [2.2]) groups (p=0.02) and lower prevalence of subjects with any symptom (29% vs 78% and 75%; p=0.01). There was no significant overall correlation between CFN dose and total symptom count (rho=0.19, p=0.23), but CDC and CTR groups did receive lower CFN doses (0.045 [0.018] and 0.049 [0.011] µg/kg) than the DEP group (0.060 [0.017]; p=0.04). Reanalysis using only the 11 COC and 12 DEP (and 12 CTR) subjects who received CFN doses of 0.03-0.07 ug/kg produced similar results (p's=0.09; all tests 2-tailed). These findings suggest that chronic cocaine use may reduce the acute response to mu-opioid agonists, although the results are potentially confounded by any other significant group differences, e.g., prior exposure to other drugs, age.

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EFFICACY OF COGNITIVE-BEHAVIOHAL THERAPY FOR COCAINE-USING METHADONE PATIENTS

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Current cocaine-dependent methadone patients (by DSM-IIIR) were randomly assigned voluntarily to six months of high intensity cognitive-behavioral therapy (5 X week individual and group) [N=140] or low intensity therapy (1 X week group) [N=58]. All regular methadone clinic services were provided. Subjects were 57% male, 43% female; 53% Hispanic, 34% African-American, 13% white/other, mean age=38; 76% unemployed; mean methadone dosage=68 mg. Therapy was completed by 61% of high intensity and 60% of low intensity patients. ANOVA with repeated measures was conducted with patients trichotomized on severity of cocaine use at baseline, therapy condition and therapy completion status as independent variables and cocaine use during four post-therapy follow-up time periods as repeated dependent measures. Cocaine use at follow-up was measured by the percentage of cocaine-positive urines during successive 12 week periods (25-36, 37-48, 49-60, and 61-72 weeks post-admission). using endpoint data for all subjects. Lower severity of cocaine use at baseline and completion of either therapy were associated with lower cocaine use at follow-up, but there was no difference between the high and low intensity conditions. There, were two interaction effects: (a) Low cocaine severity patients improved more in the low intensity condition, while mid- to high-severity patients improved more in the high intensity condition; (b) positive outcomes for therapy completers relative to non-completers increased over time. **Conclusion:** Six months of supplemental cognitive-behavioral therapy for dually addicted methadone patients had a good completion rate and reduced cocaine use primarily for patients who completed therapy. High intensity as compared with low intensity intervention was not superior overall, hut the results suggest that it may be cost-effective to match patients to levels of treatment intensity based on their severity of cocaine use.

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PROCESS EVALUATION METHODS FOR 12-STEP AND REBT DAY TREATMENT PROGRAMS

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This research evaluates and compares two intensive day treatment approaches, 12-Step and Rational Emotive Behavior Therapy (REBT), for clients with dual diagnoses. We have devised three process evaluation methods for monitoring adherence to program design and philosophy. These methods include: 1) a log system for measuring program equivalence, and 2) two systems to monitor adherence to each of the treatment orientations. The methods to be presented are transferable and could be utilized by similar programs. Both programs are designed to be the same length and have the same number and types of groups and activities. The log system was developed for daily and weekly -ding of data that may he used to compare program content and intensity. These logs capture data that are quantitative (number and types of groups, translated into two databases) and qualitative (e.g., client treatment progress and use of method). To monitor 12-Step and REBT program adherence, forms were developed that can be used by an independent observer and/or by group leaders themselves. These forms evaluate whether the major philosophies and techniques of the methods are utilized in the groups, if resource materials are available and used, staff strengths and weaknesses, and whether the individual treatment plans and notes reflect use of the method.

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MEDICATION TAKE HOME DOSES AND CONTINGENCY MANAGEMENT

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Two studies examined the effects of contingent take-home (TH) doses of methadone (Study 1) and fluoxetine (Study 2) for the treatment of opiate. and cocaine dependence, respectively. In Study 1, 32 methadone maintenance patients were randomly assigned to one of two baseline TH groups: high frequency THs (2 clinic visits with 5 TH dose/wk) or low frequency THs (5 clinic visits with 2 TH doses/wk). The 8-wk baseline period was followed by a 12-wk contingency procedure when the HFTH schedule (2 visits/S THs) could be earned for submitting urines testing negative for illicit drugs. The hypothesis that subjects in the preferred baseline condition (HFTH) would show better contingent-reinforced responding (in order to avoid elimination of this condition) was partially supported by a significant group by time interaction, indicating that the proportion of illicit drug use was lower in the HFTH group during the first six weeks of contingency. Thereafter, the two groups showed comparable levels of responding to the contingency. Drug screens at intake were related to outcome in that polydrug using methadone subjects had an overall poorer response to the contingency than single-drug users. In Study 2, TH doses of *fluoxetine* were used in a contingency management program for the treatment of cocaine dependence. Subjects (n=81) were randomly assigned to 0, 20, or 40-mg fluoxetine, then began the 12-wk trial which included a 4-wk non-contingency baseline period, a 6-wk take-home contingency period, and a 2-wk return to baseline period. All subjects received the LFTH schedule during baseline periods. Results showed that the 40-mg group used less cocaine during contingency than the other groups. There data suggest that the combination of fluoxetine and environmental contingencies may produce benefit where neither alone, is sufficient. Results of both studies are underscore the importance of behavioral and pharmacological treatment integration.

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HEALTH CARE NEED AND UTILIZATION: A COMPARISON OF INJECTION DRUG USERS, OTHER CHRONIC DRUG USERS AND NON-USERS

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Purpose: To compare the need for care, treatment-seeking health care utilization, and the failure to receive needed care among injection drug users (IDU), other chronic drug users (OCDU) and non-drug users (NDU). **Methods:** Interview data from 1,078 African-American, Hispanic/Latino, and non-Hispanic white mate and female IDUs, OCDUS, and NDUs recruited in Dade County, FL were analyzed to assess the need for care, utilization of care, and failure to receive needed care. Eight independent demographic, health status, and drug use variables were entered into three logistic regression models to determine independent factors associated with these outcomes. **Results:** Drug use (IDU and OCDU), being female, having insurance, and poorer health were independently associated with need for care. Non-use of drugs, having insurance, being female, and poorer health were independently associated with utilization of treatment-seeking care. Drug use (IDU and OCDU), having insurance, and poorer health status were independently associated with not receiving needed health care. **Conclusions:** Drug users have a demand for care, are less likely to receive care, and are less likely to receive needed care than are non-users. Interventions are needed to integrate chronic drug users into the health care system and to work with health care providers to increase their sensitivity to the needs of drug users and to emphasize the importance of establishing a continuity of care.

"THE TRI-NET STUDY" ELECTRONIC TRACKING OF NATIONAL TRENDS IN SUBSTANCE ABUSE TREATMENT

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The TRI-Net study is an ongoing, nationwide electronic system that provides standardized timely clinical and administrative information on patients entering into substance abuse treatment programs. This presentation describes the rationale, initial pilot testing and ultimate plans for this information network. Utilizing the Addiction Severity Index (ASI), information is collected on the nature and severity of patients' problems at admission, length of treatment and type of discharge. A unique feature is made possible by the electronic format; ten supplemental questions can be added via modem, based on issues of contemporary concern, and can be changed on a quarterly basis. Four primary types of treatment programs are represented: methadone maintenance. therapeutic communities. outpatient, and intensive outpatient abstinence oriented. In addition, drug court and DWI programs have been piloted. In Phase, One, a pen-based computer system and software were developed and tested. During Phase Two, nineteen programs in live major cities piloted the system, made suggestions regarding implementation, and changes were implemented. These programs (5 intensive outpatient, 5 traditional outpatient, 4 inpatient, 3 methadone programs, 1 drug court and 1 drunk driving program) continue to s-end data and provide feedback. Data transmission via modem began in September of 1996, only non-identifying data are transmitted. The information will be in the public domain. Phase Three has begun and involves expansion into approximately 100 additional programs in 25 cities. Sites are being randomly selected from the total population of treatment programs in the 26 SMSAs represented, resulting in a representative sample of various types of treatment programs.

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EVALUATION OF COMMUNITY INTERVENTIONS: THE FIGHTING BACK MODEL

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Efforts to reduce substance use and harm have widened their focus in recent years from the individual who uses (or is at risk to use) to increased emphasis on broad-based community programs, which seek to reduce substance use by addressing the continuum of care surrounding substance users and potential users: prevention, early identification. treatment, and aftercare. One of the most ambitious of these programs is Fighting Back (FB), a multi-year program designed to foster community efforts to reduce demand for and abuse of substances in fourteen communities around the U.S. In both FB and comparison communities, a set of outcome-oriented evaluation studies of the program is measuring the changes over time in community-wide indicators of substance use, abuse, and harm. Four types of studies are under way: (1) Surveys of adults and youth to address drug and alcohol use and attitudes; (2) Assessment of social indicators of harm caused by substance abuse: (3) Ethnographic studies of the communities; (4) Systematic tracking of program implementation in each community. Mid-project results validate some assumptions of the program and demonstrate that some larger sites are focusing on areas that seem likely to produce substantive changes. The complexity of the system surrounding substance abuse, however, argues that noticeable changes require long-term efforts to alter both the physical and social environments.

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LONGITUDINAL RISK-COHORT STUDY OF ONSET, COURSE, PREVALENCE AND PREVENTION OF ILLEGAL DRUG ABUSE: DRUG USE PATTERNS FOR ASSESSING THE COURSE OF DRUG USE

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Within an ongoing longitudinal study of risk-cohorts in Germany the purpose of the present analysis is to develop a system of drug consumption patterns to assess the course of drug use for time windows of 12 months. The following criteria should be fulfilled: (1) The data basis contains the CIDI with the criteria of DSM-IV diagnosis for abuse and dependence. (2) Theoretically, a person should be able to change each drug use pattern within the time window of 12 months. (3) Two dimensions should be regarded: frequency of use and consequences or problems in relation to drug use assessed by DSM-IV criteria for abuse and dependence. (4) At least the use of hard drugs should be summarized in the different drug use patterns. (5) The diagnostic drug use patterns should be validated by die self-allocation of the participants to different use categories. The suggested system of diagnostic use patterns consists of six categories: (1) seldom use 1-11) in the last 12 months and no DSM-IV diagnosis of abuse and dependence (2) regular use (12 - 100) and no diagnosis (3) heavy use and no diagnosis (4) seldom use and diagnosis of abuse or dependence (5) regular use and diagnosis (6) heavy use and diagnosis. The frequency categories of CIDI can be allocated to the frequency categories of the diagnostic drug use patterns. The results show a dominating accordance between psychic dependence and heavy use with diagnosis for opiates (87%) and cannabis (83%). but only to a less degree for cocaine users (in 58%). There is also a strong relationship between heavy use with diagnosis and physical dependence with exception of cannabis use for which 25% of the persons with physical dependence have shown a diagnostic use pattern of heavy use without DSM-IV diagnosis. The contingency coefficient care from 0.56 to 0.64 and for rank correlation (Spearman) from 0.43 to 0.62. Finally, several cluster-analyses with different predefined numbers of clusters (SPSS: Quick Cluster) were carried out to find an empiric-statistical typology to support the validity of the diagnostic drug use patterns. The four cluster solution seemed to be suitable for a plausible interpretation.

THE INCIDENCE OF POLYSUBSTANCE USE IS GREATER AMONG COCAINE USERS THAN NON-COCAINE USERS

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Although a large proportion of subjects recruited for drug abuse research studies are identified through responding to newspaper advertisements, few studies have investigated their polydrug use profiles. This study was conducted to determine the drug use profile of the typical subject who responded to the following advertisement:

Paid Volunteers, Healthy men and women,
ages 21-35, for cocaine/hormone related studies.
Blood sampling involved.

From 1990 to 1996 a total of 701 individuals responded to this advertisement and were screened using a series of structured questionnaires inquiring about drug use, health status and demographic information. The subjects (62 % male) ranged in age from 19 to 39 with a mean age of 25.7 years. Sixty-one % of the subjects reported a lifetime history of cocaine use but only 3 % reported using cocaine exclusively. Use of LSD, amphetamine, psilocybin and heroin in the cocaine using population was significantly more common than in the remaining 39 % who did not use cocaine. The incidence of reported heroin use has increased in the past 1 to 2 years while only 7 % of the subjects reported no illicit drug use at ah. These results suggest polysubstance use was significantly more common among cocaine users than individuals who have never used cocaine.

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BEHAVIORAL ADAPTATION TO CHANGES IN REINFORCEMENT CONTINGENCIES BY HUMANS: EFFECTS OF DRUG DEPENDENCE

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Two laboratory experiments investigated components of adaptation and self-control (e.g., response inhibition) in subjects with a history of drug dependence. Experiment 1:12 subjects (n=6 per group) were exposed to conditions with changing consequences. One group had a history of substance dependent: (SCID-II-NP), the other was a matched control group. On day 1, subjects were required to wait 0.25 sec between responses (button presses) to earn a monetary reward On day 2, without indication, subjects were required to wait 10 sec between each response. Dependent measures included subjects' response efficiencies (rewarded/total responses) and interresponse time distributions. Three subjects in the drug-dependence group adjusted very poorly to the transition ($p<.01$). These three subjects were all over age 35 and had long histories of substance use (>10 years): whereas other subjects either had no use or much shorter use histories. The findings prompted Experiment 2, with 18 subjects (n = 6 per group), All subjects were >35 years old. Group 1: dependence history, substance use≥10 years; Group 2: dependence history, use <5 years; Group 3: no dependence or abuse history. The high to low-rate transition procedure was repeated from Exp 1. The general finding of Exp 1 was replicated, subjects with long drug dependence histories (Group 1) showed little sign of adapting to the task requiring them to wait 10 sec between each response ($p<.01$). In both studies, these subjects tended to perseverate on the previously established high-rate response pattern. We suggest that our data measure a behavioral deficiency in adapting to contingencies that require self-controlled responding (e.g., waiting) subsequent to a history of high-rate responding.

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REINFORCING EFFECTS OF DRUG/ETHANOL COMBINATIONS RELATIVE TO ETHANOL ALONE

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The reinforcing effects of combinations of ethanol and methadone or ethanol and cocaine were examined in 6 rhesus monkeys. The monkeys had previously been trained to orally self-administer either methadone (n=4) or cocaine (n=2) in daily 3-hr test sessions. Self-administration of either drug had declined over time such that none of the subjects consistently self-administered methadone or cocaine in preference to concurrent water. However, when 0.2 mg/ml methadone or 0.2 mg/ml cocaine was combined with 1% (weight/volume) ethanol, both drug combinations were consistently prefaced to concurrently available water. In the methadone group, the methadone+ethanol combination was then compared to 1% ethanol over fixed-ratio values ranging from 1-32. At lower ratio values, ethanol alone was preferred to the methadone+ethanol combination. At higher FR values, the combination was preferred to ethanol alone. In the cocaine group, self-administration of a 0.2 mg/ml cocaine + 1% ethanol solution was also compared to concurrently available 1% ethanol. Both animals also showed an increased preference for the combination solution as fixed-ratio size increased. The results show that both ethanol+methadone and ethanol+cocaine combinations will be orally self-administered by monkeys. The findings also suggest that work requirement modifies preference for drug+ethanol combinations relative to ethanol alone.

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I.V. MORPHINE, AMPHETAMINE AND PENTOBARBITAL PRODUCE SIMILAR DEGREES OF EUPHORIA IN MALES

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To determine whether drugs of three different classes produce similar profiles, the subjective/behavioral effects of I.V. morphine, amphetamine, and pentobarbital were evaluated in eight healthy male volunteer drug users who provided informed consent and resided on a Clinical Research Unit. On 10 separate days, each subject was administered a different dose of morphine (5, 10, and 20 mg), amphetamine (5, 10, and 20 mg), pentobarbital (50, 100, and 200 mg), and placebo, in a double-blind, placebo-controlled design. Subjective drug responses were collected at 60 and 15 minutes pre- and at 30, 60, 90, 120 and 180 minutes post-injection. Amphetamine and pentobarbital produced significant elevations on the MBG Scale of the ARCI, and MBG Scale scores were significantly higher after 200 mg pentobarbital than after 50 mg pentobarbital. Amphetamine produced a greater number of discrete euphoric episodes compared to pentobarbital, and more euphoric events were reported after 200 mg pentobarbital than 50 mg pentobarbital. Latency to detect drug was shoes following 20, 10 and 5 mg morphine. Duration of drug detection was greater after pentobarbital than morphine and amphetamine, with greatest duration of drug detection reported after 200 mg pentobarbital. There were no drug-related differences in latency to detect euphoria or duration of euphoria. These results indicate that the subjective reinforcing effects of iv. morphine, amphetamine and pentobarbital have similar subjective profiles.

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METHODS FOR INCREASING FEMALE STUDY PARTICIPATION AND STUDYING COCAINE ABSTINENCE

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Ten non-treatment seeking female cocaine smokers resided on a Clinical Research Center for 4-5 days, Cocaine self-administration sessions occurred at 1200 and at 1600 on 2 consecutive days and participants could smoke up to 6 doses of 50 mg cocaine base each session. Participants immediately began a 2-week outpatient phase. They repotted to the laboratory each morning, completed questionnaires, received clinical evaluations and provided a urine specimen. Over the 2-day cocaine binge, women self-administered 20.4 out of a maximum of 24 possible doses. Compared to the 1200 session, heart rate and blood pressure were significantly increased during the 1600 session. Nine women completed the outpatient phase, attending 98% of appointments. Sixty-eight percent of urines documented the absence of cocaine use and were reinforced with $40 in merchandise vouchers. Cocaine withdrawal symptoms during the outpatient phase included increases in total scores on the Cocaine Withdrawal Questionnaire and the Opiate Symptom Checklist and increases in ratings of "Miserable" and "Tired." In contrast, scores on the Beck Depression inventory decreased over time relative to admission. These results suggest that cocaine abstinence symptoms are relatively mild in non-treatment seekers. Further, recruitment of female cocaine abusers can be enhanced by short study lengths and reduced cocaine use can be reinforced in non-treatment seekers.

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LIMITED SEX DIFFERENCES IN RESPONSE TO SMOKED COCAINE IN HUMANS

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The effects of repeated self-administration of smoked cocaine base were evaluated in 11 men and 9 women. Cocaine self-administration sessions occurred at 1200 and again at 1600 on 2 consecutive days. During each session participants could smoke up to 6 doses of 50 mg cocaine base (~ a $3 "crack" vial in NYC). Baseline systolic and diastolic blood pressure were higher in men than in women. The first cocaine dose increased HR and BP and ratings of "High" and "Stimulated" similarly in both men and women. For example, HR was 98.1 + 2.2 bpm in men and 96.2 + 1.8 bpm in women, and ratings of "high" were 58.7 + 4.7 mm in men and 54.9 + 4.9 mm in women. Women reported they would spend significantly less for that dose than men ($1.58 vs. $3.15), which may be related to the fact that the women were less likely to buy their own cocaine. Men and women self-administered a similar number (21.7 and 21.6) of doses. Although cocaine produced similar effects in men and women 4 min after each dose, HR and BP remained elevated 20 min after the last dose of the session in women, but nor in men (e.g., HR was 4 bpm above baseline for men and 11 bpm above baseline for women). Cocaine craving, estimated using ratings of "I want cocaine," also differed between men and women 20 min after the last dose: ratings were 6 mm above baseline for men, but 9 mm below baseline for women. Other ratings of drug effects were similar, however, after the last cocaine dose, despite higher cocaine plasma levels in women. Thus, smoking cocaine base pruduces similar acute subjective effects in men and women, but prolonged cardiovascular effects in women, and different effects on cocaine craving in men and women.

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GENDER DIFFERENCES IN HEROIN USE SEVERITY AMONG NON-INJECTING HEROIN USERS

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Introduction: Non-injecting users (NIUs) of heroin are an increasing proportion of heroin users. Little is known about NIUs, particularly any gender differences that may exist. It is likely that gender differences in drug use patterns and mental health that have been identified among injection drug users may also be found among NIUs. **Methods:** Street recruited NIUs in New York City who reported that they had used heroin in the past 30 days, who had never injected, and who were not currently enrolled in treatment were interviewed between March 1996 and April 1997 a part of a longitudinal study on transitions to injecting. This analysis is limited to 214 subjects for whom urine toxicology results for opiate metabolites were available. **Results:** 77% of the sample were men. 23% women, 35% were African American, 28% Latino. 30% While and 7% other race/ethnicity. The average age was 34.2 (sd 8.7). 59% of the subjects had a positive opiate toxicology result. Women were 2 times more likely to test opiate positve than were men (OR=2.3, 95% Cl=1.2, 4.7). A positive opiate toxicology was significantly associated with several self-reported measures of drug use severity including daily use (OR=8.8, 95% CI=4.6, 16.7), use in the past 3 days (OR=24.9,95% CI=l2.4, 49.9), and the mean number of bags of heroin used in the past 30 days (59 vs. 19, p=.0001). Women were significantly more likely to have higher levels of psychological distress; however, psychological distress was unable to adequately account for gender difference in heroin use severity. **Conclusion:** It appears that among NlUs, the severity of heroin use is greater in women than in men. Additionally, a positive opiate toxicology result appears to be a valid measure of heroin use severity.

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INTERCOLLEGIATE WOMEN ATHLETES, DRUG USE AND DRUG TESTING

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The drug-related attitudes and behaviors of female intercollegiate athletes and their views on drug testing were assessed and contrasted with those of male athletes at a major university (division I). Few studies have examined drug attitudes and behaviors among intercollegiate women athletes, and we could find only one study that assessed college women athletes' attitudes towards drug testing and compared attitudes towards drug testing by gender. Data used in the present analysis were derived from two sources: a questionnaire completed anonymously by 500 intercollegiate athletes on 21 teams, who were required to participate in drug testing, and 45 minute m-depth tape recorded interviews with a random sample of 57 of the 500 athletes. The questionnaire asked for demographic information, personal drug use history, and general attitudes about appropriateness and usefulness of drug testing. Results indicated that women student athletes preferred wine, and men beer; more women used coffee and over-the-counter drugs, and more men used tobacco/smokeless tobacco. Marijuana was the most commonly used illegal substance among college athletes. Intercollegiate women held more positive attitudes regarding drug testing than men and felt stronger about the importance of testing for all classes of drugs (p; chi-square tests). Only a minority of male and female college athletes felt that athletes should be tested for the use of alcohol, tobacco, and prescription drugs. The present findings have implications for drug education, counseling and drug testing programs as well as policies and procedures in colleges and universities. Prevention and intervention efforts need to target both shared and distinct characteristics of women's and men's behavior and attitudes towards substance use and drug testing for more effective policies and programs.

FURTHER ANALYSIS OF HAIR COCAINE DATA SETS: CAN HAIR SERVE AS AN AGGREGATE TREATMENT OUTCOME MEASURE?

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The extent to which cocaine-hair analysis can be used to represent levels of exposure in a sample of users is not settled. Hair is potentially of value as a long-term treatment outcome measure that could provide for more objectivity than self-report. Relating hair results to a more widely accepted concurrent exposure measure allows for an estimate of concordance. A perinatal research study provided an opportunity to study this in a sample of adult women from the beginning of a treatment/case management intervention. As part of the study protocol, samples of women's hair and urine were collected every four months from baseline out to two years beyond intake for a total of seven repeated measures by each method. Measurement of cocaine in hair and urine were performed by different commercial laboratories, each blind to other's results. A sample size of 160 were initially available, and with attrition this declined to 82 in two years. The lost cases did not bias the sample toward lower-severity users as the mean baselines for both urine and hair did not differ among the women who were either available or lost by 24 mo. Dropping obviously had no bearing on concordance. Selecting on women who provided at least 6 of the 7 specimens of both hair and urine, a strong stable relationship was found within subjects for cocaine level estimates derived from hair and urine measurement. Cocaine levels detected by the two methods were strongly correlated across all 7 sampling periods ($P<.001$) with r values ranging from a low of .41 to a high of .66. Examination of lag time between samples showed a significant linear decline in the strength of association as time between successive periods increased, this was the case both within a method (hair to hair) and across the two methods (hair to mine). The findings endorse hair as a useful AGGREGATE or cohort level estimate (especially as an alternative to self-report), but have no bearing on the use of hair measures for specific samples as is required in forensics.
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EFFECTIVENESS OF INTENSIVE CASE MANAGEMENT WITH SUBSTANCE ABUSING WOMEN: A PROCESS EVALUATION OF THE MATES PROGRAM

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Hypothesis: Intensive Case Management (ICM) can be effective in decreasing alcohol and other drug (AOD) use. increasing employment and improving physical health, mental health and social functioning. **Procedures:** The DC Metropolitan Area Treatment Enhancement System (MATES) has provided ICM to more than 900 women. Active Clients were assessed at intake and a median of 7 months post-intake with both the ASI (N=279) and SF-36, a measure of health status and functioning, (N=203). AOD agency staff provided past 30-day urinalysis results for N=209. Finally, terminated clients were compared for employment and criminal justice status between intake and discharge using case manager reported data (N=516). **Analysis:** Percentages were compared over time using the Cochran Q test. Results: Reductions in past 30 day AOD use were reported over time by 60% for alcohol, 70% for heroin, 65% cocaine and 68% marijuana. These results were consistent with urinalysis, as 9.6% of reported test results were positive. For women with children below age 18, the percentage who lived with their children increased over time by 16%. Client employment increased over time by 87%. Physical, social, role emotional and mental health functioning scores on the SF-36 significantly increased, suggesting an improvement over time relative to the general population. **Conclusions:** The results provide preliminary support for the treatment effectiveness of the ICM services.

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MULTIPLE TREATMENT OUTCOMES FOR WOMEN ENROLLED IN OUTPATIENT SUBSTANCE ABUSE TREATMENT

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Personal, social, and family outcomes were evaluated for 38 women enrolled at least 8 months in comprehensive outpatient substance abuse treatment. Comparisons of self-reported outcomes assessed with the Psychosocial History (Comfort and Kaltenbach, 1996) were conducted for intake to 4 months, 4 to 8 months, and intake to 8 months post admission. Significant declines occurred in self-reported 30-day substance use from intake to 8 months (p <.05). Increases in drug-free urine screens from the 1st to 4th months in treatment verified these reports (p <.05). The number of substance using partners decreased from intake to 4 months, then increased from 4 to 8 months, although not to the level reported at intake (p <.05). Percentages of women taking prescribed psychiatric medications showed an initial increase during the early months of treatment, followed by a decrease during later months (p <.05).Perceived needsfor housing and financial assistance decreased across both assessment intervals (p <.05). Financial assistance from partners/family doubled between intake and 4 months, then declined from 4 to 8 months (p <.05). Comparisons of the proportions of children per family who were living with their mothers showed positive outcomes in family reunification between intake and 8 months in treatment (p <.05). Reports of family legal problems (e.g., child custody or support) increased from intake to 4 and to 8 months, suggesting healthy acknowledgements of existing issues. These results demonstrate the value of assessing women's multiple needs and outcomes to effectively evaluate client progress and treatment efficacy.

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N ACTIVITY SCALE AS A PROCESS MEASURE OF TREATMENT EFFICACY

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Aims: To evaluate 1) whether patients treated with the Community Reinforcement Approach (CRA) engage in different activity patterns compared to patients treated with 12-step facilitation drug counseling (DC), and 2) whether greater involvement in pro-social activities leads to reduction in drug use. **Methods:** We developed an activity duration scale (ADS) and compared weekly activities and cocaine use, as assessed by interviewers using the ADS and the weekly drug use inventory, of cocaine-dependent pregnant and postpartum women treated for 12 weeks with CRA (n=15) or DC (n=10) in a random-assignment clinical trial comparing these treatments. The interviewer-administered ADS assesses the number of hours per day over the past week spent in activities including work/vocational; social and recreational with non-drug users; hobbies; 12 step recovery; spiritual/religious: and interactions with drug-users. **Results:** Compared to DC, CRA is associated with greater increases in social interactions with non-drug users (8.9 hrs/wk baseline to mean 13.1 hrs/wk during tx for CRA; 10.1 hrs/wk to 10.3 hrs/wk for DC) and in hobbies (9.6 hrs/wk to 12.5 hrs/wk for CRA; 6.5 hrs/wk to 7.5 hrs/wk for DC). Both CRA and DC are associated with reductions in time spent with drug users. Patients were classified as abstinent >4 weeks (n=7), 1-4 weeks (n=10), or never abstinent (n=8). Increased involvement in activities unrelated to drug use and decreased time spent with drug users were associated with abstinence. **Conclusions:** CRA and DC may be associated with differences in activity patterns, and activity patterns may be related to achievement of abstinence. A revised version of the ADS has been developed to address problems identified in the original instrument, including better definition of activity categories and specification of rating procedures.

AFTERCARE FOR WOMEN USING THE AFRICAN-AMERICAN CHURCH COMMUNITY: AN EXPLORATORY STUDY

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The African-American Church community represents one of the most influential and powerful institutions within the inner city but is usually not involved with the formal drug treatment system. This paper reports on the preliminary findings concerning a program that utilizes the African-American faith community to prevent relapse among homeless crack cocaine using women with children. The Bridges program uses a coalition of African-American churches to provide mentors and culturally-relevant educational and cultural programs in collaboration with a residential community-based treatment program. Church congregant volunteers are trained to be "community anchor persons" (CAPs), providing clients with daily individual and group fellowship and companionship, sponsorship and mentoring, as well as assistance with housing, child care, and other concerns. Because of funding limitations, less than half of those eligible for assignment to a CAP actually became involved in the aftercare program. This situation allowed for an unintended comparison group of clients who received residential treatment but did not receive the Bridges aftercare component. This paper describes the intervention, the client characteristics, and a preliminary analysis of outcomes approximately six months following discharge from residential treatment. In general, no differences were found between groups on outcomes at follow-up. However, both groups improved significantly in terms of drug and alcohol use, HIV risk behaviors, residential stability, and mood. The lack of differences may be due to a small sample size and the poor follow-up rate of the non-aftercare group. It is concluded that using an aftercare program that utilizes mentors from the faith community as well as culturally-relevant educational and group activities may represent a promising approach to maintaining long-term sobriety in the community and merits further systematic investigation.

LABORATORY MEASURES OF AGGRESSION, IMPULSIVITY AND 5-HT FUNCTION IN FEMALE PAROLEES

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Thirty female parolees participated after giving their informed consent. Subjects were divided into a violent (n=10) and nonviolent group (n=20)) based upon their criminal history. Subjects were excluded if screening indicated any history of medical or psychiatric illness, or recent drug use detected by urine drug screen analysis. Subjects participated for four days. Day 1 consisted of six 25 min sessions during which aggressive and escape responding were measured using the Point Subtraction Aggression Paradigm. Day 2 consisted of up to 10 sessions which employed an adjusting self-control procedure to measure impulsivi ty. Days 3 and 4 involved two neuroendocrine challenge tests conducted in the University's CRC. One day subjects were administered placebo and on the other day, buspirone 0.4 mg/kg. To assess CNS serotonergic activity in these subjects serial measures of prolactin were taken to determine the response to the challenge agent, buspirone. The violent and nonviolent groups differed significantly on measures of aggressive responding, but female parolees responded much less than males parolees (previous study). Impulsivity was not correlated with aggressive responding as it had been with male parolees. The prolactin response data is being analyzed. Several psychometric measures were also administered. The behavioral response data support the relationship between laboratory aggressive responding and violence history. With females the behavioral measures of aggression and impulsivity were not correlated.

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IMPACT OF VOUCHER INCENTIVES ON RESIDENTIAL LENGTH OF STAY AND OUTPATIENT TREATMENT ATTENDANCE

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Drug abstinence is particularly important for pregnant drug dependent women, as any illicit drug use cart he harmful to both mother and fetus. In the present study, we examined the efficacy of escalating voucher reinforcement schedules in retaining pregnant drug dependent women in treatment during the first 14 days (7 days residential followed by 7 days intensive outpatient), when the risk of dropout is high. Subjects were randomly assigned to escalating incentives or control groups. For subjects not in methadone maintenance (N=78), vouchers were given daily contingent on treatment attendance ($5/Day 1 with $5 increase each subsequent day; total potential earnings $525). For subjects in methadone maintenance (N=53), vouchers were given daily contingent on attendance (Days 1-7) or attendance and cocaine abstinence (Days 8-14). Vouchers bad no impact on premature dropout (AMA) from residential care. For nonmethadone subjects who did not AMA, however, attendance was greater in the incentive (mean 11.2 days) than control (mean 9.8 days) groups ($p<.02$). Similarly for methadone subjects who did not AMA, attendance and abstinence were greater in the incentive (10.9 days) as compared to the control (9.5 days) groups ($p<.05$). These data support the effectiveness of escalating voucher incentive schedules for improving treatment attendance and drug abstinence in high-risk populations such as pregnant women.

PREDICTING TREATMENT NONCOMPLIANCE IN COCAINE DEPENDENT MOTHERS

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A major problem in treating crack-cocaine addiction is the patient's noncompliance with coming to clinic visits - which is especially true early in treatment, e.g. the first 6 weeks. Noncompliance is more likely for women became they are, typically, single mothers of young children who have multiple psychosocial problems. The purpose of this study was to identify pm-treatment characteristics that predicted treatment noncompliance in the first 6 weeks of addiction treatment for 84 crack-cocaine dependent mothers, 18 years or older. who were either pregnant or had at least one child less than 4 years old. Noncompliance was defined as failing to attend any treatment for 2 or more weeks during the first 6 weeks. Using this definition. compliant and noncompliant female patient groups were distinguished and logistic regression was applied to identify attrition predictors. Results revealed that the number of high-risk sexual behaviors (i.e., HIV-related) these women had engaged in during the 6 months prior to entering treatment was the best predictor of treatment noncompliance in the first 6 weeks of treatment. That is, the Sex Index scores from the Risk for Aids Behavior (RAB) at treatment entry was 8.6 for noncompliers vs. 6.7 for compliers: Wald= 5.43, df= 1, p< .05. The second predictor of treatment attrition (i.e., a trend) was the number of days of reported cocaine use in the 30 days prior to entering treatment. That is, the number of days of cocaine use in the 30 days pre-treatment was 13.7 for noncompliers and 9.7 for compliers; Wald= 3.37, df=1, p=.07). Also, women with both cocaine and significant alcohol use were more likely to drop out of treatment. However, there was a significant correlation between number of days of cocaine use with the number of days of alcohol use in the 30 days prior to treatment (r =0.44, df= 83, p<.001). These findings have important implications for future efforts to improve treatment compliance among this population in the initial weeks of treatment. In particular, women who engage in high risk sexual behavior and have high levels of alcohol and cocaine use are more likely to drop out early in treatment. Programs with a clinical focus on alcohol treatment may improve treatment retention.
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PREDICTORS OF TREATMENT OUTCOME FOR PREGNANT WOMEN

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This study examined client characteristics predictive of retention, abstinence, and service utilization for required services and specialized services of pregnant women in outpatient and residential treatment. Retrospective data were collected from the Psychosocial History (PSH), a structured clinical interview that is an expansion of the Addiction Severity Index designed specifically to assess substance abusing women. The PSH was conducted at intake for 183 pregnant women admitted to outpatient (n=133) or residential (n=50) treatment. Factor analysis was used to reduce 42 predictor variables to 27 variables organized on 5 factors with composite scores created for the 5 factors. Multiple regression procedures were used to determine client characteristics that predict treatment outcomes. In the outpatient program, the strongest results were for Retention (p<.0001) and Required Services (p=.021). A variety of factors accounted for the variance in Retention (multiple R2=.153). Utilization of Required Services was predicted by low scores on the factor reflecting family reunification problems, parenting counseling needs, and unstable housing (multiple R2=.069). For the residential program, early drug use coupled with low scores on the composite of family history of drug and alcohol problems, psychiatric symptoms, need for prenatal and medical care and history of family conflicts predicted greater abstinence (multiple R2=252, p=.017). These findings confirm there are no simple predictors of outcome for pregnant women in treatment. Significant predictors were composites of variables that span all aspects of women's lives including medical and psychiatric needs, family and parenting issues, housing, victimization and client's perceived needs for treatment and assistance in all of these areas.
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TYPE A AND TYPE B CLUSTERS IN PREGNANT SUBSTANCE-DEPENDENT TREATMENT-SEEKING WOMEN

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Recent research has supported the validity of the Type A/Type B alcoholism typology (Babor *et al.,* 1992) in other drug abusing populations. Type As are characterized by less severe substance abuse, psychiatric and psychosocial problems and fewer premorbid risk factors while Type Bs exhibit greater impairment in these areas. The present study examined 238 opiate and/or cocaine dependent pregnant women admitted to a comprehensive drug treatment program. Cluster analyses were performed using the K-means procedure with 8% of women classified as Type B and 92% classified as Type A. The two clusters were then compared on demographic, substance use and other psychiatric and psychosocial variables using t-test and chi-square analyses. Type B women had a significantly higher incidence of premorbid factors including family history of alcohol abuse, child Conduct Disorder, and an earlier age of onset of substance dependence than Type A women. Type Bs also displayed greater substance abuse/dependence severity as well as higher severity of psychosocial problems (medical, employment, family/social) and higher levels of comorbid psychopathology. Unlike previous research, differences were found between the two subgroups for current age (Type Bs older) and race (more Caucasian Type Bs). Study findings suggest the Type A/ Type B typology has important implications for assessment and treatment of this high-risk population.

References available upon request from senior author.

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PSYCHIATRIC SYMPTOMATOLOCY IN DRUG DEPENDENT PREGNANT WOMEN

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In substance dependent patients, psychiatric symptomatology has been associated with higher rates of treatment dropout and drug relapse (Ward *et al.,* 1981; Albott, 1982). Psychiatric comorbity has also been related to unemployment. legal problems, marital distress, and lack of social support which have also been linked with increased treatment dropout (Simpson and Joe, 1993). Treatment dropout has also been associated with drug use severity (Stark and Campbell, 1988). Dropout becomes an even greater concern with pregnant women because drug use during pregnancy is associated with low infant birth weight neonatal drug withdrawal, and other complications. The present study characterized the psychiatric symptomatology in a sample of drug dependent pregnant women and examined the relationship between psychiatric symptomatology and drug abuse severity. Subjects were 110 women admitted to a comprehensive treatment program for pregnant women. Psychiatric distress was measured by the Symptom Checklist 90-Revised (SCL-90-R) and alcohol and drug abuse were measured by the Addiction Severity Index (ASI). Results indicated that 74% scored positive on at least one of the 9 subscales on the SCL-90-R upon admission to the program. Consistent with previous research (Schaefer *et al.,* 1987, Stark *et al.,* 1988) those designated as positive on the SCL-90-R for Somatization, Depression, and Anxiety had higher severity ratings on the drug subscale of the ASI when compared to those negative on the SCL-90-R for the 3 of subscales ($p=0.003$, $p=0.006$, and $p=0.004$, respectively). Given that psychiatric comorbidity is most prevelant for drug abusing populations (Smith *et al.,* 1992; Montoya *et al.,* 1994; Johnson *et al.,* 1996). it is important that upon admission these symptoms be assessed so that appropriate intervention may be taken.

CONTINUITY OF DRUG USE PATTERNS AMONG HIGH RISK WOMEN

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Postnatal drug use among mothers who have used drugs prenatally is of particular concern not only due to increased risk to the woman's health but also because of the negative impact on her caregiving capacity. Continuity of drug use after the baby's birth was examined over a 24-month period in a sample of 119 women whose primary drug was either alcohol or cocaine. Multiple samples (n=51 at 6-months, n=42 at 24-months) of low SES, urban, predominantly African-American women were drawn from a larger study. At 6-months postpartum, 82% of this sub-sample reported continued substance use. One hundred percent of those reporting alcohol as their primary drug continued, while 60% of those reporting cocaine as their primary drug continued. At 24-months postpartum, 57% reported use. 80% of those reporting alcohol as their primary drug continued to use, while among those reporting cocaine as their primary drug, the percentage was 27%. These data indicate significant behavior differences depending upon their primary drug of choice. Only a minority of women received drug treatment/intervention (16% at 6-months, and 10% at 24-months). The majority of mothers at both 6- and 24months reported that their children were home during their most recent drug and/or alcohol use. Although many demographic, social, and emotional factors were assessed, no predictors for continued drug use were identified, except for the primary drug of choice.

PARENTING SKILLS QUESTIONNAIRE-REVISED (PSQ-R): TEST-RETEST RELIABILITY

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Parenting training programs are part of comprehensive substance abuse treatment for women. No instrument has been validated in this population to measure parenting knowledge. The purpose of this study was to determine the test-retest reliability of the Parenting Skills Questionnaire-Revised (PSQ-R). The PSQ-R is a 31 self-report true-false-l don't know questionnaire developed to evaluate parenting knowledge in 3 different domains: infant care, child development, and drug abuse during pregnancy. The questionnaire was first administered to 45 pregnant or postpartum women upon entering substance abuse treatment, and administered a second time (with item order changed) 5 to 10 days later. Preliminary results showed moderate test-retest agreement for true and false items (average kappa = 0.51, $p < .05$ for 27 of 31 items), and the average percent item agreement was 87.65. These results suggest that the PSQ is a good tool to assess knowledge and beliefs among substance abusing women and to measure changes in knowledge following parenting training within this population.

COMPARISON OF MORPHINE AND METHADONE MAINTENANCE IN PREGNANT OPIATE ADDICTS

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A majority of studies demonstrate the advantage for mother and child in using methadone maintenance in pregnant opiate addicts. It is also proven, that infants born to methadone maintained mothers are more severely affected in their neonatal withdrawal syndrome as infants with an intrauterin exposure to heroin. Over a period of 50 months. the drug-addiction out-patient clinic in Vienna investigated 52 pregnant opiate addicts in administering during pregnancy either methadone or slow-release morphine. The subjects (mean age: 26 years, mean duration of pregnancy before starting maintenance treatment: 19 weeks) were consecutively enrolled in an open study design. The oral opioid at the time of delivery was in 50% of the subjects methadone (mean daily dosage 45 mg), in 43% morphine (mean daily dosage 340 mg) and 7% were successfully detoxified and drug free. The mean birth weight in the methadone group was 2850g, in the morphine group 2880g. No significant differences occurred in comparing the mean duration of withdrawal syndrome in the newborns, 16 days in the methadone group and 20 days in the morphine group. No significant correlation between withdrawal syndrome and mean daily dosage of methadone ($r = 0.53$, $p = 0.2$) and morphine ($r = 0.39$, $p = 0.14$) could be found. Born substances are safe during pregnancy and yield to a comparable out-come in regard to birth-weight of the birth-weight and neonatal withdrawal syndrome.

INCREASED SENSITIVITY TO LONG-TERM CONSEQUENCES OF EARLY EXPERIENCE FOLLOWING GESTATIONAL COCAINE EXPOSURE IN RATS

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This experiment is part of our ongoing work examining the impact of gestational cocaine exposure on later stressor responsivity. Rat offspring were derived from Sprague-Dawley dams receiving subcutaneous injections of 40 mg/kg/3cc cocaine hydrochloride (COC40) on gestational days 8-20, non-treated (NT) control dams, and dams mar had been exposed to substantial undernitrition (NC) during pregnancy. Some litters of offspring were examined in a non-invasive study of heart rate at 16 days of age (requiring approximately 5 hr of separation from me home nest), whereas other litters received no early experience. In adulthood, animals received either 0.1 or 9 daily exposures to a 15 min foot shock session (1mA, 1 sec; VI 30 sec), with all animals receiving a 5 min open field (OF) test 24 hr after the last manipulation. A number of behavioral alterations were seen in COC40 offspring, with me nature of these alterations being dependent on the early postnatal experience of the animals. COC40 offspring that did not have the early experience exhibited less immobility during their first exposure to the foot shock and in subsequent OF testing. as well as more OF locomotion man corresponding NT offspring, replicating previous findings (Molina *et al.,* 1994). In contrast. COC40 offspring given the early experience exhibited an opposite pattern, showing increased immobility and reduced OF locomotion. These dramatic effects of early experience were not seen in NT and NC offspring, despite substantial undernutrition as indexed by notable birth weight reductions in NC offspring.

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LATE ABSTRACTS

DEVELOPMENT OF NEW SCALES TO ASSESS CHANGE IN THE ADDICTION SEVERITY INDEX.

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Analyses were performed to construct and confirm the validity of new conjoint intake and 6-month follow-up scales for the Addiction Severity Index. Using a diverse sample (N=1,008) of methadone maintenance, cocaine, and alcohol dependent patients, a multistage scaling strategy identified 5 psychometrically integral addiction problem scales. Exploratory item and components analyses, confirmatory oblique item clustering, and secondarder factor analysis verified that the sales comprised relatively little common variance and that each retained a substantial amount of unique and reliable variance. Resulting scales (psychiatric, drug, alcohol, family, and legal problems, respectively) were highly internally consistent and structurally stable overall. at intake and follow-up, and across gender, age, ethnicity, and substance abuse categories. Concurrent and predictive validity were supported for clinical subsamples based on urine toxicology, criminal records, comorbid psychopathology, and personality indices. Baseline to follow-up changes on the new scale were associated with demographics and types of substance dependence. Advantages of the new scales are discussed, including provision of computer code for calculating normalized intake and follow-up standard scores and predicted change scores for use in clinical practice and treatment outcome research.

ACKNOWLEDGMENTS: Supported by NIDA Center Grant # DA05186, NIDA Grant # DA-05858, and the Department of Veterans Affairs.

PSYCHOSTIMULANTS DIFFERENTIALLY AFFECT DOPAMINE TRANSPORTER ACTIVITY

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Methamphetamine (METH) and several related analogs cause reactive oxygen species formation *in vivo,* and reactive oxygen species decrease dopamine transporter (DAT) activity *in vitro.* Hence, effects of administering METH or other pyschostimulants on DAT activity were investigated. A single administration of METH caused a rapid, but reversible, decrease in $V_{max}$of [^{3}H]dopamine uptake, as assessed in rat stiatal synaptosomes. This phenomenon was independent of the well-characterized, long-term neurotoxic effects of this stimulant, and was not caused by residual METH introduced by the original *in vivo* treatment. Administration of related psychostimulants such as methylenedioxymethamphetamine (MDMA), methcathinone or p-chloroamphetamine likewise rapidly decreased DAT activity. In contrast, cocaine administration had no effect on [^{3}H]dopamine uptake. These data demonstrate significant differences in the response of DAT to psychostimulants, and may have important implications regarding the role of oxidative events in the physiological regulation of dopaminergic neurons.

ACKNOWLEDGMENTS: Supported by NIDA grants DA-05780, DA-04222 and DA-00869.

DISCRIMINATIVE STIMULUS EFFECTS OF SELF-ADMINISTERED ETHANOL IN RATS

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Five rats were trained to discriminate 1000 mg/kg ethanol from saline injected i.p. 15 minutes prior to a 15 minute drug discrimination session. An ethanol dose response curve (100-1560 mg/kg ethanol) was completed. Complete substitution occurred at the training and higher doses. Subsequently, rats were trained to self-administer a 10% ethanol (w/v) solution. Discrimination and ethanol self-administration (SA) days were then alternated. On discrimination days, rats were injected with 1.0 g/kg ethanol or saline, placed into SA chambers for 15 minutes and then into the discrimination chamber for testing. On SA days, animals were allowed to SA ethanol for 15 minutes, then given a sham injection and returned to the chamber for 15 minutes. Three tests were completed to examine substitution of SA ethanol and water for the trained i.p. dose. First, rats SA ethanol (mean intake = 1017 mg/kg), wee given a sham injection, and tested in the discrimination procedure. Full substitution (80% ethanol lever responding) of SA for i.p. ethanol was observed. Second, rats SA water, were given a sham injection, and were tested in the discrimination procedure. Water SA resulted in 20% ethanol-level selection. A redetermination of 1000 mg/ml ethanol and saline i.p. injections reveled the training dose continued to control ethanol discrimination. Thirds, rats were allowed to SA 0.1 ml of 10% w/v ethanol prior to a discrimination session. and here was no substitution for i.p. ethanol. Finally, rats were allowed repeated access to water and response rates declined to minimal levels, indicating that ethanol was functioning as a reinforcer. These data suggest that the internal stimulus effects of self-administered ethanol are similar to stimulus effects of i.p. experimenter administered ethanol.

A CATALYTIC ANTIBODY AGAINST COCAINE ELIMINATES ITS REINFORCING EFFECTS IN RATS

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University of Michigan, Ann Arbor, Ml and *Columbia University, New York, NY

Rats were conditioned to press a lever for sweetened condensed milk, and maintained on a fixed-ratio 5 time-out 20 s schedule of reinforcement Intravenous catheters were then implanted; subsequently, lever presses delivered 0.3 mg/kg/inj cocaine under the same schedule for 1 hr daily sessions. When drug-reinforced responding was stable, saline was substituted for cocaine on occasion until responding was reduced and occurred predominantly in the early portion of the session. When the catalytic antibody, 15A1O, previously described by Yang *et al.* (1996) was administered prior to a session in which cocaine was available, the pattern of responding maintained by cocaine resembled that maintained by saline. Thus, this catalytic antibody can function *in vivo* to reduce the reinforcing effect of cocaine in rats.

Reference:

Yang, G., Chun, J., Arakawa-Uramoto, H., Wang, X., Gawinowicz, M.A., Zhao K., and Landry, D.W. Anti-cocaine antibodies: a synthetic approach to improved antibody diversity. J.Amer. Chem. Sec. (19%) 118, 25, 5881-5890.

ACKNOWLEDGMENTS: Supported by USPHS Grant DA 03228 and the Counterdrug Technology Assessment Center at the Office for National Drug Control Policy.

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXI. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1997)

A. E. Jacobson, Biological Coordinator, Drug Evaluation Committee, CPDD

Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

As previously noted (Jacobson 1997), the contemporary DEC is a direct descendent of the original analgesic testing program of the Committee on Drug Addiction of the National Research Council, National Academy of Sciences. It has only been within the past 20-25 years that the purposes and activities of DEC could be distinguished from those of CPDD. Within the past year DEC has reorganized to become an independent consortium of researchers which acts as the arm of the CPDD involved with drug testing and research. DEC activities are reported to the Chair of the the newly established Liaison Committee for Drug Evaluation and Testing.

DEC work now encompasses methodological research and physical dependence potential and abuse liability testing of drugs with analgesic, stimulant, and depressant actions. The work is done as a free public service to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. Researchers engaged in the work have grants or contracts from the National Institute on Drug Abuse, NIH, and some of DEC organizational expenses are paid by the CPDD. The DEC public service sets the CPDD apart from all other scientific membership organizations. Questions regarding this testing service can be addressed to the Biological Coordinator of DEC (fax: 301-402-0589, e-mail: aej@helix.nih.gov). Publication of the data gathered by DEC generally occurs within three years from receipt of sample, both in the NIDA Monograph (e.g., Aceto *et al.* 1997; English *et al.* 1996; Woods *et al.* 1997), as well as in various journals (Aceto *et al.* 1996; Aceto *et al.* 1989; May *et al.* 1994).

DEC MEMBERS

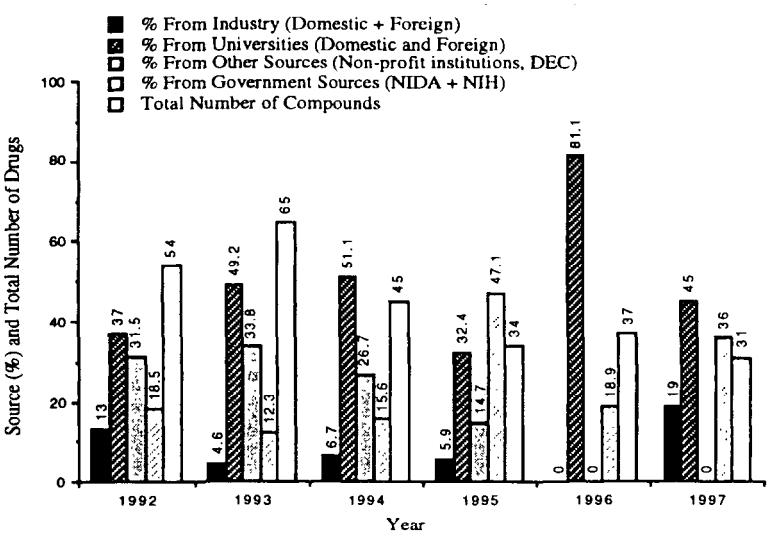
Members of DEC are those individuals who are presently associated with the Analgesic and Stimulant/Depressant Testing Programs. At this time, the DEC Members are: Drs. Mario Aceto and Louis Harris from the Medical College of Virginia Virginia Commonwealth University, James Woods, Gail Winger, and John Traynor from the University of Michigan, Ted Cicero (DEC Chair) from Washington University, St. Louis, Arthur E. Jacobson (DEC Biological Coordinator) from NIDDK, NIH, Charles France from Louisiana State University, Bill Woolverton (DEC Recording Secretary) from the University of Mississippi, and the Chair of the CPDD Liaison Committee for Drug Testing and Evaluation (James Smith, Bowman Gray School of Medicine, *ex officio).*

Membership in DEC is available to anyone who has the expertise and resources to carry out drug testing, and who is the principal investigator on a grant/contract. This drug testing must complement or extend existing drug testing programs, and the principal investigator must consider DEC drug testing as a priority for them. Their inclusion into DEC is gained by majority vote of the voting members of DEC.

STATISTICS

The sources and number of compounds released for publication from 1992 - 1997 can be seen in Fig. 1. In 1997, pharmaceutical industry once again became a major source of samples for evaluation (19%), and most of the industrial groups were foreign. The university sources (45%) were all domestic. and the governmental sources were, mostly, NIDA, with some drugs from NIDDK researchers. Additional data on four compounds

were obtained by the stimulant/depressant testing groups. The total number of compounds released for publication this year was somewhat less than the number released last year, as shown in Fig. 1, but there are several very interesting drugs (see Experimental Observations section), one of which is in phase III clinical trials for intractable pain untreatable by morphine. The sources for the examined drugs are considerably more disparate than was observed last year, although no drugs came from non-profit institutions.



EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH and CPDD numbers of the compounds examined this year, and notes the specific table number where they appear. Tables 2 - 9 present the structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from work at the Medical College of Virginia, VCU, and the University of Michigan (Aceto *et al.* 1998; Woods *et al.* 1998) and additional work on CPDD 0007, 0032, 0042, and 0044 (France *et al.* 1998) from the Stimulant/Depressant group is summarized in Table 10. The compounds in Tables 2 - 9 are grouped according to their molecular structure (e.g., endoethano- and ethenooripavines, 4,5-epoxymorphinans, 6.7-benzomorphans, etc.) in order to facilitate recognition of the relationship between their molecular structure and biological activity.

In Table 2. the DEC work is shown on the very potent endoethenoorpipavine, etorphine (NH 8068), and the even mom potent endoethanooripavine, NIH 10846, dihydroetorphine, the latter having been sent to DEC by the NIDA Medications Development Division. Both drugs are many-fold more potent than morphine as antinociceptives. The dihydroetorphine has considerably greater affinity for the μ-opioid receptor than etorphine, and is more potent *in vivo*. Since both self-administration and drug discrimination indicate that 10846 is likely to show abuse liability in man, unless its clinical efficacy is considerably better than currently used analgesics it will probably not he clinically useful as an analgesic. NIH 10846 might have utility as medication for drug abuse; it will probably be well-liked by heroin addicts, and withdrawal from the drug might be physically easier than from methadone. It is not, however, a particularly long-acting drug.

Selective, potent, opioid agonists and antagonists would be useful both as therapeutic agents and as tools for the exploration of opioid receptor systems. Such drugs are known, if not well-utilized as yet, for the the μ-, and perhaps κ--opioid receptors: less well known am drugs for the δ--opioid system. There is debate about whether the δ--opioid receptor acts independently, or interacts with the μ-receptor, or both, and whether an extremely selective δ-agonist would show physical dependence potential or abuse liability. Both a δ-agonist (NIH 10821) and antagonist (NIH 10822) were examined by DEC, and are shown in Table 3. It is interesting to note that neither drug displays an antinociceptive (or narcotic antagonist) effect in mice (sc administration), similar to our findings for other known δ–ligands such as SNC 80 (NIH 10815 (Jacobson 1996)), nor do they suppress the morphine abstinence syndrome in monkey single-dose suppression assays, unlike μ-ligands, Even more interesting is their inability to displace [^{3}H]-etorphine from rat cerebral membrane preparations. However, the actual affinity and selectivity of the δ-antagonist was shown in specific opioid receptor assays. NIH 10822 was found to be have high affinity for the δ-opioid receptor and the μ/δ ratio was found to be 37, and κ/δ was 88. Lastly, in Table 3, NIH 10875, was shown in 1930 to be a weak antinociceptive agent in the HP assay. Its binding affinity was determined, and it was found to be selective for μ-opioid receptors: its affinity is somewhat better than that of codeine, its isomer.

A series of N-substituted normetazocines were examined and the data are shown in Tables 4 and 5. It is surprising to note that the effect of various substituents on the nitrogen atom in this (or any other) class of analgesics is in large measure still quite unpredictable, although *in vivo* and *in vitro* data on many of them have been experimentally obtained (May *et al.* 1994). Of particular interest in Table 5 is the (+)-enantiomer, NIH 10898, which has weak antinociceptive activity and does not suppress morphine abstinence in the monkey single-dose suppression assay. Unfortunately, it appears to have convulsant actions. The (-) normetazocine NIH 10884 is a fairly potent antinociceptive agent, also without much effect in the SDS assay. However, like many N-substituted normetazocines, it also has high affinity at the κ-receptor.

The remaining compounds examined, in Tables 6, 7, 8, and 9 have molecular structures which do not tit into well-known analgesic classes. (-)-Eseroline (NIH 10820, in Table 6) was reexamined for pharmaceutical industry and found to be a morphine-like antinociceptive which was fairly ineffective at displacing ^{3}H-etorphine from opioid receptors; interaction with selective receptor assays was not measured. Several compounds (NIH 10833, 10838, 10839, 10840, 10841, and 10867, in Tables 6 and 7) were examined for the NIDA Medications Development Division as potential treatment agents, and ω-conotoxin (NIH 10887, Table 8) was sent to us by pharmaceutical industry. That drug was noted by the submitter to be an extremely potent intrathecal analgesic. DEC found it to have a little antinociceptive activity sc or iv and it does not appear to have affinity for any of the opioid receptors, except weak affinity for the δ-receptor. It would not be predicted to have physical dependence potential or abuse liability of the opioid-type from our self-administration and drug discrimination tests. The conotoxin family of toxins come from the cone snail and it was recently noted that the disulfide links confer its rigidity and a characteristic shape allowing the toxin to nestle in a particular channel or portion of a specific CNS receptor (Ackerman 1997). The ω-conotoxin which DEC evaluated is a synthetic peptide which was developed as a potential treatment for intractable pain, for those unresponsive to morphine It is in phase HI clinical trials (Ackerman 1997).

In Table 10, new work is shown on four compounds which were previously evaluated by the Stimulant/Depressant Group (CPDD 0007, 0032, 0042, and 0044; methaqualone, flunitrazepam, zipeprol, and γ-hydroxybutyric acid, respectively). These data are from drug discrimination studies at Louisiana State University (France *et al.* 1998). Comparative data from previous work with these compounds are also listed in that Table. the procedures used, and the complete data, will be published this year in a separate Stimulant/Depressant Group report (France *et al.* 1998).

NOTES FOR TABLES 2 - 9

Rounded numbers are used; precise values and details of the procedures are given in the MCV (Aceto *et al.* 1998) and UM (Woods *et al.* 1998) reports.

1) Antinociceptive reference data:
Morphine ED, (confidence limits): Hot Plate = 0.8 (0.3-1.8); Phenylquinone = 0.23 (0.20-0.25); Tail-Flick = 5.8 (5.7-5.9)
Tail-Flick Antagonism vs. morphine (naltrexone AD_{50}= 0.007 (0.002-0.02); naloxone AD_{50} 0.035 (0.01-0.093)).

2) *In Vitro* - Subtype selective binding affinity using monkey brain cortex membranes. Selectivity for μ, δ, and κ-opioid receptors determined with [^{3}H]-DAGO, [^{3}H]-*p*-Cl-DPDPE and [^{3}H]-U69,593, respectively.

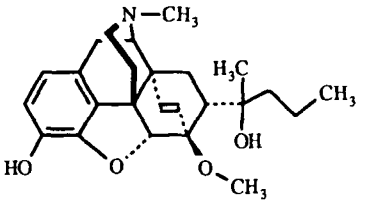
TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #-Evaluator
8068	Etorphine.HCl	2-MCV
10820	(-)-Eseroline (L)-ascorbate	6-MCV/UM
10821	3-O-Methyloxymorphindole hydrocloride	3-MCV/UM
10822	3-O-Methylnaltrindole fumarate	3-MCV/UM
10833	N-[(*R,S*)-2-Benzyl-3[(*S*)(2-amino-6-methylthio)butyldithiol]-1-oxopropyl]-L-phenylalanine benzyl ester methyl sulfite	6-MCV/UM
10838	2-Phenyl-1,3-propanediol dicarbamate (Felbamate)	6-MCV/UM
10839	3,5-Dimethyltricyclo[3.31.1^{3,7}]decan-1-amine (Memantine)	6-MCV/UM
10840	1-Aminocyclopropane carbolic acid (ACPC)	7-MCV/UM
10841	D-Phenylalanine	7-MCV/UM
10846	Dihydroetorphine hydrocloride	2-MCV/UM
10860	(-)-5,9α-Dimethyl-2-heptyl-2'propionoxy-6,7-benzomorphan hydrocloride	4-MCV/UM
10864	(-)-5,9α--Dimethyl-2'-hidroxy-2-(2-hydroxyethyl)-6,7-benzomorphan oxalate	4-MCV/UM
10867	7-Nitroindazole	7-MCV/UM
10869	(-)-2-Cyanomethyl-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan hydrocloride	4-MCV/UM
10870	(+)-2-Cyanomethyl-5,9 α--dimethyl-2'hydroxy-6,7-benzomorphan hydrochloride	4-MCV/UM
10871	(-)-2-(5-Chloropentyl)-5,9 α-dimethyl-2'hydroxy-6,7-benzomorphan hydrochloride	4-MCV
10874	7-Benzoyl-2-piperidinomethyl-1,6-benzodioxane hydrochloride	7-UM
10875	Pseudocodeine hydrocloride	3-UM
10884	2*R*,5*R*,9*R*-(-)-2-(3-Cyanopropyl)-5.9 α-dimethyl-2'-hydroxy-6,7-benzomorphan	5-MCV/UM

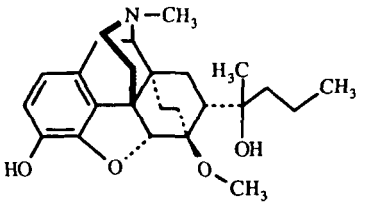
TABLE 1. CONTINUED - NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #-Evaluator
10885	2*S*,5*S*,9S-(+)-2-(3-Cyanopropyl)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan	5-MCV
10886	(±)-Isonicotine oxalate	8-MCV/UM
10887	w-Conotoxin MVIIA (reduced cyclic (1-16), (8-20), (15-25) - SNX-111)	8-MCV/UM
10895	(-)-Isonicotine oxalate	8-MCV/UM
10896	(+)-Isonicotine oxalate	8-MCV/UM
10897	2*R*,5*R*,9*R*-(-)-2-(6-Chlorohexyl)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	5-MCV
10898	2*S*,5*S*,9*S*-(+)-2-(6-Clorohexyl)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	5-MCV
10899	2-Methyl-5-(3-pyridyl)morphan oxalate	9-UM
10900	11-[6-Hydroxy-6-(3-trifluoromethyl)piperidin-1-yl]-2-methyl-6,11-dihydrodibenz[b,e]oxepine sulfuric acid	9-MCV
10901	11-(6-Hydroxy-6-phenylpireridin-1-yl)-2-methyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid	9-MCV
10902	11-[6-Hydroxy-6-(3-trifluoromethylphenyl)piperidin-1-yl]-2-dihydrodibenz[b,e]oxepine fumaric acid	9-MCV
10903	11-(6-Hydroxy-6-phenylpiperidin-1-yl)-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine	9-MCV
CPDD 0007	Methaqualone	10-S/D:LSU
CPDD 0032	Flunitrazepam	10-S/D:LSU
CPDD 0042	Zipeprol dihydrochloride	10-S/D:LSU
CPDD 0044	γ-Hydroxybutyric acid sodium salt	10-S/D:LSU

TABLE 2. ENDOETHENO- AND ENDOETHANOORIPAVINES



8068 (Etorphine)



10846 (Dihydroetorphine)

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for-Morphine (sc, mg/kg)
8068	0.00096[a]	0.0004	0.002[b]	Inactive	μ=0.6; δ=1.13[c]	-	Complete substitution (~ 2000x morphine)
10846	0.0002	0.0002	0.00015[d]	Inactive	μ=0.088; δ=2.54 κ=0.197	0.34 (100) [antagonized by naltrexone]	Complete substitution (~ 2000x morphine)

a) Previously reported, with high physical dependence capacity noted in Substitution-for Morphine assay (Deneau and Seevers 1964).

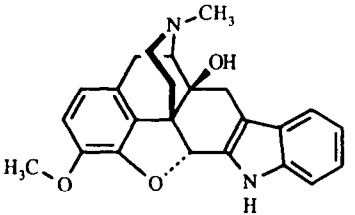
b) Tail flick assay with nor-BNI or naltrindole antagonism: μ-selective and devoid of δ for κ activity. Extended duration in morphine-dependent animals. Low pA_2 (0.09) suggests multiple drug properties.

c) Previously reported (displacement of ^{3}H-sufentanil and ^{3}H-DPDPE, [(Woods *et al.* 1997), see p 400]).

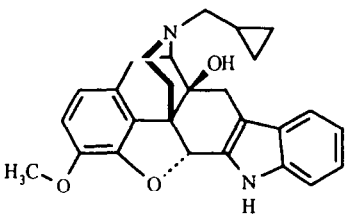
d) Naloxone AD_{50} = 0.04

e) Rat Infusion (Substitution-for-Morphine): suppression less than with morphine; Rat Infusion (Primary Physical Dependence): withdrawal milder than morphine, but same behavioral signs; Monkey primary physical dependence: μ-like withdrawal syndrome, but body weight constant; Self-administration (monkey): >460x heroin, >20,000x codeine.

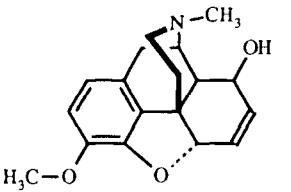
TABLE 3. 4,5-EPOXYMORPHINANS



10821
(3-O-Methyloxymorphindole fumarate)



10822
(3-O-Methylnaltrindole .HCl)



10875 (Pseudocodeine .HCl)

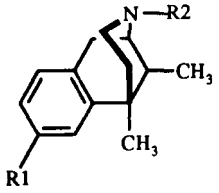
	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg)				IN VITRO	MONKEY	
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for Morphine (sc, mg/kg)
10821	Inactive	Inactive	Inactive	Inactive	^{3}H-etorphine>6000	1300 (100) [antagonized by naltrexone][a]	Partial substitution (20)
10822	Inactive	Inactive	Inactive	Inactive	3H-etorphine>6000 μ=66.4; δ=1.8; κ=158	-	No substitution, possible exacerbation of withdrawal (4,16)
10875 00003	431[b]	-	-	-	μ = 427;δ = >6000; κ=>6000	14800 (63)[c]	-

a) Typical δ-agonist.

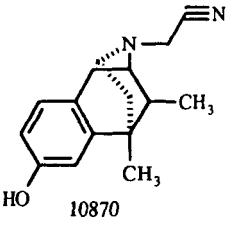
b) Determined in 1930 at NIDDK, MH.

c) Very weak agonist with unusual activity at μ-opioid receptors (naltrexone decreased maximum response without shift in concentration-effect curve).

TABLE 4. 6,7-BENZOMORPHANS



10860: R1 = OCOEt, R2= $(CH_2)_6CH_3$
10864: R1 = OH, R2 = $(CH_2)_2OH$
10869: R1 = OH, R2 = CH_2CN
10871: R1 = OH, R2 = $(CH_2)_5Cl$



10870

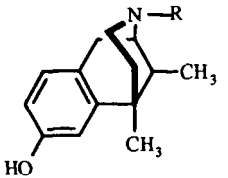
	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg)				IN VITRO		MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for-Morphine (sc, mg.kg)
10860	5.5	0.31	3.13	Inactive	μ=28.2, δ=47, κ=47.5[a]	No effect[a,b]	No substitution (2-12); convulsant, lethal
10864	Inactive	Inactive	Inactive (sc and icv)	Inactive	μ=41, δ=316, κ=16	1290 (68) Slight antagonism) by naltrexone; weak δ-agonist	No substitution (3,12)
10869	8.5	1.52	11.6	Inactive	μ=166, δ=574, κ=69	1720 (83)	Complete substitution [0.25x morphine]
10870	Inactive	6.0	Inactive	Inactive	μ=4490, δ=>6000, κ=1310	7930 (35); not antagonized by naltrexone	Complete substitution (1)[k]
10871	3.6	0.5	0.84	Inactive	-	-	Complete substitution

a) Previously reported ((Woods *et al.* 1997) - see p 416).

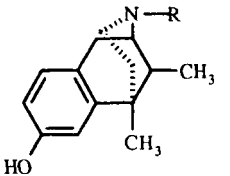
b) Unusual agonist decreased magnitude of twitch, but did not suppress it at any concentration. Very weak, non-selective, antagonist.

c) Severe ataxia; possible κ--opioid.

TABLE 5. 6,7-BENZOMORPHANS (CONTINUED)



10884 (-): R = $(CH_2)_3CN$
10897 (-): R = $(CH_2)_6Cl$



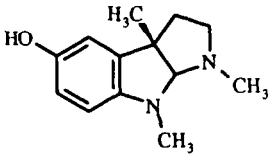
10885 (+): R = $(CH_2)_3CN$
10898 (+): R = $(CH_2)_6Cl$

	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg)				IN VITRO		MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for-Morphine (sc, mg/kg)
10884	1.1	0.1	0.36[a]	Inactive	μ=6.5, δ=21.6, κ=0.34	42.7 (100) [antagonized by naltrexone]	Non-dose-dependent
10885	Inactive	Inactive	Inactive	Inactive	-	-	Non-dose-dependent
10897	1.59	0.67	2.03	Inactive	-	-	Partial substitution (2,8)[b]
10898	Inactive	6.32	11.56	Inactive	-	-	No substitution (3,12); convulsions at 12 mg/kg.

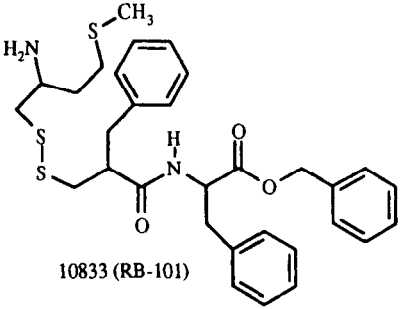
a) High naloxone AD_{50} = 0.28, and effects in monkeys suggest heterogenous opioid properties.

b) Nearly suppresses morphine-withdrawal, potency>morphine; appears μ-opioid-like.

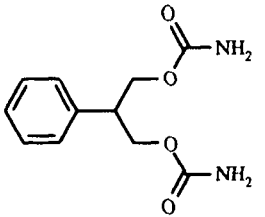
TABLE 6. MISCELLANEOUS



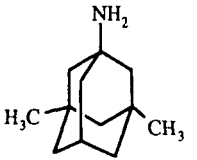
10820 ((-)-Eseroline (L)-ascorbate) (10398[a])



10833 (RB-101)



10838 (Felbamate)



10839 (Memantine)

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for-Morphine (sc.) mg/kg)
10820	3	0.3	2.4[b]	Inactive	1600 (^{3}H-etorphine]	3.9 (49) [Antagonized by naltrexone]	Complete substitution (2.5-10)
10833	-	-	39 (iv); ip inactive[c]	-	μ=2100, δ=>6000, κ=>6000	977 (23) [Not antagonized by naltrexone]	Solvent-like partial substitution (iv)
10838	Inactive	Inactive	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	670 (29) [Not antagonized by naltrexone]	No substitution (3,15)
10839	Inactive	15.1	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	47 (35) [Not antagonized by naltrexone]	No substitution (2,8)[d]

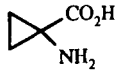
a) Previously reported (Aceto *et al.* 1987)

b) High naloxone AD_{50}= 0.16; pA_2: not typical opioid agonist non-competitive or non-equilibrium steady slate. No antagonism with norBNI.

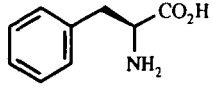
c) Drug has no acute or chronic effect on morphine's ED_{50}.

d) No exacerbation of withdrawal. Excitability seen in tail flick and phenylquinone assays; some signs suggest PCP-like behavior in monkeys.

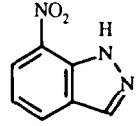
TABLE 7. MISCELLANEOUS (CONTINUED)



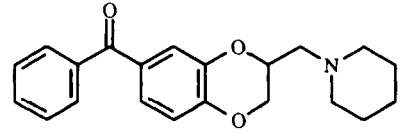
10840



10841



10867



10874

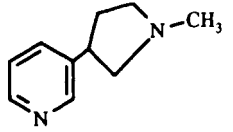
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, SC, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antanonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-For-Morphine (sc, mg/kg)
10840	Inactive	Inactive	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	3290 (34) [Not antagonized by naltrexone]	No substitution (5,25)[a]
10841	Inactive	Inactive	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	185 (56) [Not antagonized by naltrexone]	No substitution (9,45)[b]
10867	Inactive	Inactive	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	1500 (47) [Not antagonized by naltrexone]	-
10874	7.4	-			μ=>6000, δ=>6000, κ=>6000	21 (100) [Not antagonized by naltrexone]	No substitution (5,40)

a) A single (200 mg/kg) dose had no effect When a 200 mg/kg sc was given for 4 days and the monkeys placed in withdrawal, followed by another 200 mg/kg sc dose, neither substitution nor exacerbated withdrawal was observed.

b) No exacerbation of withdrawal. Rat Infusion (Substitution-for-Morphine): no substitution. Heroin discrimination: no attenuation of heroin disciminitive stimulus.

TABLE 8. MISCELLANEOUS (CONTINUED)



10886: (±)-Isonicotine oxalate
10895: (-)-Isonicotine oxalate
10896: (+)-Isonicotine oxalate

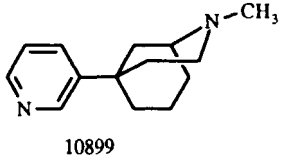
H-Cys-Lys-Gly-Lys-Gly- Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2 cyclic (1-16), (8-20), (15-25)-tris(disulfide)

10887 [ω-Conotoxin MVIA (reduced)]

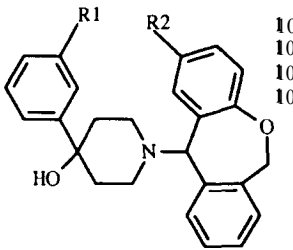
	ANTINOCICEPTIVE/ANTAGONIST ASSAYS				IN VITRO		MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution-for-Morphine (sc, mg/kg)
10886	Inactive	3.2	Inactive	Inactive	μ=>6000, δ=>6000, κ=>6000	Very weak antagonist at μ, and possibly δ	No substitution (3,12)
10887	-	3.16	17.7 (iv)	-	μ=>6000, δ=>1190, κ=>6000	4.8 (100) [Not antagonized by naltrexone]	Partial substitution (0.25,1)[a]
10895	Inactive	3.8	Inactive	Inactive	-		Partial substitution (non-dose related)
10896	Inactive	1.63	Inactive	Inactive	-		No substitution (2.5,10)

a) Self-administration: no reinforcing effect; drug discrimination (naltrexone-saline): did not attenuate discrimination of morphine withdrawal.

TABLE 9. MISCELLANEOUS (CONTINUED)[a]



10899



10900: R1 = CF_3, R2 = CH_3
10901: R1 = H, R2 = CH_3
10902: R1 = CF_3, R2 = CH_2OH
10903: R1 = H, R2 = CH_2OH

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, K^i, nM	Substitution-for Morphine (sc, mg/kg)
10899	-	-	-	-	μ=>1175, =>10000, =>10000	-
10900	Inactive	Inactive	Inactive[a]	Inactive	-	Non-dose related suppression of withdrawal
10901	-	7.6	Inactive[a]	Inactive	-	Complete substitution (0.2x morphine)
10902	0.98	1.13	12.86[b,c]	Inactive	-	
10903	2.2	0.6	1.11[d]	Inactive	-	Complete substitution - morphine-like

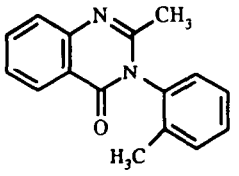
a) Also, orally with 20 or 40 min pretreatment: inactive

b) Possible pro-drug in mouse.

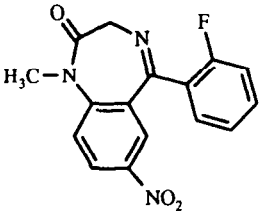
c) Naloxone AD50: 0.12 (high - suggests heterogenous activity)

d) Also, orally with 20 min pretreatment 1.0 mg/kg; 40 min pretreatment: 0.98 mg/kg.

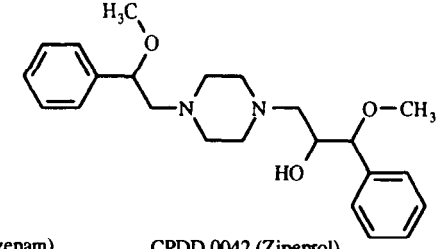
TABLE 10. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



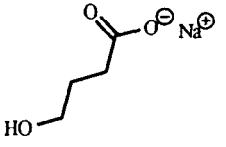
CPDD 0007 (Methaqualone)



CPDD 0032 (Flunitrazepam)



CPDD 0042 (Zipeprol)



CPDD 0044
(γ-Hydroxybutyric Acid)

CPDD#	Discriminative Stimulus Effects In Monkeys, Comparison To Flumazenil & Triazolam (sc)[a]	Monkey Self-Administration (iv)	Monkey Drug Discrimination (Intragastric)
0007	No benzodiazepine agonist or antagonist action	Reinforcer[b]	Substitutes for pentobarbital[b]
0032	Benzodiazepine-like agonist potency similar to triazolam	Reinforcer in 1/3 monkeys[c]	Pentobarbital-trained: 100% Drug-appropriate responding at 0.3-1.0 mp/kg[c]
0042	No benzodiazepine agonist or antagonist action	Reinforcer in methohexital- and alfentanil-trained monkeys[d]	Pentobarbital-trained: No drug-appropriate responding Amphetamine-trained: No drug-appropriate responding[d]
0044	No benzodiazepine agonist or antagonist action	Did not maintain behavior. No reinforcing effect[e]	Pentobarbital-trained: No drug-appropriate responding Amphetamine-trained: Maximum of 50% drug-appropriate responding, probably not dose-related; may have weak amphetamine-Iike subjective effects[e]

a) See Stimulant/Depressant report (France *et al.* 1998)

b) Previously reported (Jacobson 1988a; Jacobson 1988b; Johanson 1986)

c) Previously reported (Jacobson 1991; Patrick *et al.* 1992; Winger *et al.* 1992)

d) Previously reported (English *et al.* 1996)

e) Previously reported (Jacobson 1997)

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DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1997)

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All compounds, except etorphine, dihydroetorphine, NIH 10917 and 10918 were unknown to us when submitted by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. These studies were conducted under the auspices of the Drug Evaluation Committee in association with of the College on Problems of Drug Dependence. See summary of new data in Table 1.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were. used, and they received 3 mg/kg, s.c., of morphine•SO_4 every 6 h. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that bad not received morphine for 14-15 h and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-h observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated the data were analyzed using the Kruskal-Wallis Anova and posthoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 h after the last dose of morphine. These animals were not in withdrawal. Naloxone•HCI (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodicahy challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with antagonist or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 h. Occasionally, when deemed necessary, as with cocaine, infusions were given *via* the right jugular vein.

Substitution-for-Morphine (SM) Test. The rats received morphine•SO_4 (50 mg/kg/24 h on the first day, 100 mg/kg/24 h on the second day, and 200 mg/kg/24 h from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 h at 6, 24, 48, 72 and/or 96 h after stopping the infusion of morphine.

Table 1. SUMMARY OF NEW DATA

NIH No.	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		TF	TFvsM	PPQ	HP	pA_2	SM	PPD	SDS	PPT-W	PPD
8068	Etorphine·HCl	T[a,b]	T	T	T	T			T		
10820	(-)-Eserline (L)-ascorbate	T[c,d]	T	T	T	T			T		
10821	3-O-Methylmorphindole·HCl	T	T	T	T				T		
10822	3-O-Methylnaltrindole·HCl	T	T	T	T				T		
10833	L-Phenylalanine	T	T	T	T				T		
10838	1,3-Propanediol	T	T	T	T				T		
10839	Memantine	T	T	T	T				T		
10840	Cyclopropane amine	T	T	T	T				T		
10841	D-Phenylalanine	T[e,f,g,h]	T	T	T				T		
10846	Dihydroetorphine·HCl	T[i,j,k]	T	T	T	T			T[l]		T
10860	6,7-Benzomorphan	T	T	T	T				T		
10864	6,7-Benzomorphan	T	T	T	T				T		
10867	7-Nitroindazole	T	T	T	T						
10870	6,7-Benzomorphan	T	T	T	T				T		
10871	6,7-Benzomorphan	T	T	T	T				T		
10884	6,7-Benzomorphan	T	T	T	T				T		
10885	6,7-Benzomorphan	T	T	T	T				T		
10886	(±)-Isonicotine oxalate	T	T	T	T				T		
10887	ω-Conotoxin MVIIA	T	T	T	T				T		
10895	(-)-Isonicotine oxalate	T	T	T	T				T		
10896	(+)-Isonicotine oxalate	T	T	T	T				T		
10897	6,7-Benzomorphan	T[m]	T	T	T				T		
10898	6,7-Benzomorphan	T	T	T	T				T		
10900	4-Piperidinol	T[n]	T	T	T				T		
10901	4-Piperidinol	T[o]	T	T	T				T		
10902	4-Piperidinol	T[p]	T	T	T				T		

Table 1. SUMMARY OF NEW DATA

(continued)

NIH No.	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		T F	TFvsM	P P Q	HP	pA_2	SM	PPD	SDS	PPt-W	PPD
10903	4-Piperidinol	T[o,q]	T	T	T				T		
10917	(+)-Pyrroloisoquiniline[1]	T[r]	T	T	T						
10918	(-)-Pyrroloisoquinoline[2]	T	T	T	T						

T=TEST PERFORMED

[a]Special interaction study of NIH 8068 and antagonist subtypes in mouse TF test. [b]Special time-course study in mouse TF test. [c]Special naloxone vs ED80 of NIH 10820 in TF test. [d]Special Nor-binaltorphimine (NlH 10588, kappa antagonist, vs ED80 of NIH 10820 in TF test. [e]Special intravenous study in mouse TF test. [f]NIH 10841 and morphine given simultaneousiy in mouse TF test. [g]Special chronic NIH 10841 (i.v.) plus morphine (s.c.) in mouse TF test. [h]Special chronic NIH 10841 (s.c.) plus morphine (s.c.) in mouse TF test. [i]Special naloxone vs ED80 of NIH 10846 in TF test. [j]Special time-course study of morphine and NIH 10846 in mouse TF. test. [k]Special interaction study of NM 10846 and opioid antagonists subtypes in mouse TF test. [l]Special preliminary study-repeated dose-suppression, abrupt and precipitated withdrawal. [m]Special naloxone vs ED80 of NIH 10897 in mouse TF test. [n,o]Speciai oral pretreatment of mice with NIH 10900 in TF test. [p]Special naloxone vs ED80 of NIH 10902 in mouse TF test. [q]Special naloxone vs ED80 of NIH 10903 in mouse TF Test. [r]Special naloxone vs ED80 of NIH 10817 in TF test. [s]Special mecamylamine vs ED80 of NIH 10817 in mouse PPQ test. [t]Special mecamylamine vs ED80 of NIH 10817 in HP test. [1](+)-Bridged Nicotine. [2](-)-Bridged Nicotine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested and 6-10 animals per dose were used. When applicable, ED50's were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally or i.v. and the pretreatment tunes are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 s under control conditions. Mice were injected with drug or vehicle and tested 20 m later. In the assay for antagonism of the antinociceptive effect, the potential antagonists were administered 10 m before the agonist, and evaluation occurred 20 m later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drugs and 10 m later received 2.0 mg/kg ip of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten minutes after the PPQ injection, the total number of stretches per group were counted over a 1-m period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, a-d extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 s or more, but no more than 30 s beyond the control time.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-flick	Tail-flick	Phenylquinone	Hot-Plate
		Antagonist		
Pentazocine	15% at 10.0	18 (12-26) (1.0-2.5)	1.7	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02-0.78)	0.01 (0.005-0.03)	25% at 9.0
Nalorphine•HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03- 1.44)	13% at 30.0
Naloxone•HCl	None at 10.0	0.04 (0.0-0.09)	No Activity	----
Naltrexone•HCl	None at 10.0	0.007 (.002-0.02)	No Activity	----
Morphine•SO_4[b]	1.92 (0.89-4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39-1.86)
Codeine•PO_4	----	Inactive	8.25 (5.12-13.29)	6.4 (2.4-16.8)
Meperidine•HCl	8.37 (4.59-15.27)	Inactive	----	4.6 (1.18-11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2. Using the tail-flick assay, the apparent pA_2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 m later by an injection of agonist. The mice were tested 30 m after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED50s were, estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96.399, 1949). Bach dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-1) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x-1) were plotted. The pA_2 values for the antagonist were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

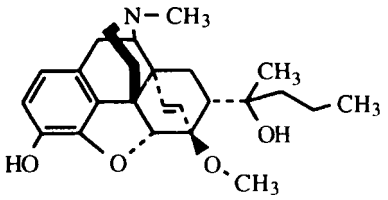
Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2 (95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1-7.6)
2) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
3) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
4) (-)Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 -0 7.6)
5) Naloxone/Sufentanil	7.0 (6.9 - 7.1)-1.0	7.0 (6.9 - 7.0)
6) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
7) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-1.7	7.2 (6.9 - 7.5)
5) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	7.0 (6.9 - 7.0)
9) Naloxone/U-50,488	6.6 (6.3 - 6.9)-1.1	7.2 (6.9 - 7.5)
kappa agonist		6.6 (6.3 - 7.0)
10) Naloxone/NIH 10672	6.1 (5.6 - 6.6)-1.2	6.2 (5.9 - 7.3)
selective kappa agonist		
11) (-) Quadazocine/NIH 10672	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
12) nor BNI/NIH 10672	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
13) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	6.5 (6.4 - 6.6)

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve the the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a costrained plot, the slope of the regression line is restricted to slope = -1.

Special Intracerebroventricular Tail-Flick and PPQ Assays. In order to develop an *in-vivo* agonist and antagonist model to correlate with the *in vitro* binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accomodate the fact that no delta agonist is available which is active by peripheral mutes of administration.

NIH 8068 Etorphine•HCI



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.002 (0.001 - 0.004)
2) TF vs. M - Inactive
3) PPQ - 0.0004 (0.00002 - 0.0009)
4) HP - 0.001 (0.0004 - 0.003)

5) Naloxone vs NIH 8068 in Tail-Flick Test (Apparent pA_2).

The naloxone pA_2 estimate for etorphine of 6.5 (6.5 - 6.5) with a slope of - 0.9 is lower than obtained for morphine (7.2) and fentanyl (7.0). When the slope is constrained to - 1, the pA_2 is 6.45 (6.33 - 6.57).

6) Interaction of opioid agonist and antagonist subtypes in the mouse T.F. Test.

The data indicate that etorphine is a selective mu agonist devoid of kappa and delta activity (see Table 1).

Table 1. The interaction of NIH 8068 (etorphine) with selective opioid antagonists subtypes in the mouse T.F. test.

Antagonist s.c.	Pretreatment Time	Agonist i.c.v./s.c.	Pretreatment Time	ED_{50} or AD_{50}
Naloxone ((s.c.) 0.03, 0.1 and 0.3 mg/kg	30 m	Etorphine (s.c.) ED_{80} - 0.005 mg/kg	20 min	AD50 - 0.09 mg/kg (0.04 - 0.25) Slope = 2.68
Nor-BNI (NIH 10588) (s.c.) 1.0, 10.0 and 30.0 mg/kg	2 h	Etorphine (s.c.) ED_{80} - 0.005 mg/kg	20 min	30 mg/kg : 0% antagonism 10 mg/kg : 0% antagonism 1 mg/kg : 0% antagonism
Naltrindole (NIH10589) (s.c.) 1.0, 10.0 and 30.0 mg/kg	30 m	Etorphine (s.c.) ED_{80} - 0.005 mg/kg	20 min	30 mg/kg : 0% antagonism 10 mg/kg : 0% antagonism 1 mg/kg : 0% antagonism
β-FNA (i.c.v.) 1.0, 3.0, 10.0 and 30.0 µg/brain	4 h	Etorphine (s.c.) ED_{80} - 0.005 mg/kg	20 min	AD50 - 4.7 µg/brain (2.5 - 8.6)

7) Time Course.

As shown in Table 2, etorphine has a rapid onset of action and relatively short duration of action. The half-life estimate is 40 m. The half life of morphine is approximately 2 hr.

Table 2. Time-course study for etorphine tail-flick ED_{80}s in the mouse tail flick assay

% Inhibition of Nociception ± SEM	Pretreatment Time (min)
82 ± 12	20
66 ± 18	40
18 ± 8	60
4 ± 4	90

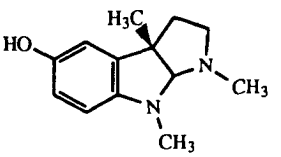
NIH 8068 (Continued)

MONKEY DATA
(SDS)

Etorphine dose-dependently substituted completely for morphine with a potency range of 1.500 to 6,000 times that of morphine sulfate. Etorphine acted promptly and, at the high dose, duration of action was at least 2.5 h.

Comment: In the mouse etorphine behaved essentially as a short-acting-selective mu agonist. In the morphine-dependent monkey in withdrawal, etorphine completely substituted for morphine suggesting that it had mu agonist properties. However, the duration of action was longer in a state of opioid dependency

NIH 10820 (NIH 10398) (-)-Eseroline (L)-ascorbate



MOUSE DATA - ED50 OR AD50, mg/kg/s.c. (95% C.L.) or % change

1) TF - 2.4 (1.2 - 4.5)[a]
2) TF vs. M - Inactive at 1.0. 10.0 and 30.0[a]
3) PPQ - 0.3 (0.1 - 0.7)[a]
4) HP - 3.0 (1.5 - 6.0)[a]

5) Special: Naloxone vs ED80 of 10820 in TF AD50 = 0.16 (0.05 - 0.55)

6) Special: Naloxone-NIH 10820 pA_2 = 6.9 (4.2 9.6) Slope - 0.33 (see Fig Naloxone-NIH10820)

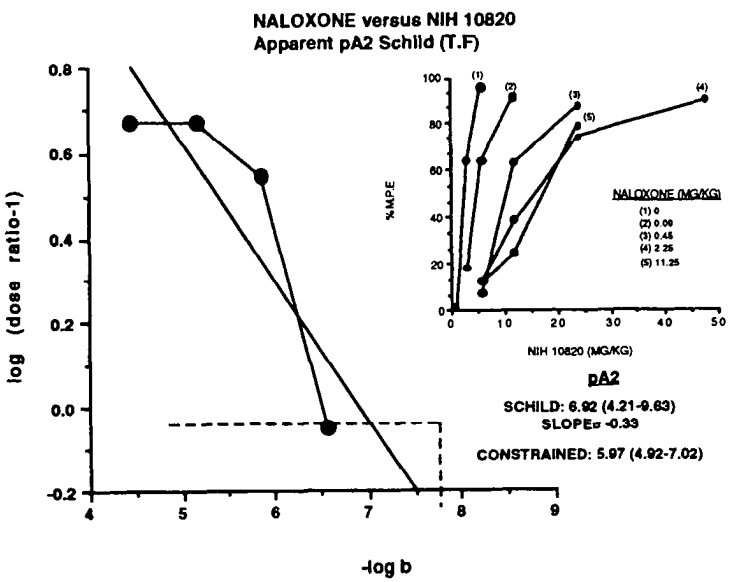


Fig Naloxone-NIH 10820. Naloxone vs NIH 10820 apparent pA_2.

NIH 10820 (Continued)

7) Special: Nor-binaltorphimine (NIH 10588, kappa antagonist) vs ED80 of 10820 in TF (0% antagonist at 1.0, 10.0, 30.0 and 60.0 mg/kg).

MONKEY DATA
(SDS)

NIH 10820 dose dependently substituted completely for morphine at 2.5 and 10.0 mg/kg (see Fig MH 10820)

Comment: This compound was originally studied in the mouse for antinociceptive properties the results of this study are in accord with those reported earlier (see NIDA Monog. 76, 1986).

The fact that this compound was reported not to bind to mu receptors and yet showed *in vivo* mu activity prompted the additional studies. The pA_2 is similar to that obtained with naloxone/morphine interaction. However, the slope of the regression was less than unity suggesting a non competitive or nonequilibrium steady state. In addition, NIH 10820 was devoid of kappa agonist properties.

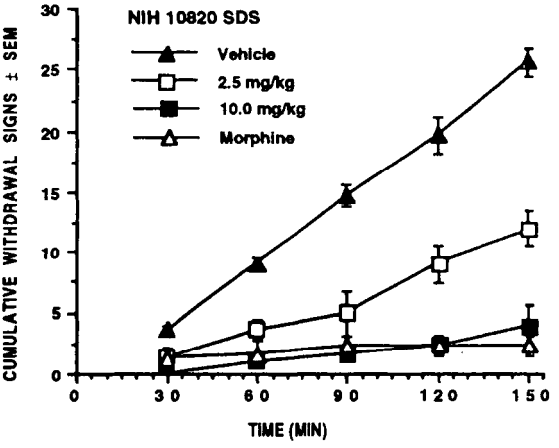
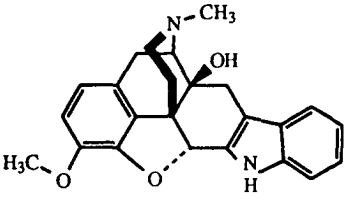


Fig NIH 10820 Results of single-dose substitution of NIH 10820 for morphine in dependent monkeys in withdrawal.

NIH 10821 3-O-Methylmorphindole•HCl



MOUSE DATA - ED50 OR AD50, mg/kg/s.c. (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0% at 1.0, 17% at 10.0 and 23% at 30.0
4) HP - 13% at 1.0, 25% at 10.0 and 38% at 30.0

MONKEY DATA
(SDS)

As shown in the figure (NIH 10821), apparently it suppressed withdrawal. However, the results are equivocal because the number of subjects per dose was only 2. Drug supply was exhausted. The solution had a garlic-like odor.

Comment: The results in monkeys contrast sharply with those observed in mice, Because of limited supplies a definitive study in monkeys was not possible.

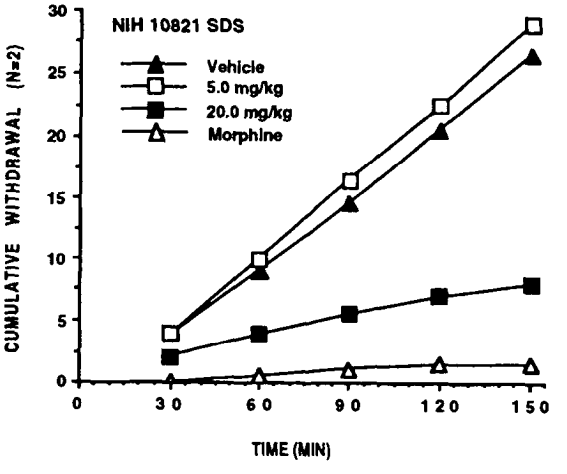
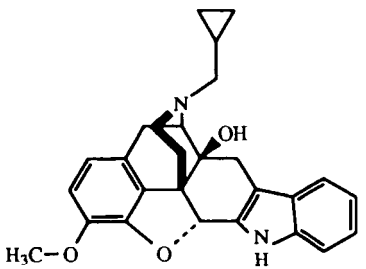


Fig NIH 10821. Results of single-dose suppression of NIH 10821 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10822 3-O-Methylnaltrindole•fumarate



MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 6% at 1.0, 14% at 10.0 and 23% at 30.0
4) HP - 13% at 1.0, 25% at 10.0 and 38% at 30.0

MONKEY DATA
(SDS)

At doses of 4 and 16 mg/kg, NIH 10822 did not substitute for morphine. Instead, there appeared to be a non-significant trend indicating exacerbation of withdrawal (see Fig. NIH 10822). Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.

Comment: This compound does not display remarkable pharmacological properties in the assays tested.

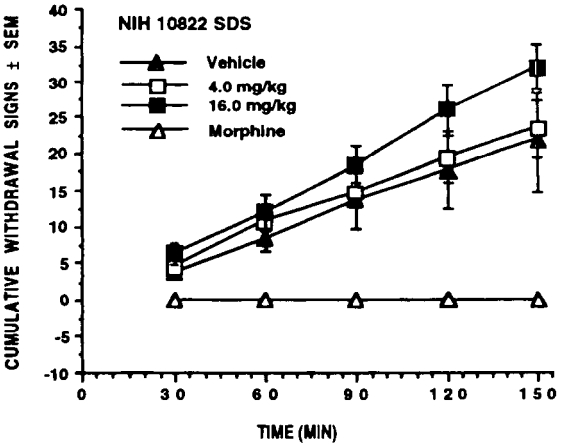
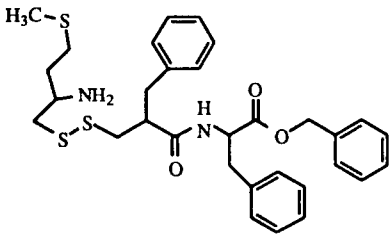


Fig NIH 10822. Results of single-dose substitution of NIH 10822 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10833 N-[(R,S)-2-Benzyl-3[(S)(2-amino-4-methylthio)butyldithiol]-1=oxopropyl]-L-phenylalanine benzyl ester methyl sulfite



MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF - (i.v.) - 39.0 (13.9 - 85.0) at 30.0 increased locomotor activity and 60.0 Straub tail[a]

TF- (i.p.) 15% at 60.0, 20% at 120 and 54% at 200.0[a]

[a]Vehicle 3% Tween 80 in saline

[b]Eyelid ptosis at 60.0 and 120.0

MONKEY DATA
SDS - Special i.v. study

NIH 10833 was dissolved in a minimal amount of dimethylsulfoxide (DMSO). Sterile saline was added, quantum sufficiat, to obtain the desired final volume of 3 ml. The solution was injected into a saphenous vein over a 40-60 second interval. During the first 30-m observation period, some of the monkeys receiving NIH 10833 vocalized as if getting relief (calling) and began eating. However, they also retched and vomitted. An examination of the data illustrated in (figure NIH 10833) suggested that NIH 10833 exacerbated withdrawal. However, the DMSO vehicle controls suppressed two important withdrawal signs termed rigid abdominal muscles and vocalization when palpated. As a result, the control cumulative score was low.

Comment: The results in the mice suggest that given i.v., NIH 10733 produced signs indicative of opioid action (Straub tail and increased locomotor activity). However, the different behavioral signs obtained after i.p. administration suggest that it was rapidly metabolized. Although some indications for opioid action were noted in monkeys, the effect was fleeting and was not reflected in the cumulative scores. Finally, DMSO may have some actions of its own.

NIH 10833 (Continued)

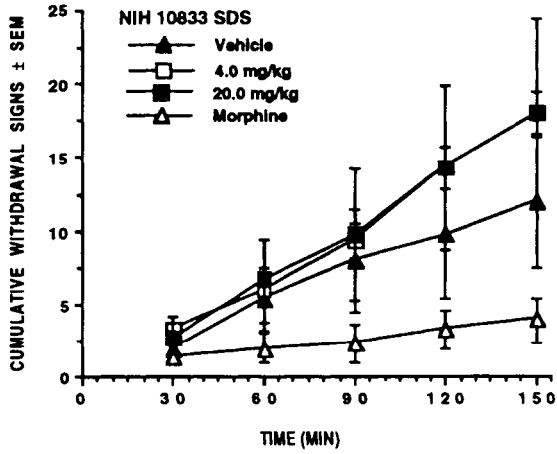
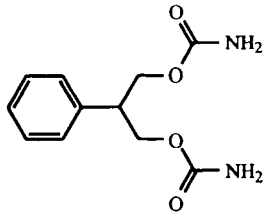


Fig NIH 10833. Results of single-dose. substitution of NIH 10833 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10838 2-Phenyl-1.3-propanediol dicarbamate (Felbamate)



MOUSE DATA - ED50 OR AD50, mg/kg (95% C.L.) or % change

Subcutaneously

1) TF (s.c.) - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M (s.c.) - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ (s.c.) - 6% at 1.0, 14% at 10.0 and 6% at 30.0
4) HP (s.c.) - 13% at 1.0,10.0 and 30.0[a]

Intravenously

1) TF (i.v.) - 15% at 1.0, 2% at 10.0 and 8% at 30.0[a]
2) TF vs. M (i.v.) - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ (i.v.) - Inactive at 1.0, 20% at 10.0 and 34% at 30.0

[a]Vehicle-5% hydroxypropyl-β-cyclodexhin in saline

NIH 10838 (Continued)

MONKEY DATA
(SDS)

Inactive at 3 and 15 mg/kg s.c. (See Fig NIH 10838).

Comment NIH 10838 appears to be avoid of antinociceptive activity in the mouse and neither substituted for nor exacerbared withdrawal in morphine-dependent monkeys in withdrawal. Apparently, NIH 10838 lacks opioid properties.

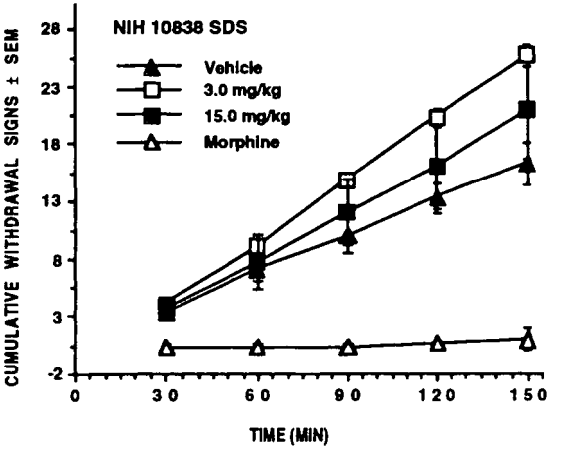
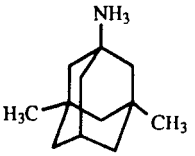


Fig NIH 10838. Results of single-dose substitution of NIH 10838 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10839 3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine (Memantine)



MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF (s.c.) - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M (s.c.) - Inactive at 1.0, 10.0 and 30.0[b]
3) PPQ (s.c.) - 15.1 (11.2 - 20.5)
4) HP (s.c.) - Inactive at 1.0, 10.0 and 30.0[c]

[a]Mice were extremely excited and jumping at 10.0 and 30.0. Test latencies (MPEs) were shorter than control latencies.

[b]Increased locomotor activity and Straub tail at 10.0 and 30.0. Clonic convulsions in 1 of 6 mice at 30.0. Also, tremors and ataxia noted.

[c]At 30.0 mg/kg ataxia increased locomotor activity and Straub tails were noted. Latencies (MPEs) where shorter than control.

MONKEY DATA
(SDS)

As shown in the accompanying fig., NIH 10839 did not substitute for morphine or exacerbate withdrawal at doses of 2 and 8 mg/kg. A number of signs designated slowing, ataxia, chewing, eyelid ptosis, disorientation, walking in circles were noted at both doses.

Comment: It is unlikely that NIH 10839 has mu or kappa-like properties. The drug displays prominent CNS effects in mice and monkeys. Some of the signs noted in monkeys suggest PCP-like behavior.

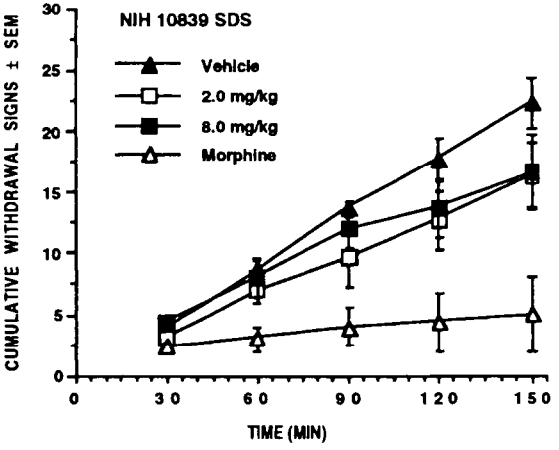
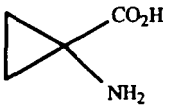


Fig NIH 10839. Results of single-dose replacement of NIH 10839 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10840 1-Aminocydopropane carboxylic acid (ACPC)



MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF - Inactive at 1.0 10.0 and 30.0
2) TF vs. M - Inactive at 1.0 10.0 and 30.0
3) PPQ - Inactive at 1.0, 10.0 and 30.0
4) HP - Inactive at 1.0, 10.0 and 30.0

MONKEY DATA
SDS

Study 1 At doses of 5 and 25 mg/kg, NIH 10840 neither suppressed nor exacerbated withdrawal (see Fig NIH 10840). No overt behavioral effects were seen at these doses.

Study 2 A single dose of 200 mg/kg s.c. was without effect in an abruptly withdrawn morphine-dependent monkey. The dose was administered at 2 sites. Drug supply exhausted.

Comment: NIH 10840 does not display remarkable mu opioid suppressive properties in the monkey at 5 or 25 mg/kg. In the dose range tested in the mouse, NIH 10840 did not demonstrate antinociceptive properties.

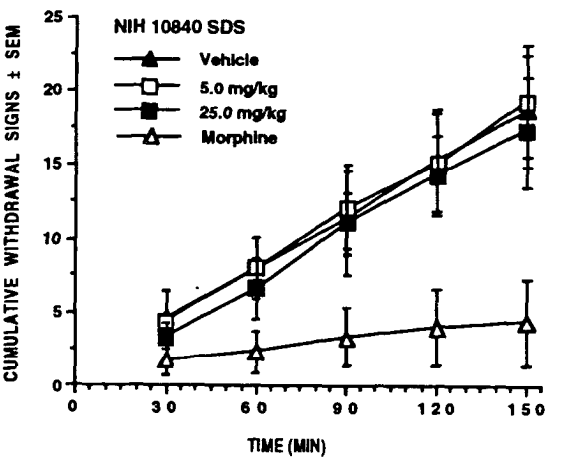
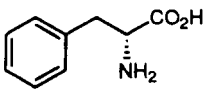


Fig NIH 10840. Results of replacement of NIH 10840 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10841 D-Phenylalanine



MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF (i.v)[a] - Inactive at 1.0, and 30.0, 14% at 10.0
(s.c.) Inactive at 1.0, 10.0 and 30.0
2) TF vs. M (i.v.)[a] - Inactive at 1.0, 10.0 and 30.0
(s.c.) Inactive at 1.0, 10.0 and 30.0
3) PPQ (i.v)[a] - 14% at 1.0, 11% at 10.0 and 23% at 30.0
(s.c.) 9% at 1.0 and 10.0, 51% at 30.0 and 37% at 30.0
4) HP (i.v.)[a] - Inactive at 1.0, 10.0 and 30.0
(s.c.) 13% at 1.0, 10.0 and 30.0

[a]Vehicle-Sterile Saline

MOUSE DATA - ED50 OR AD50, mg/kg
(95% C.L.) or % change

1) TF (s.c.) - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M (s.c.) - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ (s.c.) - 9% at 1.0 and 10.0, 51% at 30.0, 37% at 60.0[a]
4) HP (s.c.) - 13% at 1.0, 10.0 and 30.0[a]

[a]Vehicle - Sterile water

Special Mouse Data

Special acute and chronic interaction studies of NIH 10841 with morphine in the tail-flick test.

A) Acute NIH 10841 (i.v.) Plus Morphine (s.c.)

Mice were given 30 mg/kg of NIH 10841 followed 10 min later by morphine. Latency measurements were conducted 20 min later (see Fig NIH 10841 Mouse Acute Treatment).

B) Chronic (3 day) NIH 10841 Plus Morphine (s.c.)

Mice were given NIH 10841 i.v. or vehicle once a day for 3 days. On the third day, NIH 10841 was given 10 min before morphine. Results were obtained 20 min later.

As shown in the figure (Fig NIH 10841 Mouse Chronic Treatment (i.v.), chronic treatment with NIH 10841 caused a suppression of morphine's dose-response curve.

C) Chronic (3 days) NIH 10841 (s.c.) Plus Morphine (s.c.)

Essentially, the same procedure as described in B above was followed. except NIH 10841 was given subcutaneously Results obtained are shown in Fig NIH 10841 Mouse Chronic Treatment (s.c.)

The results are consistent, but not as pronounced as those reported in B above.

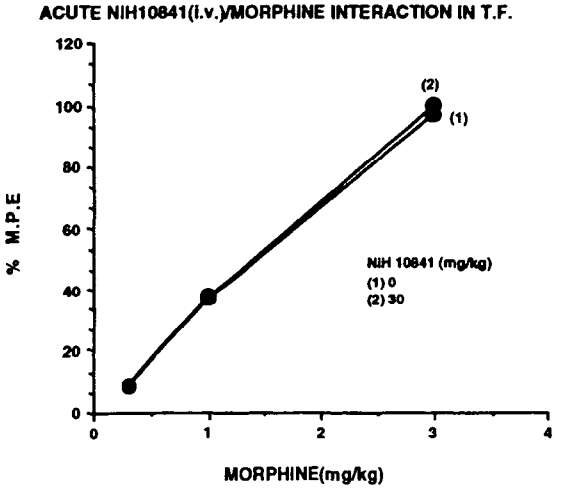


Fig NIH 10841. Mouse Acute Treatment. Results of study on the effect of acute treatment of mice with NIH 10841 prior to receiving morphine. Note lack of suppression of morphine dose-response curve.

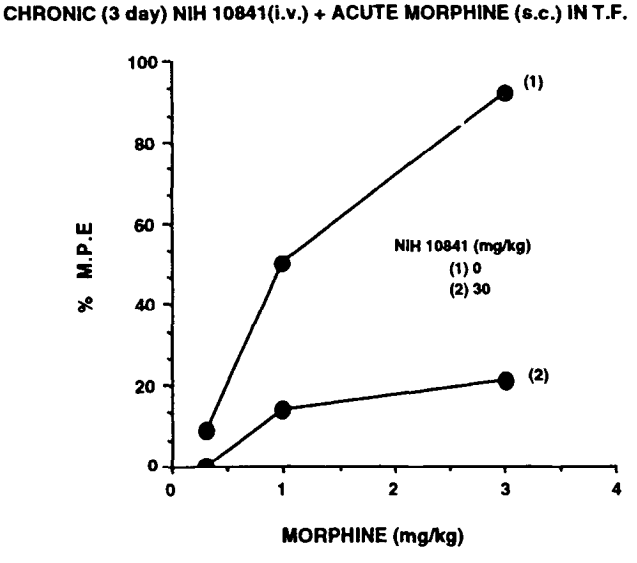


Fig NIH 10841. Mouse Chronic Treatment (i.v.). Results of study on the effect of chronic treatment of mice with NIH 10841 prior to receiving morphine. Note suppression of morphine dose-response curve.

NIH 10841 (Continued)

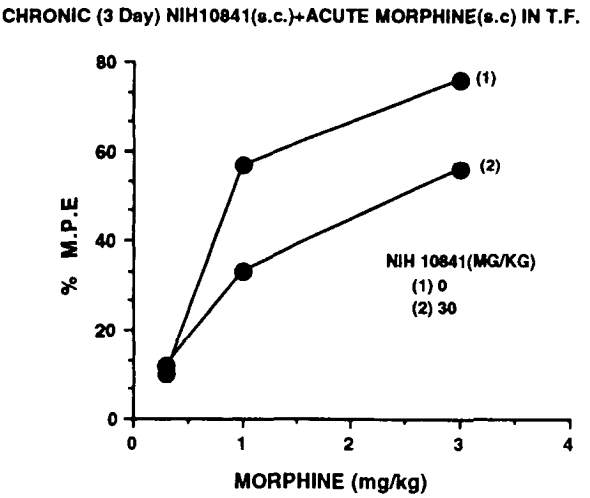


Fig NIH 10841. Mouse Chronic Treatment (s.c.). Results of study on the effect of chronic treatment of mice with NIH 10841 prior to receiving morphine. Note suppression of morphine dose-response curve.

MONKEY DATA
SDS

The data did not demonstrate or indicate that NIH 10841 suppressed withdrawal in morphine-dependent monkeys (see Fig NIH 10841). Neither did it show significant exacerbation of withdrawal at either 9 or 45 mg/kg. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: It appears that given chronically, NIH 10841 suppressed morphine's antinociceptive action. The action appears non-competitive. The intravenous route is the most effective. Apparently, NIH 10841, per se, was without significant opioid effect in the mouse and monkey studies.

NIH 10841 (Continued)

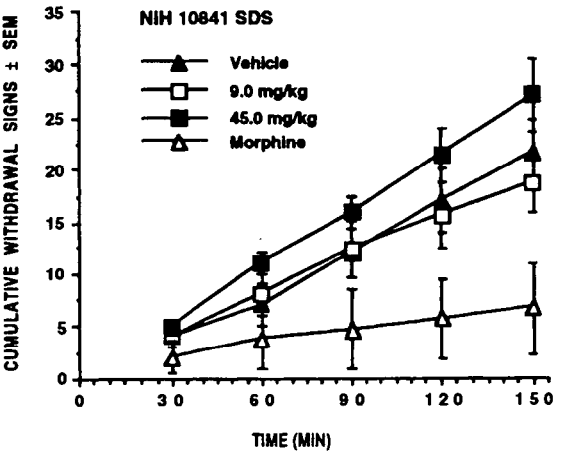
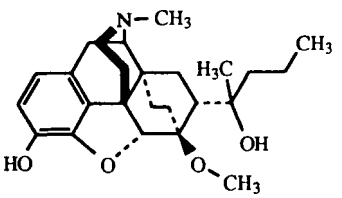


Fig NIH 10841. Results of study in which NIH 10841 was substituted for morphine in morphine-dependent monkeys in withdrawal

NIH 10846 Dihydroetorphine•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.00015 (0.00006 - 0.0004)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,b]
3) PPQ - 0.0002 (0.00005 - 0.0008)
4) HP - 0.0001 (0.00005 - 0.0003)[a]

[a]5% hydroxypropyl-β-cyclodextrin in water
[b]At 10 and 30 mice convulsed and lost their righting reflex

1. Special Test: Nalxone AD50 vs ED80 of NIH 10846 in TF = 0.04 (0.01 - 0.08)

2. Special Time-Course Study: Dihydroetorphine's half-life (in Table 1) is estimated to be 40 min.

NIH 10846 (Continued)

Table 1. Time-course study for the ED_{80} of NIH 10846 in the tail-flick test.

% Inhibition of Nociception ± SEM	Pretreatment Time (min)
77 ± 13	20
41 ± 10	40
4 ± 2	60
1 ± 0.8	90

3. Special Test: Naloxone vs DHE pA_2 in TF = 6.65 (5.79 - 7.51) Slope - 0.93. When the slope is constrained to - 1, the pA_2 is 6.5 (6.3 - 6.8).

In mice DHE and etorphine have similar and short durations of action compared with morphine. The apparent pA2s for naloxone versus DHE or ET are also similar to but lower than that calculated for morphine (see Table 3 in Introduction).

4. Interaction of opioid agonist and antagonist subtypes in mouse T.F. test

Table 1. The interaction of NM 10846 (dihydroetorphine) (DHE) with selective opioid antagonists subtypes in the mouse T.F. test.

Antagonist s.c.	Pretreatment Time	Agonist i.c.v./s.c.	Pretreatment Time	ED_{50} or AD_{50}
Naloxone ((s.c.) 0.03, 0.1 and 0.3 mg/kg	30 m	DHE (s.c.) ED_{80} - 0.001 mg/kg	20 m	AD50 - 0.01 mg/kg (0.01 - 0.03) Slope = 2.60
Nor-BNI (NIH 10588) (s.c.) 1.0, 10.0 and 30.0 mg/kg	2 h	DHE (s.c.) ED_{80} - 0.001 mg/kg	20 m	1.0 mg/kg: 11% antagonism 10.0 mg/kg: 8% antagonism 30.0 mg/kg: 8% antagonism
Naltrindole (NIH10589) (s.c.) 1.0, 10.0 and 30.0 mg/kg	30 m	DHE (s.c.) ED_{80} - 0.001 mg/kg	20 m	1.0 mg/kg: 0% antagonism 10.0 mg/kg: 3% antagonism 30.0 mg/kg: 21% antagonism
β-FNA (i.c.v.) 1.0, 3.0, 10.0 and 30.0 µg/brain	4 h	DHE (s.c.) ED_{80} - 0.001 mg/kg	20 m	AD50 - 9.27 µg/brain (3.44 - 24.97) Slope = 1.51

NIH 10846 (Continued)

MONKEY DATA

A. SDS

NIH 10846 dose-dependently substituted for morphine at doses of 3×10^{-5} and 15×10^{-5} mg/kg. There was a subjective feeling that the onset of action was slightly delayed. Duration appeared similar to that of morphine. Potency estimates is at least 20,000 x morphine. Some drowsiness, slowing, and sagging were noted at the high dose.

Comment: The drug has a profile of activity commonly associated with mu agonists. The potency is impressive. Activity was noted in the potency range of 20.000 to 100.000 x morphine. Comments regarding primary physical dependence in monkeys may be found under PPD below.

MONKEY DATA

B. PPD

Initially, dihydroetorphine produced the usual agonist behavioral signs asssociated with the administration of opiates to non tolerant subjects such as body sag, ataxia, slowing, ptosis, and scratching. Because dihydroetorphine had a relatively short duration of action, the frequency of injections was increased from every 6 h to 6 times a day on weekdays (at 6, 10 and 12 a.m. and 2.6 and 12 p.m.). On day 8, when the dose had been raised to 1,200 ng/kg, one monkey lost consciousness for a brief period. The following day, 2 monkeys lost consciousness briefly. As a result, the dose was reduced to 600 ng/kg at the noon injection. Fewer agonist signs were noted at the lowered dose indicating some tolerance had developed.

On day 16, approximately 2 h after the 6 AM injection of DHE, the monkeys were challenged with naloxone (0.05 mg/kg/s.c.). This dose would normally precipitate a severe withdrawal syndrome in morphine-treated monkeys receiving 3 mg/kg every 6 4 for at least 90 days (Aceto *et al.,* 1977). However, naloxone was ineffective. One-half h later, the dose of naloxone was raised by a factor of 10 and the monkeys were challenged again. As described in Table 4, a very mild withdrawal syndrome developed. Nevertheless, two critically important withdrawal signs were not seen; namely, rigid abominal muscles and vocalization associated with palpation of the abdomen. We concluded that only a very mild degree of physical dependence had developed. After the precipitated withdrawal test was conducted, dihydroetorphine was given and the dose was raised to 900 ng/kg. The usual agonist signs were recorded The following day the dose of DHE was raised to 1,200 ng/kg and maintained at that level until day 21 when loss of consciousness was again observed in 2 monkeys. The dose was reduced to 900 ng/kg for the remainder of the study. Agonist signs were noted throughout this period.

On day 31, the monkeys were again challenged with a very high dose (0.55 mg/kg s.c.) of naloxone. Only a very mild withdrawal syndrome was elicited. DHE was abruptly withdrawn (Abrupt Withdrawal) on day 41 and the animals were evaluated for signs of withdrawal. Again, very mild withdrawal behavior was noted. Sixteen h after abrupt withdrawal (day 42), dihydroetorphine (900 ng/kg) was again administered and 0.5 4 later, the monkeys were challenged for the third time with naloxone (0.55 mg/kg s.c.). Wet-dog shakes were elicited in only 1 of 5 subjects. Interestingly, during the 0.5 h-observation period, some DHE agonist signs were still evident. Throughout the study no remarkable body weight changes were observed (Data not shown.).

NIH 10846 (Continued)

MONKEY DATA (Preliminary Study)

C. Chronic Replacement of DHE for Morphine and Subsequent Abrupt and Precipitated Withdrawal Studies

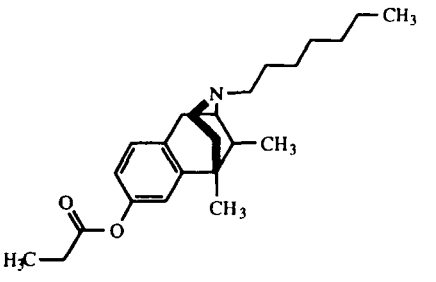
NIH 10846 was substituted for morphine in 3 maximally-dependent monkeys for 7 days. It substinned completely for morphine during this interval at a dose of 0.00006 mg/kg 4 x per day. Fifteen h after DHE was withdrawn, some abstinence signs were apparent (see Table 4). However, the incidence and number of abstinence signs are considered low. One day later, 2 h after DHE (0.00006 mg/kg), the monkeys were challenged with a dose of 0.05 mg/kg of naloxone, a dose which would have precipitated a full-blown abstinence syndrome. Few signs (as shown in table) were observed during a 1/2 h observation period. The monkeys wee challenged a second time with a double dose of naloxone (0.1 mg/kg) and again only a few abstinence signs were noted. Additionally, at the end of the experiment the monkeys were again treated with the usual regimen of morphine (3.0 mg/kg) some of the animals were scratching. The results suggest that DHE alters the course of tolerance and physical dependence on morphine and may be useful in the therapy of opioid abuse in human addicts.

Table 4. Signs observed in three morphine-dependent monkeys IN whom NIH 10846 was substituted for 7 days and then subjected to precipitated withdrawal.

	WITHDRAWAL CONDITION		
Withdrawal Signs	Abrupt[a]	Precipitated 1[a,b]	Precipitated 2[a,c]
Lying on Side or Abdomen	2 of 3 (7)	1 of 3 (1)	2 of 3 (3)
Fighting	1 of 3 (2)	0 of 3 (0)	0 of 3 (0)
Restless (Pacing)	0 of 3 (0)	1 of 3 (1)	0 of 3 (0)
Wet Dog Shakes	2 of 3 (3)	1 of 3 (1)	2 of 3 (3)
Retching	0 of 3 (0)	0 of 3 (0)	1 of 3 (1)
Masturbation	1 of 3 (4)	2 of 3 (1)	2 of 3 (4)

[a]Denotes number responding of possible 3. It should be noted that one monkey expired six days after experiment was completed On gross necropsy the monkey appeared to have abnormal kidneys.
[b]Naloxone 0.05 mg/kg as initial dose.
Naloxone 0.10 mg/kg after 1/2 hr.
Numbers in parentheses denote total number of signs observed during 2.5 h observation of abrupt withdrawal and during 30 m precipitated withdrawals 1 and 2.

NM 10860 (-)-5.9α-Dimethyl-2-heptyl-2'-propionoxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3.13 (1.55 - 6.30)[a]
2) TF vs. M - Inactive at 1.0. 10.0 and 30.0[a]
3) PPQ - 0.31 (0.07 - 1.3)[a]
4) HP - 5.5 (3.5 - 8.8)[a]

[a]Vehicle - 2.5% Hydroxypropyl-β-cyclodextrin in water

NIH 10860 (Continued)

MONKEY DATA
(SDS)

As shown in Figure NIH 10860, this compound produced a dose-related but non-significant reduction in withdrawal signs at 2 and 8 mg/kg. One monkey convulsed and died 5 m after receiving 12 mg/kg. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Results in mice suggest an opioid profile of activity. Because the drug produced convulsions and was lethal, higher doses were not investigated in me monkey. Perhaps this compound is a delta agonist.

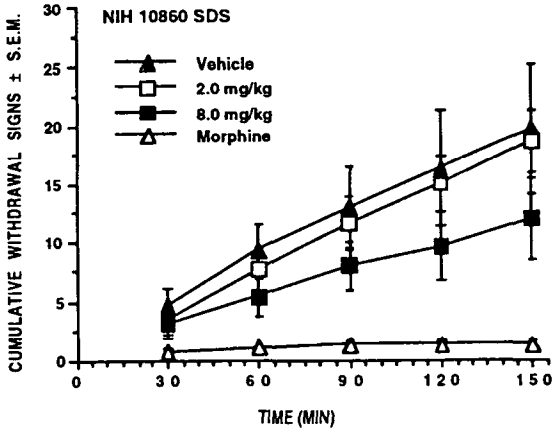
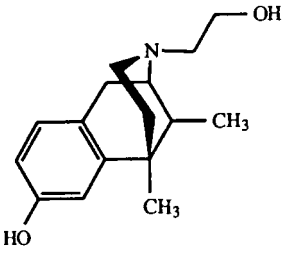


Fig NIH 10860. Results of study involving the substitution of a single dose of NIH 10860 in morphine-dependent monkeys in withdrawal.

NIH 10864 (+)-5,9α-Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphanoxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - Inactive at 1.0, 14% at 10.0 and 26% at 30.0[a]
4) HP - 13% at 1.0, 25% at 10.0 and 20% 30.0[a]

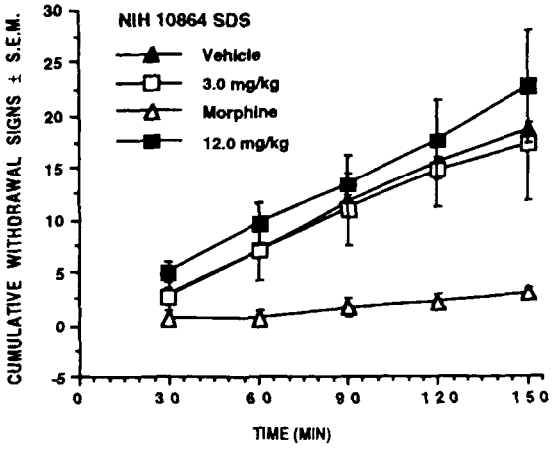
[a]Vehicle - 2.5% hydroxypropyl-β-cyclodextrin in water

NIH 10864 (Continued)

MONKEY DATA
(SDS)

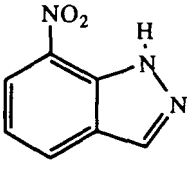
NIH 10864 neither substituted for morphine nor exacerbated withdrawal at doses of 3 and 12 mg/kg (see Fig NIH 10864). Vehicle was 10% hydroxypropyl-β--cyclodextrin in water.

Comment: Apparently, NIH 10864 was without significant opioid effect in me mouse and monkey studies.



Pig NIH 10864. Results of study involving the substitution of a single dose of NIH 10864 in morphine-dependent monkeys in withdrawal.

NIH 10867 7-Nitroindazole (7-Nitro-1H-indazole)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF- 6% at 1.0, 1% at 10.0 and 4% at 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - Inactive at 1.0, 46% at 10.0 and 51% at 30.0[a]
4) HP - Inactive at 1.0, 13% at 10.0 and 25% at 30.0[a]

[a]Vehicle - 20% hydroxypropyl-β--cyclodextrin-15% Tween 80 in water

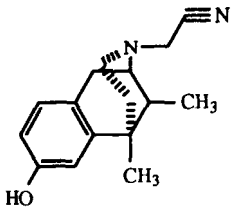
NIH 10867 (Continued)

MONKEY DATA
(SDS)

Not tested Drug supply exhausted

Comment: NIH 10867 is not active antinociceptively and apparently lacks opioid properties.

NIH 10870 (+)-Cyanomethyl-5.9a-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 5% at 1,6% at 10 and 12% at 30[a]
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 6.0 (4.2 - 8.4)[b]
4) HP - Inactive at 1 and 10, and 30[a,b,c]

[a]Loss of righting reflex al 30
[b]ataxia at 10,
[c]popcorn convulsions (6 of 8) and difficulty in breathing in all; at 30, 1 of 8 died.

MONKEY DATA
(SDS)

NIH 10870 produced a dose related and significant reduction in withdrawal signs at 0.25 and 1.0 mg/kg (see Fig NIH 10870). However, suppression at the higher dose was accompanied by the signs designated as slowing, ataxia and eyelid ptosis. In addition, in the preliminary study, in one monkey receiving a cumulative dose of 5.5 mg in 45 min, profuse salivation and severe ataxia were noted.

Comment: The results in the mouse and monkey are at variance. In the monkey, kappa opioid activity is suspected.

NIH 10870 (Continued)

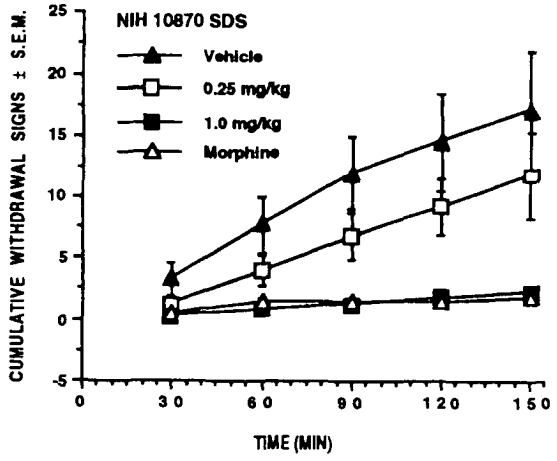
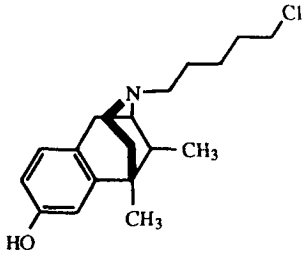


Fig NIH 10870. Results of study in which NIH 10870 was substituted for morphine in morphine-dependent monkeys in withdrawal,

NIH 10871 (-)-2-(Chloropentyl)-5,9α-dimethyl-2'-bydroxyd,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.84 (0.43 - 1.63)
2) TF vs. M - inactive at 1, 10 and 30
3) PPQ - 0.5 (0.25 - 1.0)
4) HP - 3.6 (2.3 - 5.8)[a]

[a]Vehicle - 5% Hydroxypropyl-β-cyclodextrin in water
[b]Straub tails and increased locomotor activity at 6 and 10

NIH 10871 (Continued)

MONKEY DATA
(SDS)

NIH 10871 significantly suppressed withdrawal for about 90 m at the high dose (see Fig NIH 10871). Onset was rapid and offset was short Vehicle was 10% hydroxypropylβ--cyclodextrin in water.

Comment: The profile of activity for NIH 10871 in mice and in monkeys was typical of a morphine-like drug.

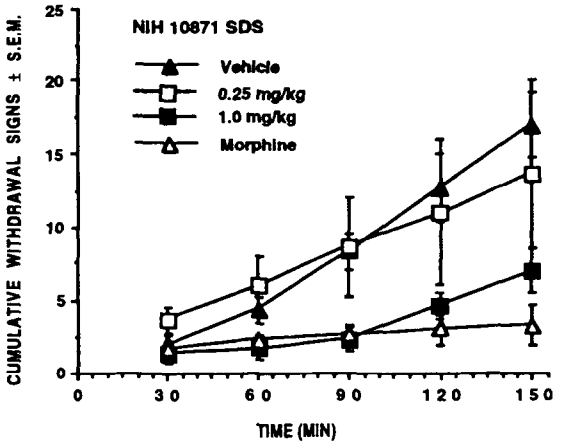
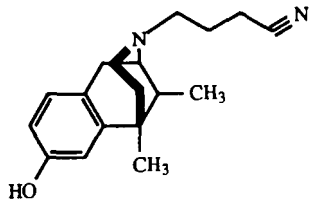


Fig NIH 10871. Effects of NIH 10871 acutely substituted for morphine in dependent monkeys in withdrawal.

NIH 10884 (-)-2-(3-Cyanopropyl)-5,9a-dimethyl-2'hydroxy-6,7-benzomorphan



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.36 (0.18 - 0.72)[a]
2) TF vs. M - Inactive at 1, 10 and 30[a]
3) PPQ - 0.1 (0.05 - 0.27)[a]
4) HP - 1.1 (0.37 - 3.4)[a]

[a]Vehicle was lactic acid in water.

NIH 10884 (Continued)

Special Test: Naloxone AD50 vs NIH 10884 ED80 in TF = 0.28 (0.12 - 0.67)

MONKEY DATA
(SDS)

A non dose-related reduction of withdrawal signs (see Fig NIH 10884) accompanied by jaw sag, ataxia, salivation and sagging in some of the monkeys at the high dose was the signature of NIH 10884. However, the drug did not completely substitute for morphine.

Comment: The relatively high naloxone AD50 in mice and the results in monkeys suggest heterogenous opioid properties.

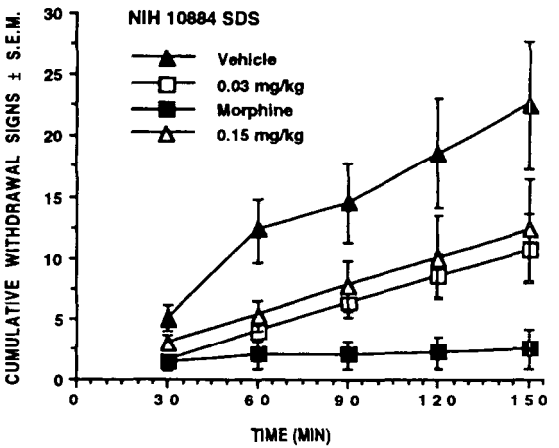
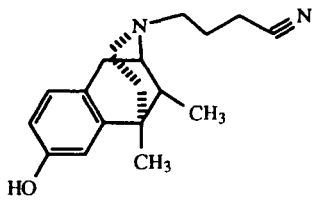


Fig NIH 10884. Results of study involving the single-dose substitution of NIH 10884 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10885 (+)-2-(3-Cyanopropyl)-5,9a-dimethyl-2'hydroxy-6,7-benzomorphan



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1,13% at 10,9% at 0[a]

2) TF vs. M - Inactive at 1, 10 and 30[a]

3) PPQ - 3% at 1.9% at 10 and 60% at 30[a]

4) HP - Inactive at 1, 10 and 30[a]

[a]Vehicle - 1 drop Lactic acid + water

NIH 10885 (Continued)

MONKEY DATA
(SDS)

As shown in Fig NIH 10885. at doses of 4 and 16 mg/kg, NIH 10885 non-dose dependently attenuated withdrawal. At both doses, behavioral signs designated jaw sag, slowing and ptosis were noted. Salivation was also observed at the high dose.

Comment: The mouse data and monkey data suggest that NIH 10885 is devoid of opioid properties. The attenuation of withdrawal signs is probably associated with nonspecific CNS/and autonomic properties. Vehicle was dilute HCl in water.

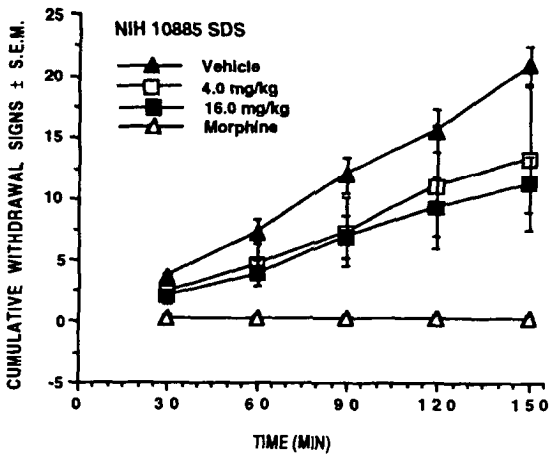
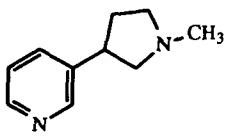


Fig NIH 10885. Results of study in which single doses of NIH 10885 were substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10886 (±)-Isonicotin•oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1 and 10, 17% at 30
2) TF vs. M - Inactive at 1.10 and 30
3) PPQ - 3.24 (1.18 - 8.89)
4) HP - Inactive at 1 and 10.25% at 30

NIH 10886 (Continued)

MONKEY DATA
(SDS)

As indicated in Fig. NIH 10886, at doses of 3.0 and 12.0 mg/kg, NIH 10886 neither substituted for nor exacerbated withdrawal. The number of withdrawal signs seen with the vehicle controls were abnormally low.

Comment: The results obtained with NIH 10886 provide little evidence that it has opioid properties. Slight activity was noted in the paraphenylquinone and hot plate tests at 30 mg/kg.

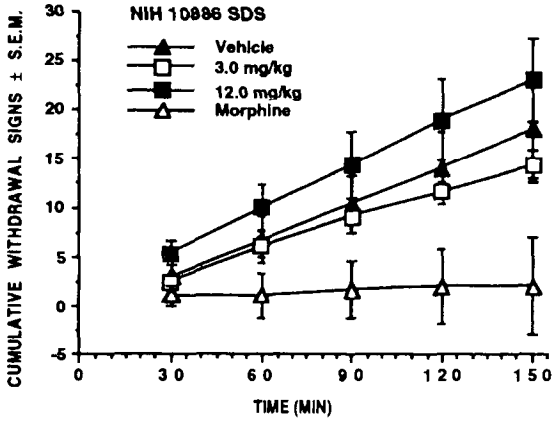


Fig NIH 10886. Results of study in which NIH 10886 in single doses was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10887 ω--Conotoxin MVIIA (reduced, cyclic (1-16), (8-20), (15-25))

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Dir-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2 cyclic (1-16), (8-20), (15-25)-tris(disulfide)

MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)
1) TF - 17.7 (11.0-28.2)[a] Intravenously
2) TF vs. M - Not Tested
3) PPQ - 3.16 (1.0 - 9.7)[a] Intravenously
4) HP - Not Tested

[a]Clonic convulsions and eyelid ptosis at 20 and 30

NIH 10887 (Continued)

MONKEY DATA

(SDS) Intravenuously

NIH 10887 produced a dose-related reduction of withdrawal signs (see Fig NIH 10887). However, it never substituted completely for morphine. Drug supply precluded testing higher doses. Additionally, eyelid ptosis was noted in all monkeys at both doses and jaw sag was seen in one monkey receiving the high dose. Vehicle was sterile saline solution.

Comment: There is insufficient data to characterize this drug. It may have opioid properties.

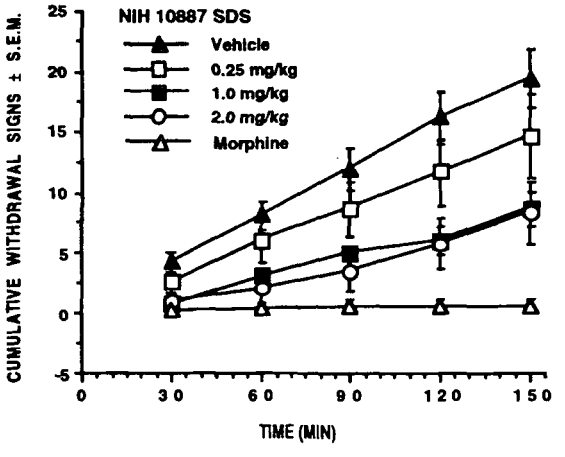
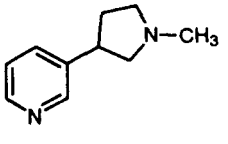


Fig NIH 10887. Results of study involving single-dose substitution of NIH 10887 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10895 (-)-Isonicotine•dioxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3% at 1.8% at 10 and 32% at 30[a]
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 3.80 (1.99 - 7.30)
4) HP - Inactive at 1.38% at 10 and 38% at 30

[a]Mobility diminished at 10 and 30.

NIH 10895 (Continued)

MONKEY DATA

(SDS)

As shown in the figure, NIH 10895 produced a non-dose related attenuation of withdrawal signs. The effect was not remarkable.

Cornment: NIH 10895 did not provide results indicative of opioid properties. The only biological activity noted was in the paraphenylquinone antinociceptive test.

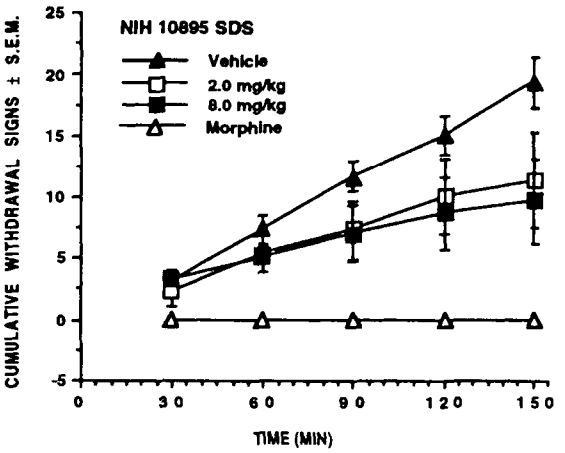
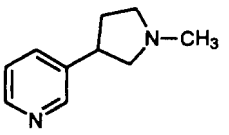


Fig NIH 10895. Results of a study involving the single-dose substitution of NIH 10895 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10896 (+)-Isonicotine•oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3% at 1, 11% at 10 and 64% at 30[a]
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 1.63 (0.57 - 4.70)
4) HP - Inactive at 1, 13% at 10 and 13% at 30

[a]Mobility diminished at 10 and 30

NIH 10896 (Continued)

MONKEY DATA
(SDS)

NIH 108% neither substituted for morphine nor examined withdrawal at doses of 2.5 and 10.0 mg/kg (see Fig NIH 108%).

Comment: Except for some antinociceptive activity in the pataphenylquinone test, the results with NIH 10896 in mice and monkeys were not rermarkable. This compound produced little evidence regarding opioid activity.

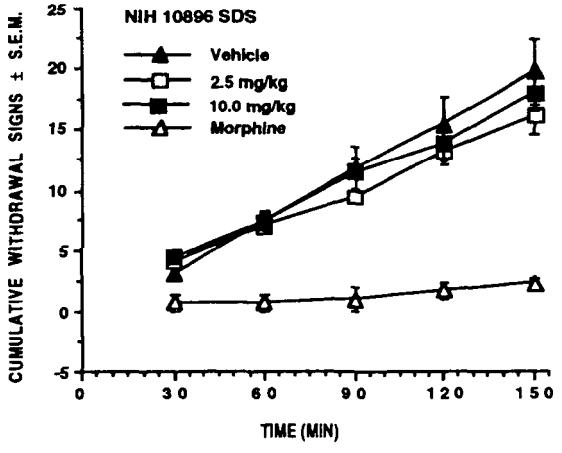
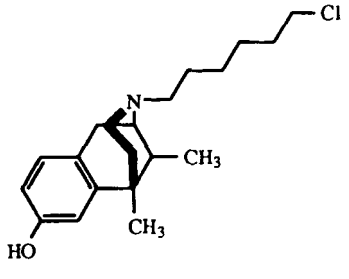


Fig NIH 108%. Results of single-dose substitution of NIH 10896 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10897 (-)-(6-Chlorohexyl)-5.9α-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 2.03 (1.16 - 3.57)
2) TF vs. M - Inactive at 1, 10 and 30[a,b]
3) PPQ - 0.67 (0.33 - 1.35)[a]
4) HP - 1.59 (0.87 - 2.92)

[a]Vehicle - 5% hydroxypropyl-β-cyclodextrin in water.
At 10 mg/kg decreased locomotor activity.

NIH 10897 (Continued)

Special Test: Naloxone AD50 vs ED80 of NIH 10897 in TF = 0.02 (0.01 - 0.04)[a]

MONKEY DATA
(SDS)

Both doses appeared equally effective in nearly suppressing withdrawal in morphine-dependent monkeys (see Fig NIH 10897). At the high dose, ataxia slowing, and pale faces were noted. Lower doses might provide a dose response relationship. The compound acts quickly and has a duration of action at least as long as that of morphine. Potency cannot be determined on the basis of the data available. However, it is probably greater than that of morphine.

Comment: Based on the results in mice and monkeys, it is concluded that NIH 10897 appears to have mu-opioid properties.

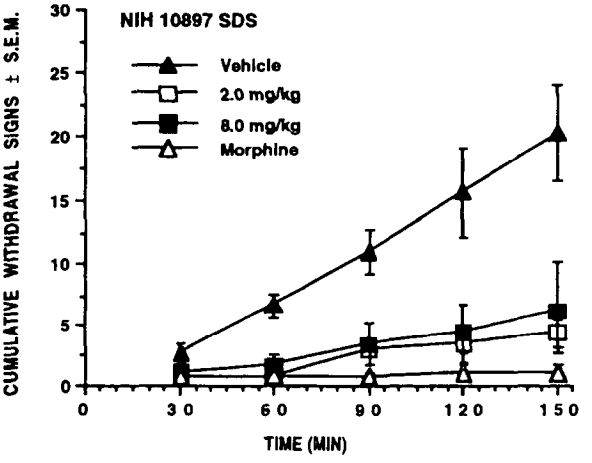
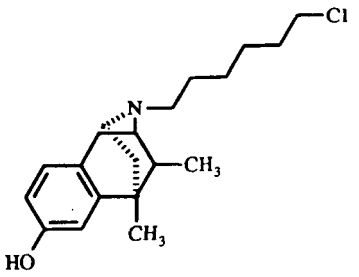


Fig NIH 10897. Results of study involving the substitution of single doses of NIH 10897 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10898 2*S*,5*S*,9*S*-(+)-2-(6-Chlorohexyl)-5-9α-dimethyl-2'-hydroxy-benzomorhan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 11.56 (4.00 - 33.37)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 5.32 (2.92 - 9.68)
4) HP - Inactive at 1.0, 38% at 10.0 and 50% at 30.0[a]

[a]5% hydroxypropyl-β-cyclodextrin in water

MONKEY DATA
(SDS)

This compound did not substitute for morphine (see Fig NIH 10898) at doses of 3 and 12 mg/kg. At the high dose, 2 monkeys convulsed. The convulsions were quickly terminated using pentobarbital (30 mg, i.p.). The vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Although some antinociception was observed in the mouse, mu opioid activity was probably not a significant factor in either species.

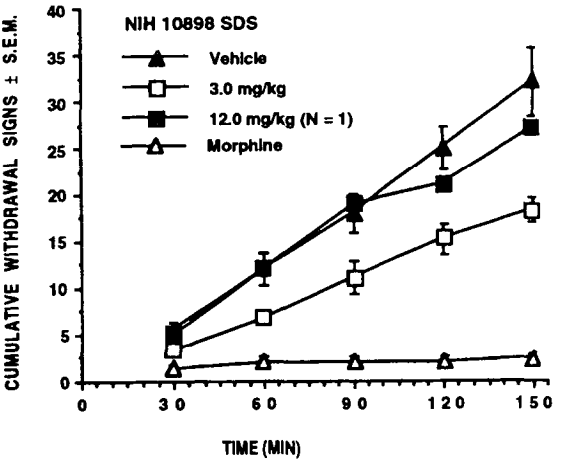
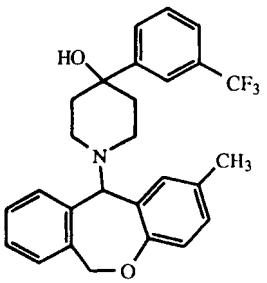


Fig NIH 10898. Results of study involving the substitution of NIH 10898 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10900 11-[4-Hydroxy-4(3-triflouromethylphenyl)-piperidin-1-yl]-2-methyl-6,11-dihydrobenz[b,e]oxepine sulfuric acid



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

A. Subcutaneously

1) TF - Inactive at 1.0, 10.0 and 30.0

B. Subcutaneously

1) TF vs. M - Inactive at 1.0, 10.0 and 30.0
2) PPQ - 9% at 1.0, 23% at 10.0 and 39% at 30.0
3) HP - Inactive at 1.0, 10./0 and 30.0

C. Orally (20 min pretreatment)

1) TF - 7% at 1.0, 14% at 10.0 and 12% at 30.0

D. Orally (40 min pretreatment)

1) TF - 7% at 1.0, 14% at 10.0 and 57% at 30.0

MONKEY DATA
SDS

As shown in the Figure NIH 10900, the drug produced a non-dose-related suppression of withdrawal signs. It should be noted that the results of the high dose are not significantly different from those of vehicle (7% hydroxypropyl-β--cyclodextrin in water). The small number of subjects preclude a definite conclusion in this study. Insufftcient supplies prevented additional testing.

Comment: The results suggest that NIH 10900 has a delayed onset of action in the mouse. Possibly, it is a pro drug. Taken together, these results in both species indicate weak, if any, mu opioid activity.

NIH 10900 (Continued)

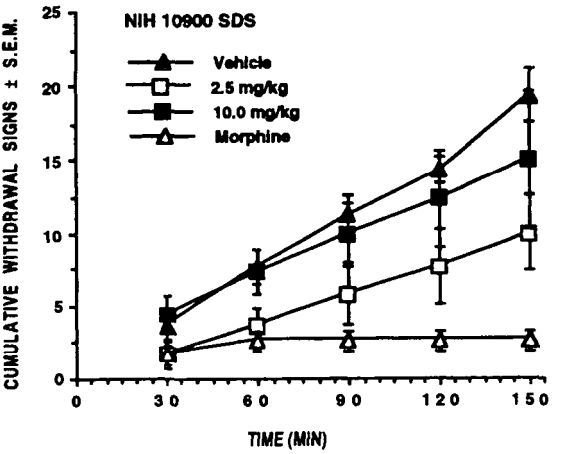
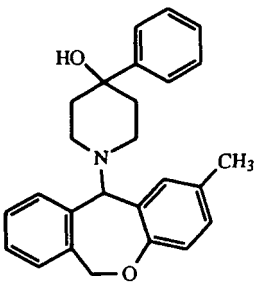


Fig NIH 10900. Results of study involving the substitution of single doses of NIH 10900 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10901 11-(4-Hydroxy-4-phenylpiperidin-l-yl)-2-methyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)
A. Subcutaneously[a]

1) TF - Inactive at 1.0, 10.0 and 30.0

B. Subcutaneously[a]

1) TF vs. M - Inactive at 1.0, 10.0 and 30.0
2) PPQ - 7.6 (3.7 - 15.4)
3) HP - Inactive at 1.0, 10./0 and 30.0

C. Orally (20 min pretreatment)

1) TF - 5% at 1.0, 9% at 10.0 and 45% at 30.0

D. Orally (40 min pretreatment)

1) TF - 0% at 1.0, 8% at 10.0 and 25% at 30.0

[a]2.5% Hydroxypropyl-β-cyclodexodextrin in water

NIH 10901 (Continued)

MONKEY DATA
(SDS)

Because drug supply was exhausted, a complete evaluation could not be conducted. The results shown in the figure suggest that NIH 10901 substituted for morphine. Onset was slow and duration of action was 90-120 min. Potency was estimated at 1/5 that of morphine. Vehicle was 10% hydroxypropyl-β--cyclodextrin in water.

Comment: NIH 10901 does not show significant antinociceptive activity in the TF or HP tests when given s.c. Neither does it show remarkable activity when given orally with pretreatment times of 20 or 40 min. Some antinocicepcive activity was observed in the PPQ test. Possible opioid activity is suggested in the morphine-dependent monkey.

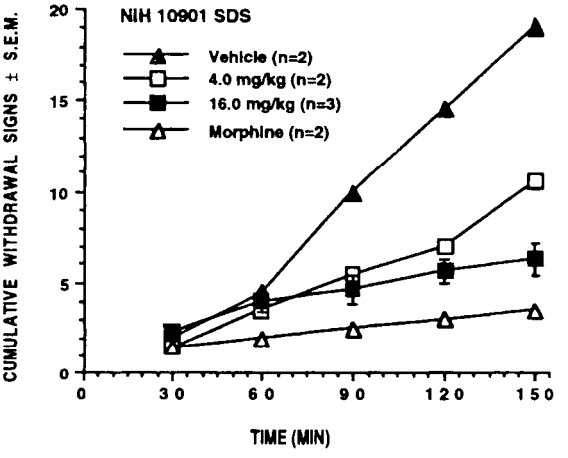
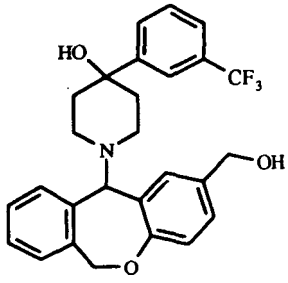


Fig NIH 10901. Results of replacement study involving NIH 10901. Single doses of NIH 10901 were substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10902 11-[4-Hydroxy-4-(trifluoromethylphenyl)piperidin-l-yl]2-hydroxymethyl]2-hydroxymethyl-6,11 dihydro-dibenz[b,e]oxepine fumaric acid



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

A. Subcutaneously

1) TF - 12.86 (6.28 - 26.33)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 1.13 (0.45 - 2.88)
4) HP - 2.4 (1.1 - 5.0)

B. Orally [a] (20 min pretreatment)

1) TF - 1.0 (0.4 - 2.5)

C. Orally [a] (40 min pretreatment)

1) TF - 0.98 (0.28 - 3.40)

[a]Vehicle - 5% hydroxypropyl-β--cyclodextrin in water

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10902 in TF = 0.12 (0.06 - 0.24)

MONKEY DATA
(SDS)

As shown in Fig NIH 10902, this compound dose-dependently substituted for morphine. Onset was rapid and duration of action was at least 2.5 h. At the high dose, the signs scratching, sagging, slowing, salivation and yawning were noted. Vehicle was 10% hydroxypropyl-β--cyclodextrin.

Comment: The compound appears to be a pro drug in the mouse. The relatively high AD50 for naloxone coupled with salivation in the monkey suggested that NM 10902 may possess heterogenous opioid activity.

3NIH 10902 (Continued)

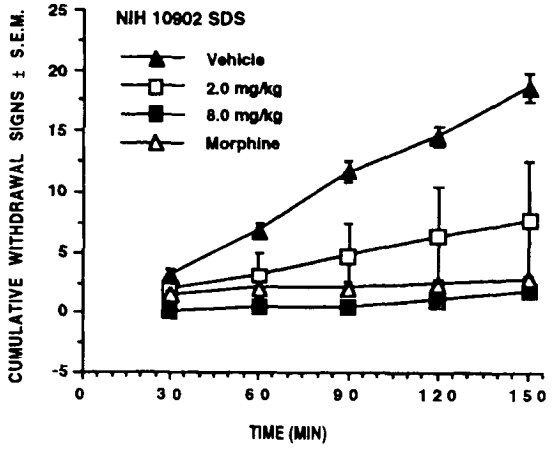
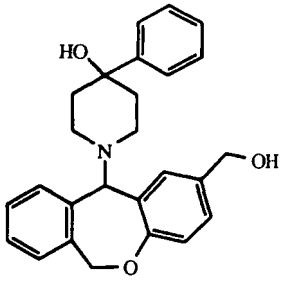


Fig NIH 10902. Results of single-dose substitution of NIH 10902 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10903 11-(4-Hydroxy-4-phenylpiperidin-l-yl)-2-hydroxymethyl-6,11-dihydrodibenz(b,e]oxe-pine fumaric acid



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

A. Subcutaneously[a]

1) TF - 1.1 (0.45 - 2.76)

B. Subcutaneously[a]

1) TF vs. M - Inactive at 1.0, 10.0 and 30.0
2) PPQ - 0.6 (0.4 - 1.0)
3) HP - 2.2 1.2 - 4.2)

C. Orally[a] (20 min pretreatment)

1) TF - 1.0 (0.45 - 2.5)

D. Orally[a] (40 min pretreatment)

1) TF - 0.98 (0.28 - 3.40)

[a]15% Hydroxypropyl-β-cyclodcxtrin in water

NIH 10903 (Continued)

Special Test: Naloxone AD50 vs ED80 of NIH 10903 in TF = 0.06 (0.03 - 0.12)

MONKEY DATA
(SDS)

As shown in the Figure NIH 10903, this drug dose-dependently substituted completely for morphine in the dose range of 0.2 to 0.8 mg/kg s.c. Onset was prompt and offset was about 2 h. Potency is estimated as 3 x that of morphine. Eyelid ptosis was noted in one monkey at the high dose. Vehicle was 25% hydroxypropyl-β-cyclodextrin in water.

Comment: Given subcutaneously or orally and at 20 min or 40 min before testing, NIH 10903's effects are the same. The naloxone AD50 and the results in monkeys suggest that NIH 10903 is a mu agonist and its potency in monkeys is approximately 3 x that of morphine.

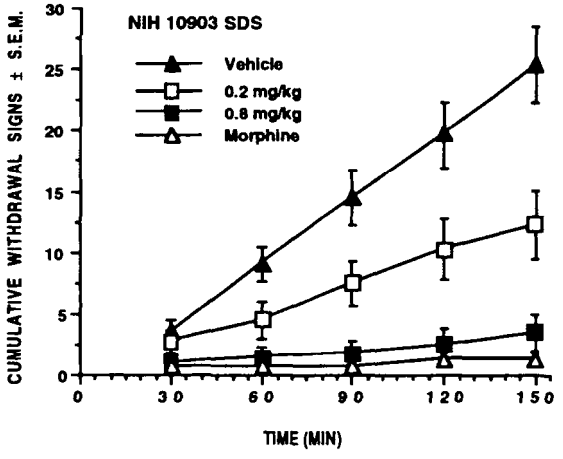
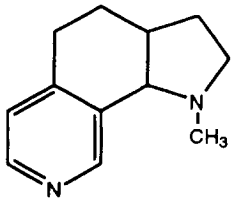


Fig NIH 10903. Results of study involving the substitution of single doses of NIH 10903 for morphine in morphine-dependent monkeys in withdrawal.

NIH 10917 (+)-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[3,2-h]-isoquinoline•HBr (+)-Bridged Nicotine



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

Special: 5 mm Pretreatment

1) TF - 4.1 (1.7 - 9.8)
2) TF vs. M - Inactive at 0.1, 1.0 and 10.0[b]
3) PPQ - 1.6 (0.6 - 4.1)
4) HP - 3.1 (1.6 - 6.0)

[a]Convulsions at 10.0 and 20.0 mg/kg
[b]Convulsions at 10.0 mg/kg

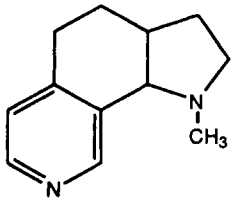
Special Tests: 1) Naloxone AD50 vs ED80 of NIH 10917 in TF: 2% at 0.1, 24% at 0.3, 62% at 1.0, 37% at 3.0 and 41% at 10.0.
2) Mecamylamine AD50 vs ED80 of NIH 10917 in PPQ: 0% at 5 and 10.0 mg/kg.
3) Mecamylamine AD50 vs ED80 of NIH 10917 in HP: 0% at 1.0 and 10.0 mg/kg.

MONKEY DATA
(SDS)

Not tested.

Comment: This is a (+)-"bridged nicotine" with antinociceptive properties similar to those of nicotine. However, mecamylamine was ineffective in suppressing antinociception in the TF and PPQ tests.

NM 10918 (-)-2,3.3a,4,5,9b-Hexahydro-1-methyl-1 *H*-pyrrolo[3,2-*h*]-isoquinoline-2HBr (-)-Bridged Nicotine



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0 and 10.0; 8% at 30.0
2) TF vs. M -
3) PPQ - 11% at 1.0, 14% at 10.0 and 57% at 30.0
4) HP - 0% at 1.0, 13% at 10.0 and 38% at 30.0

MONKEY DATA
(SDS)

Not tested.

Comment: Surprisingly, this (-)-"bridged nicotine" did not show antinociceptive activity. See NIH 10917 the (+)-enantiomer.

ACKNOWLEDGMENTS:

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EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (1997)

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This report contains information on opioid abuse liability evaluations on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained can involve both *in vitro* evaluation in opioid binding assays and smooth muscle preparations. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys. Each of these assays is described below. Usually when limited information is provided (*e.g., in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD. The compounds, which come originally from pharmaceutical companies, universities, government laboratories, and international organizations are submitted to Dr. Jacobson.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. After the evaluation is complete and the report submitted to Dr. Jacobson, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported herein

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts 15-min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-

appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These are are also named and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food. an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete. 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively (i.e., fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one tune out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.,* irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.,* alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone *(i.e.,* precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (i.e., withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40°C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or fess and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.,* alfentanil) or κ (*e.g.,* U-50,488) opioid agonist.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 l/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g.,* alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989).

DISPLACEMENT OF RADIOLABELED LIGAND BINDING

Details of the binding assay based on the displacement of ^{3}H-etorphine in rat brain membranes have been described previously (Medzihradsky et al., 1984). Briefly, aliquots of a membrane preparation from rat cerebrum are incubated with ^{3}H-etorphine in the presence of 150 mM NaCI, and in the presence of different concentrations of the drug under investigation. Specific, i.e., opioid-receptor-related interaction of ^{3}H-etotphine is determined as the difference in binding obtained in the absence and presence of an appropriate excess of unlabeled etorphine. The potency of the drugs in displacing the specific binding of ^{3}H-etorphine is determined from log-probit plots of the data. See table I for representative results with different opioids.

TABLE I

EC_{50}'s of representative opioids for displacement of 0.5 nM ^{3}H-etorphine from rat brain membrane, and inhibition of the twitch of the mouse vas deferens preparation.

Compound	BINDING* EC_{50} (nM)	MVD
DPDPE	---	5.52
U50,488	---	6.29
Fentanyl	36.2	37.1
DAMGO	23.9	81.3
Etorphine	0.37	0.0068
(-)Cyclazocine	0.53	11.9
Naltrexone	0.63	—
Bremazocine	1.42	0.29
UM 1071R**	1.55	—
Sufentanil	1.60	4.43
(-)SKF 10047	3.93	
Ethylketazocine	6.60	11.6
Ketazocine	14.1	1.18
Morphine	23.6	395
DSLET	43.0	1.71
Dextrorphan	<6000	1010

* In the presence of 150 mM NaCl.

** IR-5R-9R-2"R-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride

To enhance the characterization of novel opioids, we are also investigating their selectivity in binding to μ-, δ-, and κ-opioid receptors in membranes from monkey brain cortex. Thus, we are now providing K_i values of the tested compounds in displacing the following radiolabeled opioid ligands:

etorphine (nonselective, reflects opioid character).
sufentanil or Tyr-D-Ala-Gly-(Me)Phe-Gly-ol (DAMGO); (μ selective),
[D-Pen^2-D-Pen^5]enkephalin (DPDPE; δ selective),
U-69,593 (κ selective).

Using the receptor-specific assays, we have described the selectivity of various established opioids in brain membranes of different species (Clark et al., 1988). The selection of monkey brain as the tissue for the selective binding assays strengthens the correlation between this in vitro assessment and the behavioral evaluation of the tested compounds. In

the **ANNUAL REPORT**, the results of the selective binding assays are listed under "Binding in monkey brain cortex." See table II for representative results with different opioids in rat and monkey brain.

ISOLATED, ELECTRICALLY-STIMULATED MOUSE VAS DEFERENS PREPARATION

The development of new, highly selective antagonists such as the reversible κ receptor antagonist norbinaltorphimine (Smith et al., 1989) and the competitive δ receptor antagonist ICI-174864 have made possible the evaluation of selectivity of opioid agonists and antagonists by use of the mouse vas deferens preparation. Male, albino ICR mice, weighing between 25 and 30 g, are used. The mice are decapitated, the vasa deferentia.

TABLE II

Inhibition of radiolabeled sufentanil, DPDPE and U69,593 binding in rat and monkey brain. In membranes from rat cerebrum and monkey brain cortex, the inhibition of specific equilibrium binding of 0.5 nM [^{3}H]sufentanil, 1.5 nM [^{3}H]DPDPE and 1.5 nM [^{3}H]U69,593 by five different concentrations of the listed compounds was investigated in the presence of 150 mM NaCl (modified from Clark et al., 1988).

Compound	EC_{50} (nM) [^{3}H]Sufentanil	[^{3}H]DPDPE	[^{3}H]U69,593
Rat cerebrum			
DAMGO	13.2	690	
Sufentanil	1.25	45.0	
Morphine	31.4	422	
β-FNA	6.99	43.9	
β-CNA	1.29	7.48	
Naloxone	6.37	14.3	
Etorphine	0.60	1.13	
Buprenorphine	1.07	1.12	
Bremazocine	1 .19	1.12	
Superfit	576	16.5	
DSLET	121	1.05	
ICI-174,864	58900	59.0	
DPDPE	7720	6.44	
U50,488	7230	13100	
U69,593	38000	13400	
Monkey cortex			
Sufentanil	1.18	81.1	>10000
DPDPE	18900	4.21	>10000
U69,593	10700	17000	8.41

removed, and 1.5 cm segments are suspended in organ baths which contain 30 ml of a modified Kreb's physiological buffer. The buffer contains the following (mM): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; $MgSO_4$, 1.19; KH_2PO_4, 1.19; glucose, 11; $NaHCO_3$, 25; pargyline HCl, 0.3; and disodium edetate, 0.03. The buffer is saturated with 95% O_2 - 5% CO, and kept at 37° C. The segments are attached to strain gauge transducers and suspended between two platinum electrodes. After a 30-min equilibration period, the segments are stimulated once every 10 sec with pairs of pulses of

2 msec duration, 1 msec apart and at supramaximal voltage. See table III for potencies of representative agonists,

The following antagonists are studied: naltrexone MCI, ICI- 174864 [N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH] and norbinaltorphimine. The antagonists are added to the organ baths 15 minutes before the determination of cumulative concentration-effect relationships for the various agonists. See table III for the potencies of different competitive antagonists studied in relation to prototypic agonists. EC_{50}'s are calculated by probit analysis, and pA_2 values are determined to assess relative potencies of antagonists.

All drugs which are submitted for evaluation are studied in the following manner: 1) the submitted drug is tested on the vas deferens preparation in the absence and in the presence of a concentration of naltrexone sufficient to block μ, κ and δ receptors. 2) If the submitted drug inhibits the twitch and its actions are blocked by naltrexone, it is evaluated further in the absence and presence of ICI-174864 and norbinaltorphimme used in concentrations at which these antagonists are selective for δ and κ receptors, respectively. 3) If the submitted drug is a partial agonist or devoid of agonistic activity at opioid receptors, it is evaluated further as an antagonist against the following agonists: sufentanil (μ selective), DSLET (δ ;selective) and U50,488 (κ selective). If the submitted drug has antagonistic activity against any or all of the receptor-selective agonists or upon any of the other preparations used in the Drug Evaluation Unit, the type of antagonism (competitive, noncompetitive, irreversible) is determined. For further details of the procedure and for a description of experiments in which β-funaltrexamine was used see Smith (1986). Drugs studied in the preparation prior to 1987 were evaluated with the protocol reported in the 1985 Annual Report.

TABLE III

Potencies of antagonists assessed in the mouse vas deferens

	pA_2 values* determined with three agonists		
	Sufentanil (μ)	U50,488 (κ)	DSLET (δ)
Antagonist			
Naltrexone	8.76	7.74	7.41
Naloxone	7.99	6.90	7.35
Cyprodime	7.41	6.15	5.98
Nalbuphine	7.23	6.31	5.76
Naltrindole	7.71	7.38	9.44
ICI-174,864	<5.00	<5.00	7.90

*The pA_2 value is the negative logarithm of the molar concentration of antagonist necessary to shift the agonist concentration-effect curve to the right by a factor of 2-fold.

SUMMARY OF TESTS PERFORMED

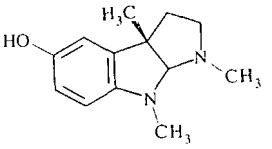
The compounds which were evaluated at the University of Michigan during the past year, and the individual tests which were performed are shown in table IV. Also shown are dates of Reports to the Biological Coordinator, Dr. A.E. Jacobson, in which results are reported.

TABLE IV
SUMMARY OF TESTS PERFORMED

NIH #	SA	MVD	BIND	DD	ANLG	RSP	REPORT*
10820		X	X				2/14/94
10821		X	X				7/6/94
10822		Insol	X MCB				4/14/95 8/2/95
10833		X	MCB				3/24/95
10838		X	MCB				8/2/95
10839		X	MCB				8/2/95
10840		X	MCB				8/2/95
10841		X	MCB				8/23/95
10846		X	MCB				2/15/95
10867		X	MCB				1/2/96
10869		X	MCB				8/13/96
10870		X	MCB				8/13/96
10874		X	MCB				7/2/96
10875		X	MCB				7/26/96
10884		X	MCB				9/10/96
10886		X	MCB				7/2/96
10887	X	X	MCB				6/7/96 6/4/96
10899		X	MCB				2/19/97

* Date report was submitted to CPDD Biological Coordinator. MCB = Monkey Cortex Binding

NIH 10820



(-)-Eseroline (L)-ascorbate
(Also see 10398, 1986 Annual Report)

DISPLACEMENT OF [3H]ETORPHINE BINDING

EC_{50} of 1604 nM in the presence of 150 nM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	3.89 ± 0.40	49.2 ± 3.9		3
Naltrexone (100 nM)	3.87 ± 0.72	37.3 ± 0.8	1.0	3

Second Phase

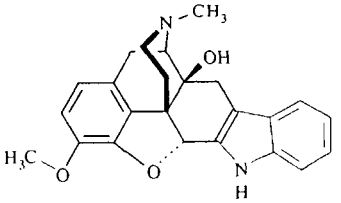
Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	3.88 ± 0.62	55.7 ± 3.0		3
Naltrexone (100 nM)	4.74 ± 1.73	23.3 ± 2.9	1.2	3

SUMMARY

NIH 10820 had very low affinity in the binding assay. In the electrically-stimulated mouse *vas deferens* preparation, NIH 10820 decreased the magnitude of the twitch in concentrations of 0.1 nM to 100 μM. Naltrexone, 100 nM, did not shift either phase of the NIH 10820 concentration effect curve but did decrease the maximum response. Thus, NIH 10820 did not display characteristics typical of opioid agonists. In concentrations up to 10 μM, NIH 10820 was devoid of antagonist activity at μ, δ, and κ receptors.

* * *

NIH 10821



3--O-Methyloxymorphindole.HCl

DISPLACEMENT OF [^{3}H]ETORPHHINE BINDING

EC_{50} of >6000 nM (19% inhibition) in the presence of 150 mM NaCl.

NIH 10821 (continued)

MOUSE *VAS DEFERENS* PREPARATION

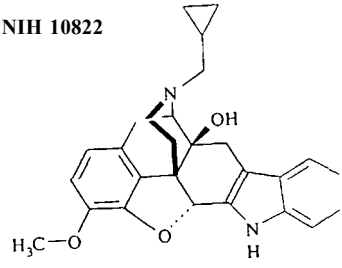
Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.29 ± 0.26	100		9
Naltrexone (100 nM)	9.48 ± 2.12	100	1.4	3
ICI 174.864 (100 nM)	5.83 ± 1.09	99.2 ± 0.8	4.5	3
Nor-BNI (10 nM)	2.13 ± 0.43	100	1.7	3

SUMMARY

NIH 10821 had little opioid activity in the binding assay. In concentrations of 10 nM to 100 μM, NIH 10821 decreased the magnitude of the twitch of the electrically stimulated moose *vas deferens* preparation. Both naltrexone (100 nM, a μ-opioid selective receptor antagonist) and ICI 174864 (100 nM, a δ-opioid receptor antagonist) shifted the NIH 10821 concentration-effect curve to the right. Neither antagonist decreased maximum responses to this drug. Nor-binaltorphimine (10 nM, a κ-opioid receptor antagonist) did not shift the NIH 10821 concentration-effect curve significantly. Thus, NIH 10821 had characteristics typical of a δ-opioid receptor agonist.

* * *

NIH 10822 **3-O-Methylnaltrindole.fumarate**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6000 nM (38% inhibition) in the presence of 150 mM NaCI.

MONKEY CORTEX BINDING (nM)*

μ-receptor:	66.4
δ-receptor:	1.8
κ-receptor:	158.0

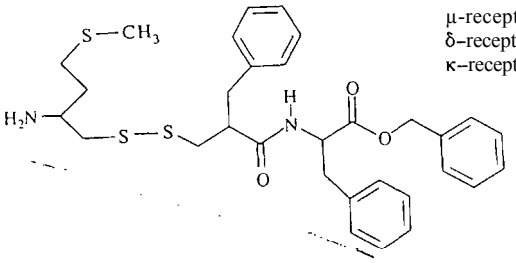
*For this assay 0.6 N HCl, 10% ethanol, and 28% DMSO were used as vehicle.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10822 was insoluble.

NIH 10833

N-[(*R*,*S*)-2-Benzyl-3[(*S*)(2-amino-4-methyithio)butyldithiol]-1-oxopropyl]-Lphenylalanine benzyl ester methyl sulfite



MONKEY CORTEX BINDING (nM)

μ-receptor: 2100
δ–receptor: 0% inhibition at 6000 nM
κ–receptor: 42% inhibition at 6000 nM

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	977.3 ± 350.0	23.1 ± 1.3		3
Naltrexone (100 nM)	1565.3 ± 103.5	25.0 ± 0.6	1.6	3

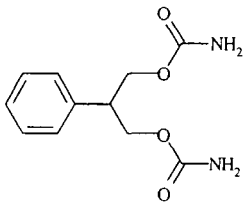
SUMMARY

NIH 10833, in concentrations of 100 nM to 30 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. In a concentration of 30 μM, NIH 10833 was devoid of antagonist activity at μ, δ and κ receptors. In the monkey cortex binding assay, NIH 10833 was active in displacing the ligand at the μ site only at high concentrations.

* * *

NIH 16838

2-Phenyl-1,3-propanediol dicarbamate (Felbamate)



MONKEY CORTEX BINDING (nM)

μ-receptor: 5% inhibition at 6 μM
δ–receptor: 0% inhibition at 6 μM
κ–receptor: 7% inhibition at 6 μM

NIH 10838 continued

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	670.1 ± 15.6	29.7 ± 3.3		3
Naltrexone (100 nM)	659.4 ± 33.7	28.5 ± 3.7	1.0	3

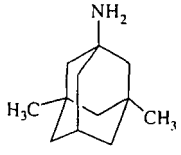
Solubility: 3 mM in H_2O

SUMMARY

NIH 10838, in concentrations ranging from 100 nM to 30 µM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. In the monkey cortex binding assay, NIH 10838 had insignificant affinity for the binding sites.

* * *

NIH 10839 **3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine (Memantine)**



MONKEY CORTEX BINDING (nM)

µ-receptor: 21% inhibition at 6 µM
δ--receptor: 0% inhibition at 6 µM
κ--receptor: 9% inhibition at 6 µM

MOUSE *VAS DEFERENS* PREPARATION

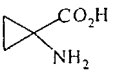
Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	47.7 ± 7.1	34.8 ± 3.5		3
Naltrexone (100 nM)	57.2 ± 8.1	26.7 ± 1.1	1.2	3

Solubility: 3 mM in H_2O

SUMMARY

NIH 10839, in concentrations ranging from 10 nM to 3 µM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. In the monkey cortex binding assay, NIH 10839 had insignificant affinity for the binding sites.

NIH 10840 **1-Aminocyclopropane carboxylic acid (ACPC)**



MONKEY CORTEX BINDING (nM)

μ-receptor:	1% inhibition at 6 μM
δ-receptor:	2% inhibition at 6 μM
κ-receptor:	3% inhibition at 6 μM

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	3.29 ± 1.41	33.8 ± 8.1		3
Naltrexone (100 nM)	2.56 ± 1.60	28.5 ± 10.2	0.8	3

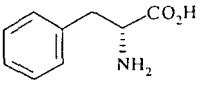
Solubility: 3 mM in H_2O

SUMMARY

NIH 10840, in concentrations ranging from 1 μM to 30 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. Higher concentrations could not be evaluated because of an insufficient supply of the drug. In the monkey cortex binding assay, NIH 10840 had insignificant affinity for the binding sites.

* * *

NIH 10841 **D-Phenylalanine**



MONKEY CORTEX BINDING (nM)

μ-receptor:	0% inhibition at 6 μM
δ-receptor:	3% inhibition at 6 μM
κ-receptor:	2% inhibition at 6 μM

MOUSE *VAS DEFERENS* PREPARATION

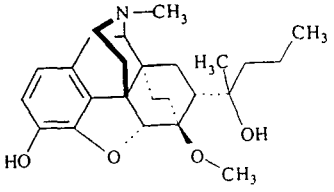
Condition	EG_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	185.5 ± 35.2	55.8 ± 2.9		3
Naltrexone (100 nM)	182.1 ± 16.7	46.9 ± 1.1	1.0	3

SOL: 3 mM in H_2O

SUMMARY

NIH 10841, in concentrations of 10 nM to 30 μM slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked by naltrexone. NIH 10841, at a concentration of 30 μM, was devoid of significant antagonist activity at μ,κ and δ-opioid receptors. In the monkey cortex assay, NIH 10841 had insignificant effects.

NIH 10846 Dihydroetorphine.HCl



MONKEY CORTEX BINDING (nM)

μ-receptor: 0.088
δ-receptor: 2.54
κ-receptor: 0.197

MOUSE *VAS DEFERENS* PREPARATION

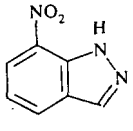
Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	0.34 ± 0.06	100.0		9
Naltrexone (100 nM)	2.84 ± 0.56	100.0	8.3	3
ICI-174864 (100 nM)	0.43 ± 0.20	100.0	1.3	3
Nor-BNI (10 nM)	0.51 ± 0.10	100.0	1.5	3

SUMMARY

NIH 10846, in concentrations ranging from 1 nM to 100 mM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone, 100 nM, shifted the NIH 10846 concentration-effect curve to the right. Neither nor-binaltorphimine (a κ-opioid receptor antagonist) nor ICI-174864 (aδ-opioid receptor antagonist) shifted the NIH 10846 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10846. Therefore, in the mouse *vas deferens* preparation, NIH 10846 acted as an extremely potent μ-opioid receptor agonist. In the monkey cortex binding assay, NIH 10846 also had quite high affinity and some selectivity for the μ recognition site.

* * *

NIH 10867 **7-Nitroindazole (7-nitro-1H-indazole)**



MONKEY CORTEX BINDING (nM)

μ-receptor: 0% inhibition at 6 μM
δ-receptor: 0% inhibition at 6 μM
κ-receptor: 0% inhibition at 6 μM

NIH 10867 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.5 ± 0.15	47.4 ± 8.8		3
Naltrexone (100 nM)	2.48 ± 0.58	43.6 ± 1.2	1.7	3

SOL: 3 mM in methanol

SUMMARY

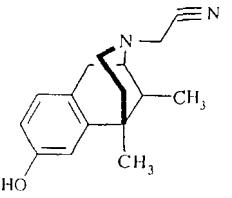
NIH 10867, in concentrations of 30 nM to 10 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation - a response not blocked by naltrexone. NIH 10867,30 μM, was devoid of significant antagonist activity at μ-, κ- and δ–opioid receptors. In the monkey cortex binding assay, it failed to displace any of the ligands.

* * *

NIH 10869 (-)2-Cyanomethyl-5,9 'α-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MONKEY CORTEX BINDING (nM)

μ-receptor: 166
δ--receptor: 574
κ--receptor: 68.5



MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.72 ± 0.13	83.0 ± 2.3		9
Naltrexone (100 nM)	5.41 ± 0.49	42.8 ± 1.4	3.1	3
ICI-174864(100 nM)	3.03 ± 0.12	80.4 ± 3.7	1.8	3
Nor-BNI (10 nM)	3.03 ± 0.77	76.0 ± 5.0	1.8	3

SOL: 3 mM in H_2O

SUMMARY

NIH 10869, in concentrations of 300 nM to 30 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone (100 nM) shifted the concentration-effect curve to the right. Neither

NIH 10869 (continued)

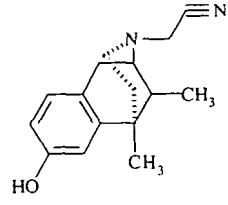
ICI-174864 (100 nM) nor nor-binaltorphimine (10 nM) shifted the NM 10869 concentration-effect curve significantly. In the presence of NIH 10869,30 μM, there was a 4.6-fold shift to the right in the sufentanil concentration-effect curve, a 10.7-fold shift to the right in the DSLET concentration effect curve, and a 3.8-fold shift to the right in the U50,488 concentration-effect curve. Thus, NIH 10869 was a weak, mixed agonist-antagonist with some selectivity as an antagonist at delta opioid receptors. In the monkey cortex binding assay, the compound had moderate affinity for each binding site, with highest affinity for kappa sites. These data suggest that NIH 10869 is likely to be an opioid agonist-antagonist of moderate potency; it's agonist effect may be exerted through different receptor types.

* * *

NIH 10870 **(+)-2-Cyanomethyl-5,9α--dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor: 4490
δ-receptor: 13.7% inhibition at 6 μM
κ-receptor: 1310



***MOUSE VAS DEFERENS* PREPARATION**

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	7.93 ± 1.11	35.4 ± 3.7		3
Naltrexone (100 nM)	12.56 ± 0.93	25.9 ± 5.2	1.6	3

SOL: 3 mM in H2O

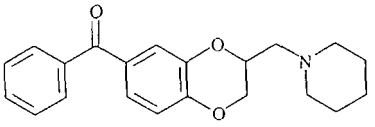
SUMMARY:

NIH 10870, in concentrations of 1 nM to 30 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation - a response not blocked by naltrexone. NIH 10870,30 μM, was devoid of significant antagonist activity at μ-,κ-- and δ-opioid receptors. In the monkey cortex binding assay, although IC_{50}'s were obtained for mu- and kappa-binding sites, they are unlikely to be predictive of in vivo narcotic activity, except perhaps at very high doses.

NIH 10874 **7-Benzoyl-2-piperidineomethyl-1,4-benzodioxane.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor: 0% inhibition at 6 μM
δ-receptor: 3% inhibition at 6 μM
κ--receptor: 4% inhiblion at 6 μM



MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	20.6 ± 2.2	100		9
Naltrexone (100 nM)	45.5 ± 6.1	100	2.2	3
ICI-174864 (100 nM)	27.2 ± 4.0	100	1.3	3
Nor-BNI (10 nM)	27.9 ± 4.2	100	1.4	3

SOL: 3 mM in H_2O

SUMMARY

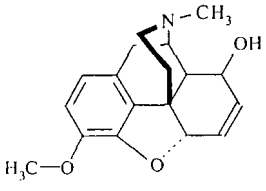
NIH 10874, in concentrations of 10 nM to 1 μM. decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone (100 nM), ICI-174864 (100 nM), and nor-binaltorphimine (10 nM) failed to shift the NIH 10874 concentration-effect curve significantly. Thus, NIH 10574 was a potent agonist dcvoid of opioid activity on the isolated mouse *vas deferens* preparation. In the monkey cortex binding assay, the compound had no significant activity.

* * *

NIH 10875 **Pseudocodeine.HCl**

MONKEY CORTEX BINDING (nM)

(a) μ-receptor: 427
(b) δ--receptor: 27.3% inhibition at 6 μM
(c) κ-receptor: 20.5% inhibition at 6 μM



NIH 10875 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	14.8 ± 4.5	62.9 ± 7.4		10
Naltrexone (100 nM)	3.9 ± 0.5	17.2 ± 1.9	0.3	4
ICI-174864 (100 nM)	25.8 ± 17.5	76.1 ± 6.5	1.7	3
Nor-BNI (10 nM)	17.2 ± 75	51.9 ± 6.7	1.2	3

SOL: 3 mM in H_2O

SUMMARY

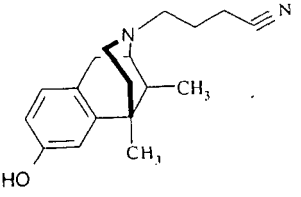
NIH 10875 is a complex drug with low affinity for mu-binding sites. In concentrations of 1 μM to 100 μM, it decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. The maximum response was a 62.9% inhibition of the twitch. Because of limitations in solubility, higher concentrations could not be evaluated. Naltrexone (100 nM) decreased markedly the maximum response to NIH 10875 but did not shift the concentration-effect curve to the right or left. Naltrexonc, 100 nM, also reversed the inhibition produced by NIH 10875. Neither ICI 174864 (100 nM) nor nor-binaltorphimine (10 nM) shifted the NIH 10875 concentration-effect curve significantly. Thus, in the mouse *vas deferens* preparation, NIH 10875 was a very weak agonist with unusual activity at mu opioid receptors.

* * *

NIH 10884 (-)-2-(3-Cyanopropyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan

MONKEY CORTEX BINDING (nM)

μ-receptor: 6.52
δ--receptor: 21.6
κ--receptor: 0.34



MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	42.7 ± 4.0	100		9
Naltrexone (100 nM)	631.5 ± 229.8	100 ± 6.3	14.8	3
ICI-174864 (100 nM)	67.8 ± 10.0	100	1.6	3
Nor-BNI (10 nM)	335.4 ± 56.9	100	7.9	3

NIH 10884 (continued)

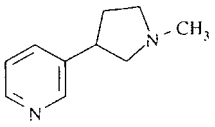
SUMMARY

NIH 10884 in concentrations of 10 nM to 1 μM decreased the magnitude of the twitch of the electrically stimulated mouse vas deferens preparation. Naltrexone (a mu opioid receptor antagonist) shifted the NIH 10884 concentration effect curve to the right. Nor-binaltorphimine (a kappa opioid receptor antagonist) also shifted the NM 10884 concentration-effect curve to the right. ICI-174864 (a delta-opioid receptor antagonists) did not shift teh NIH 10884 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10884. Thus, NIH 10884 has characteristics typical of a kappa-opioid receptor agonist. In the monkey cortex binding assay, NIH 10884 was highly potent and selective for kappa binding sites, as well.

* * *

NIH 10886 (±)-Isonicotine oxalate

MONKEY CORTEX BINDING (nM)



μ-receptor:	15.8% inhibition at 6 μM
δ-receptor:	0.0% inhibition at 6 μM
κ-receptor:	9.6% inhibition at 6 μM

MOUSE *VAS DEFERENS* PREPARATION

NIH 10886 was devoid of significant agonist activity on the isolated, electrically stimulated mouse vas deferens preparation when tested in concentrations from 100 nM to 30 μM. At a concentration of 30 μM, NIH 10886 caused a 5.07-fold shift to the right in the sufentanil concentration-effect curve, a 2.17-fold shift to the right in the DSLET concentration-effect curve, and a 1.51-fold shift to the right in the U50,488 concentration-effect curve. Higher concentrations could not be studied due to an insufficient supply of the drug. NIH 10886 did not alter the maximum response obtained with any of the agonists. Thus, NIH 10886 appears to be a very weak antagonist at mu, and possibly delta-opiold receptors.

SUMMARY

NIH 10886 had no significant activity in the binding assay: and there was weak evidence of antagonist activity in the mouse *vas deferens* preparation. NIH 10886 probably had no significant opioid activity in these assays.

* * *

NIH 10887 ω-Conotoxin MVIIA (reduced, cyclic (1-16), (8-20), (15-25))

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-
Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2
cyclic (1-16), (8-20), (15-25)-tris(disulfide)

MONKEY CORTEX BINDING (nM)

μ-receptor: 1% inhibition at 6 μM δ-receptor: 1190 κ-receptor: 0.3% inhibition at 6 μM

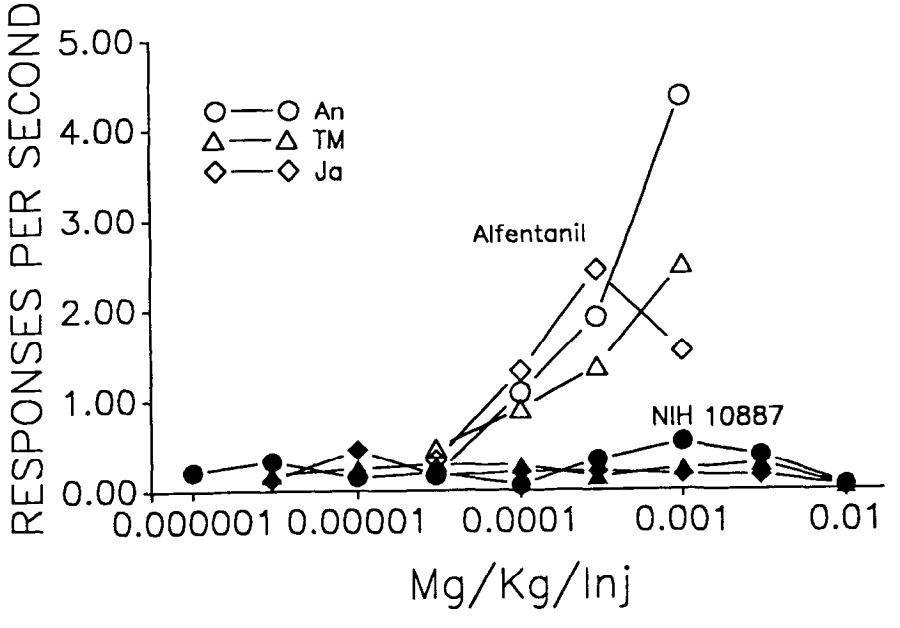
NIH 10887 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	4.78 ± 0.58	100		3
Naltrexone (100 nM)	5.02 ± 0.47	100 ± 6.3	1.0	3

REINFORCING EFFECTS IN RHESUS MONKEYS

NIH 10867 was evaluated across a wide range of doses. Four doses could be evaluated in a single session, and in different sessions, the concentration of drug was adjusted so that the dose range was altered as well. Doses of from 0.000001 to 0.01 mg/kg/inj were tested. We did not go to higher doses because of concerns about hypotensive effects of the drug. (As many as 20 injections can be taken at each dose). The reason such small doses were tested was because slightly higher rates seemed to be maintained by the smaller doses of each dose series that was tested. Therefore, the possibility that low rates were maintained because the drug was especially potent was evaluated. As can be observed in the accompanying figure, although alfentanil maintained a dose-related increase in rates of responding that were greater than 2.0 responses/sec at peak, NIH 10887 did not maintain rates of responding that indicated a reinforcing effect of this drug. Observation of the animals after self-administration sections did not indicate that the drug had any effects at the doses taken. Therefore, across the range of doses tested, there was no indication that this drug had any effects that were different from saline. In other studies ongoing in the laboratory, an intravenous dose of 0.1 mg/kg was observed to produce a distinctly pale appearance in a monkey, indicating a hypotensive effect.



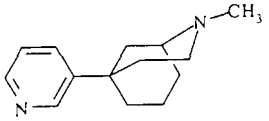
NIH 10887 (continued)

SUMMARY

NIH 10887, in concentrations of 1 nM to 30 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone (100 nM) did not shift the NIH 10887 concentration effect curve. Thus, NIH 10887 is a potent, highly efficacious agonist on the mouse *vas deferens* preparation. Opioid agonist properties were not detectable. In the monkey cortex binding assay, it failed to produce significant displacement of any of the tritiated ligands. It also did not act as a reinforcer in the rhesus monkey over a very wide range of doses up to 0.01 mg/kg/inj

* * *

NIH 10899 **2-Methyl-5-(3-pyridyl)morphan.2 oxalate**



MONKEY CORTEX BINDING (nM)

μ-receptor:	
δ-receptor:	28.8 ± 5.2% inhibition at 10 μM
κ-receptor:	29.1 ± 3.0% inhibition at 10 μM

SUMMARY

NIH 10899 had weak affinity for the μ-opioid receptor, approximately 1500 times less than the standard μ-peptide DAMGO. In contrast, it does appear to have some degree of selectivity for μ- over δ- and κ--receptors.

* * *

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (1996)

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INTRODUCTION

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately 13 years. The group now includes laboratories at Louisiana State University Medical Center (France, Gerak), University of Mississippi Medical Center (Woolverton, Rowlett), and the University of Michigan (Winger, Woods) and is part of the Drug Evaluation Committee (Dr. T. Cicero, Chair) of the College on Problems of Drug Dependence (CPDD) which is supported by both CPDD and the National Institute on Drug Abuse (NIDA). One of the purposes of the group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and physical dependence potential. Compounds are received, coded and distributed by Dr. A. Jacobson at the National institute of Diabetes, Digestive and Kidney Diseases (NIDDK). National Institutes of Health (NIH), for blind testing in the various laboratories. They are evaluated for discriminative stimulus effects in pentobarbital-trained monkeys (UMMC), amphetamine-trained monkeys (UMMC), triazolam-trained monkeys (LSUMC), flumazenil-trained monkeys that receive diazepam daily (LSUMC) and also for reinforcing effects in monkeys that previously self-administered methohexital (UM). This report includes the results of evaluation of the following compounds: CPDD-0007, CPDD-0032, CPDD-0042 and CPDD-0044.

METHODS

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects

Subjects were rhesus monkeys (Macaca mulatta) experienced with self-administration of sodium methohexital and saline. Animals were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. Catheters passed subcutaneously (s.c.) to the mid-scapular region, exited the body and continued, through a hollow restraining arm, to the outside rear of the cage.

Apparatus

The restraint and catheter protection devices are described in detail by Deneau et al. (1969). Each monkey wore a tubular stainless steel harness that protected the exit site of the catheter and allowed relatively unrestricted movements within the cage. A Teflon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection for animals who tended to locate and pull their catheters. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 1.5 cm apart, were three circles, 2.5 cm in diameter. covered with translucent plastic and capable of being illuminated from behind by 5 W colored bulbs. The two side lights could be illuminated red and the center light green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by a force of 0.010 to 0.0 15

N. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairheld, VT) software and located in an adjoining room.

Procedure

Reinforcing effects of CPDD-0044 were evaluated in a substitution self-administration procedure with methohexital serving as the baseline drug. Test sessions and baseline sessions had the same general structure. At the start of each session, a red light was illuminated over one of two levers. When a monkey completed the fixed-ratio requirement of 10 presses on that lever (fixed-ratio [FR] 10), a 5-second, 1.0 ml injection of saline solution, sodium methohexital (0.1 mg/kg), or a test compound was delivered. The red light was extinguished and a center green light illuminated for the duration of the infusion. Each injection was followed by a 10-second timeout during which all stimulus lights were extinguished and responding had no programmed consequence

Twice daily experimental sessions lasted 130 mm each. On approximately half of the baseline sessions, the monkeys could respond for saline. All animals showed clear and consistent differential responses to saline and methohexital before test compounds were substituted.

In test sessions a dose of the test compound was made available for one session. Other conditions were similar to those of the baseline sessions.

Drugs

Both drugs were given in an injection volume of 1.0 ml. The methohexital training dose was 0.1 mg/kg/injection. Four doses of CPDD-0044 were evaluated (0.00 1.0.01, 0.1 and 1.0 mg/kg/injection); not all monkeys received all doses, but each of the three monkeys were evaluated at the two largest doses (0.1 and 1.0 mg/kg/injection). In most cases, two observations were made at the tested doses in each monkey.

Discriminative Stimulus Effects of CPDD-4044 in Rhesus Monkeys (pentobarbital and amphetamine discriminations, UMMC)

Subjects

The subjects were seven adult rhesus monkeys (Macaca mulatta) weighing between 6.4 and 12.2 kg. Monkeys were housed individually in stainless steel cages in which water was available continuously. They were fed 150 to 200 g of Teklad monkey chow after each session and were given a chewable vitamin tablet 3 days/week.

The monkeys had been trained previously to discriminate d-amphetamine (Ou3, 7739, 8515 and 8405) or pentobarbital (AQ63, 8814 and 8902) from saline in a two-lever, discrete-trial shock avoidance procedure. All monkeys had received other test drugs prior to testing with CPDD-0044.

Apparatus

During experimental sessions animals were seated in primate restraint chairs and placed inside sound-attenuating cubicles. All chains were fitted with shoes containing brass plates in the soles that permitted delivery of electric shock produced by a shock generator (SG 903 BRS/LVE, Laurel, MD). Chambers were equipped with two response levers (PRL-001, BRS/LVE, Laurel, MD) mounted on one wall. There were four white lights above each lever. Chambers were illuminated with ceiling-mounted 40w incandescent house lights. Experimental events were programmed and recorded with an Apple Macintosh II computer in a room adjacent to the one in which animals were tested.

Procedure

The training and test procedures have been reported in detail elsewhere (Woolverton et al., 1994). A monkey was placed in the restraint chair and either saline (1-2 ml) or the training drug was administered intragastrically

(i.g.) via a nasogastric tube, followed by a 1.5 ml saline flush Fifty-five minutes after infusion, the monkey was placed into the experimental chamber.

The session began with a S-minute time-out which was followed by 30 trials. On each trial the house tight and lever lights were illuminated and responding on the correct lever postponed scheduled shock and extinguished the lights. Incorrect responses reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR 1, 2 or FR 5) was not satisfied on the correct lever within 5 seconds (1 0 seconds for FR 5) of the onset of the lights, shock (250 msec duration, 3 or 7 mA intensity) was delivered. If the response requirement was not satisfied within 2 additional seconds (4 seconds for FR 5) of this shock, a second shock was delivered and the trial automatically ended. The session was terminated when 2 shocks were delivered during 2 consecutive trials. Trials were separated by 30-see timeouts.

Training sessions were conducted five days a week according to the following schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline and D denotes sessions preceded by drug. Discrimination training continued until at least 90% of the responses in the first trial were on the correct lever and subjects avoided shock on at least 90% of the trials (27/30) for seven out of eight consecutive sessions. When subjects failed to satisfy criteria, the training sequence was conducted until the criteria were once again satisfied.

Test sessions were identical to training sessions except that test drugs were administered and completing the response requirement on either lever avoided shock.

Drugs

A stock solution of d-amphetamine sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in saline in a concentration of 5.0 mg/ml. The training dose of amphetamine was either 0.56 or 1.0 mg/kg i.g. Pentobarbital was mixed daily by diluting Nembutal (Abbott Laboratories, N. Chicago, IL). The training dose was 10 mg/kg for all pentobarbital-trained monkeys. CPDD-0044 was dissolved in 0.9% saline immediate before administrations doses of 1.0, 3.0, 10.0 and 30.0 mg/kg were evaluated at an infusion volume of 0.25 mg/kg.

Discriminative Stimulus Eflects in Rhesus Monkeys (triazolam and flumazenil discriminations, LSUMC)

Subjects

The subjects were five adult and three juvenile rhesus monkeys (*Macaca mulatta*) weighing between 3.0 and 9.0 kg. Two juvenile monkeys participated in the flumazenil discrimination study and four adults participated in the triazolam discrimination study. Monkeys were housed individually in stainless steel cages in which water was continuously available (except for monkey LU who was water restricted to facilitate drinking punch that contained drug). Monkeys received primate chow (Harlan Teklad, Madison, WI) daily as well as fresh fruit and peanuts several days per week. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee. Louisiana State University Medical Center. New Orleans. and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Apparatus

Monkeys were seated in chairs that provided restraint at the neck. Chairs were equipped with shoes containing brass electrodes, to which brief (250 msec) electric shock could be delivered an an a.c. shock generator located adjacent to the chambers. During experimental sessions, chairs were located in sound-attenuating, ventilated chambers that were equipped with several response levers, a food cup and an array of stimulus lights.

Procedure

Flumazenil Discrimination. Monkeys consumed 5.6 mg/kg of diazepam in 45-50 ml of fruit punch 3 hrs prior to daily sessions in which they discriminated between s.c. injections of 0.32 mg/kg of flumazenil and vehicle

while responding under a FR 5 schedule of stimulus-shock termination. Daily training sessions consisted of several discrete, 15-minute cycles. Each cycle comprised a 10-minute pretreatment period, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and monkeys could postpone scheduled shock for 30 seconds by responding five times on the appropriate lever as determined by the s.c. injection administered during the first minute of the 10-minute timeout (e.g., left lever after vehicle, right lever after flumazenil). Failure to satisfy the response requirement within 10-seconds resulted in the delivery of a brief shock. The response period ended after 5 minutes or the delivery of 4 shocks, whichever occurred first. Responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were identical to training sessions except that various doses of flumazenil or the test compound were administered during the first minute of each timeout and five consecutive responses on either lever postponed scheduled shock.

Triazolam Discrimination. Monkeys discriminated between s.c. injections of 0.032 (subject MA) or 0.1 mg/kg of triazolam and vehicle while responding under a FR 5 schedule of stimulus-shock termination. Daily sessions comprised a single cycle that included a 15-minute pretreatment period, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and monkeys could postpone scheduled shock for 30 seconds by responding five times on the appropriate lever, as determined by the s.c. injection administered 45 minutes prior to the beginning of the session, 60 minutes prior to the beginning of the response period (e.g., left lever after vehicle, right lever after triazolam). Failure to satisfy the response requirement within 10 seconds resulted in the delivery of a brief shock. The response period ended after 5 minutes or the delivery of 4 shocks, whichever occurred first. Responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were identical to training sessions except that various doses of triazolam or the teat compound were administered 45 minute3 prior to the session and five consecutive responses on either lever postponed scheduled shock.

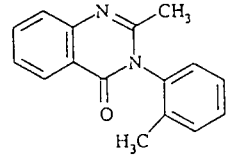
Drugs

Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 45-50 ml (depending on body weight) of fruit punch or apple juice containing suspending Agent K to yield a dose of 5.6 mg/kg/daily drinking episode. Fhunazenil (F. Hoffman LaRoche, LTD, Basel, Switzerland) was dissolved in a vehicle of 10% ethanol, 40% propylene glycol and 50% saline; triazolam (Upjohn, Kalamazoo, MI), CPDD-0007, and CPDD-0032 were dissolved in a vehicle of 10% ethanol, 20% emulphor and 70% water. CPDD-0007 was studied up to a dose of 32.0 mg/kg s.c.; limited solubility precluded studies of larger doses. CPDD-0032 was studied up to a dose of either 0.32 (triazolam study) or 3.2 (flumazenil study) mg/kg s.c.; limited solubility precluded studies on larger doses in the flumazenil study. CPDD-0042 and CPDD-0044 were dissolved in sterile water. CPDD-0042 was studied up to a dose of 5.6 mg/kg s.c.; larger doses of this compound were not studied and were reported to produce convulsions in other studies (1). CPDD-0044 was studied up to a dose of 32.0 mg/kg s.c.

RESULTS

CPDD-0007

Methaqualone (2-methyl-3-o-tolyl-4(3H)-quinazolinone)



Discriminative Stimulus Effects In Rhesus Monkeys (triazolam and flumazenil discriminations)

Up to a dose of 32.0 mg/kg, CPDD-0007 failed to substitute (i.e.. did not produce at least 80% drug-lever responding) for the flumazenil discriminative stimulus (Table 1). Moreover, rates of responding were greater than 70% of control rates with all doses of CPDD-0007 (data not shown).

Up to a dose of 32.0 mg/kg, CPDD-0007 failed to occasion triazolam-lever responding (Table 2). Moreover, rates of responding were not altered by any dose of CPDD-0007 (data not shown).

TABLE 1. Discriminative stimulus effects of flumazenil and CPDD-0007 in diazepam-treated monkeys discriminating between flumazeail and vehicle.

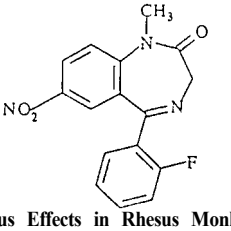
		Flumazenil (mg/kg)				CPDD-0007 (mg/kg)			
Subject	Vehicle	0.0032	0.1	0.32	1.0	1.0	3.2	10.0	32.0
DU	0	8.2	11.1	75.0	87.5	0	0	0	0
LU	0	3.5	0	37.7	84.0	10.0	0	0	0

TABLE 2. Discriminative stimulus effects of triazolam and CPDD-0007 in monkeys discriminating between triazolam and vehicle.

		Triazolam (mg/kg)				CPDD-0007 (mg/kg)			
Subject	Vehicle	0.0032	0.01	0.032	0.1	1.0	3.2	10.0	32.0
SA	0	0	11.1	54.4	95.0	n.s.	0	0	20.0
R O	0	0	0	0	100	n.s.	0	0	0

n.s. = not studied

CPDD-0032
Flunitrazepam



Discriminative Stimulus Effects in Rhesus Monkeys (triazolam and flumazenil discriminations)

Up to a dose of 3.2 mg/kg, CPDD-0032 failed to occasion flumazenil-lever responding (Table 3). Moreover, rates of responding were above 80% of control rates with all doses of CPDD-0032 (data not shown).

CPDD-0032 substituted (i.e., produced at least 80% drug-lever responding) for triazolam in a dose-related manner in both monkeys with doses of CPDD-0032 larger than 0.032 mg/kg occasioning greater than 80% triazolam-lever responding (Table 4). Average rates of responding were decreased to less than 50% of control after s.c. injection of 0.1 mg/kg of CPDD-0032 (data not shown).

TABLE 3. Discriminative stimulus effects of flumazenil and CPDD-0032 in diazepam-treated monkeys discriminating between flumazenil and vehicle.

		Flumazenil (mg/kg)				CPDD-0032 (mg/kg)			
Subject	Vehicle	0.032	0.1	0.32	1.0	0.1	0.32	1.0	3.2
DU	0	8.2	11.1	75.0	87.5	0	0	0	0
LU	0	3.5	0	37.7	84.0	0	0	4.0	0

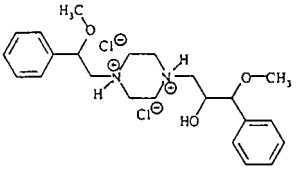
TABLE 4. Discriminative stimulus effects of triazolam and CPDD-0032 monkeys discriminating between triazolam and vehicle.

		Triazolam (mg/kg)				CPDD-0032 (mg/kg)				
Subject	Vehicle	0.0032	0.01	0.032	0.1	0.0032	0.01	0.032	0.1	0.32
MA	0	0	100	97.8	95.2	0	50.0	40.0	97.6	*
CA	0	0	0	0	100	0	9.3	45.4	90.0	91.8

* = no responding

CPDD-0042

Zipeprol [4-(2-methoxy-2-phenylethyl)- α-mehoxyphenylmethyl)-1-piperezineethanol.2HCl]



Discriminative Stimulus Effects ln Rhesus Monkeys (triazolam and flumazenil discriminations)

Up to a dose of 5.6 mg/kg, CPDD-0042 failed to substitute for the flumazenil discriminative stimulus (Table 5). Rates of responding were increased modestly by CPDD-0042 (to 141% and 123% of control in monkeys DU and LU, respectively, at a cumulative dose of 1.0 mg/kg, data not shown).

Up to a dose of 5.6 mg/kg, CPDD-0042 tailed to occasion triazolam-lever responding (Table 6). Moreover, CPDD 0042 did not alter rates of responding in one monkey (MA) and increased rates modestly (to 128% of control at a cumulative dose of 5.6 mg/kg) in another (RO; data not shown).

TABLE 5. Discriminative stimulus effects of flumazenil and CPDD-0042 in diazepam-treated monkeys discriminating between flumazenil and vehicle

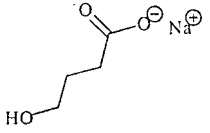
		Flumazenil (mg/kg)				CPDD-0042 (mg/kg)			
Subject	Vehicle	0.032	0.1	0.32	1.0	0.32	1.0	3.2	5.6
DU	4.3	8.2	11.1	75.0	87.5	2.0	0	0	0
LU	0	3.5	0	37.7	84.0	0	0	0	0

TABLE 6. Discriminative stimulus effects of triazolam and CPDD-0042 in monkeys discriminating between triazolam and vehicle.

		Triazolam (mg/kg)				CPDD-0042 (mg/kg)		
Subject	Vehicle	0.0032	0.01	0.032	0.1	1.0	3.2	5.6
MARG	0	0	11.8	90.0	100	0	0	0
RO	0	0	0	0	100	0	0	0

CPDD-0044

γ-Hydroxybutyric acid, sodium salt



Reinforcing Effects in Rhesus Monkeys

Four doses of CPDD-0044 (0.001, 0.01, 0.1 and 1.0 mg/kg/injection) were evaluated in three monkeys. CPDD-0044 maintained very little self administration behavior; the number of injections taken of CPDD-0044 was not greater than the number of injections of saline and was considerably less than the number of injections taken of methohexital.

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital and amphetamine discriminations)

CPDD-0044 engendered a maximum of 50% drug-appropriate responding in amphetamine-trained monkeys (Table 7) and no drug-appropriate responding in pentobarbital-trained monkeys (Table 8). The amphetamine-appropriate responding that was engendered by CPDD-0044 was not dose related and response rates were not systematically altered by CPDD-0044 in either group of monkeys (data not shown).

TABLE 7. Discriminative stimulus effects of amphetamine and CPDD-0044 in monkeys discriminating between amphetamine and vehicle.

			CPDD-0044 (mg/kg)			
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	30.0
Ou3	0	100	0	47	50	0
7739	0	100	n.s.	0	0	0
8515	0	100	n.s.	0	48	0
8405	0	92	n.s.	22	18	50

n.s. = not studied

Discriminative Stimulus Effects in Rhesus Monkeys (triazolam and flumazenil discriminations)

Up to a dose of 32.0 mg/kg, CPDD-0044 failed to substitute for the flumazenil discriminative stimulus (Table 9). Rates of responding were increased modestly by CPDD-0044 (to an average of 142% of control at a dose of 32.0 mg/kg; data not shown).

In two monkeys (RO and CA), CPDD-0044 failed to occasion any triazolam-lever responding up to a dose of 32.0 mg/kg s.c. Moreover, CPDD-0044 did not alter rates of responding in these two monkeys. In a third monkey (MARG), CPDD-0044 produced 81 and 40% triazolam-lever responding at doses of 3.2 and 10.0 mg/kg, respectively. A retest with 10.0 mg/kg in monkey MARG confirmed the initial finding with this dose occasioning 6 1% triazolam-lever responding. Rate of responding was decreased to 76% of control in monkey MARG at a dose of 32.0 mg/kg of CPDD-0044.

TABLE 8. Discriminative stimulus effects of pentobarbitnl and CPDD-0044 in monkeys discriminating between pentobarbital and vehicle.

			CPDD-0044 (mg/kg)			
Subject	Vehicle	Pentobarbital	1.0	3.0	10.0	30.0
AQ63	0	100	0	0	0	0
8814	0	100	n.s.	0	0	0
8902	0	100	n.s.	0	0	0

n.s. = not studied

TABLE 9. Discriminative stimulus effects of flumazenil and CPDD-0044 in diazepam-treated monkeys discriminating between flumazenil and vehicle

		Flumazenil (mg/kg)					CPDD-0044 (mg/kg)			
Subject	Vehicle	0.01	0.032	0.1	0.32	1.0	1.0	3.2	10.0	32.0
DU	4.3	n.s.	8.2	11.1	75.0	87.5	2.2	0	0	8.2
IG	0	0	74.5	57.7	100	n.s.	11.1	0	0	0

n.s. = not studied

TABLE 10. Discriminative stimulus effects of triazolam and CPDD-0044 in monkeys discriminating between triazolam and vehicle

		Triazolam (mg/kg)				CPDD-0044 (mg/kg)			
Subject	Vehicle	0.0032	0.01	0.032	0.1	1.0	3.2	10.0	32.0
MARG	10	0	11.8	90.0	100	3.9	81.5	40.0	0
RO	0	0	0	0	100	0	0	0	0
CA	0	0	32.3	81.8	93.8	0	0	0	0

CONCLUSIONS

CPDD-0007

CPDD-0007 (methaqualone) failed to substitute for for flumazenil in diazepam-treated monkeys and also failed to substitute for triazolam in otherwise untreated monkeys. While it is possible that doses larger than 32.0 mg/kg of CPDD 0007 might have discriminative stimulus effects under the conditions described above or under conditions different from those used in the current study, it is clear that for doses up to and including 32.0 mg/kg. CPDD-0007 fails to exert either benzodiazepine antagonist or benzodiazepine agonist actions in rhesus monkeys (also see 3, 4, 8 for results from other procedures).

CPDD-0032

CPDD-0032 (flunitrazepam) failed to substitute for flumazenil in diazepam-treated monkeys discriminating between flumazenil and vehicle; however, CPDD-0032 substituted completely for triazolam in monkeys discriminating between triazolam and vehicle. Up to a dose of 3.2 mg/kg. CPDD-0032 failed to alter rates of lever pressing in monkeys treated daily with 5.6 mg/kg (p.o.) of diazepam. In contrast, in otherwise untreated monkeys (i.e., those discriminating triazolam), CPDD-0032 dose-dependently decreased response rates with a potency that was not different from triazolam. Collectively these results demonstrate that CPDD-0032 shares discriminative stimulus and rate-decreasing effects with and has a potency similar to triazolam. That CPDD-0032

was less effective in decreasing rates of responding in diazepam-treated monkeys could indicate that daily treatment with diazepam generated cross-tolerance to the rate-decreasing effects of CPDD-0032. In summary, CPDD-0032 appears to be a benzodiazepine-like agonist with a potency similar to triazolam (also see 5 for results from other procedures).

CPDD-0042

CPDD-0042 (zipeprol) failed to substitute for flumazenil in diazepam-treated monkeys and also failed to substitute for triazolam in otherwise untreated monkeys. While it is possible that CPDD-0042 might have discriminative stimulus effects under conditions different from those used in the current study, it is clear that, for doses up to and including 5.6 mg/kg, CPDD-0042 fails to exert either benzodiazepine antagonist or bcnsodiazepine agonist actions in rhesus monkeys (also see 2,6 for results from other procedures).

CPDD-0044

CPDD-0044 (γ-hydroxybutyric acid) did not maintain self-administration responding in any of the three monkeys tested. In drug discrimination studies, CPDD-0044 had, at most, partial amphetamine-like discriminative stimulus effects and no pentobarbital-like discriminative stimulus effects. CPDDW failed to substitute for flumazenil in diazepam-treated monkeys and also failed to substitute for triazolam in two of three untreated monkeys. One dose of CPDD-0044 substituted for triazolam in one monkey, although the effects of CPDD-0044 in this monkey, over a 32-fold dose range, were not dose related. While it is possible that CPDD-0044 might have discriminative stimulus effects under conditions different from those used in the current study, for doses up to and including 32.0 mg/kg, CPDD-0044 fails to reliably exert either amphetamine-like, pentobarbital-like, triazolam-like or benzodiazepine antagonist actions in rhesus monkeys (also see 7).

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STANDARD BINDING AND FUNCTIONAL ASSAYS RELATED TO MEDICATIONS DEVELOPMENT DIVISION TESTING FOR POTENTIAL COCAINE AND OPIATE NARCOTIC TREATMENT MEDICATIONS

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INTRODUCTION

One of the key missions of the National institute on Drug Abuse is the development of drugs for the treatment of drug abuse. Although there are presently three drugs approved for treatment of opiate narcotic addiction (methadone, naltrexone, and LAAM), second and third generation compounds are desired. Because of the absence of any clinically used medications, of particular importance is the identification and development of treatment compounds for the psychostimulant cocaine.

The Medications Development Division at NIDA has established an Opiate Treatment Discovery Program (OTDP). and a Cocaine Treatment Discovery Program (CTDP) with the purpose of using simple preclinical tests for the identification and evaluation of compounds that may be of use in the treatment of opiate narcotic and cocaine abuse. Tests in these programs include *in vitro* binding and biochemical assays, and *in vivo* pharmacological studies, designed to inexpensively select the most promising compounds for further evaluation and possible development as treatment medications. The strategy chosen was to test a large number of unknown compounds at molecular targets (receptors or transporters) that may be involved in the addiction process for opiates and cocaine.

The potential sites for treatment of opiate addiction have been reasonably well defined over the past several years. The approved medications act as either very long-lasting μ opiate agonists (methadone and LAAM), or a μ opiate antagonist (naltrexone). In addition, μ partial agonists, such as buprenorphine, have had indications of some usefulness in preclinical studies, and clinical trials (Kosten *et al.,* 1992). Accordingly, for the OTDP, the binding affinity and activity of a large number of opiate compounds have been tested at μ-, δ--, and κ--opiate receptors. Binding studies were originally conducted in guinea pig brain membranes, and subsequent studies have been carried out in CHO cells transfected with human receptors. Activity has been determined using the *in vitro* bioassays guinea pig ileum (GPI) and mouse vas deferens (MVD). Additional studies have been carried out by measuring stimulation of [^{35}S]GTPγS binding in transfected ceils.

The sites of action for potential cocaine treatment medications are significantly less well defined. Cocaine is a local anesthetic that has pharmacological actions throughout the body. However, the CNS stimulant actions of cocaine are known to be mediated by its ability to block the reuptake of the biogenic amines dopamine, norepinephrine, and serotonin (5-hydroxytryptamine, 5-HT) (Ritz *et al.* 1990; Reith, 1988). The addictive property of cocaine appears to be related to its ability to block dopamine reuptake (Kuhar *et al.,* 1988). Accordingly, cocaine mediates its effects by increasing synaptic levels of dopamine and the other biogenic amines. Based upon the success of opiate addiction medications, potential cocaine treatment medications could include long-lasting cocaine analogs, long-lasting dopamine receptor agonists, dopamine receptor antagonists, dopamine receptor partial agonists. Unfortunately, unlike opiates, for which we know the it receptor mediates the rewarding actions, we don't know which of the five dopamine receptors mediate the rewarding aspects of cocaine administration.

The objective of one CIDP contract was to evaluate a large number of compounds that interact with biogenic amine receptors for potential cocaine treatment medications. We characterized compounds at dopamine (D_1, D_2, and D_3), 5-HT (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3), phencyclidine (PCP), and sigma (σ) binding sites. The characterization included both determination of binding affinities and, where possible, an evaluation of the agonist or antagonist potencies of compounds at the dopamine and 5-HT receptors. Activity at D_1 receptors has been determined by measuring stimulation of cAMP accumulation. Activity at D_2 and D_3 was determined by measuring stimulation of mitogenic activity. Activity at 5-HT_{2A} receptors was measured in the rat aorta spiral, *in vitro.* and activity at the 5-HT_3 receptor was measured in the GPI.

Prior to the study of unknowns at each site discussed above, our binding and functional assays were validated by the characterization of a large number of known standard compounds. In this manuscript. we will list binding affinities and activities of standard compounds derived for both OTDP and CTDP programs.

METHODS

Receptor Binding

Serotonin Receptors

Human 5-HT_{1A} receptors on HA7 cells were donated by Dr. Marc Caron. NIH-3T3-GF6 cells containing rat $5HT_{2A}$ receptors and NIH-3T3-Pø‹cells containing rat 5-HT_{2C} receptors were obtained from Dr. David Julius. Each cell line is grown in Dulbecco's minimum essential medium (DMEM) containing 10% fetal calf serum, 0.05% pen-streptomycin, and 400 µg/ml G418. The cells are scraped from the 100 x 20 mm plates and centrifuged at 500 x g for 5 min. The pellet is homogenized in 50 mM Tris-HCl, pH 7.7, with a polytron, centrifuged at 27.000 x g, and resuspended in the same buffer, washed once and resuspended in 25 mM Tris-HCl containing 100 µM ascorbic acid and 10 µM nialamide at pH 7.4 for 5-HT_{1A} receptors, 25 mM Tris-HCl, pH 7.7 for 5-HT_{2A} receptors, and 50 mM Tris-HCl, pH 7.7, 4 mM $CaCl_2$, 10 µM pargyline, and 0.1% ascorbic acid for 5-HT_{2C} receptors. The binding assays contain [^{3}H]8-0H-DPAT (0.5 nM final concentration), and 30 µg protein/tube, [^{3}H]kctanserin (0.40 nM final concentration) with 30 µg protein/tube, or [^{3}Hlmesulergine (0.4 nM final concentration), and 8 µg protein/tube, in a volume of 1.0 ml for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors respectively. The tubes are incubated at 25°C for 60 min before filtration.

5-HT_3 receptors are found in the neuroblastoma x glioma hybrid cells NG108-15, which are grown in DMEM with HAT supplement and 10% fetal calf serum. The cell membranes are prepared as described above and resuspended in 25 mM Tris-HCl, pH 7.7 with 1 mM EDTA. The assay is performed in 0.5 ml with [^{3}H]GR65630 (1.6 nM final concentration), and 0.13 mg protein to each tube. The tubes are then incubated at 25°C for 45 min. Nonspecific binding is defined by 1 µM of zacopride. Filters are soaked in 0.1% polyethyleneimine (PEI) before filtering.

Dopamine Receptors

Human D_1 receptors in L cells, obtained from, Dr. David Grandy, are grown and prepared as described for the HA7 cells. The final pellet is resuspended in 50 mM Tris-HCl containing 120 mM NaCI, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 7.7. Binding is conducted as described above using [^{3}H]SCH 23,390 (0.18 nM final concentration) and 70 µg protein/ tube. Human D_2- and D_3-receptor-containing CHOp- cells were obtained from Dr. Robert MacKenzie, and are grown in a minimum essential medium (α MEM) containing 10% fetal calf serum. 0.05% penicillin-streptomycin, and 600 µg/ml G418. Membranes are prepared as described above. The final pellet is resuspended in 50 mM Tris containing 120 mM NaCl, 5 mM of KCl, 1.5 mM $CaCl_2$, 4 mM of $MgCl_2$, and 1 mM EDTA, pH 7.4. The binding incubation is in 2.0 ml and contains 30 µg protein/tube, and [^{3}H]YM-09151-2 (0.2 nM final concentration). Filters are soaked in 0.1% PEI before filtering.

µ, δ, and κ Opioid Receptors

Receptor binding studies were initially conducted on Hartley guinea pig brain membranes. Guinea pigs were decapitated and the brains quickly removed and weighed, then homogenized in 50 mM Tris HCl, pH 7.5, using a Polytron homogenizer. The homogenate was centrifuged at 40,000 x g for 15 min, rehomogenized, and centrifuged once more. The final pellet was resuspended in Tris HCl, pH 7.5. at a final concentration of 6.67 mg original wet weight of tissue per milliliter.

Routine binding assays are conducted using [^{3}H]DAMGO, [^{3}H]Cl-DPDPE, [^{3}H]U69,593 for binding to µ, δ, κ receptors, respectively. Binding is conducted in a total volume of 2.0 ml. usually for 1 h at 25°C. Samples are filtered and counted as described above.

Binding was also conducted on cloned receptors. Humanκ-opioid receptor-containing CHO cells were obtained from Dr. Lee-Yuan Liu-Chen, and are grown in DMEM with 10% fetal calf serum, 0.4 mg/ml G418, and 0.1% penicillin/streptomycin. Human µ-opioid receptor-containing CHO cells were obtained from Dr. George Uhl, and are grown in F12 medium containing 10% fetal calf serum and 0.4 mg/ml G418. Human δ-opioid receptor-

containing CHO cells were obtained from Dr. Hank Yamamura, and are grown in F12 medium containing 10% fetal calf serum and 0.5 mg/ml hygromycin B. Cell membranes are prepared as described above. For binding, 30 mg protein is incubated in 50 mM Tris buffer pH 7.7, with approximately 0.5 nM of the radioligand. Incubation volume is 1.0 ml. Samples were filtered and counted as described above.

Functional Biochemical Assays

cAMP Production

C6 cells containing monkey D_1 receptor were obtained from Dr. Kim Neve, and were grown on 96-well plates in DMEM containing 10% FBS and 2 µg/ml of puromycin. D_1 receptors stimulate adenylyl cyclase, so for these receptors an increase in cAMP accumulation in intact cells is measured. When the cells in each well have learned confluence, the medium is removed and each well is rinsed with 0.1 ml of Krebs-HEPES buffer (130 mM of NaCl, 4.8 mM of KCl, 1.2 mM of KH_2PO_4, 1.3 mM of $CaCl_2$, 1.2 mM of $MgSO_4$, 25 mM of HEPES, and 10 mM of glucose, pH 7.3). The test drug is diluted in Krebs-HEPES buffer containing 0.1% ascorbic acid, 10 µM of pargyline, and 50 µM of 3-isobutyl-1-methylxantine (IBMX) and 0.1 ml is added to each well. The plates am preincubated for 20 mm at 37°C with or without antagonist, then incubated for an additional 10 min with the test compound. After incubation, the medium is removed and 0.1 ml of 0.5 M formic acid is added, then the supernatant is removed and 1yophilized. cAMP is quantitated using the protein kinase binding assay of Gilman (1970).

Stimulation of Mitogenesis

To measure D_2 and D_3 stimulation of mitogenesis (Chio *et al.,* 1994). CHOp- cells are used in a 96-well mate containing approximately 5.000 cells/well. The cells are incubated at 37°C in a MEM with 10% FBS, 0.05 penicillin-streptomycin, and 200 µg/ml Geneticin (G418 sulfate). After 48 h, the wells are rinsed twice with 100-µl aliquots of serum-free a MEM and incubated for 24 h at 37°C in serum-free α MEM. The medium is then removed and replaced with 90 µl of serum-free a MEM and 10 µl of drug in sterile water. After another 24 h of incubation at 37°C, 0.25 µCi of [^{3}H]thymidine is added to each well. The cells are incubated for 2 h at 37°C. Then, 10 µl/well of 10x trypsin is added to remove the cells, and the plate is filtered using a Tomtec cell harvester, and counted in a Betaplate Reader (Wallac).

[^{35}S]GTPγS Binding
[^{35}S]GTPγS binding is used to measure activity of µ, δ,, and κ opioid receptors. Binding is conducted basically as described by Traynor and Nahorski (1995). Cells are prepared as described above, and suspended in Buffer A, containing 20 mM HEPES, 10 mM $MgCl_2$, 100 mM NaCl, pH 7.4. For the binding assay, membranes (15 mg protein) are incubated with [^{35}S]GTPγS (50 µM). GDP (usually 10 µM), and the desired compound, in a total volume of 1 ml, for 60 mm at 25°C. Samples are filtered over glass fiber filters and counted as described for the binding assays above. Dose-response curves with the full agonists DAMGO, DPDPE, and U69,593 are determined in each experiment to identify full and partial agonist compounds at µ-δ-, and κ-opioid receptors, respectively.

***In Vitro* Functional Smooth Muscle Bioassays**

5-HT_{2A} Receptor
Rat Aorta Spiral (RAS) Tissue Preparation
Male albino Wistar rats (200-300 g body weight) are sacrificed and their aortas quickly removed, cleaned, and cut into a spiral. The spiral is mounted in an 8-ml water-jacketed tissue bath containing Krebs-bicarbonate solution (118 mM NaCl, 2.5 mM $CaCl_2$, 4.7 mM KCl, 25 mM NaHCO3, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, and 11.5 mM glucose). The spiral is first incubated with oxygenated (5% CO_2 in oxygen) Krebs solution at 37°C under 2.0 g tension for 30 min, then an additional 30 min in the presence of 500 µM of pargyline, a monoamine oxidase inhibitor, and 10 µM of benextramine tetrahydrochloride, an a_1-adrenoceptor inhibitor (Marin *et al.,* 1981). Excess unreacted pargyline and benextramine are then removed from the bath by flushing the system several times with the Krebs solution.

Serotonin (5-HT) Standard Curve

For standardization purposes, the spiral is cumulatively contracted with increasing concentrations of 5-HT in the presence of 10^{-4} M ascorbic acid. The 5-HT-induced contractions are recorded using an isometric transducer (Metrigram) coupled to a Gould multichannel polygraph.

Agonist Determinations

A concentration-response curve is generated for the test compound, and an ED_{50} (agonist concentration that produces half of the maximum contraction attainable by the agonist) value determined. To verify the test compound's agonist activity at 5-HT_{2A} receptors, assays are conducted in the presence of 100 nM ketanserin.

Antagonist Determinations

Test compounds that do not produce a contraction of the spiral on their own are tested for 5-HT_{2A} antagonist activity. The test compound is incubated with the spiral for 30 mm, and then the 5-HT standard curve is repeated in the presence of the drug. Antagonist activities are calculated for each single tissue from full concentration-response curves before and after addition of a single antagonist concentration. At least three different concentrations are used, and only one antagonist concentration is tested on each tissue. pA_2 values are determined from Schild plots (Schild, 1949) using a statistical analysis program developed by B. Eynon (SRI International).

5-HT_3 Receptor

Longitudinal Muscle Strip of Guinea Pig Ileum (GPI) Preparation

Male Hartley guinea pigs weighing 350-40 g are decapitated and the small intestine removed. The longitudinal muscle, with the myenteric plexus attached, is gently separated from the underlying circular muscle by the method of Paton and Vizi (1969). The muscle strips are mounted in an 8-ml, water-jacketed organ bath containing Krebs-bicarbonate solution. The tissues are kept at 37°C and bubbled with 5% CO_2 in oxygen, An initial tension of 1.0 g is applied to the strips. The tissues are equilibrated for 60 min before the start of the experiments. The contractions are recorded as described above.

Agonist and Antagonist Determinations

Concentration-response curves are constructed with the selective 5-HT_3 agonist 2-methyl-5-HT at concentrations from 1 to 100 μM. hrdividual doses are given 20 min apart. Then the test compound is injected into the tissue bath. If the compound contracts the GPI preparation, a concentration-response curve is constructed and the ED_{50}, value is determined both in the absence and presence of 100 nM ICS 205-930, a selective 5-HT_3 antagonist. Antagonist determinations using the Schild method are conducted as described above for the 5-HT_{2A} receptor, using the selective 5-HT_3 agonist 2-methyl-5-HT.

Opioid Receptors

Longitudinal Muscle Strip of Guinea Pig Ileum (GPI)

The tissue is prepared as described above for the 5-HT_3 receptor except that the muscle strip is stimulated for 60 mm before the start of each experiment Field electrical stimulation is delivered through platinum wire electrodes positioned at the top and bottom of the organ bath and kept a ftxed distance apart (3.5 cm). The upper electrode is a ring 4 mm in diameter. The parameters of rectangular stimulation are supramaximal voltage, 1-ms impulse duration at 0.1 Hz. A Grass S-88 electrostimulator is used for stimulation.

Electrically Stimulated Mouse Vas Deferens (MVD)

Swiss-Webster mice weighing 30-35 g are used The vasa deferentia are prepared according to the method of Hughes *et al.* (1975), bathed at 31°C in Mg^{2+} -free Krebs solution, and bubbled with a mixture of oxygen and CO_2 (95:5). An initial tension of 200-350 mg is used. The parameters of field stimulation have been modified slightly from the original description (Ronai *et al.,* 1977); paired shocks of 100-ms delay between supramaximal rectangular pulses of 1-ms duration are delivered at a rate of 0.1 Hz.

Kinetics

The agonist potencies of lest compounds are determined from concentration-response curves and characterized by their IC_{50} values. IC_{50} is defined as the concentration of the agonist that causes 50% inhibition of the electrically induced contractions.

Compounds with antagonist activity are characterized by the equilibrium dissociation constant (K_e) calculated from the following equation:

$$K_e = a/(DR - 1)$$

where "a" is the nanomolar concentration of antagonist and DR is the virtual shift of the agonist concentration-response curve to the right in the presence of a given concentration of antagonist. In the case of mixed agonist-antagonist compounds, the dose ratios are determined by the "single-dose method" introduced by Kosterlitz and Watt (1968).

A standard ratio with respect to a reference compound is also determined. The reference compound for μ- agonists is DAMGO. that for κ- agonists is U69,593 and that for δ- agonists is DPDPE. Their K_e values with the respective/selective antagonists are taken as 1.0.

RESULTS AND DISCUSSION

Cocaine Treatment Discovery Program

Binding affinities derived at serotonin and dopamine receptors are shown in Table 1. Affinities are given as $K_{0.5}$ values ± Standard Deviation of, in general, two experiments. Also shown are Hill coefficients derived in those two experiments. $K_{0.5}$ values are derived from the Cheng-Prusoff equation: $K_i = IC_{50}/(1 + [L]/K_d)$. This equation is only strictly valid for inhibition curves with Hill coefficients of 1.0. Because binding experiments have generally used [^{3}H]antagonists that bind to high and low affinity conformations, Hill coefficients of unlabeled agonists are often less than 1.0, necessitating the designation $K_{0.5}$.

Activity at D_1 receptors was determined by measuring agonist-stimulated increase in cAMP accumulation. One problem encountered with this assay was that compounds known to he partial agonists exhibited full agonist activity when measured in the D_1 receptor-containing cells first obtained. Subsequently, we obtained C6 cells containing either high or low copy number of the monkey D_1 receptor. As seen in Table 2, both cell lines could be successfully used to measure an agonist-stimulated increase in cAMP accumulation. However, in the high expressing cells both full agonists dopamine and SKF-81297, and partial agonists SKF-38393 and SKF-77434 acted as full agonists. In the low expressing cells, both partial agonists clearly produced significantly less cAMP than the full agonists tested. In addition, as would be predicted for low expressing cells with no receptor reserve, each of the agonists was fess potent, as demonstrated by a higher value for the EC_{50}. To identify partial agonist compounds, all further experiments were conducted on the low expressing cells.

Activity at D_2 and D_3 receptors was determined by measuring stimulation of mitogenic activity (Table 3). All experiments were done in comparison to stimulation of mitogenesis by the D_2/D_3 full agonist quinpirole, conducted on the same day. In this way percent maximal stimulation could he accurately determined. This method has been useful for the identification of full and partial agonists at D_2 and D_3 receptors.

Functional activity at 5-HT_{2A} and 5-HT_3 receptors have been determined using smooth muscle bioassays (Table 4), as described in Methods. Most of the standards tested have been antagonists at one or both of the 5-HT receptors. For each antagonist, K_e values were determined by full Schild analysis.

Opiate Treatment Discovery Program

Table 5 shows values derived from binding to the μ-, δ-, and κ-opioid receptors. At the beginning of the contract, all opioid binding studies were conducted on guinea pig brain membranes. With the cloning of the opioid receptors, and the subsequent availability of human receptors, recent experiments were conducted on human opioid receptor containing CHO cells. A comparison of guinea pig brain and human receptor binding indicates a very close correlation between the two species. These affinities are listed as K_i values and were also derived from the Cheng-Prusoff equation. Because [^{3}H]agonists were used in all of these binding experiments, Hill coefficients were uniformly close to 1.0, and the designation K_i is appropriate.

Historically, smooth muscle bioassays have been used extensively for the characterization of opioid compounds. The guinea pig ileum can be used for characterization of compounds at μ and κ receptors. The mouse vas deferens has μ, δ,, and κ receptors. However, it is apparently highest in δ receptors, and has often been used to characterize compounds at the δ opioid receptor. The activities of standard compounds at μ and κ receptors in the GPI, and at δ receptors in the MVD are shown in Table 6. The values shown are: IC_{50}, concentration at which the compounds

inhibits 50% of the magnitude of the electrically-induced contractions; the dose ratio (DR), the shift in IC_{50} in the presence of 200 nM CTAP, 1 nM Nor-BNI, or 1 nM naltrindole; the K_e of the antagonist and the ratio with respect to the prototypical agonist. Together, these values show the activity of each compound, as well as the selectivity of each compound.

Table 7 shows a biochemical method for determining activity and potency of opioid compounds, stimulation of [^{35}S]GTPγS binding in membranes from cells transfected with human μ, δ, or κ receptors. As with the mitogenesis assay, a standard prototypical agonist (DAMGO, DPDPE, and U69,693 for μ, δ, and κ receptors) is tested in every experiment so that percent maximal stimulation, with respect to the standard agonist, can be determined for each compound. In general, values determined in the GTPγS assays correspond quite well with the data derived from the smooth muscle bioassays. Compounds that are listed as flat at any particular site either are antagonists, or have low affinity for that particular site. K_e values of antagonists have not yet been determined in this assay. The advantages of this assay are that one measures activity in tissue containing a single receptor type, so that the use of selective antagonists is not necessary to clearly identify the site of action. In addition, GTPγS binding seems to clearly identify the efficacy of compounds. For instance, compounds such as buprenorphine and pentazocine can easily be identified as partial agonists.

The values listed in each of these tables have also been incorporated into NIDA's Medications Development Database. NIDA's OTDP and CTDP programs are still active, and we encourage the delivery of compounds into these programs for the continued identification of potential addiction medications.

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Table 1

AFFINITIES OF STANDARD COMPOUNDS AT DOPAMINE AND SEROTONIN RECEPTORS

	$K_{0.5}$ ± S.D. (nM) and Hill Coefficient						
Cold Ligand	D_1 [^{3}H]SCH 23390	D_2 [^{3}H]YM-09151-2	D_3 [^{3}H]YM-09151-2	5-HT_{1A} [^{3}H]8-OH-DPAT	5-HT_{2A} [^{3}H]Ketanserin	5-HT_{2C} [^{3}H]Mesulergine	5-HT_3 [^{3}H]GR65630
d-Amphetamine	>10,000	>10,000	>10,000	6606 ± 1327 0.9	>10,000	>10,000	>10,000
SKF-82958	22 ± 3.0 0.7	136 ± 64.3 0.6	68 ± 5.9 1	1781 ± 383 1	1295 ± 19.1 0.9	4626 ± 764 1	>10,000
Apomorphine	400 ± 55.3 0.8	42 ± 8.2 1.6	27 ± 6.3 1	4929 ± 3048	4377 ± 1217 1	1103 ± 345 1	>10,000
(+)Bromocriptine	2070 ± 392 1.3	8.2 ± 1.1 1.2	7.1 ± 1.5 1.5	25 ± 14.7 2.1	117 ± 8.4 1.4	4674 ± 256	>10,000
(+)Butaclamol	4.2 ± 1.55 1.1	1 ± 0 1.3	1.4 ± 0 0.9	528 ± 162 0.7	5.2 ± 1.2 1.1	1064 ± 338 1	>10,000
Carbamazepine	>10,000	>10,000		>10,000	>10,000	>10,000	>10,000
CGS-12066B	1529 ± 700 1.4	1739 ± 343 1.5	580 ± 281 1.4	44 ± 0.45 1.1	3134 ± 1347 1.5	6601 ± 574 1.1	>10,000
Chlorpromazine	44 ± 1.4 0.8	3 ± 0.65 0.8	1.8 ± 0.25 1.1	3115 ± 260 0.8	3.6 ± 1.7 0.8	39 ± 2.4 1.1	820 ± 13.9 3.3
Clomipramine	219 ± 5.1 1	162 ± 2 0.8	30 ± 5.6 1	>10,000	11 ± 2.6 0.8	52 ± 13.4 1.1	985 ± 302 1
Cocaine	>10,000*	>10,000		>10,000	>10,000	>10,000	>10,000
Cyproheptadine	117 ± 14.6 0.9	112 ± 53 1	8 ± 2.8 0.5	59 ± 23.6 0.9	0.7 ± 0.1 1.2	15 ± 3.7 1	228 ± 23.3 1.1
Deprenyl	>10,000	>10,000		>10,000	5638 ± 1350 1.1	>10,000	>10,000
Desipramine	5465 ± 461 0.6	1561 ± 237 1.6		>10,000	106 ± 8.3 0.9	748 ± 57.4 1.1	4402 ± 385 1.6
Dihydroergotamine	2779 ± 186 1	5 ± 0.8 1.1	16 ± 3.4 1	1.5 ± 0.55 1.6	38 ± 14.1 1.7	298 ± 115 1	>10,000

Table 1 (continued)

AFFINITIES OF STANDARD COMPOUNDS AT DOPAMINE AND SEROTONIN RECEPTORS

	$K_{0.5}$ ± S.D. (nM) and Hill Coefficient						
Cold Ligand	D_1 [^{3}H]SCH 23390	D_2 [^{3}H]YM-09151-2	D_3 [^{3}H]YM-09151-2	5-HT_{1A} [^{3}H]8-OH-DPAT	5-HT_{2A} [^{3}H]Ketanserin	5-HT_{2C} [^{3}H]Mesulergine	5-HT_3 [^{3}H]GR65630
L-DOPA	>10,000	>10,000		>10,000	>10,000	>10,000	>10,000
Dopamine	4470 ± 1598 0.8	422 ± 9.2 0.7	20 ± 1.2 0.6	8248 ± 1454 1	>10,000	>10,000	>10,000
8-OH-DPAT	>10,000	1788 ± 265		6.9 ± 2.6 0.6	>10,000	>10,000	>10,000
S(-)-Eticlopride	>10,000	0.1 ± 0 1.3	0.1 ± 0.05 0.8	1790 ± 160 1.2	705 ± 76.8 0.8	>10,000	>10,000
cis(Z)Flupentixol	3 1.2	1.5 ± 0.2 0.9	1.7 ± 1.3 1.1	8028 ± 159 0.6	13 ± 0.35 1.2	295 ± 15.5 1.2	>10,000
Fluphenazine	7 ± 1.4 1.2	0.9 ± 0.15 1	0.9 ± 0.1 1	2829 ± 1135 0.8	17 ± 1.8 1.3	1011 ± 331 1.1	>10,000
GBR-12909	>10,000	737 ± 231 1.1	109 ± 44.9 0.7	4677 ± 598 0.9	161 ± 10.2 1.1	>10,000	>10,000
GR-38032F	>10,000	>10,000		>10,000	>10,000	>10,000	15 ± 1.9 0.4
Haloperidol	58 ± 5.3 1	0.5 ± 0 1	2.1 ± 0.85 0.5	5084 ± 956 0.7	34 ± 5.2 0.7	>10,000	>10,000
Ibogaine	>10,000	>10,000		>10,000	>10,000	>10,000	>10,000
ICS 205-930	>10,000	>10,000		>10,000	5607 ± 240 1	>10,000	0.5 ± 0.25 0.9
Idazoxan	>10,000	>10,000		662 ± 216 1.1	>10,000	>10,000	>10,000
Imipramine	>10,000	726 ± 134 1.1	387 ± 108 0.9	>10,000	102 ± 8.0 1.1	106 ± 11.7 1.3	3651 ± 238 0.7
Ketanserin	464 ± 90.2 1.1	>10,000		>10,000	1.6 ± 0.05 1	69 ± 16.4 1.3	>10,000

Table 1 (continued)

AFFINITIES OF STANDARD COMPOUNDS AT DOPAMINE AND SEROTONIN RECEPTORS

	$K_{0.5}$ ± S.D. (nM) and Hill Coefficient						
Cold Ligand	D_1 [^{3}H]SCH 23390	D_2 [^{3}H]YM09151-2	D_3 [^{3}H]YM09151-2	5-HT_{1A} [^{3}H]8-OH-DPAT	5-HT_{2A} [^{3}H]Ketanserin	5-HT_{2C} [^{3}H]Mesulergine	5-HT_3 [^{3}H]GR65630
MDL-72222	>10,000	>10,000		>10,000	2852 ± 1318 0.9	>10,000	14 ± 1.5 0.9
(-)MDA	>10,000	>10,000		>10,000	3296 ± 2104 0.5	2598 ± 1476 0.9	>10,000
(-)MDMA	>10,000	>10,000		>10,000	3911 ± 81.9 1	>10,000	>10,000
(+)Methamphetamine	>10,000	>10,000		>10,000	>10,000	>10,000	>10,000
2-Methyl-5-HT	>10,000	>10,000		3074 ± 72.2 0.9	>10,000	1367 ± 184 1.4	995 ± 80.0 1.1
Methylphenidate	>10,000	>10,000		>10,000	>10,000	>10,000	>10,000
Metoclopromide	>10,000*	64 ± 38.4 1	16 ± 5.1 0.7	>10,000	2063 ± 117 0.9	3859 ± 62.6 1.2	353 ± 62.3 1.3
Mianserin	426 ± 29.2 0.8	1274 ± 380 1.5		2592 ± 185 0.8	2.3 ± 0.05 1.1	11 ± 0.05 1.2	300 ± 72.8 1.1
NAN-190	4510 ± 911 1	47 ± 12.6 0.8	3.4 ± 1.4 0.4	3 ± 1.8 0.8	549 ± 79.6 1.3	4117 ± 843 1	>10,000
Nomifensine	>10,000	>10,000		1183 ± 261 1	874 ± 203 1	>10,000	>10,000
Norepinephrine	>10,000	>10,000		>10,000	>10,000	>10,000	
Phentolamine	>10,000	>10,000		2151 ± 183 0.7	222 ± 33.6 1	459 ± 82.7 1	4294 ± 407 1.1
Pimozide	>10,000*	2.2 ± 0.45 1	2.3 ± 1.0 1.8	650 ± 62.2 1.2	49 ± 0.8 1.2	5787 ± 1679 1.3	3292 ± 108 3.2
S(-)-3-PPP	>10,000*	192 ± 11.4 1	262 ± 25.6 1.1	4174 ± 1706 0.4	5988 ± 797 1	>10,000	>10,000
(+/-)Propranolol	>10,000*	>10,000		272 ± 96.5 1	1047 ± 321 0.6	2457 ± 137 1	>10,000

Table 1 (continued)

AFFINITIES OF STANDARD COMPOUNDS AT DOPAMINE AND SEROTONIN RECEPTORS

	$K_{0.5}$ ± S.D. (nM) and Hill Coefficient						
Cold Ligand	D_1 [^{3}H]SCH 23390	D_2 [^{3}H]YM-09151-2	D_3 [^{3}H]YM-09151-2	5-HT$_{1A}$ [^{3}H]8-OH-DPAT	5-HT$_{2A}$ [^{3}H]Ketanserin	5-HT$_{2C}$ [^{3}H]Mesulergine	5-HT$_3$ [^{3}H]GR65630
Quinpirole	>10,000	1185 ± 265 0.5	43 ± 19.7 1	1713 ± 285 1.2	>10,000	>10,000	>10,000
Quipazine	>10,000	>10,000		>10,000	92 ± 19.2 0.4	653 ± 58.8 1.2	3.2 ± 0.9 1.1
Reserpine	3849 ± 1297	586 ± 339 1.7	598 ± 51.7 3.9	1832 ± 694 1.7	3057 ± 231	3098 ± 267 2.1	>10,000
Ritanserin	933 ± 371 0.9	84 ± 46.2 1.1	24 ± 3 1.8	2919 ± 45.9 0.9	4.7 ± 1.6 1.1	11 ± 7.3 1.9	>10,000
R(+)SCH-23390	0.8 ± 0.1 1.1	431 ± 9.2 1.1	2421 ± 417 1.5	661 ± 172 0.6	12.2 ± 0.85 1	51 ± 3.8 0.8	3912 ± 1904 1.3
Serotonin	>10,000	>10,000		1.3 ± 0.15 1.1	96 ± 10.0 0.6	44 ± 5.8 0.7	292 ± 74.8 1
(+/-)SKF-38393	987 ± 56.7 0.9	>10,000	>10,000	3096 ± 0.35 0.8	6160 ± 1176 1	>10,000	>10,000
SKF-77434	73 ± 2.0 0.9	580 ± 25 0.6	10 ± 0.35 0.7	2107 ± 1084 1.7	2700 ± 78.6 1.3	3037 ± 387 1.1	
SKF-81297	112 ± 13.9 1.2	>10,000	792 ± 153 1.1	5516 ± 1888 1.4	3083 ± 977 1.2	1510 ± 781 1.4	
Spiperone	577 ± 50.8 1	0.1 ± 0 1.2	0.2 ± 0.05 1.5	61 ± 36.6 0.7	0.6 ± 0.15 1.1	4094 ± 1778 1.2	>10,000
Sulpiride	>10,000*	4.2 ± 1.8 0.8	15 ± 2.4 1	>10,000	>10,000	>10,000	>10,000
Tranylcypromine	>10,000	>10,000		5963 ± 412 0.7	>10,000	>10,000	>10,000
YM-09151-2	2602 ± 1066 1.99	0.1 ± 0.05 1.1	0.2 ± 0.1 1.5	15 ± 5.4 1.2	58 ± 5.3 0.7	3118 ± 2070 1.2	526 ± 7 0.9
Yohimbine	>10,000*	280 ± 52.1 1	2489 ± 521 1.1	642 ± 309 1.1	2258 ± 98.1 0.9	>10,000	>10,000
Zimelidine	>10,000*	1874 ± 38.6 0.9		>10,000	875 ± 329 1	482 ± 9.3 1.1	>10,000

Table 2

AGONIST POTENCIES FOR STIMULATION OF cAMP ACCUMULATION IN C6D1L (Low Expressor) AND C6D1H (High Expressor) CELLS

	C6D1L		C6D1H	
Compound	**EC_{50} (nM)**	**% Max Stim.**	**EC_{50} (nM)**	**% Max. Stim.**
Apomorphine	180	92		
Dopamine	52	100	2.3	100
SKF-38393	44	34	6.4	95
SKF-77434	22	10	5.6	89
SKF-81297	3.4	113	0.14	94
SKF-82958	5.2	88		

Table 3

AGONIST POTENCIES FOR STIMULATION OF MITOGENESIS IN CHOp-D_2 and D_3 CELLS

Compound	D_2 EC_{50} (nM)	% Max Stim	D_3 EC_{50} (nM)	% Max Stim
Apomorphine	11.00 ± 3.75	66	8.3 ± 2	100
(+)Bromocriptine	0.34 ± 0.2	81	23.0 ± 12	119
Dihydroergocristine	0.82 ± 0.015	99	22.0 ± 2	98
Dihydroergotamine	1.20 ± 0.48	59	3.1 ± 0.7	100
Dopamine	65.00 ± 15	90	6.1 ± 0.4	100
N-0437	0.45 ± 0.28	76	1.4 ± 0.4	90
Quinpirole	19.00 ± 16	100	8.4 ± 5.74	100
S(-)-3-PPP	64.00 ± 7	90		
SKF-82958	158.00 ± 56.5	52		
7-OH-DPAT	2.80 ± 0.55	102	1.0 ± 0.24	86
Terguride	0.28 ± 0.13	96	0.72 ± 0.06	88

Table 4

BIOASSAY RESULTS AT 5-HT_{2A} AND 5-HT_3 RECEPTORS

	RAT AORTA SPIRAL 5-HT_{2A}			GUINEA PIG ILEUM 5-HT_3		
COMPOUND	ED_{50} [μM] Agonist	DR with Ketanserin	K_e [nM] Antagonist	ED_{50} [μM] Agonist	DR with ICS 205-930	K_e [nM] Antagonist
d-Amphetamine				[a]		No inhibition from 10^{-8} to 10^{-5} M
(+)Bromocriptine			28.62 ± 4.65 (4)			
(+)Butaclamol	[a]		0.27 ± 0.10 (4)			
Chlorpromazine			4.04 ± 1.45 (5)			
Clomipramine			10.31 ± 4.87 (4)			
Cocaine	[a]		No inhibition from 10^{-8} to 10^{-5} M	[a]		1,517 ± 585 (7)
Cyproheptadine			0.017 ± 0.004 (4)			9.46 ± 4.04[b] (4)
Desipramine			225.23 ± 72.80 (4)			
Dihydroergotamine			1.11 ± 0.54 (5)			
cis(Z)Flupentixol	[a]		2.82 ± 1.33 (6)			
Fluphenazine			5.64 ± 2.47 (4)			
GBR-12909	[a]		41.84 ± 27.26 (7)			
Granisetron						3.85 ± 1.42 (8)

[a]No agonist activity was found from 10^{-9} to 10^{-5}M.

[b]There was a maximum depression at each concentrations, studied.

Table 4 (continued)

BIOASSAY RESULTS AT 5-HT_{2A} AND 5-HT_3 RECEPTORS

	RAT AORTA SPIRAL 5-HT_{2A}			GUINEA PIG ILEUM 5-HT_3		
COMPOUND	ED_{50} [μM] Agonist	DR with Ketanserin	K_e [nM] Antagonist	ED_{50} [μM] Agonist	DR with ICS 205-930	K_e [nM] Antagonist
GR-38032F						62.52 ± 16.0 (14)
Haloperidol	a		18.57 ± 4.02 (3)			
Imipramine			172.85 ± 74 (4)			
ICS 205-930						9.51 ± 1.13 (11)
Ketanserin			0.68 ± 0.31 (4)			
Mianserin			0.38 ± 0.18 (7)			352.84 ± 130.95[c] (3)
MDL 72222						272 ± 89 (6)
Phentolamine			552.19 ± 178 (8)			
Pimozide			8.61 ± 2.63 (5)			
Quipazine	0.302 ± 0.018 (3)			0.31 ± 0.04 (3)		
Ritanserin	a		0.026 ± 0.01 (4)			
R(+)SCH-23390	a		7.26 ± 1.72 (6)			

[a]No agonist activity was found.

[c]There was a maximum depression at 2.5 x 10^{-6} M concentration, studied.

Table 4 (concluded)

BIOASSAY RESULTS AT 5-HT_{2A} AND 5-HT_3 RECEPTORS

	RAT AORTA SPIRAL 5-HT_{2A}			GUINEA PIG ILEUM 5-HT_3		
COMPOUND	**ED_{50} [μM] Agonist**	**DR with Ketanserin**	**K_e [nM] Antagonist**	**ED_{50} [μM] Agonist**	**DR with ICS 205-930**	**K_e [nM] Antagonist**
Serotonin	0.447 ± 0.26 (11)			0.64 ± 0.25[d] (6)		
2-Me-Serotonin				2.95 ± 1.29 (15)		
Spiperone			0.38 ± 0.11[e] (6)			
YM-09151-2			17.87 ± 5.57 (8)			254.79 ± 58.61[b] (4)

[b]There was a maximum depression at each concentrations, studied.

[d]Determined in the presence of 100 nM ketanserin.

[e]EDTA was used in the experiment instead of ascorbic acid.

Table 5

AFFINITIES OF STANDARD COMPOUNDS AT μ/δ/κ-OPIOID RECEPTORS OF GUINEA-PIG BRAIN MEMBRANES AND HUMAN RECEPTORS ON CHO CELLS

	K_i (nM)					
Cold Ligand	μ in μ-CHO [^{3}H]DAMGO	μ in GP Brain [^{3}H]DAMGO	δ in δ-CHO [^{3}H]DPDPE-Cl	δ in GP Brain [^{3}H]DPDPE-Cl	κ_1 in κ-CHO [^{3}H]U69,593	κ_1 in GP Brain [^{3}H]U69,593
DAMGO	0.5 ± 0.05	1.1 ± 0.2	300.0 ± 58.6	180.4 ± 16	305.5 ± 46	1,841 ± 22
Morphine - sulfate	1.1 ± 0.05	2.0 ± 0.3	140.0 ± 1.5	50.0 ± 0.6	46.9 ± 14.5	33.9 ± 9
Normorphine-$HClO_4$	1.7 ± 0.25	3.9 ± 0.03	85.5 ± 1.0	60.5 ± 0.3	16.3 ± 2.2	64.5 ± 14
Fentanyl - HCl	0.7 ± 0.3	1.0 ± 0.1	152.7 ± 38.3	73.8 ± 3.5	84.8 ± 19.4	151.2 ± 5.2
Etonitazene	0.2 ± 0.1	1.6 ± 0.15	184.6 ± 121	141.9 ± 1.3	116.3 ± 11.7	595.0 ± 9.2
PL017	7.0 ± 1.0	8.1 ± 0.1	>10,000	>10,000	>10,000	>10,000
Dihydromorphine	1.7 ± 0.4	0.8 ± 0.2	203.4 ± 67.2	46.7 ± 4.9	83.8 ± 6.7	79.0 ± 8.7
Codeine Sulfate	135.2 ± 10.7	152.0 ± 33	>10,000	>10,000	-	>10,000
(-)Methadone - HCl	0.6 ± 0.2	1.4 ± 0.05	132.2 ± 10.7	37.3 ± 2.3	323.5 ± 18.3	728.0 ± 120
Nalmefene - HCl	0.3 ± 0.15	0.3 ± 0.08	7.3 ± 3.6	2.6 ± 0.1	0.3 ± 0.15	0.3 ± 0.1
Levorphanol -tartarate	0.3 ± 0	0.3 ± 0.02	14.7 ± 3.2	4.2 ± 0.3	1.5 ± 0.25	3.4 ± 0.7
Diprenorphine - HCl	0.8 ± 0.05	0.2 ± 0.06	0.5 ± 0.1	0.3 ± 0.05	0.2 ± 0.05	0.4 ± 0.2
Buprenorphine	1.5 ± 0.8	1.3 ± 0.15	4.5 ± 0.4	1.6 ± 0.07	0.8 ± 0.05	1.5 ± 0.25
CTAP - NH_2	2.3 ± 0.65	0.5 ± 0.05	365 ± 82	6.5 ± 1.3	>10,000	1,054 ± 4

Table 5 (continued)

AFFINITIES OF STANDARD COMPOUNDS AT μ/δ/κ-OPIOID RECEPTORS OF GUINEA-PIG BRAIN MEMBRANES AND HUMAN RECEPTORS ON CHO CELLS

	K_i (nM)					
Cold Ligand	μ in μ-CHO [^{3}H]DAMGO	μ in GP Brain [^{3}H]DAMGO	δ in δ-CHO [^{3}H]DPDPE-Cl	δ in GP Brain [^{3}H]DPDPE-Cl	κ_1 in κ-CHO [^{3}H]U69,593	κ_1 in GP Brain [^{3}H]U69,593
(-)Naloxone - HCl	1.4 ± 0.05	1.5 ± 0.02	67.5 ± 40	19.8 ± 0.7	2.5 ± 0.3	3.8 ± 0.9
Naltrexone - HCl	0.2 ± 0	0.4 ± 0.05	10.8 ± 3.0	6.5 ± 1.3	0.4 ± 0.1	0.6 ± 0.1
β-FNA - HCl	0.3 ± 0.05	0.4 ± 0.05	12.8 ± 0.95	7.7 ± 2.4	0.2 ± 0	0.9 ± 0.05
TIPPΨ	>10,000	>10,000	1.0 ± 0.7	0.6 ± 0.1	>10,000	>10,000
DPDPE - Cl	-	180.0 ± 1.2	0.3 ± 0.05	0.3 ± 0.1	-	>10,000
DPDPE - OH	503.6 ± 10.0	>10,000	1.7 ± 0.1	2.8 ± 0.04	>10,000	>10,000
DSLET - OH	6.9 ± 0.7	20.6 ± 3.6	0.5 ± 0.1	0.5 ± 0.1	>10,000	>10,000
DADLE - OH	1.8 ± 0.25	3.2 ± 0.05	0.7 ± 0.1	0.3 ± 0.01	>10,000	>10,000
Deltorphin-II	2,082 ± 998		1.5 ± 0.1		>10,000	>10,000
Leu-Enkephalin	7.4 ± 0.45	21.7 ± 1.4	2.1 ± 0.4	1.6 ± 0.5	>10,000	>10,000
β-Endorphin - OH	1.6 ± 0.1	2.3 ± 0.5	5.4 ± 0.45	1.6 ± 0.45	11.4 ± 1.2	43.5 ± 4.1
Naltrindole	6.3 ± 2.3	0.2 ± 0.01	0.2 ± 0.05	0.09 ± 0	10.1 ± 0.65	7.8 ± 0.1
BNTX	1.7 ± 0.05	1.9 ± 0.5	3.7 ± 2.5	4.2 ± 0.1	3.7 ± 1.35	7.1 ± 1.7
NTB	12.5 ± 2.1	6.5 ± 1.1	0.1 ± 0.04	0.06 ± 0	4.1 ± 0.7	10.2 ± 2.4
U69,593	1,145 ± 335	692.0 ± 97	>10,000	1,358± 118	0.3 ± 0	0.7 ± 0.05

Table 5 (continued)

AFFINITIES OF STANDARD COMPOUNDS AT μ/δ/κ-OPIOID RECEPTORS OF GUINEA-PIG BRAIN MEMBRANES AND HUMAN RECEPTORS ON CHO CELLS

	K_i (nM)					
Cold Ligand	μ in μ-CHO [^{3}H]DAMGO	μ in GP Brain [^{3}H]DAMGO	δ in δ-CHO [^{3}H]DPDPE-Cl	δ in GP Brain [^{3}H]DPDPE-Cl	κ_1 in κ-CHO [^{3}H]U69,593	κ_1 in GP Brain [^{3}H]U69,593
U50,488H	290.0 ± 14.3	294.0 ± 49	>10,000	>10,000	0.2 ± 0.05	0.2 ± 0.05
(-)EKC	0.3 ± 0.15	0.4 ± 0.04	3.4 ± 0	2.0 ± 0.07	0.1 ± 0.03	0.1 ± 0.01
(-)Bremazocine	0.2 ± 0.04	0.1 ± 0	0.9 ± 0.5	0.3 ± 0.07	0.03 ± 0.005	0.1 ± 0.03
Etorphine - HCl	0.3 ± 0.05	1.5 ± 0.35	1.5 ± 0.6	0.7 ± 0.07	0.2 ± 0.05	0.8 ± 0.20
Nalorphine - HCl	1.2 ± 0.2	1.9 ± 0.25	44.5 ± 2.9	19.3 ± 4.3	0.8 ± 0.05	1.7 ± 0.1
Nor-BNI $(HCl)_2$	21.0 ± 5	8.3 ± 1.2	5.7 ± 0.9	6.3 ± 0.4	0.2 ± 0.05	0.3 ± 0.10
Dynorphin (1-8)-OH	4.0 ± 0.9		3.6 ± 0.05	1.5 ± 0.7	0.2 ± 0.1	1.4 ± 0.4
Dynorphin (1-11) - OH	1.5 ± 0.5	2.3 ± 0.5	10.4 ± 0	1.8 ± 0.2	0.2 ± 0.05	0.1 ± 0
Dynorphin (1-13) - OH	4.5 ± 0.1	3.3 ± 0.1	14.3 ± 0.8	16.3 ± 0.9	0.5 ± 0.05	0.4 ± 0.1
Dynorphin (1-17) - OH	7.7 ± 2.2	8.1 ± 0.2	42.7 ± 8.6	5.8 ± 0.8	1.7 ± 0.85	1.7 ± 0
Dynorphin B - OH	3.0 ± 0.6	5.5 ± 0.2	14.7 ± 5.1	4.2 ± 0.25	0.3 ± 0.05	0.9 ± 0.1
(-) Cyclazocine	0.1 ± 0	0.1 ± 0.0	0.8 ± 0.05	0.6 ± 0.05	0.1 ± 0	0.1 ± 0.02
(-) Pentazocine	3.9 ± 0.7	5.7 ± 0.9	49.3 ± 15.1	32.7 ± 3.15	2.2 ± 0.2	4.4 ± 0.1
NalBzoH	1.8 ± 0.45	0.2 ± 0	6.0 ± 1.4	1.4 ± 0.13	0.3 ± 0.1	0.4 ± 0.1
(-) WIN 44,441	0.1 ± 0	0.1 ± 0.03	1.4 ± 0.5	0.9 ± 0.07	0.2 ± 0.1	0.2 ± 0

Table 6

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50} (nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
DAMGO	8.25 ± 2.0 (13)	4.98 ± 0.3 (4)	25.31 ± 2.54 (4)	1.000	1.74 ± 0.14 (6)	27.67 ± 4.52 (6)	0.002	177.60 ± 134 (7)	0.93 ± 0.10 (4)	N.D.	
Morphine	24.75 ± 2.4 (4)	4.27 ± 0.18 (2)	30.67 ± 1.66 (2)	0.707	1.05 ± 0.06 (2)	222.22 (1)	0.003	2,131 ± 904 (4)	0.92 ± 0.38 (4)	N.D.	
Normorphine	47.30 ± 13 (15)	3.02 ± 0.28 (4)	50.25 ± 6.6 (4)	0.500	1.90 ± 0.39 (4)	26.47 ± 13.6 (4)	0.002	511.9 ± 51 (4)	1.06 ± 0.07 (4)	8.38 ± 0 (2)	0.0025
Dihydromorphine	42.39 ± 6.61 (3)	12.46 ± 0.15 (2)	17.46 ± 0.23 (2)	1.354	1.12 ± 0.18 (2)			8,113 ± 2,729 (3)	2.67 ± 0.82 (2)		
Fentanyl	1.86 ± 0.64 (8)	3.12 ± 0.82 (4)	53.86 ± 23.10 (4)	0.403	1.18 ± 0.09 (2)	132.6 ± 69.6 (2)	0.001	18.07 ± 3.0 (3)	0.87 ± 0.07 (3)	N.D.	
Etonitazene	0.89 ± 0.16 (4)	10.38 ± 0.67 (2)	10.69 ± 0.76 (2)	2.028	1.70 ± 0.27 (2)	30.84 ± 11.84 (2)	0.002	1.85 ± 0.07 (2)	0.82 ± 0.11 (2)	N.D.	
A-PL017	18.11 ± 2.83 (4)	7.19 ± 0.74 (2)	16.29 ± 1.96 (2)	1.331	1.49 ± 0.15 (2)	43.27 ± 13.2 (2)	0.001	240.5 ± 63 (2)	0.89 ± 0.11 (4)	N.D.	
(-)Methadone	45.83 ± 3.6 (3)	1.19 ± 0.14 (4)	408 ± 100 (3)	0.062	1.20 ± 0.06 (2)	108.3 ± 35.4 (2)	0.001	452.5 ± 251 (2)	0.94 ± 0.09 (2)	N.D.	
Oxycodone	323.80 ± 116 (4)	2.30 ± 0.25 (2)	78.66 ± 15 (2)	0.322	1.45 ± 0.10 (3)	45.84 ± 11.5 (3)	0.001	6,330 ± 3,140 (3)	0.79 ± 0.08 (2)	N.D.	

Table 6 (continued)

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50} (nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
Nalorphine	29.20 ± 15[a] (9)	0.90 ± 0.14 (2)	N.D.		643.9 ± 83.5 (2)	0.03 ± 0.004 (2)	2.000	a			
β-Endorphin	59.43 ± 6.26 (4)	5.86 ± 0.79 (2)	20.87 ± 3.37 (2)	0.928	4.24 ± 1.55 (2)	6.98 ± 3.34 (2)	0.007	67.99 ± 19.0 (3)	7.98 ± 2.3 (4)	0.156 ± 0.05 (4)	0.147
NalBzoH	b				b			b			
Nalmefene	c				c			c			
Naloxone	d				d			d			
Naltrexone	e				e			e			
CTAP	f										
Buprenorphine	8.13 ± 3.55[g] (4)							21.39 ± 14.3 (3)			

[a]Nalorphine is a κ-opioid receptor agonist and a μδ receptor antagonist. In the GPI the μ antagonist activity was determined in the presence of 20 nM Nor-BNI. Its pA_2 value at μ is 7.49/-0.87, and at δ is 6.79/-1.05.

[b]NalBzoH is an antagonist at all three opioid receptors. The pA_2 value at μ is 8.81/-1.02, at δ is 7.76/-0.96, and at κ is 7.76/-1.19.

[c]Nalmefene is an antagonist at all three opioid receptors. The pA_2 value at μ is 9.38/-1.05, at δ is 7.82/-1.15, and at κ is 8.48/-1.01.

[d]Naloxone is an antagonist at all three opioid receptors. The pA_2 value at μ is 8.51/-1.07, at δ is 7.30/-1.05, and at κ is 7.73/-0.99.

[e]Naltrexone is an antagonist at all three opioid receptors. The pA_2 value at μ is 9.19/-1.08, at δ is 8.08/-1.09, and at κ is 8.11/-1.03.

[f]CTAP is a very selective μ receptor antagonist. Its pA_2 value is 7.65 and the slope is -1.02.

[g]The agonist activity could not be reversed neither with CTAP nor with nor-BNI. In β--FNA treated GPI the compound is a κ antagonist. The pA_2 value at the κ is 9.16/-1.28.

Table 6 (continued)

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50} (nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
DPDPE	4,130 ± 870 (6)	5.84 ± 2.6 (3)	25.83 ± 15.3 (3)	0.980	1.54 ± 0.31 (4)	50.68 ± 35.1 (4)	0.001	4.11 ± 1.32 (80)	53.11 ± 17.6 (8)	0.021 ± 0.007 (8)	1.000
DSLET	59.30 ± 3.78 (4)	5.36 ± 1.35 (4)	24.50 ± 6.9 (4)	1.030	1.72 ± 0.13 (4)	28.55 ± 5.6 (4)	0.002	1.23 ± 0.40 (11)	46.84 ± 8.0 (3)	0.022 ± 0.004 (3)	0.955
DTLET	41.70 ± 14.52 (4)	5.33 ± 0.04 (2)	23.12 ± 0.19 (2)	0.938	1.57 ± 0.03 (2)	35.13 ± 1.74 (2)	0.002	0.32 ± 0.14 (4)	31.25 ± 6.7 (4)	0.034 ± 0.007 (4)	0.612
DADLE	13.39 ± 7.4 (3)	4.33 ± 0.60 (2)	30.58 ± 5.5 (2)	0.709	1.53 ± 0.02 (2)	38.13 ± 1.54 (2)	0.002	1.60 ± 0.30 (4)	16.22 ± 4.01 (3)	0.069 ± 0.016 (3)	0.304
Leu - Enkephalin*	87.35 ± 9.90 (4)	4.63 ± 1.26 (2)	29.38 ± 10.26 (2)	0.659	1.94 ± 0.04 (2)	21.41 ± 0.81 (2)	0.002	7.38 ± 2.40 (6)	28.07 ± 4.45 (6)	0.038 ± 0.001 (6)	0.577
Met - Enkephalin*	27.44 ± 3.75 (4)	5.08 ± 0.17 (2)	24.50 ± 1.06 (2)	0.791	6.07 ± 0.26 (2)	3.95 ± 0.20 (2)	0.012	1.52 ± 0.26 (3)	13.63 ± 2.74 (4)	0.082 ± 0.016 (4)	0.305
Dynorphin (1-9)*	4.69 ± 2.34 (4)	1.13 ± 0.20 (2)	357.14 (1)	0.054	75.48 ± 26.20 (2)	0.29 ± 0.10 (2)	0.161	12.22 ± 2.59 (4)	5.71 ± 2.90 (4)	0.281 ± 0.154 (4)	0.082
Naltrindole	h				h			h			
NTB					i			i			

*Experiments with dynorphins, Met- and Leu-enkephalins were done in the presence of enzyme inhibitors.

[h]Naltrindole is an antagonist at all three opioid receptors. The pA_2 value at μ is 7.53/-1.13, at δ is 10.92/-0.83, and at κ is 7.61/-0.85.

[i]NTB is an antagonist at all three opioid receptors. The pA_2 value at μ is 7.95/-0.94, at δ is 10.55/-1.03, and at κ is 7.22/-1.02.

Table 6 (continued)

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50}(nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
BNTX	j				j			j			
TIPPΨ								k			
U 69,593	1.66 ± 0.63 (12)	0.68 ± 0.11 (4)	N.D.		363.0 ± 97.0 (7)	0.06 ± 0.017 (8)	1.000	208.30 ± 139 (8)	0.40 ± 0.10 (4)	N.D.	
U 50,488H	1.57 ± 0.50 (6)	0.52 ± 0.06 (2)	N.D.		430.1 ± 85.7 (4)	0.05 ± 0.01 (4)	1.250	94.33 ± 16.2 (3)	0.94 ± 0.20 (2)	N.D.	
(-)Bremazocine	0.067 ±0.015 (4)	0.83 ±0.12 (2)	N.D.		226.3 ± 34.3 (2)	0.09 ± 0.014 (2)	0.445	I			
Etorphine	0.055 ±0.016 (4)	1.54 ±0.04 (2)	185.76 ± 14.6 (2)	0.104	2.34 ±0.18 (2)	15.03 ± 2.02 (2)	0.003	1.39 ± 0.20 (4)	0.82 ± 0.11 (4)	N.D.	
(±)EKC	0.44 ± 0.14 (8)	0.60 ± 0.09 (4)	N.D.		61.20 ± 6.8 (8)	0.36 ± 0.11 (8)	0.170	18.98 ± 7.0 (8)	0.88 ± 0.09 (4)	N.D.	
(-)EKC	0.15 ± 0.01 (4)	0.62 ± 0.01 (2)	N.D.		35.09 ± 8.47 (2)	0.61 ± 0.15 (2)	0.076	5.31 ± 1.89 (4)	0.90 ± 0.15 (4)	N.D.	
CI -977	0.15 ± 0.06 (6)	0.64 ± 0.10 (2)	N.D.		275.90 ± 25.0 (3)	0.07 ± 0.06 (3)	0.630	3.71 ± 2.40 (4)	0.89 ± 0.10 (4)	N.D.	

[j]BNTX is an antagonist at all three opioid receptors. The pA_2 value at in is 8.56/-0.93, at δ is 8.90/-1.01, and at κ is 7.43/-0.78.

[k]TIPPΨ is a very selective, competitive δ-opioid receptor antagonist. The pA_2 value at δ is 9.17/-0.99.

[l]IC_{50} could not be determined. Very shallow dose-response curve.

Table 6 (continued)

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50} (nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
CI -977	0.15 ± 0.06 (6)	0.64 ± 0.10 (2)	N.D.		275.90 ± 25.0 (3)	0.07 ± 0.06 (3)	0.630	3.71 ± 2.40 (4)	0.89 ± 0.10 (4)	N.D.	
Dynorphin (1-8)	71.76 ± 45.5 (7)	0.98 ± 0.17 (2)	N.D.		18.44 ± 4.53 (4)	1.21 ± 0.34 (4)	0.050	56.40 ± 5.0 (3)	2.77 ± 0.68 (3)	0.64 ± 0.29 (3)	0.033
Dynorphin (1-11)	1.03 ± 0.40 (4)	0.34 ± 0.02 (2)	N.D.		116.49 ± 21.2 (4)	0.18 ± 0.03 (2)	0.261	368.92 ± 56.0 (4)	0.75 ± 0.12 (4)	N.D.	
Dynorphin (1-13) OH	0.17 ± 0.07 (4)	1.05 ± 0.57 (2)	222.22 (1)	0.098	425.30 ± 40.4 (3)	0.05 ± 0.01 (4)	0.979	5.28 ± 2.2 (4)	0.89 ± 0.33 (4)	N.D.	
Dynorphin (1-13) NH_2	0.38 ± 0.18 (4)	1.33 ± 0.17 (2)	349.21 ± 179 (2)	0.056	125.81 ± 14.3 (2)	0.16 ± 0.02 (2)	0.286	7.02 ± 2.44 (4)	0.99 ± 0.09 (4)	N.D.	
Dynorphin A (1-17)	0.95 ± 0.08 (2)	1.52 ± 0.21 (2)	209.89 ± 86 (2)	0.121	102.20 ± 11.0 (2)	0.20 ± 0.02 (2)	0.302	29.30 ± 24.9 (2)	1.15 ± 0.05 (2)	7.32 ± 2.5 (2)	0.003
Dynorphin B	4.40 ± 1.54 (4)	1.08 ± 0.30 (2)	344.83 (1)	0.056	75.48 ± 26.2 (2)	0.28 ± 0.10 (2)	0.161	39.14 ± 7.39 (4)	2.10 ± 0.30 (4)	0.95 ± 0.21 (4)	0.024
Nor-BNI	[m]				[m]			[m]			

[m]Nor-BNI is a selective κ_1 antagonist. Its pA_2 value at the κ_1 receptor is 10.02 and the slope is -1.14. The pA_2 value at μ receptor is 7.26/-1.19, and at δ receptor is 7.87/-1.04.

Table 6 (concluded)

RESULTS OF STANDARD COMPOUNDS IN THE OPIATE BIOASSAYS

	Guinea Pig Ileum							Mouse Vas Deferens			
Compound	IC_{50} (nM)	DR with CTAP	K_e of CTAP	Ratio	DR with Nor-BNI	K_e of Nor-BNI	Ratio	IC_{50} (nM)	DR with Naltrindole	K_e of Naltrindole	Ratio
(-)SKF10,047	10.50 ± 3.9[n] (7)	0.44 ± 0.02 (2)	N.D.		273.10 ± 47 (2)	0.08 ± 0.01 (2)	0.800	n			
(-)Pentazocine	170.30 ± 69.2 (4)	0.73 ± 0.38 (2)	N.D.		6.10 ± 1.00 (2)	4.00 ± 0.8 (2)	0.015	o			
(-)Cyclazocine	1.05 ± 0.4 (4)	1.00 ± 0.00 (2)	N.D.		33.39 ± 25.2 (2)	0.89 ± 0.69 (2)	0.067	p			

[n] In the GPI the μ antagonist activity was determined in the presence of 20 nM Nor-BNI.The pA_2 value in the GPI is 7.69/-1.22. In the MVD from 10^{-9} to 10^{-6} M slight inhibition; from 5 x 10^{-6} to 5 x 10^{-5} M enhancement.The pA_2 value in the MVD at the μ receptor is 8.20/-1.20, and at the δ is 7.55/-0.99.

[o] IC_{50} could not be determined.

[p] IC_{50} could not be determined from 10^{-9} to 5 x 10^{-5} M (maximum inhibition = 17%).The pA_2 value in the MVD at the μ receptor is 9.02/-1.01, and at the δ is 8.23/-0.95. The experiments were done in the presence of 5 nM nor-BNI to block any agonist effect on the tissue.

Table 7

STIMULATION OF [^{35}S]GTPγS BINDING TO μ, δ, AND κ RECEPTORS

	Human μ-CHO Cell Membranes		Human δ-CHO Cell Membranes		Human κ-CHO Cell Membranes	
Cold Ligand	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation
DAMGO	13.7 ± 5.28	100	flat		4,365 ± 1,661	62 ± 21
Morphine	15.6 ± 0.5	93 ± 2.8	316.5 ± 4.9	103 ± 7	484 ± 213	62 ± 7
Normorphine	47.4 ± 11	114 ±11	418.0 ± 48.8	96 ± 24	1,443 ± 504	86 ± 3
Fentanyl	8.1 ± 0.4	100 ± 12	515.0 ± 102	86 ± 19	2,368 ± 534	30 ± 4
Etonitazene	1.0 ± 0	119 ± 19	300.5 ± 96	114 ± 23	7,312 ± 3,774	24 ± 1
PL017	97.5 ± 21.9	109 ± 22	flat			
Dihydromorphine	35.9 ± 15	109 ± 5	225 ± 128	106 ± 4	1,015 ± 347	47 ± 3
(-)Methadone	26.6 ± 14.3	116 ± 20	980 ± 99	106 ± 21	4,943 ± 400	25 ± 16
Nalmefene	flat		30.5 ± 20	66.5 ± 13	flat	
Diprenorphine	flat		0.8 ± 0.2	98.5 ± 3.5	0.26 ± 0.06	47 ± 4
Buprenorphine	2.3 ± 1.7	66 ± 36	flat		flat	
CTAP	flat		flat		flat	
(-)Naloxone	flat		flat		flat	

% Stimulation compared to DAMGO, DPDPE or U69,593, respectively.

Table 7 (continued)

RESULTS ON HUMAN μ/δ/κ-CHO CELL MEMBRANES USING GTPγS BINDING

	Human μ-CHO Cell Membranes		Human δ-CHO Cell Membranes		Human κ-CHO Cell Membranes	
Cold Ligand	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation
Naltrexone	flat		flat		flat	
β-FNA	3.1 ± 1.3	19 ± 0	flat		5.1 ± 1.4	78 ± 9
β-CNA	flat		flat		3.9 ± 1.2	52 ± 22
DPDPE	flat		1.3 ± 0.5	100	flat	
DSLET	74.6 ±15	134 ± 65	0.7 ± 0.4	116 ± 22	flat	
DADLE	14.0 ± 2.8	89 ± 15	0.6 ± 0.12	107 ± 9	12,780 ± 6,300	69 ± 9
Deltorphin-II	flat		0.35 ±0.07	134 ± 16		
Leu-Enkephalin	25.5 ± 0.8	11 ± 4	1.35 ± 0.2	104 ± 21	4,160 ± 1,683	89 ± 15
β-Endorphin	24.5 ± 3.5	116 ± 17	13.6 ± 11.8	82.5 ± 11	971 ± 175	77
Naltrindole	flat		flat		flat	
NTB	flat		flat		flat	
U69,593	flat		flat		26.15 ± 10.7	100
U50,488H	flat		flat		9.31 ± 2.54	93 ± 11
(-)EKC	1.3 ± 0.4	146 ± 85	2.3 ± 1.3	99 ± 1	0.41 ± 0.14	88 ± 11

% Stimulation compared to DAMGO, DPDPE or U69,593, respectively.

Table 7 (continued)

RESULTS ON HUMAN μ/δ/κ-CHO CELL MEMBRANES USING GTPγS BINDING

	Human μ-CHO Cell Membranes		Human δ-CHO Cell Membranes		Human κ-CHO Cell Membranes	
Cold Ligand	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation	EC_{50} (nM)	% Stimulation
(-)Bremazocine	flat		3.8 ± 1.7	101 ± 8	0.053 ± 0.008	84 ± 13
Etorphine	0.66± 0.06	117 ± 24	1.5 ± 0.2	107 ± 2	2.02 ± 0.57	95 ± 16
Nalorphine	flat		59.7 ± 22	58 ± 15	2.56 ± 0.06	14 ± 0
Nor-BNI	flat		flat		flat	
Dynorphin (1-8)	58.5 ± 27.6	105 ± 9	3.4 ± 0.7	76 ± 22	116 ± 37	94 ± 4
Dynorphin (1-9)	24.0 ± 0	96 ± 0.7	6.6 ± 1.3	84 ± 5	9.50 ± 6.0	66
Dynorphin (1-11)	43.0 ± 2.8	95 ± 2.8	39.2 ± 1.3	85 ± 5	1.43 ± 0.66	92 ± 4
Dynorphin (1-13)	68.5 ± 4.9	115	81.4 ± 10.4	120	2.46 ± 0.93	93 ± 10
Dynorphin (1-17)	65.0 ± 34	99 ± 1.4	72.0 ± 12	99 ± 3	5.65 ± 2.08	97 ± 5
Dynorphin B	63.5 ± 3.5	112 ± 23	54.8 ± 0.8	97	5.80 ± 1.4	82
(-) Cyclazocine	1.2 ± 0.07	33 ± 18	2.9 ± 1.9	82 ± 9	0.80 ± 0.2	80
	flat		9.4 ± 2.3	70 ± 9	5.38 ± 2.3	49 ± 13
(-) Pentazocine	36.0 ± 7.1	35 ± 4	148.5 ± 40.3	85 ± 10	27.5 ± 7.8	39 ± 14
NalBzoH	flat				6.14 ± 4.19	42 ± 6

% stimulation compared to DAMGO, DPDPE or U69,593, respectively.

AUTHOR INDEX

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