National Institute on Drug Abuse

Research 65

MONOGRAPH SERIES

Women and Drugs: A New Era for Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

Women and Drugs: A New Era for Research

Editors:

Barbara A. Ray, Ph.D.

Division of Clinical Research
National Institute on Drug Abuse

Monique C. Braude, Ph.D.

Division of Preclinical Research
National institute on Drug Abuse

NIDA Research Monograph 65
1986

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, Maryland 20857

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

NIDA Research Monographs are prepared by the research divisions of the National Institute on Drug Abuse and published by its Office of Science. The primary objective of the series is to provide critical reviews of research problem areas and techniques, the content of state-of-the-art conferences, and integrative research reviews. Its dual publication emphasis is rapid and targeted dissemination to the scientific and professional community.

Editorial Advisors

NIDA Research Monograph Series

Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857

Women and Drugs:
A New Era for Research

This monograph is based upon papers and discussion from the technical review on research issues related to women which took place on May 1 and 2, 1985, at Bethesda, Maryland. The review was sponsored by the Division of Clinical Research of the National Institute on Drug Abuse.

DHHS Publication No. (ADM)90-1447
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1966, Reprinted 1967, 1990

NIDA Research Monographs are indexed in the Index Medicus. They are selectively included in the coverage of American Statistics Index, BioSciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.

Preface

Barbara A. Ray and Monique C. Braude

The history of drug abuse research shares with other sciences a relative paucity of knowledge about females in particular and about gender effects in general. This bias in knowledge stems from the tradition of using male subjects for animal and human experiments and an unexamined assumption that gender is not an important experimental variable.

The Public Health Service is now charged with correcting this cumulated imbalance in knowledge, and the PHS Women's Task Force has developed specific recommendations for achieving the goal, including targets for the future of drug- and alcohol-related research. The history and significance of the Task Force is here described by Dr. Chatham, and mechanisms and guidelines for correcting gaps in knowledge about new and marketed drugs are referenced in Dr. Danello's overview of the Food and Drug Administration and its role in drug-related research.

Among the culturally embedded but inaccurate assumptions about gender is that reproductive functioning is somehow an entirely female matter. Consideration must now be given to the possible assault on both male and female gametes by drug and alcohol abuse. Not only can the female ovum possibly be damaged by substance abuse, but male sperm can likewise be damaged and subvert healthy fetal development.

Another false assumption about gender is that sex differences are relevant only to reproductive processes. Dr. Hamilton provides an extensive and well-documented story of the many ways that gender affects health, including the gonadal steroid influences on brain neurochemical substrate. A host of new discoveries make it clear that differences in brain structure and physiology exist that are attributable to a masculine or feminine patterning of hormones occurring at critical periods during development.

As the chapter by Dr. Baum makes quite clear, sex hormones are not male or female, but interact at critical stages to produce profound differences in anatomy and behavior. Dr. Baum leads us

through an intricate trail of detection to show that, in the ferret. It is ultimately estrogen that permits the formation of a male brain nucleus that then seems to permit sensitivity to testosterone, leading to characteristic male behavior. Although Dr. Baum describes brain dimorphism in the ferret, an extensive literature is emerging that strongly suggests that brain dimorphism exists between the human female and male.

For the purposes of scientific research, studying just women is as meaningless as studying just men. Rather, gender as an experimental variable needs to become standard in studies of drug abuse and drug effects. Dr. Mendelson shows us that the picture for women and drug abuse changes markedly when nature and extent figures are broken out for men and women separately. Looking only at how many substance abusers are women, their problem seems small compared to the numbers of men abusing drugs and alcohol. But among women needing mental health support services, drug and alcohol abuse problems rank second only to depressive illness. From a female perspective, substance abuse appears as an important threat to health.

Dr. Mello presents evidence indicating that women who suffer dysphoria associated with the menstrual cycle may self-medicate during the dysphoric period. That the menstrual cycle involves coordinated and repeated hormonal secretions in the central nervous system makes the female possibly a useful model for studying drugs of abuse, as abused drugs typically act on central neural events.

Going back to reanalyze epidemiologic data by gender, Dr. Clayton uses NIDA's 1982 National Survey to show certain stable differences in drug use by gender as well as a trend toward convergence in age-of-first-use for females and males. Dr. Clayton directs our attention to the changing role of women in society and sees a need to track how this may affect substance abuse patterns in the future.

For the purpose of preventing drug abuse, it is important to understand how societal, economic, and physiological pressures differ for subpopulations. Several contributors address this question. Dr. Gritz outlines the correlation between a post World War II decision by cigarette manufacturers to target the female consumer and a gradual increase in cigarette smoking by women, beginning in their teens, at a time when men were decreasing their smoking. Dr. Braude provides an overview of the many important changes in biology and life circumstances that confront the older woman, who composes approximately 60 percent of the elderly population. Dr. Braude also points out the especially high risk In this population of harmful effects resulting from the taking of multiple medications that may have unknown and possibly dangerous interactions. In a related chapter, Dr. Barry, drawing upon her geriatric expertise, gives details of the changing response to drugs that accompanies the aging process and how this differs for men and women.

Gender research is in its infancy and promises to challenge accepted ideas as the accumulating data sort fact from fiction. The NIDA conference on women and drugs and this monograph are one step in the process of opening the scientific community to new ideas and knowledge about gender as it relates to substance abuse.

Contents

The PHS Task Force on Women's Health Issues

Lois Chatham

I have been asked to convey to you the background and significance of the Public Health Service (PHS) Task Force on Women's Health Issues. As background I would like to discuss the reasons why a task force is created. It is my impression that a task force usually is created to work on a specific, well-defined problem or subject--hence the term task force. The establishment of such a work group provides visibility and enables the appointing official to cut across organizational lines for the purpose of pooling resources. The creation of a task force also usually implies speedy action.

A task force frequently is created in response to some perceived emergency or threat. The event may be a national or regional emergency, such as an outbreak of Legionnaire's disease, the eruption of Mt. St. Helen, the flooding of Johnstown, Pennsylvania, or, more recently, the outbreak of Acquired Immune Deficiency Syndrome (AIDS). On the other hand, such a group may be established in response to perceived political pressures such as the concerns of the aging, the Vietnam veterans, the handicapped, or minority populations.

The PHS Task Force on Women's Health Issues obviously was not created in response to an emergency health event. In fact, women's overall health status, like the Nation's health, has improved over the past decade. However, it also is apparent that the treatment of many chronic diseases and devastating illnesses has not improved significantly over the past decade.

Because the Task Force report was scheduled for submission to the Assistant Secretary for Health in October prior to the 1984 Presidential election, many of us wondered if the Task Force had been created in response to political pressure. However, this concern proved unfounded. To the contrary, the Task Force was the attempt of the Assistant Secretary for Health, Dr. Edward Brandt, to direct the Public Health Service to reexamine its activities for the purpose of significantly improving women's health.

To assess the significance of a task force, one must examine the organizational placement of the unit and the stature of the members. One also must assess the resources allocated to the activity. In this case, although no funds were provided, the Office of the Assistant Secretary for Health assigned a staff member to serve as Executive Secretary for the Task Force. It also is significant that the Chairperson of the Task Force is the highest ranking woman in the Public Health Service, namely, Ruth Kirschstein, M.D., Director of the National Institute of General Medical Sciences. Other Task Force members were appointed by the respective PHS agency heads. All members, by virtue of organizational location or personal characteristics, were in a position to speak for the agency they represented in matters of policy and resources. This is essential to the effective operation of such a unit.

A task force put together to work quickly on a single task faces certain dangers. First, because of the singlemindedness of the assignment, a task force may create organizational threats to existing agencies that feel the work being performed lies within their agency's scope of responsibility. Second, the task force may make impractical or impossible recommendations because of bureaucratic naivete. Third, the report may not be read by the right people, or, if read, the recommendations may not be implemented. To increase the likelihood that the recommendations of the task force would be used, all recommendations were carefully analyzed for feasibility and appropriateness by the organizational units expected to implement them.

In October, 1984, the Task Force Report was submitted to the Assistant Secretary for Health, Dr. Edward Brandt. In November, 1984, Dr. Brandt issued a memorandum to all Health and Human Services (HHS) agency heads, directing them to develop plans for implementing the Task Force recommendations. To ensure continuity and oversight of these plans, in December, 1984, the Assistant Secretary for Health established the Coordinating Committee on Women's Health Issues. Thus, in June, 1985, agency representatives reported for the first time to the Assistant Secretary for Health on the progress being made to implement the Task Force recommendations. These plans, in turn, will be reviewed by the Coordinating Committee as the first step in providing a continuing review of the implementation of the Task Force Report and Recommendations.

To give you an historical perspective, the following lists have been developed. These outline the history of the Task Force. They outline its areas of responsibility and the recommendations it has made. The chronological sequence of events is outlined below:

PHS TASK FORCE ON

WOMEN'S HEALTH ISSUES

1983

Summer

Dr. Edward Brandt, DHHS, Assistant Secretary for Health, appoints Task Force.

PHS agencies assemble information on diseases/conditions:

- Unique to women
- More prevalent in women
- More serious in women
- Having different risk factors for women

Fall

Task Force establishes six committees.

1984

January-March

PHS Regional Offices hold public hearings.

April-August

Reports and recommendations are prepared and edited.

September

Executive Summary and Recommendations plans developed by PHS agencies.

December

PHS Coordinating Committee on Women's Health Issues is established.

1985

February

Volume I of Women's Health: Report of the Public Health Service Task Force on Women's Health Issues published (USPHS 1985).

May

Volume II of Women's Health report published (USPHS 1985).

The members of the Task Force encompassed all PHS agencies, as follows:

- Office of Disease Prevention and Health Promotion (OPDHP)
- Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)
- Centers for Disease Control (CDC)
- Food and Drug Administration (FDA)
- Office of Public Affairs (OPA)
- National Institutes of Health (NIH)
- Health Resources and Services Administration (HRSA)

These agencies have divergent responsibilities, all of which address the broad mandate of the Public Health Service. For ease in implementation, recommendations were grouped according to which of the six PHS missions they most clearly addressed. The PHS missions are:

I. Promoting a Safe and Healthful Physical and Social Environment

II. Providing Services for the Prevention and Treatment of Illness

III. Conducting Research and Evaluation

IV. Recruiting and Training of Health Care Personnel

V. Educating and Informing the Public and Disseminating Research Information

VI. Designing Guidance for Legislative and Regulatory Measures

Similarly, for ease in accomplishing the task, subcommittees were formed to write reports for the full Task Force. After much thought, six subcommittees were formed as outlined below:

- Social Factors Affecting Women's Health
- Women's Physical Health and Well-Being
- Health Concerns of Older Women

- Issues Related to Alcohol and Drug Abuse and the Mental Health of Women

- Assessment of Women's Health Issues as Presented at Regional Meetings

- Inventory of Public Health Service Programs Related to Women's Health

The first four are substantive in nature. The fifth subcommittee report summarizes the recommendations made at the meetings held in the PHS regional offices, and the sixth subcommittee report is a repository of all relevant women's health activities and resources identified during the life of the Task Force.

Since the Task Force was to address health issues of women in the broadest sense, it became apparent that the Federal Government was responsible for implementing only a portion of the recommendations. Indeed, if women's health issues were to be effectively and efficiently addressed, the following sectors needed to be involved:

- The Public Health Service

- Other Federal, State, and local government agencies

- Private and voluntary organizations

- Women themselves

Below, the recommendations are displayed within the six-part mission of the Public Health Service.

I. PROMOTING A SAFE AND HEALTHFUL PHYSICAL AND SOCIAL ENVIRONMENT

A. Use the law and regulations to ensure a safe, healthful physical and social environment for all.

B. Encourage women to learn about health issues and take personal and political action to Improve their health.

II. PROVIDING SERVICES FOR THE PREVENTION AND TREATMENT OF ILLNESS

A. Make chronic disease management a priority for the Public Health Service.

B. Increase access to health care for women who are underinsured, elderly, or isolated.

III. CONDUCTING RESEARCH AND EVALUATION

A. Expand research on conditions that are unique to women or that are more prevalent in women.

B. Use longitudinal research to assess the interaction of behavioral, social, and biological factors.

C. Collect and analyze health data by age, sex, and race.

D. Study workplace hazards for women.

E. Study how culture and socialization affect women's and men's health differently.

IV. RECRUITING AND TRAINING OF HEALTH CARE PERSONNEL

A. Increase the number of women in key health positions in services, research, administration, and education.

B. Address continuing education programs in health to women's needs.

V. EDUCATING AND INFORMING THE PUBLIC AND DISSEMINATING RESEARCH INFORMATION

A. Communicate the importance of a healthful lifestyle through outreach programs.

8. Organize a group from television, films, publishing, and advertising to examine the effects of media images on women's health.

C. Disseminate, via the Public Health Service, up-to-date research information.

VI. DESIGNING GUIDANCE FOR LEGISLATIVE AND REGULATORY MEASURES

A. Encourage organizations interested in women's well-being to keep informed, promote information exchange and education, and advocate improved health conditions for women.

B. Use law and regulations to ensure a safe, healthful physical and social environment for all.

Finally, the Task Force report consists of many recommendations beyond the 16 displayed above. Since the purpose of this meeting is to look at women's health as affected by drug and alcohol abuse, some additional recommendations have been identified as a useful framework for conceptualizing presentations and potential recommendations which may come from this conference.

SPECIAL EFFORTS SHOULD BE MADE TO GAIN KNOWLEDGE ABOUT THOSE DISEASES RELATED TO ALCOHOL AND DRUG ABUSE, AND ABOUT MENTAL ILLNESSES OF IMPORTANCE TO WOMEN, BY THE INITIATION OF:

(1) Research to study depression in women when it occurs alone or in conjunction with alcohol or drug abuse problems.

(2) Studies of the significant factors related to the onset, continuation, and cessation of smoking, drinking, and drug taking by women.

(3) Studies of the role of the family and of cultural attitudes in the maintenance of mental health or the development of mental illness, as well as in the use or misuse of alcohol, drugs, and tobacco.

A SYSTEMATIC EFFORT MUST BE MADE TO ADDRESS ISSUES RELATING TO GENDER BIAS IN RESEARCH AND CLINICAL PRACTICE THAT LEAD TO INADEQUATE ATTENTION TO THE NEEDS OF WOMEN.

Ways to effect such change include:

(1) The issuance of a comprehensive Public Health Service policy directing all operating units to review their research guidelines to ensure that sex differences are routinely studied, wherever feasible. Such instructions should be included in grant application kits.

(2) The requirement that postmarketing surveillance of all prescription drugs should include reporting of the adverse effects in women of drug interactions with alcohol, commonly used psychotherapeutic drugs, and drugs commonly used in relation to hormonal changes in women.

(3) The requirement that adequate numbers of women be included in clinical trials of drugs that will be used by women, and that results be separately reported by gender for all new drugs that are to be recommended for use by women.

(4) The commissioning of an interdisciplinary panel of senior scientists, including women, to review existing research and research methodology to develop a comprehensive plan for addressing any gender bias identified in research in general, but in particular in alcohol, drug abuse, and mental health research.

(5) The establishment of a task force to review mental health issues related to women and to make recommendations for change in the Fourth Revision of the Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (APA), in order to promote adequate diagnosis and treatment of women with alcohol, drug abuse, and mental health problems. Such a task force should work closely with

the APA Task Force on Nomenclature and Statistics. In addition, a similar review mechanism should be established for the International Classification of Diseases (ICD-10).

This summarizes the progress and significance of the PHS Task Force on Women's Health Issues. I am confident that our meeting and collaborative publication reflect an awareness that research on drug and alcohol use by women is crucial to improving the health status of women. With the impetus provided by the Task Force Report, it is anticipated that the research community will be stimulated to explore aspects of women's health previously neglected.

REFERENCES

U.S. Public Health Service. Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I. Supplement to Public Health Reports, 100(1):73-106, January-February 1985.

U.S. Public Health Service. Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume II. DHHS Publication No. (PHS)85-50206, May 1985.

AUTHOR

Lois Chatham, Ph.D.
Director of Extramural Research
National Institute on Alcohol Abuse and Alcoholism
Parklawn Building, Room 14C-10
5600 Fishers Lane
Rockville, MD 20857

FDA's Perspective on Women and Drugs

Mary Ann Danello

Many of you are probably familiar with the Food and Drug Administration's (FDA) requirements for new drug approval. However, for the benefit of those who are not as familiar with this process, let me give you a brief overview as well as some idea of when women are included in these clinical trials.

The FDA provides guidance for investigators performing clinical evaluations of new drugs in an Agency publication entitled, "General Considerations for Clinical Evaluation of Drugs" (HEW publication no. FDA-77-3040). The purpose of this publication is to present acceptable current approaches to the study of investigational drugs in humans. The document, in part, contains recommendations for clinical studies, which are recognized as desirable approaches to be used in arriving at conclusions concerning the safety and effectiveness of a new drug, and includes the following basic information:

- A description of institutional review boards (IRBs) and principles of informed consent
- Clinical trial design and analysis considerations
- Selection of subjects
- Numbers of and randomization of patients
- Study control
- Patient compliance
- Dosage considerations
- Drug dynamic studies

In addition to that document, there are 25 clinical guidelines available concerning the design of adequate and well-controlled

studies on different classes of drugs. These guidelines have been developed largely or entirely by the FDA's advisory committees and consultants.

The FDA's drug review and approval process involves two stages--the investigational new drug application stage (IND) and the new drug application stage (NDA). The IND process begins after animal data on the drug have been collected and analyzed and the testing in humans is ready to commence. Once an IND is submitted to the FDA, and the Agency is satisfied that the study does not pose unreasonable risks to human subjects, then the sponsor may begin testing the drug in humans.

The testing of investigational drugs occurs in three phases:

PHASE 1

These are clinical pharmacologic studies which include the initial introduction of the drug into humans and involve a range of about 20 to 80 persons in a trial. Phase 1 trials include early dose-ranging studies as well as determination of toxicity levels and pharmacologic effects. Drug dynamic and metabolic studies are also considered to be Phase 1 clinical pharmacologic studies in whichever stage of the clinical investigation they are performed. It is recommended that females who are pregnant, or are at risk of becoming pregnant, should be excluded from early dose-ranging studies.

PHASE 2

These clinical investigations consist of controlled clinical trials designed to demonstrate effectiveness and relative safety of the investigational drug. These studies are normally performed on a limited number (100 to 200) of closely monitored patients. Women may be included in Phase 2 clinical trials if adequate information on relative safety and efficacy has been amassed and certain animal experiments described in the FDA animal reproduction guidelines (Segment 1 for females and Segment 2) have been completed. These experiments determine the teratogenic potential of the investigational drug. There are instances in which women of childbearing potential may receive investigational drugs in the absence of adequate reproduction studies in animals. These include: the use of the drug as a lifesaving or life-prolonging measure; use of the drug which belongs to a class of drugs the teratogenic potential of which has already been determined; use of women who may have been institutionalized for a time period adequate to establish a nonpregnant state.

PHASE 3

These clinical trials are expanded controlled and uncontrolled trials. They are performed after the drug's effectiveness has been established (to a certain degree) and are intended to gather

additional evidence of effectiveness for specific indications and a more precise definition of drug-related adverse effects. Since Phase 3 trials are large-scale trials, it is recommended that women of childbearing age be included only if all three segments of the FDA animal reproduction guidelines are completed to determine the teratogenic potential of the investigational drug. As with Phase 2 trials, there are circumstances in which an investigational drug may be administered to women in the absence of adequate reproduction studies in animals.

Data from the Phase 1, 2, and 3 studies, as well as additional information (supplements, amendments, progress reports, and reviews), are compiled by the sponsoring pharmaceutical firm and comprise the NDA (New Drug Application). After these data have been analyzed and assessed by the FDA to determine that the investigational drug is safe and effective for what it claims to do, the drug can be approved for marketing. Following the marketing of a drug, the drug's sponsor should submit to the FDA reports on adverse reactions, data from additional studies, or manufacturing information.

PHASE 4

These studies are clinical trials which are undertaken after the new drug has been marketed. Included in this category are:

- additional studies to elucidate the incidence of adverse reactions or to obtain more information on a pharmacologic effect;
- large-scale, long-term morbidity or mortality studies;
- clinical trials in a patient population not adequately studied in the premarketing stage;
- clinical trials for an indication for which the presumed drug, once available, will be used; and
- additional Phase 3-type trials to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to the acquisition of all data normally obtained before marketing.

Subpopulations

While the Agency has developed separate guidelines for clinical evaluation of drugs in infants and children and is in the process of addressing some of the special problems of clinical evaluation of drugs in the elderly, there are presently no similar guidelines for women of childbearing potential. However, the "General Considerations" publication includes a brief section on the inclusion of women of childbearing potential in studies of investigational drugs.

The salient features of these general considerations are as follows:

- Women of childbearing potential should be excluded from the earliest dose-ranging studies.

- If adequate information on efficacy and relative safety data are present (including certain animal reproduction studies), women of childbearing potential may be included in Phase 2 and Phase 3 trials.

- Women of childbearing potential may receive Phase 2 or Phase 3 investigational drugs in the absence of adequate reproduction studies in animals under certain circumstances (e.g., the drug is lifesaving or life prolonging, or it belongs to a class of drugs for which the animal teratogenic potential is known).

- When an investigational drug for which there are no animal reproduction data is used in women for the treatment of a serious disease, the lack of animal data should be pointed out and fully informed consent obtained.

- Pregnancy tests should be performed prior to the introduction of investigational drugs in women and they should be advised of contraceptive measures.

- For drugs that are absorbed systemically, transplacental passage of the drug and its secretion in milk should be assumed. Fetal followup should be conducted in women who become pregnant while on an investigational drug. Excretion of the drug or its metabolites in the milk of lactating women should be determined, when feasible, prior to the use of the drug in nursing mothers.

This is a brief overview of the FDA new drug approval process and the avenues for testing drug effects on women and their offspring, including the current considerations for the use of women in clinical trials for investigational drugs. As you have seen, women of childbearing age can be included in clinical trials, but under a prescribed set of circumstances. Older women (i.e., postmenopausal) can also be included in clinical trials for investigational drugs according to draft Agency guidelines for testing drugs in the elderly.

FOOTNOTE

[1]Segments of FDA animal reproduction studies:

Segment 1 - Single generation studies to assess gonadal function, estrous cycle, mating behavior, and early stages of gestation

Segment 2 - Assessment of teratogenesis

Segment 3 - Effects of the investigational drug on the late fetal development, labor, delivery, lactation, and health of the newborn

AUTHOR

Mary Ann Danello, Ph.D.
Special Assistant to the Commissioner
Food and Drug Administration
HF5/Room 1490
5600 Fishers Lane
Rockville, MD 20857

An Overview of the Clinical Rationale for Advancing Gender-Related Psychopharmacology and Drug Abuse Research

Jean A. Hamilton

Gender correlates with naturally occurring patterns of drug use, misuse, and abuse (Russo et al. 1985). In studying gender as a variable in clinical pharmacology, we must move beyond overly simplistic laboratory studies of single agents and recognize the drug combinations that women actually use. For example, women frequently combine the use of drugs--legal and illegal--with the use of exogenous steroid hormones, i.e., oral contraceptives or estrogens for postmenopausal replacement therapy. These combinations are sometimes used in conjunction with alcohol or cigarettes, which are known to affect endogenous hormones (MacMahon et al. 1982; Sepkovic et al. 1984). Certain drugs have side effects that are known to alter the menstrual cycle or other gender-related reproductive functioning (Mendelson and Mello, this volume).

Despite this evidence, which provides a clinical rationale for a more gender-related pharmacology, investigators have too often behaved as though these effects are trivial and do not merit systematic attention. That a gender-related blind spot may occur in drug research is suggested, for example, by the relative neglect of gender as a variable, even when there is evidence that gender is related to the actual disease process (Raskin 1974; Kinney et al. 1981; Hamilton and Parry 1983; Hamilton et al. 1984b).

One example of the biased attitudes that operate against the appropriate recognition of gender as a research variable is the preference for "basic" as opposed to "applied" advances in scientific knowledge. Clinical pharmacologists have behaved as though gender-related drug effects, even if they occurred, would be "only metabolic." Implicit in this belief is the assumption that gender-related effects will not help to clarify the basic mechanisms of drug action.

While this belief may have been tenable in the previous decade, it runs counter to the most recent evidence. For example, the existence of gender-related differences in brain structures--and perhaps in localized functioning--could have consequences for the

effects of certain drugs on the brain (Baum, this volume). Moreover, there is increasing evidence that gonadal steroids affect the ongoing neurochemical substrate underlying the mechanisms of drug action in the brain (Murphy and Hamilton 1983; Hamilton and Conrad, in press). While speculative, these trends in the data now provide a basic science rationale for gender-related drug research, which reinforces the purely clinical argument.

In considering the implications for drug abuse research, I am impressed that both prescription psychoactive drugs and drugs of abuse are often used to alter the quality of our thinking and experiences. As one example, for reasons that are not understood, antidepressants are rarely drugs of abuse (while speculative, this may be related to side effects, or to an effect of the initial baseline in terms of mood), but alcohol, opiates, and stimulants are likely to be used or abused in order to avoid dysphoria, if not to actually self-medicate a clinically significant depression. At least from the standpoint of regulating affect, this suggests a certain degree of motivational overlap. In addition, several prescription psychoactive drugs share with drugs of abuse some of the side effects on reproductive functioning. From the perspective of these observations, I will briefly review some of the gender-related data for two types of psychoactive drugs, antidepressants and antipsychotics.

My purpose in this chapter is to highlight gaps in knowledge and to identify several methodological requirements for advancing gender-related psychopharmacology. Many of these observations will have parallels for drug abuse research. I will further address some of the attitudinal and conceptual barriers to moving gender-related methods into the mainstream of clinical psychopharmacology and drug abuse research.

GENDER-RELATED DATA FOR SELECTED PSYCHOACTIVE DRUGS

Antidepressants

About 10 years ago, Raskin (1974) reviewed the existing data and concluded that: "Although twice as many women as men are treated for depression, the depression literature suggests that it is the men rather than the women who benefit most from antidepressant drugs." When I attempted to update Raskin's review, I was especially interested in the literature on MAO-inhibiting antidepressants, due to the suggestion of sex-related differences in responsivity in the animal literature. But my review of the existing clinical data on phenelzine, a nonspecific MAO-inhibiting antidepressant, demonstrated important gaps in knowledge, since only 3 out of 25 studies (12 percent) tabulated the data by either gender or age (Hamilton et al. 1984). It is likely that other gender-related effects might be observed in psychopharmacology, but without the adequate inclusion and reporting of gender as a research variable, it is impossible to know (Hamilton and Hirschfeld 1984).

Also of interest with regard to possible abuse or misuse of stimulants is Gerner's (1983) observation that amphetamine may be more effective as an antidepressant in females or the elderly than in males. This example highlights the need to clarify gender-related effects in order to maximize therapeutic responsivity and to minimize untoward side effects in subgroups that are defined by gender and age.

Antipsychotics

As we reevaluate gender as a variable in psychopharmacology, the literature on antipsychotics and tardive dyskinesia demonstrates the need to clarify gender by age effects in the light of hormonal effects. Tardive dyskinesia is a movement disorder that occurs in association with the use of antipsychotic drugs. The well-known gender difference in the distribution of this side effect (Tepper and Haas 1979; Kane and Smith 1982) is confirmed even when controlling for age; that is, the female excess is not simply an artifact of comparing older women with younger males, since it persists in studies with a similar male-female age distribution, and it has also been observed in younger age groups (Brandon et al. 1971; Degkwitz and Wenzel 1967).

There does not appear to be a simple or trivial explanation for the gender-related difference in tardive dyskinesia. For example, the finding is probably not simply a function of gender differences in absolute dosage (Odejide 1980; Simpson et al. 1978; Yassa et al. 1983), relative dosage, length of drug use, or polypharmacy (Simpson et al. 1978). Future studies of possible gender and hormonal effects on neuroleptic blood levels (Stevens 1973), optimal dosages required for control of symptoms (Chouinard et al. 1980; Seeman 1983), and subtype of movement disorder can clarify the observed gender-related effects.

At present, the evidence for a hormonal account of the gender-related distribution of tardive dyskinesia is mixed, but there is some literature suggesting an effect of menstrual status and of circulating levels of gonadal hormones (Stevens 1973). For example, when the gonadal hormone, estrogen, is extremely high in premenopausal women--as with oral contraceptive use (Barber et al. 1976) or during pregnancy--a choreiform movement disorder may arise, perhaps from excess functioning of the brain neurotransmitter, dopamine (Gordon et al. 1980; Klawans et al. 1980).

With menopause, estrogens diminish gradually, often over the course of years. Moderate levels of estrogen are thought to be protective for tardive dyskinesia, partly through a presynaptic mechanism (Klawans et al. 1980). Particularly for women who have been on antipsychotic medication, the loss of the protective effect of estrogen at menopause may, in effect, "unmask" tardive dyskinesia. Although there is not an increase in the prevalence of tardive dyskinesia in the menopausal age group, the greatest increase in the severity of tardive dyskinesia does occur in the forties and fifties Smith and Baldessarini 1980).

Another investigational finding connecting tardive dyskinesia with estrogen levels is that exogenous estrogens improve dyskinesia in both animals (Gordon et al. 1980) and humans. For example, standard doses of Premarin (.625 mg/d) resulted in marked improvement in a repeated on-off clinical trial involving two women (Villeneuve et al. 1978; Bedard et al. 1977).

METHODOLOGICAL REQUIREMENTS FOR ADVANCING GENDER-RELATED PSYCHOPHARMACOLOGY AND DRUG ABUSE RESEARCH

Both of these examples highlight the need to select subjects in a way that will clarify, rather than obscure, possible gender by age and hormonal status effects on drug responsivity and on drug use. A further methodological guideline is for investigators to report the exact statistical significance (p value) by gender, in order to allow for subsequent combining of statistics for meta-analysis of several clinical trials.

The example of neuroleptic-related tardive dyskinesia reminds us to examine not only gender-related trends in therapeutic efficacy, but also in the patterning of side effects. As detailed elsewhere (Hamilton et al. 1984). investigators must control, or at least describe carefully, gender-related effects on known pharmacokinetic variables, e.g., body composition and serum levels. The menstrual cycle must also be recognized consistently as a potential source of variance in psychopharmacological studies (Shader and Harmatz 1982; Mendelson and Mello, this volume).

Finally, we must address the fact that confounding variables may also be gender-related. Such variables may include baseline levels of severity, placebo versus spontaneous remission rates, or side effects related to rates of dropping-out. As mentioned earlier, the complexity of people's lives must also receive recognition in psychopharmacology and drug abuse research; for example, there are gender-related differences in cigarette smoking and alcohol use, and these may interact with other variables pertinent to our research. Only by greater attention to naturally occurring patterns of drug use or abuse--including the social ecology of drug combination--will we begin to clarify the mechanisms for gender-related effects on drug responsivity and usage (Russo 1985).

ON BARRIERS TO MOVING GENDER-RELATED METHODS INTO THE MAINSTREAM OF DRUG RESEARCH

The scientific rationale for gender-related drug research is simply to advance knowledge and to improve the quality of research clinically, theoretically, and empirically. From a policy point of view, however, there are several conceptual barriers to moving gender-related research into the mainstream (Hamilton, in press).

For example, this area is likely to be trivialized as though it pertains only to a special "subpopulation." There is also a persistent notion among basic pharmacologists that gender is such an

obvious, almost simple-minded variable, that its study will result only in clinical applications, as opposed to the possibility that it will provide windows on mechanisms of drug action.

The problem with these attitudes is one of perspective. If you speak with front-line clinicians--or with the women who actually suffer from the perhaps needless excess of tardive dyskinesia or with their families--even rather simple "metabolic" factors seem less trivial. Theoretically, in fact, the study of gender-related effects may advance a new thread of basic research, aimed at understanding drug-hormone interactions, as one example.

Finally, we need to understand better the connections between seemingly simple-minded variables like a e, and profound concepts like "development," or "evolution." As the variable age is to the concept development, so the variable gender may stand in relation to some as yet unknown, but perhaps groundbreaking, concept in drug research.

In summary, the use of gender comparisons is based on the long empirical tradition of comparative methods in physiology and in neuroscience (Bullock 1984). At its best, gender-comparative research will both sharpen our skills in assessing the mechanisms of drug action, and improve clinical care--not just for a single subpopulation, but for all subgroups defined by gender, age, and hormonal status.

REFERENCES

Barber, P.V.; Arnold, A.G.; and Evans, G. Recurrent hormone dependent chorea: Effects of oestrogens and progestogens. Clin Endocrinol 5:291-293. 1976.

Bedard, P.; Langelier. P.; and Villeneuve, A. Oestrogens and extrapyramidal system. Lancet 2:1367, 1977.

Brandon, S.; McClelland, H.A.; and Protheroe, C. A study of facial dyskinesia in a mental hospital population. Br J Psychiatry 118: 71-184, 1971

Bullock, T.H. Comparative Neuroscience holds promise for quiet revolutions. Science 225: 473-478. 1984

Chouinard, G.; Jones, B.D.; Annable, L.; and Ross-Chouinard, A. Sex differences in tardive dyskinesia. Am J Psychiatry 137(4):50, 1980.

Degkwitz, R., and Wenzel, W. Persistent extrapyramidal side effects after long-term application of neuroleptics. Neuropsychopharmacol 129:608-615, 1967.

Gerner, R.H. Systematic treatment approach to depression and treatment-resistant depression. Psychiatr Ann 13:37-49, 1983.

Gordon. J.H.; Borison, R.L.; and Diamond, B.I. Estrogen in experimental tardive dyskinesia. Neurol 30:551-554, 1980.

Hamilton, J.A. Avoiding methodological and policy-making biases in gender-related research. In: Report of the Public Health Service Task Force on Women's Health. Vol. II. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., in press.

Hamilton, J.A., and Conrad, C. Toward a developmental psychopharmacology: The physiological basis of age, gender and hormonal effects on drug responsivity. In: Call, J., ed. Update, Handbook of Child Psychiatry. New York: Basic Books, in press.

Hamilton, J.A., and Hirschfeld, R.M.A. An additional recommendation on reporting depression. Am J Psychiatry 141(9):1134-1135, 1984.

Hamilton, J.A., and Parry, B. Sex-related differences in clinical drug response: Implications for women's health. J Am Med Wom Assn 38(5):126-132, 1983.

Hamilton, J.A.; Alagna, S.W.; and Pinkel, S. Gender differences in antidepressant and activating drug effects on self-perceptions. J Aff Dis 7:235-243, 1984b.

Hamilton, J.A.; Lloyd, C.; Alagna, S.W.; Phillips, K.; and Pinkel, S. Gender, depressive subtypes, and gender-age effects on antidepressant-response: Hormonal hypotheses. Psychopharm Bull 20(3):475-480, 1984a.

Kane,J.M.,and Smith, J.M. Tardive dyskinesia. Prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 39:473-481, 1982.

Kinney, E.L.; Trautmann, J.; Gold, J.A.; Vesell. E.S.; and Zelis, R. Underrepresentation of women in new drug trials. Ann Int Med 95:495-499, 1981.

Klawans, H.L.; Goetz, C.G.; and Perlik, S. Tardive dyskinesia: Review and update. Am J Psychiatry 137(8):900-908, 1980.

MacMahon, B.; Trichopoulos, D.; Cole, P.; and Brown, J. Cigarette smoking and urinary estrogens. N Engl J Med 307:1062-1065, 1982.

Murphy, D.L., and Hamilton, J.A. Gender-related differences in neuropharmacologic responsivity: Contributions from neuro-chemical and drug metabolism studies. Proceedings of the American College of Neuropsychopharmacologists, San Juan, Puerto Rico, 1983. (Abstract)

Odejide, A.O. Prevalence of persistent abnormal involuntary movements among patients in a Nigerian long-stay psychiatric unit. Int Pharmacopsychiat 15:292-300, 1980.

Raskin, A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis 159:120-130, 1974.

Russo, N.F. Developing a national agenda to address women's mental health needs. Washington, DC: American Psychological Association, 1985. pp. 19-22.

Seeman, M.V. Interaction of sex, age, and neuroleptic dose. Compr Psychiatry 24(2):125-128, 1983.

Sepkovic, D.W.; Haley, N.J.; and Wynder, E.L. Thyroid activity in cigarette smokers. Arch Int Med 144:501-503, 1984.

Shader, R.I., and Harmatz, J.S. Premenstrual tension in biochemical and psychotropic drug assessment. Psychopharm Bull 18(3):113-120, 1982.

Simpson. G.M.; Varga, E.; Lee, J.H.; and Zoubok, B. Tardive dyskinesia and psychotropic drug history. Psychopharmacol 58:117-124. 1978.

Smith, J.M., and Baldessarini, R.J. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. Arch Gen Psychiatry 37:1368-1373, 1980.

Stevens, J.R. An anatomy of schizophrenia? Arch Gen Psychiatry 29:177-189, 1973.

Tepper, S.J., and Haas, J.R. Prevalence of tardive dyskinesia. J Clin Psychiatry 40:508-516, 1979.

Villeneuve, A.; Langlier, P.; and Bedard, P. Estrogens, dopamine and dyskinesias. Can Psychiatr Assn J 23(1):68-70, 1978.

Yassa, R.; Ananth, J.; Cordozo, S.; and Ally, J. Tardive dyskinesia in an outpatient population. Prevalence and predisposing factors. Can J Psychiatry 28:391-394, 1983.

AUTHOR

Jean A. Hamilton, M.D.
Institute for Research on
Women's Health, Inc.
1616 Eighteenth Street, N.W.
Suite 109 (B)
Washington, DC 20009

Clinical Investigations of Drug Effects in Women

Jack H. Mendelson and Nancy K. Mello

INTRODUCTION

Because prevalence of drug abuse problems in men is generally greater than for women in the United States (Cisin et al. 1983), it is not surprising that most of our information about process and outcome of drug dependence treatment has been obtained in studies with male patients. However, recent data obtained in the National Institute of Mental Health Epidemiologic Catchment Area Survey revealed that drug abuse and dependence was the second most commonly reported mental health disorder for women between the ages of 18 and 24 (Regier et al. 1984; Eaton et al. 1984; Robins et al. 1984; Myers et al. 1984). During 1984, 37 of the 137 patients admitted to the Drug Dependence Unit at the McLean Hospital were women. The percentage (27 percent) of female patients admitted to McLean Hospital for treatment of drug dependence is consistent with a general impression that approximately one out of four patients diagnosed as having drug abuse or dependence problems in the United States is a woman (Myers et al. 1984).

The role of gender factors in determining both safety and efficacy of pharmacotherapy for drug dependence remains largely unexplored. Since gender differences have been shown to influence a wide range of pharmacologic therapies in medical practice (Vesell 1979), a more intensive assessment of pharmacologic treatment for drug dependence of women should be carried out.

PHARMCOLOGIC TREATMENT OF COCAINE ABUSE

In a recent review of current and experimental treatments for cocaine abuse, Kleber and Gawin (1984) note that there are many problems associated with criteria currently used for the diagnosis of cocaine abuse. The importance of antecedent or consequent psychiatric illness associated with cocaine abuse is not clear. Kleber and Gawin (1984) as well as Gold (1983) have argued that cocaine abusers may be more heterogeneous with respect to variations in drug self-administration behavior than other patients who

request treatment for substance abuse problems. Marked heterogeneity has also been observed with respect to dosage, drug self-administration patterns, presence of intercurrent illness, and other social, biologic, and psychologic factors that appear to have an important role in initiating and perpetuating drug abuse (Mendelson and Mello 1982).

Our recent studies with women who have significant polydrug abuse problems strongly suggest that the appearance of heterogeneity among persons who are substance abusers may be accounted for, in part, by gender differences (Lex et al. 1984; Mendelson et al. 1985; Mendelson et al., submitted for publication). Thus, targeted studies with women patients who have a diagnosis of cocaine abuse, or cocaine abuse associated with alcohol abuse and dependence, may assist in identifying more precisely specific factors that may contribute to variance in biologic and behavioral indices as well as provide a basis for more rational and therapeutic interventions for drug abuse problems in women.

We have been able to locate only two reports of use of antidepressant medication for the treatment of cocaine abuse (Tennant and Rawson 1983; Gawin and Kleber 1984). Both these studies were "open trials" and did not utilize placebo control, double-blind crossover procedures for determination of treatment efficacy. However, the initial data obtained in these studies encourage more rigorous and systematic assessment of antidepressant pharmacotherapy for cocaine abuse by women.

The first report of the use of the antidepressant drug desipramine for treatment of cocaine dependence was presented by Drs. Tennant and Rawson (1983) at the 44th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, in 1982. A summary report of the outcome of this study was published in the National Institute on Drug Abuse Research Monograph 43 in April, 1983 (Tennant and Rawson 1983). Drs. Tennant and Rawson stated that the rationale for selecting desipramine for the treatment of cocaine abuse was based upon research reported in 1961 by Dr. Julius Axelrod, which demonstrated that amphetamines and cocaine inhibit the reuptake of norepinephrine (Axelrod et al. 1961). Subsequent studies showed that desipramine had the greatest degree of selectivity for blockade of norepinephrine uptake by tricyclic antidepressants (Hollister 1978). These data suggested to Tennant and Rawson (1983) that desipramine might be an effective drug for treating patients with cocaine abuse.

Tennant and Rawson (1983) reported outcome data for 14 cocaine abusers, including 4 women. Desipramine was administered on an outpatient basis for a period of 7 to 52 days. Daily dosage of desipramine ranged from 50 to 125 mg. Outcome data for this study did not describe any gender differences; this was not surprising since only 4 females out of a total of 14 patients participated in the clinical trial. The general outcome results, however, were encouraging since 28 percent of all patients reported total

abstinence from cocaine use 30 to 45 days following the initiation of the study. Tennant and Rawson (1983) cautioned that

> the study must not be over-interpreted due to its non-blind nature, the possibility of placebo effect, and the inherent difficulty of controlling drug-dependent research subjects. Further clarification of the role of desipramine in the treatment of amphetamine and cocaine dependence must await double-blind trials. (Tennant and Rawson 1983, p. 354)

The second report describing an open pilot trial with desipramine for the treatment of cocaine abuse was published by Gawin and Kleber in the September 1984 issue of the Archives of General Psychiatry (Gawin and Kleber 1984). In this study, six patients, three males and three females, were administered desipramine in doses of 200 mg/day and also received psychotherapy in individual sessions once or twice weekly. Some patients also participated in 1-hour group therapy sessions and in family therapy group meetings.

Gawin and Kleber reported that

> administration of desipramine was associated with abstinence from cocaine in all subjects so treated with this sample, regardless of the diagnosis. It was also associated with an anticraving effect whose time course was similar to the delayed effects of tricyclic antidepressants in major depression and neuroreceptor studies. (Gawin and Kleber 1984, p. 907)

Gawin and Kleber noted that any conclusions derived from the study were limited because of the open nature of the trial and the lack of double-blind placebo controls. Specific gender differences in treatment responses and outcome were not described, although one illustrative case report highlighted the efficacy of desipramine pharmacotherapy for a 21-year-old female treated for cocaine free-base smoking.

In retrospect, it is surprising that there have not been more attempts to evaluate the efficacy of desipramine treatment for cocaine abuse. Kleber and Gawin have noted findings derived from many basic and clinical neuroscience studies that would support the rationale for this approach (Colpaert et al. 1979; Ellinwood 1977; Fischman et al. 1976; Kosman and Unna 1968; Smith and Wesson 1980; Wesson and Smith 1977). Additional support for the potential efficacy of desipramine in the treatment of cocaine abuse may be inferred from recent studies that have shown that tricyclic antidepressants interact with the ionic channel moiety of acetylcholine receptors at the motor endplate (Eldefrawi et al. 1981; Shaker et al. 1981) and that cocaine inhibits sodium uptake into PC12 cells by binding to the open channel form of the receptor (Karpen et al. 1982). In studies of the receptor-associated ionic

channels involved in catecholamine release, Cena and his associates found that imipramine and cocaine inhibit noradrenalin release by selective inactivation of the acetylcholine receptor ionophore (Cena et al. 1983). Cocaine and the tricyclic antidepressant desipramine may have a very similar mode of action on nerve cell receptor sites and membrane ion channel function, which regulate neuronal activity and behavior. Desipramine may act as a pharmacologic substitute for cocaine by inhibiting norepinephrine release via selective inactivation of the acetylcholine receptor ionophore (Cena et al. 1983).

PHARMACOLOGIC TREATMENT OF OPIOID ABUSE AND DEPENDENCE--NALTREXONE

During 1984, naltrexone was approved by the Food and Drug Administration (FDA) for use as an adjunctive pharmacotherapy for the treatment of opioid dependence. FDA approval of naltrexone followed extensive clinical investigations that documented both the safety and limited efficacy of naltrexone treatment for opioid-dependent persons (Ginzberg 1984; Ginzberg and Glass 1984; Judson et al. 1981; Julius and Renault 1976; Resnick et al. 1974; Tennant et al. 1984; Washton et al. 1984).

A pioneering study of the effects of naltrexone on self-determined patterns of heroin self-administration by heroin-dependent men was initiated at the Harvard-McLean Alcohol and Drug Abuse Research Center (Meyer et al. 1976a; Meyer et al. 1976b; Meyer and Mirin 1979). Naltrexone (75 mg/day) effectively reduced heroin use in comparison to Glacebo controls (Meyer and Mirin 1979). The safety of chronic naltrexone therapy was also evaluated in these studies with particular emphasis on naltrexone effects on neuroendocrine function (Mello et al. 1981; Mendelson et al. 1980; Ellingboe et al. 1980).

The vast amount of data obtained concerning safety and efficacy of naltrexone treatment has been attained in studies with men (Ginzberg 1984; Ginzberg and Glass 1984; Judson et al. 1981; Julius and Renault 1976: Resnick et al. 1974; Tennant et al. 1984: Washton et al. 1984). Women were infrequently studied because the largest number of opiate-dependent persons who received naltrexone in protocol-based studies were primarily men with compromised social and economic resources. In studies with more affluent persons (Washton et al. 1984; Tennant et al. 1984), women represented one-quarter to one-third of the patients treated with naltrexone, but data obtained in these studies did not describe any gender similarities or differences for either the safety or efficacy of naltrexone treatment. This may be especially important since it has been shown that opioid antagonists are potent stimulators of both luteinizing hormone (LH) and prolactin in women (Ropert et al. 1981; Quigley and Yen 1980). Since naltrexone has been shown to stimulate gonadotropin secretion in males (Mendelson et al. 1979), it is likely that women may develop abnormalities of menstrual cycle and reproductive function as a consequence of chronic naltrexone therapy.

PHARMACOLOGIC TREATMENT OF OPIOID DEPENDENCE--BUPRENORPHINE

Since buprenorphine is an oripavine derivative of etorphine (Lewis 1974), a potent opioid agonist, and diprenorphine, an opiate antagonist (Jasinski et al. 1982; Jasinski et al. 1983; Mello and Mendelson 1980; Mello et al. 1982), buprenorphine combines the characteristics of both opioid agonists and antagonists. However, unlike opiate agonists, buprenorphine does not produce severe and protracted withdrawal signs and symptoms in man (Mello and Mendelson 1980; Mello et al. 1982; Jasinski et al. 1978). Buprenorphine is also safer than opiate agonists since its antagonistic component appears to prevent lethal overdose even at approximately 10 times the analgesic therapeutic dose (Banks 1979). This reduces the possibility of opiate overdose deaths observed with methadone use (Kreek 1978). Buprenorphine is equivalent to naltrexone in the duration of opiate antagonist action (Martin et al. 1973). A sublingual preparation of buprenorphine further enhances its potential clinical utility for the treatment of opioid dependence (Jasinski et al. 1984).

The effects of maintenance on buprenorphine, a mixed opioid agonist-antagonist, or placebo on patterns of operant acquisition of heroin and money were studied under double-blind conditions (Mello and Mendelson 1980; Mello et al. 1982). Male volunteers with histories of heroin abuse lived on a clinical research ward for 40 days. After a 5-day drug-free period, buprenorphine or placebo was given in gradually ascending doses (0.5 to 8 mg/day SC) over 14 days. Subjects were maintained on 8 mg/day of buprenorphine for 10 days during which they could earn money ($1.50) or heroin (7 or 13.5 mg/injection IV) by responding on a second order schedule of reinforcement [FR 300 (Fl 1 sec:S)] for approximately 90 minutes. Buprenorphine-maintained subjects took significantly less heroin than subjects maintained on placebo ($p<.001$). Of the total amount of heroin available, buprenorphine-maintained subjects took only between 2 and 31 percent, whereas placebo-maintained subjects took between 93 and 100 percent. One subject maintained on a somewhat smaller dose of 4 mg/day of buprenorphine took 55 percent of the available heroin: Tolerance to the opiate agonist-like somatic and sedative effects of buprenorphine developed gradually. Buprenorphine maintenance did not impair operant performance for money, Placebo subjects also showed no impairment of operant performance for heroin and money during heroin intoxication; they titrated operant work to acquire the desired amount of heroin and then resumed working for money. There were no significant differences between the buprenorphine and the placebo group in total operant points earned or total hours worked during any phase of the study. These data indicate the effectiveness of buprenorphine in suppressing heroin self-administration and illustrate the value of using direct measures of drug self-administration to evaluate new pharmacotherapies for the treatment of opiate abuse.

Buprenorphine also suppressed plasma luteinizing hormone (LH) and increased prolactin levels after 12 consecutive days of ascending dose administration in comparison to drug-free control conditions (Mendelson et al. 1982). During a subsequent 10-day period of buprenorphine maintenance at a dose of 8 mg SC, LH levels remained suppressed and prolactin continued to be elevated. Tolerance to buprenorphine effects on LH and prolactin levels did not occur during chronic drug administration (Mendelson et al. 1982). Buprenorphine-induced changes in plasma LH and prolactin after chronic administration to human males were smaller than those observed with less potent opiate agonist drugs (Mendelson et al. 1982).

We have been unable to locate any reports of buprenorphine effects on pituitary and gonadal hormones in females. Therefore, studies for determining safety (in addition to efficacy) of buprenorphine pharmacotherapy for opioid-dependent women should be conducted in the near future.

REFERENCES

Axelrod, J.; Whitby, L.G.; and Hertiling, G. Effect of psychotropic drugs on the uptake of H^3-norepinephrine by tissues. Science 133:183, 1961.

Banks, C.D. Overdose of buprenorphine: Case report. NZ Med J 89:255-256, 1979.

Cena, V.; Nicolas, G.P.; Sanchez-Garcia, P.; Kirpekar, S.M.; and Garcia, A.G. Pharmacological dissection of receptor-associated and voltage-sensitive ionic channels involved in catecholamine release. Neuroscience 10:1455-1462, 1983.

Cisin, I.; Miller, J.; and Abelson, H. The National Household Survey on Drug Abuse 1982. National Institute on Drug Abuse. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1983.

Colpaert, F.C.; Niemegeers, C.J.; and Janssen, P.A. Discriminative stimulus properties of cocaine: Neuropharmacological characteristics as derived from stimulus generalization experiments. Pharmacol Biochem Behav 10:535-546, 1979.

Eaton, W.W.; Holzer, C.E., III; Von Korff, M.; Anthony, J.C.; Helzer, J.E.; George, L.; Burnam, M.A.; Boyd, J.H.; Kessler, L.G.; and Locke, B.Z. The design of the Epidemiologic Catchment Area Survey. Arch Gen Pyschiatry 41:942-948, 1984.

Eldefrawi, M.E.; Warnick, J.E.; Schofield, G.G.; Albuquerque, E.X.; and Eldefrawi, A.T. Interaction of imipramine with the ionic channel of the acetylcholine receptor of motor endplace and electric organ. Biochem Pharmacol 30:1391-1394, 1981.

Ellingboe, J.; Mendelson, J.H.; and Kuehnle, J.C. Effects of heroin-and naltrexone on plasma prolactin levels in man. Pharmacol Biochem Behav 12:163-165, 1980.

Ellinwood. E.H. Amphetamine and cocaine. In: Jarvik, M.E., ed. Psychopharmacology in the Practice of Medicine. New York: Appleton Century Crofts, 1977. pp.467-476.

Fischman, M.W.; Schuster, C.R.; Resnekov, I.; Shik, J.F.E.; Krasnegor, H.; Fennel, W.; and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 33:983-989, 1976.

Gawin, F.H., and Kleber, H.D. Cocaine abuse treatment. Arch Gen Psychiatry 41:903-909, 1984.

Ginzberg, H.M. Naltrexone: Its Clinical Utility. National Institute on Drug Abuse Treatment Research Report. DHHS Pub. No. (ADM) 84-1358. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984.

Ginzberg, H.M., and Glass, W.J. The role of the National Institute on Drug Abuse in the development of naltrexone. J Clin Psychiatry 45(9):section 2:2-6, 1984.

Gold, M.S. 800 Cocaine/The first two weeks. Mimeographed report. Fair Oaks Hospital, Summit, NJ, 1983.

Hollister, L.E. Tricyclic antidepressant. N Engl J Med 299:1106-1109, 1978.

Jasinski, D.R.; Boren, J.J.; Henningfield, J.E.; Johnson, R.E.; Lange, W.R.; and Lukas, S.E. Progress Report of the NIDA Addiction Research Center. In: Harris, L.S., ed. Problems of Drug Dependence 1983. National Institute on Drug Abuse Research Monograph 49. DHEW Pub. No. (ADM) 84-1316. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 69-76.

Jasinski, D.R.; Haertzen, C.A.; Henningfield, J.E.; Johnson, R.E.; Makhzoumi, H.M.; and Miyasato, K. Progress Report of the NIDA Addiction Research Center. In: Harris, L.S., ed. Problems of Drug Dependence 1981. National Institute on Drug Abuse Research Monograph 41. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1982. pp. 45-52.

Jasinski, D.R.; Henningfield, J.E.; Hickey, J.E.; and Johnson, R.E. Proqress Report of the NIDA Addiction Research Center. In: Harris, L.S.; ed. Problems of Drug Dependence 1982. National Institute on Drug Research Monograph 43. DHEW Pub. No. (ADM) 83-1264. Washington, DC: Supt: of Docs., U.S. Govt. Print. Off., 1983. pp. 92-98.

Jasinski, D.R.; Pevnick, J.S.; and Griffith, J.D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 35:601-616, 1978.

Judson, B.A.; Carney, T.M.; and Goldstein, A. Naltrexone treatment of heroin addiction: Efficacy and safety in a double-blind dosage comparison. Drug Alcohol Depend 7:325-346, 1981.

Julius, D., and Renault, P., eds. Narcotic Antagonists: Naltrexone Progress Report. National Institute on Drug Abuse Research Monograph 9. DHEW Pub. No. (ADM) 76-387. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1976. 181 pp.

Karpen, J.W.; Aoshima, H.; Abood, L.G.; and Hess, G.P. Cocaine and phencyclidine inhibition of the acetylcholine receptor: Analysis of the mechanisms of action based on measurements of ion flux in the millisecond-to-minute time region. Proc Natl Acad Sci USA 79:2509-2513, 1982.

Kleber, H.D., and Gawin, F.H. Cocaine abuse: A review of current and experimental treatments. In: Grabowski, J., ed. Cocaine: Pharmacology, Effects, and Treatment of Abuse. National Institute on Drug Abuse Monograph Series 50. DHEW Pub. No. (ADM) 84-1326. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 111-129.

Kosman, M.E., and Unna, K.R. Effects of chronic administration of the amphetamines and other stimulants on behavior. Clin Pharmacol Ther 9:240-254, 1968.

Kreek, M.J. Medical complications in methadone patients. In: Kissen, B.; Lowinson, J.; and Millman, R., eds. Recent Developments in Chemotherapy of Narcotic Addiction. Ann NY Acad Sci 311:110-134, 1978.

Lewis, J.W. Ring C-bridged derivatives of thebaine and oripavine. In: Braude, M.C.; Harris, L.S.; May, E.L.; Smith, J.P.; and Villarreal, J.E., eds. Narcotic Antagonists Advances in Biochemical Psychopharmacology Vol. 8. New York: Raven Press, 1974. pp. 123-136.

Lex, B.W; Mendelson, J.H.; Bavli, S.; Harvey, K.; and Mello, N.K. Effects of acute marijuana smoking on pulse rate and mood states in women. Psychopharmacology 84:178-187, 1984.

Martin, W.R.; Jasinski, D.R.; and Mansky, P.A. Naltrexone, an antagonist for the treatment of heroin dependence effects in man. Arch Gen Psychiatry 28:784-791, 1973.

Mello, N.K.. and Mendelson. J.H. Buprenorphine suppresses heroin use by heroin addicts. Science 207:657-659, 1980.

Mello, N.K.; Mendelson, J.H.; and Kuehnle, J.C. Buprenorphine effects on human heroin self-administration: An operant analysis. J Pharmacol Exp Ther 223:30-39, 1982.

Mello, N.K.; Mendelson, J.H.; Kuehnle, J.C.; and Sellers, M.S. Operan; analysis of human heroin self-administration and the effects of naltrexone. J Pharmacol Exp Ther 216:45-54, 1981.

Mendelson, J.H.; Ellingboe, J.; Kuehnle, J.C.; and Mello, N.K. Heroin and naltrexone effects on pituitary-gonadal hormones in man: Interaction of steroid feedback effects, tolerance, and supersensitivity. J Pharmacol Exp Ther 214:503-506, 1980.

Mendelson, J.H., and Mello, N.K. Commonly abused drugs. In: Harrison's principles of Internal Medicine. New York: McGraw Hill, 1982. pp. 1541-1546.

Mendelson, J.H.; Ellingboe, J.; Kuehnle, J.C.; and Mello, N.K. Effects of naltrexone on mood and neuroendocrine function in normal adult males. Psychoneuroendocrinology 3:231-236, 1979.

Mendelson, J.H.; Ellingboe, J.; Mello, N.K.; and Kuehnle, J.C. Buprenorphine effects on plasma luteinizing hormone and prolactin in male heroin addicts. J Pharmacol Exp Ther 220:252-255, 1982.

Mendelson, J.H.; Mello, N.K.; and Ellingboe, J. Acute effects of marihuana smoking on prolactin levels in human females. J Pharmacol Exp Ther 232:220-222, 1985.

Mendelson, J.H.; Mello, N.K.; Ellingboe, J.; Skupny, A.S.T.; Lex, B.W.; and Griffin, M. Marihuana smoking suppresses luteinizing hormone in women. Submitted for publication.

Meyer, R.E., and Mirin, S.M. The Heroin Stimulus. New York: Plenum. 1979. 254 pp.
Meyer, R:E.; Mirin, S.M.; Altman, J.C.; and McNamee, H.B. A behavioral paradigm for the evaluation of narcotic antagonists. Arch Gen Psychiatry 33:371-377, 1976a.
Meyer, R.E.; Randall, M.; Mirin, S.M.; and Davies, M. Heroin self-administration: The effects of prior experience, environment, and narcotic blockade. In: Problems of Drug Dependence 1976, presented at the NAS-NRC Meeting, Committee on Problems of Drug Dependence, Richmond, VA, 1976b. pp. 272-295.
Myers, J.K.; Weissman, M.M.; Tischler, G.L.; Holzer, C.E., III; Leaf, P.J.; Orvaschel, H.; Anthony, J.C.; Boyd, J.H.; Burke, J.D., Jr.; Kramer, M.; and Stoltzman, R. Six-month prevalence of psychiatric disorders in three communities. Arch Gen Psychiatry 41:959-970 1984.
Quigley, M.E., and Yen, S.S.C. The role of endogenous opiates on LH secretion during the menstrual cycle. J Clin Endocrinol Metab 51:179, 1980.
Regier, D.A.; Myers, J.K.; Kramer, M.; Robins, L.N.; Blazer, D.G.; Hough, R.L.; Eaton, W.W.; and Locke, B.Z. The NIMH Epidemiologic Catchment Area Program. Arch Gen Psychiatry 41:934-941, 1984.
Resnick, J.; Volavka, J.; Freedman, A.; and Thomas, M. Studies of EN-1639A (naltrexone): A new narcotic antagonist. Am J Psychiatry 131:646-650, 1974.
Robins, L.N.; Helzer, J.E.; Weissman, M.M.; Orvaschel, H.; Gruenberg, E.; Burke, J.D., Jr.; and Regier, D.A. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 41:949-958, 1984.
Ropert, F.; Quigley, M.E.; and Yen, S.S.C. Endogenous opiates modulate pulsatile luteinizins hormone release in humans. J Clin Endocrinol Metab 52:583, 1981.
Shaker, N.; Eldefrawi, A.T.; Miller, E.R.; and Eldefrawi. M. Interactions of tricyclic antidepressants with the ionic channels of the acetylcholine receptor of Torpedo electric organ. Mol Pharmacol 20:511-518, 1981.
Smith, D.E., and Wesson, D.R. Cocaine. In: Jeri, F.R., ed. Cocaine 1980. Lima, Peru: Pacific Press, 1980. pp. 49-61.
Tennant, F.S., Jr., and Rawson, R.A. Cocaine and amphetamine dependence treated with desipramine. In: Harris, L.S., ed. Problems of Drug Dependence 1982. National Institute on Drug Abuse Research Monograph 43. DHEW Pub. No. (ADM) 83-1264. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1983. pp. 351-355.
Tennant, F.S., Jr.; Rawson, R.A.; Cohen, A.J.; and Mann, A. Clinical experience with naltrexone in suburban opioid addicts. J Clin Psychiatry 45(9):section 2:42-45, 1984.
Vesell, E.S. Pharmacogenetics - multiple interactions between genes and environment as determinants of drug response. Am J Med 66:183-187, 1979.
Washton, A.M.; Pottash, A.C.; and Gold, M.S. Naltrexone in addicted business executives and physicians. J Clin Psychiatry 45(9):section 2:39-41, 1984.

Wesson, D.R., and Smith, D.E. Cocaine: Its use for central nervous system stimulation including recreational and medical uses. In: Peterson, R.C., and Stillman, R.C., eds. Cocaine: 1977. National Institute on Drug Abuse Research Monograph DHEW Pub. No. (ADM) 77-432. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1977. pp. 137-152.

ACKNOWLEDGEMENTS

This research was supported, In part, by Grants DA 00064, DA 00101, and DA 02905 from the National Institute on Drug Abuse.

AUTHORS

Jack H. Mendelson, M.D.
Alcohol and Drug Abuse Research Center
McLean Hospital
115 Mill Street
Belmont, MA 02178

Nancy K. Mello, Ph.D.
Alcohol and Drug Abuse Research Center
McLean Hospital
115 Mill Street
Belmont, MA 02178

Drug Use Patterns and Premenstrual Dysphoria

Nancy K. Mello

The issue of how gender differences may affect drug use patterns or the consequences of drug abuse has been largely ignored. There appears to be an implicit assumption that information obtained from men will be completely generalizable to women and that any possible gender differences are of little consequence. In the absence of data to the contrary, such attitudes are likely to persist. Yet unless both women and men are studied, the prevalent notion that gender differences are inconsequential cannot be adequately tested. This essay will consider some possible implications of gender differences for our understanding of the proximal determinants and consequences of alcohol and drug abuse. The intent is not to construct a bastian of militant feminism with a mindless insistence on examination of women qua women--many fundamental biological processes are unlikely to be gender specific. Rather the intent is to suggest some areas of investigation that are relevant to the unique attributes of women and may present special problems as well as special research opportunities for studies of substance abuse.

The serious health risks associated with cigarette smoking, alcohol and drug abuse are widely recognized, and educating women about the health consequences of substance use has become an issue of increasing concern. This technical review on women and drugs initiated by the National Institute on Drug Abuse (NIDA) is an important first step towards implementation of the recommendations of the 1985 DHHS Task Force on Women's Health Issues concerning substance abuse-related research. The Task Force urged that

> special efforts should be made to gain knowledge about those diseases related to alcohol and drug abuse, and about mental illnesses of importance to women, by the initiation of: (1) research to study depression in women when it occurs alone or in conjunction with alcohol or drug abuse problems; (2) studies of the significant factors related to the onset, continuation and cessation of smoking, drinking, and drug taking by

> women; and (3) studies of the role of the family and of cultural attitudes in the maintenance of mental health or the development of mental illness, as well as in the use or misuse of alcohol, drugs, and tobacco. (Report of the Public Health Service Task Force on Women's Health Issues 1985, p. 81)

The Task Force report and its implications are discussed more fully elsewhere in this monograph (Chatham, this volume).

Increased Federal attention to the health problems of women generally, and the impact of substance abuse in particular, is an encouraging development. In 1978, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) was among the first to sanction the notion that alcohol abuse problems may be different in men and women in their first research monograph, "Alcoholism and Alcohol Abuse Among Women: Research Issues" (NIAAA 1980). In 1984, the NIAAA sponsored a second National research conference on women and alcohol. Since 1980, several important books on alcohol and drug abuse problems in women have been published (Wilsnack and Beckman 1984; Kalant 1980; Sandmaier 1980; Eddy and Ford 1980). Despite evidence of progress in reversing the longstanding tendency to assume that women are just like men, this attitude is deeply imbedded in our culture. Its myopic adherents appear to be afflicted with "the Adam's Rib syndrome!" A fundamentalist's interpretation of genesis subscribes to the belief that Adam was "formed from the dust of the ground" and Eve from one of his ribs. Although this is not the dominant hypothesis in contemporary biomedical science, many people still behave as if this were a guiding assumption. Calling attention to the possible importance of gender differences (except in reproductive biology) can evoke reactions ranging from incredulity to indifference.

SUBSTANCE ABUSE: RISK AND RECURRENCE

Risk for development of substance abuse problems is influenced by many interacting variables. The great diversity of individuals with alcohol and drug abuse problems argues against a search for constant etiological factors (Mello 1980; Mello 1983a). Trying to analyze the events that maintain drug abuse behavior may be more important than attempting to recapture the distant antecedents of that behavior. We understand very little about the way in which alcohol and drugs come to control behavior leading to their repeated administration. Drinking and drug abuse problems may develop for many reasons, but once established, there may be similarities in the way abuse patterns are maintained that transcend the specific pharmacological properties of the drug (Mello 1983b).

A once common belief was that certain drugs inevitably led to repetitive compulsive use, motivated in part by the avoidance of withdrawal signs and symptoms. Yet direct observations of drug users have not supported this notion. Alcohol-dependent men alternated between drinking and abstinence, over periods of 30 to

60 days, despite the occurrence of withdrawal signs and symptoms (Mello and Mendelson 1972; Mello and Mendelson 1978). Similar cyclic patterns of alcohol self-administration were seen in rhesus monkeys (Winger and Woods 1973). Occasional intermittent use of heroin is also reported (Harding and Zinberg 1983). Given that drugs are often used intermittently, it would be useful to identify the proximal determinants of drug use and clarify the extent to which these may differ in men and women.

Behavior is maintained by its consequences, but clinical research has shown that the consequences of chronic alcohol and drug abuse are considerably more complex and varied than was once believed. Traditionally, the purported "positive" effects of intoxication (mood elevation, rush, high, euphoria) have been considered as a primary explanation for repeated drug abuse. Although intoxication may initially induce pleasant feeling states and diminish feelings of anxiety and depression, chronic intoxication with alcohol and opiates is often associated with increased anxiety and depression (Mello 1983b). The elusive effects of chronic drug intoxication may be reflected in microcosm in the acute effects of drug intoxication. Biphasic changes in mood state appear to parallel the ascending and descending phase of drug concentrations in plasma. The transient positive changes in mood usually occur during the rising phase of the drug concentration curve. Opiates and cocaine may produce positive changes in feeling states within seconds or minutes after intravenous administration. Alcohol may produce similar effects within 30 to 90 minutes after drinking, as the blood alcohol curve rises. But dysphoric changes in feelings may occur after the heroin rush, after smoking cocaine paste, and during the falling phase of the blood alcohol curve. Higher drug doses are more likely to be associated with dysphoric changes in subjective states. However, this generalization is qualified by the fact that many nonpharmacological factors including expectancy, drug experience, and social context modulate the perceived consequences of intoxication (Mello 1983b; Marlatt and Rohsenow 1980).

Naive users of alcohol, opiates, and nicotine often experience dysphoria, nausea, vomiting, dizziness, and some impairment of concentration and thinking. Although tolerance to the adverse effects of initial drug use may develop, another possibility is that the initial adverse drug reactions (dysphoria, nausea, vomiting) will persist and become an integral part of the reinforcing properties of subsequent drug use (Mello 1983b).

To the extent that dysphoric consequences are associated with both acute and chronic intoxication, the explanatory value of "euphoria" is diminished. One advantage of the term "reinforcement" is that it does not imply anything about the nature of the reinforcing event. Rather reinforcement describes a functional relationship between events and behavior. If occurrence of an event increases behavior leading to that consequence, the event can be defined as a reinforcer. If the removal of an event

increases behavior leading to it, the event can also be defined as a reinforcer. However, if either the presentation or removal of an event decreases behavior leading to it, the event can be defined as a punisher (Morse and Kelleher 1977).

The maintenance of behavior by aversive or noxious events is not unusual. There is considerable evidence that aversive consequences such as electric shock will maintain shock self-administration behavior in animals under certain conditions (Morse et al. 1977). Opiate-dependent monkeys will work to produce injections of a narcotic antagonist which, in turn, precipitate opiate abstinence signs (Goldberg et al. 1972; Woods et al. 1975). Within this context, the fact that the increased despondency and anxiety often associated with chronic drug abuse are part of the complex that maintains the drug use behavior is less surprising.

The challenge of analyzing the mercurial reinforcing effects of drugs is further illustrated by patterns of polydrug use which involve the concurrent use of substances with different pharmacological actions. Polydrug use of stimulants and depressants has prompted the speculation that a change in state may be the critical reinforcing component of drug intoxication. The direction of that change in state, up or down, may be far less important than the change itself. Insofar as drugs are stimuli leading to some change in subjective state, to think of drug self-administration as a form of stimulus administration may be useful (Mello 1977; Mello 1983b). It is possible that any drug which has definite stimulus properties, i.e., behavioral effects for the user, is a drug which has abuse potential (Mello 1983b).

Since expectancy is a powerful determinant of the perceived consequences of intoxication, "placebo effects" may be as salient in maintaining behavior as actual consequences (Mendelson et al. 1984). Alcoholic men recalled only the anticipated positive effects of a drinking experience and none of the dysphoric events during a subsequent episode of sobriety (McGuire et al. 1966; Tamerin et al. 1970). Anticipation of a positive intoxication experience, aided by selective recall of past intoxication, is likely to remain an important determinant of drug use. Intoxication is a common strategy for coping with problems of all types. However, whether or not the periodic recurrence of certain definable problems reliably predicts episodes of drug use is unclear.

GENDER DIFFERENCES THAT MAY EFFECT DRUG USE PATTERNS

There is little question that the menstrual cycle uniquely differentiates women of childbearing age from men. Until very recently, the psychological concomitants of phases of the menstrual cycle and the impact on women's health and behavior have received very little scientific attention. The emergence of the women's liberation movement in the early sixties was-accompanied by definitions of social equality which often involved denial of sexual differences: Attention to sexual differences was regarded as

perniciously sexist by some. This militant extremism has gradually evolved towards the recognition that there may be important sexual differences which have significant consequences for women's health, a position most recently exemplified in the 1985 Task Force on Women's Health Issues. Indeed it could be argued that the time-honored tradition of assuming that sex-related differences are unimportant reflects a profound sexism with more potentially adverse implications for women than objective examination of these differences.

The menstrual cycle is controlled by a complex interaction between hypothalamic, pituitary, and ovarian hormones. The synthesis and secretion of hypothalamic and pituitary hormones is regulated by the central nervous system and modulated by the ovarian steroid hormones. Hypothalamic LHRH (luteinizing hormone-releasing hormone) stimulates the production and release of pituitary gonadotropins, LH (luteinizing hormone) and FSH (follicle-stimulating hormone). Changes in the levels of pituitary gonadotropins and ovarian steroid hormones (estrogens and progesterone) define the successive phases of the menstrual cycle (Knobil 1980; Wilson and Foster 1985). A schematic diagram of the hypothalamic-pituitary-gonadal interrelationships appears in figure 1.

The menstrual cycle is usually divided into two phases which correspond to the development of the ovarian follicle and ovulation (the follicular phase) and transformation of the follicle into a corpus luteum (the luteal phase). The onset of menses defines the beginning of a menstrual cycle and the beginning of the follicular phase. During the follicular phase, FSH and LH stimulate maturation of the ovarian follicle and secretion of estrogen, an ovarian steroid hormone. As the follicle matures, there is a rapid increase in estrogen secretion with a surge of estrogen at midcycle. This estrogen surge is followed by a surge in LH and FSH which triggers ovulation, i.e., release of the ovum from the ovarian follicle into the fallopian tube. After ovulation, the ovarian follicle is transformed into the corpus luteum which produces progesterone, another ovarian steroid hormone. The corpus luteum continues to synthesize and secrete progesterone for approximately 13 days unless fertilization of the ovum and pregnancy occurs. Increased progesterone levels prepare the uterus for implantation of the ovum by inducing uterine glandular and vascular proliferation. If pregnancy does not occur, the endometrial lining of the uterus is sloughed off during the process of menstruation. Demise of the corpus luteum marks the end of a menstrual cycle.

The average menstrual cycle lasts for 28 days (+ 4 days). The follicular phase includes menses, which usually last 3 to 5 days, and the period of follicular development, 7 to 10 days. Variations in the length of the follicular phase account for variations in length of the normal menstrual cycle. The 2 days before and after ovulation are usually designated as the periovulatory phase.

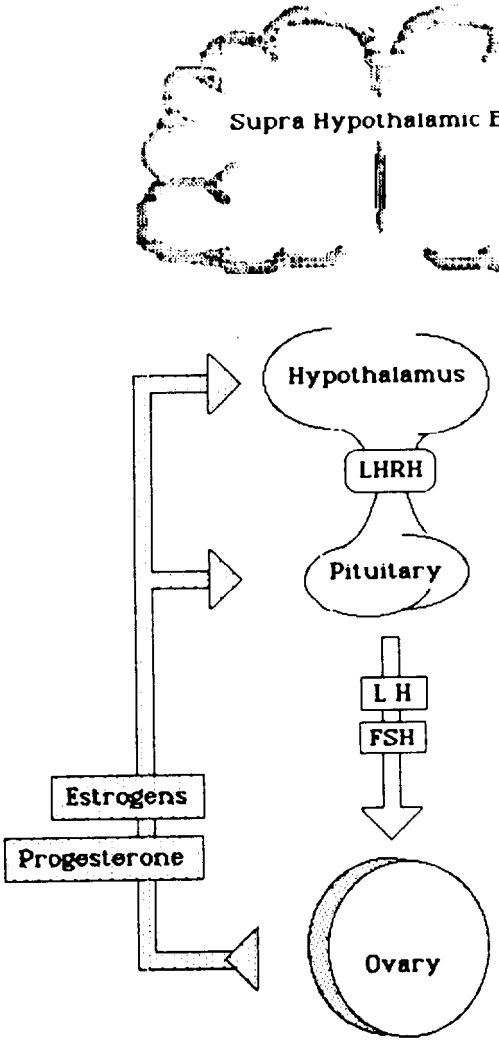

FIGURE 1. *A schematic diagram of the interrelationships between the hypothalamus, the anterior pituitary, and the ovary*

NOTE: Hypothalamic secretion of LHRH Is responsible for maintaining the tonic secretion of LH and FSH by the pituitary. Gonadotropin (LH and FSH) stimulation of the ovary leads to follicular development and the secretion of estrogens. When circulating estrogen levels reach 200 to 300 pg/ml, the pituitary releases a surge of LH and FSH which causes the ovarian follicle to rupture and release its ovum. The follicle Is then luteinized and secretes progesterone. The feedback relationships between hypothalamic LHRH, the pituitary gonadotropins, and ovarian steroid hormones are shown by the arrows. The contribution of the central nervous system to hypothalamic regulation is indicated by the suprahypothalamlc brain.

The length of the luteal phase is quite consistent from cycle to cycle, varying between 13 and 15 days. The midluteal phase, when progesterone levels are highest, usually occurs about 8 days after ovulation. The end of the luteal phase, 3 to 5 days before menstruation, is commonly referred to as the premenstruum. However, definitions of the premenstruum vary, and symptoms usually associated with the premenstruum can occur as early as 13 days prior to the onset of menstruation (Halbreich et al. 1982).

There is abundant clinical evidence that dysphoric mood states are correlated with the premenstrual phases of the menstrual cycle. A syndrome often referred to as "premenstrual tension" is characterized by increased anxiety, depression, tension, irritability, sleep disturbances, lethargy, impaired concentration, headaches, constipation, bloating, backaches, breast tenderness, weight changes, and changes in sexual feeling and activity (Moos 1969; Smith 1975; Steiner and Carroll 1977; Wilcoxon et al. 1976). Although the premenstruum is most commonly associated with dysphoria and lability of affect, menstruation and the periovulatory phase may also be associated with increased anxiety and depression. These symptoms may not occur in all women at every cycle, and all are not specific to women or to the menstrual cycle process. However, the periodic recurrence of this constellation of symptoms in concert with phases of the menstrual cycle has been implicated in an exacerbation of psychotic disorders, especially depression (Smith 1975; Steiner and Carroll 1977), as well as increased abuse of alcohol (Podolsky 1963; Belfer and Shader 1976; Belfer et al. 1971). It should be emphasized that premenstrual tension often occurs in normal women, independently of a concomitant depressive disorder (Steiner et al. 1980; Haskett et al. 1980).

The existence of a premenstrual tension syndrome has been challenged on ideological as well as methodological grounds (Wilcoxon et al. 1976; Rubinow and Roy-Byrne 1984). For example, it has been argued that women experience discomfort because they have been taught that they should feel premenstrual tension and anxiety (Ruble 1977). The influence of social expectancy on reports of menstrual-cycle-related symptoms has often been emphasized (AuBuchon and Calhoun 1985). At the other end of the spectrum are those who postulate that the cyclic changes in pituitary gonadotropins and ovarian steroid hormones, which define the phases of the menstrual cycle, may contribute to changes in affective states (Bardwick 1974; Steiner and Carroll 1977; Reid and Yen 1981), but the pathophysiology of the premenstrual tension syndrome is not understood (Vaitukaitis 1984; Rubinow and Roy-Byrne 1984). These discrepant views point to the obvious conclusion that the premenstrual tension syndrome is multiply determined, and simplistic, single-factor explanations are unlikely to adequately account for the syndrome. How subjective changes in feeling states are influenced by expectancy or modulated by concurrent changes in pituitary and gonadal hormone secretory patterns is unknown; however, it is generally agreed that these dysphoric changes in feeling

states are not necessarily associated with dysmenorrhea (Smith 1975; Moos 1969).

An association between mood fluctuations and menstrual cycle phases has been consistently established despite a wide diversity of methods and subjects. One recent study examined changes in mood and physical symptoms in women in treatment for severe premenstrual tension and compared them with women with a history of premenstrual tension and with asymptomatic women (Sanders et al. 1983). Phases of the menstrual cycle were defined by measurement of pituitary and gonadal hormones. All women showed similar changes in mood and physical states as a function of cycle phase. Feelings of well-being were greatest during the late follicular phase and declined during the luteal phase. Self-ratings of depression, irritability, and physical complaints began to increase during the early luteal phase and were maximal at the premenstruum. The magnitude of these changes was greatest in the groups that reported premenstrual tension. Women in treatment for premenstrual tension reported intense negative experiences often beginning early in the luteal phase and increasing significantly at the premenstruum (Sanders et al. 1983).

Since some women do experience anxiety and dysphoria in association with the late luteal (premenstrual) phase of the menstrual cycle, it is tempting to postulate that these may be accompanied by various forms of self-medication behavior including increased use and abuse of alcohol and other drugs. A schematic diagram illustrating this hypothesis appears in figure 2. Recurrent menstrual cycles are shown at the top of the figure, and the onset of premenstrual dysphoria is shown as a dark bar in the second row. The hypothesis that menstrual cycle mood changes may be associated with increased alcohol and drug use is shown in the third and fourth rows.

ALCOHOL USE AND MENSTRUAL CYCLE PHASE

The evidence relating to this hypothesis is somewhat sparse, but provocative. Podolsky (1963) was one of the first to state this hypothesis explicitly on the basis of clinical observations of seven female patients with alcohol problems. Each patient reported that she drank most heavily during the premenstrual period, and each patient suffered from severe premenstrual tension. Podolsky (1963) concluded that

> in general, such women drink in order to alleviate the symptoms of premenstrual tension. The tempo of drinking is increased during the premenstruum. Alcohol is utilized partly to relieve tension, but for the most part to allow acting out and verbalization of passivity demands. (Podolsky 1963, p. 818)

The clinical impression that alcohol use is related to premenstrual tension was confirmed by Belfer and coworkers in 1971.

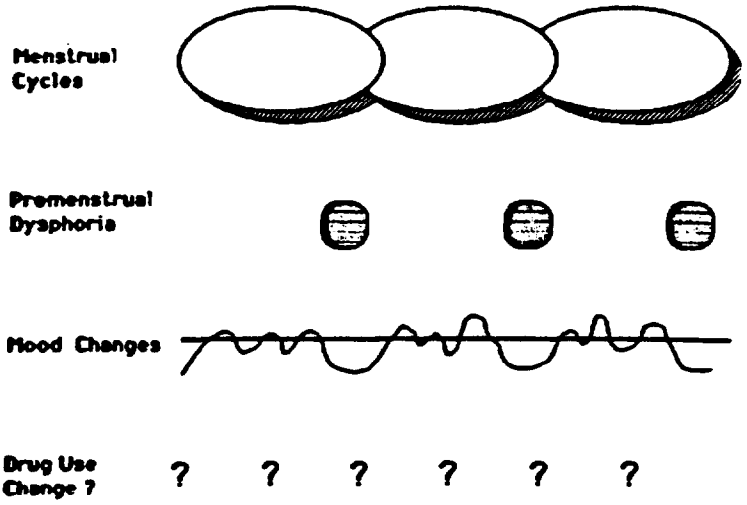

FIGURE 2. *Schematic diagram of possible association between menstrual cycle, mood changes, and drug/alcohol intake*

Self-reports of the relation of premenstrual tension and/or menopause to drinking patterns were obtained from 34 alcoholic women and 10 nonalcoholic women who accompanied their alcoholic husbands to an alcohol clinic. Over half of the alcoholic women related drinking to the menstrual cycle, especially to the premenstrual period. Belfer and coworkers (1971) commented that

> this association was made in the absence of obvious disturbances in sexual or menstrual function and in lieu of any difference in the scores of women who experienced maximal versus minimal task interference, physical discomfort or psychological discomfort during their menstrual cycle. (Belfer et al. 1971, p. 543)

MARIJUANA USE AND MENSTRUAL CYCLE PHASE

Marijuana is probably the most frequently used illicit drug in this country today (Clayton 1984) and marijuana use among women appears to be increasing (Abelson et al. 1977; Smart 1983). The possible effects of chronic marijuana use on pulmonary and

reproductive function is an issue of continuing concern (Fehr and Kalant 1983; Marijuana and Health 1982; Braude and Ludford 1984). In the context of a series of studies designed to examine marijuana effects on female reproductive function and behavior, we examined the extent to which marijuana acquisition and use patterns covaried with specific phases of the menstrual cycle (Mello and Mendelson 1985). Twenty-one young women (average age 26.7 ± 1.15 years) who reported smoking marijuana for an average of 8.1 (± 0.89) years gave informed consent for participation in clinical research studies. Each woman was in good health as determined by clinical and laboratory examinations. Women were studied in groups of three or four and lived on a clinical research ward for 35 days. A 7-day drug-free baseline was followed by 21 days of marijuana availability and a postmarijuana drug-free period of 7 days. Operant techniques were used to provide an objective and quantitative measure of performance for two alternative reinforcers, marijuana and money. Women could work for money throughout the study and for marijuana during the period of marijuana availability by pressing a button on a simple operant manipulandum. Women could earn either one marijuana cigarette (1 gm containing approximately 1.83 percent delta-9-THC) or 50 cents by 30 minutes of operant work on a second-order FR 300 (FI 1 sec: [S]) schedule of reinforcement. A fixed ratio (FR) of 300 responses on the fixed interval (FI) 1-second component of the schedule was required to earn a single purchase point. The FI 1-second schedule specified that only the first response after 1 second had elapsed was recorded as an effective response by the programming circuitry. Approximately 5 minutes of operant performance was required to earn 300 effective responses, or one purchase point on the FI 1-second schedule. Six purchase points were required to buy one marijuana cigarette or to earn 50 cents upon completion of the study.

Since subjects were studied in groups, scheduling admissions to coincide with any specific phase of the menstrual cycle was not possible. However, the period of marijuana availability extended over most of a complete menstrual cycle in 7 women and coincided with the premenstruum, defined as 3 days immediately before menstruation, in 15 women. Five of these fifteen women increased marijuana use during the premenstruum; five women decreased marijuana use during the premenstruum; and five women showed no change in marijuana use during the premenstruum.

Examination of scores on the Premenstrual Assessment Form (PAF) (Halbreich et al. 1982) showed a striking concordance between premenstrual dysphoria and marijuana use during the premenstruum. Women who increased marijuana use at the premenstruum reported significantly greater depression, anxiety, mood lability, anger, irritability, and impaired social functioning ($p<.05$) than women whose marijuana use decreased or stayed the same. Severity of premenstrual dysphoria appeared to be more important in differentiating the three groups of women than physical discomfort associated with the premenstruum. Although women who increased

marijuana use reported greater physical discomfort, pain, nausea, dizziness, and general malaise than the other two groups, with the exception of signs of water retention, these differences were not statistically significant. These data suggest that the dysphoric component of premenstrual tension is probably more closely associated with increased drug use than dysmenorrhea (Mello and Mendelson 1985).

An association between increased use of marijuana and alcohol and premenstrual dysphoria lends support to the notion that depression and anxiety associated with the premenstruum may be one proximal determinant of episodic increases in drug use by women. However, the experience of premenstrual dysphoria appears to be a critical factor, since recent studies indicate that drug use does not covary with menstrual cycle phase in women who do not report premenstrual dysphoria. Daily marijuana use did not covary with menstrual cycle phase in 30 women who reported no significant increase in Moos Menstrual Distress Questionnaire (MDQ) factors reflecting negative affect, decreased concentration, behavior change, or arousal (Griffin et al. 1985). Women completed daily diaries reporting drug use and MDQ (Form T) scores for three consecutive menstrual cycles, and 2,715 of a possible 2,741 diaries were returned. The group reported smoking an average of 1.4 (± 2.0) marijuana cigarettes per day, and individuals smoked between 7.3 (± 3.8) and 0.1 (± 0.4) marijuana cigarettes per day (Griffin et al. 1985). Both marijuana and alcohol use increased on weekends, and day of the week predicted drug use more reliably than any other variable in this sample. Neither unusual life events nor sexual activity were associated with concurrent alcohol and marijuana use (Lex et al. 1985).

The lack of significant variation of these MDQ factors across phases of the menstrual cycle was surprising since these female marijuana users were similar to the Moos normative sample in age, education, and menstrual cycle characteristics (Moos 1969). However, Moos' normative sample differed from women studied by Griffin and coworkers (1985) in that 9.7 percent were pregnant during standardization of the MDQ and over half were currently using a contraceptive pill.

DO DRUG EFFECTS DIFFER AT DIFFERENT PHASES OF THE MENSTRUAL CYCLE?

An issue related to the question of whether or not menstrual cycle phases affect drug self-administration is whether drug effects remain constant across the menstrual cycle. The literature concerning changes in the effects of alcohol in women at different phases of the menstrual cycle is conflicting and inconsistent (Mello 1980). According to reports in 1976, women develop higher blood alcohol levels at the premenstruum than during menstruation or at midcycle after equivalent doses of alcohol (Jones and Jones 1976a; Jones and Jones 1976b). Women absorbed alcohol more rapidly and developed significantly higher blood alcohol levels at the premenstrual period (80 mg/dl) than during menstruation or cycle

days 13 through 18 (64 and 68 mg/dl). Three women were studied daily throughout a single menstrual cycle and given a moderate dose of alcohol (0.66 ml/kg) at the same time each morning. There was considerable variation in blood alcohol levels, but the highest peak blood alcohol levels occurred during the premenstruum and at the periovulatory phase of the menstrual cycle (Jones and Jones 1976b). The investigators hypothesized that these data might be related to more rapid alcohol absorption (Jones and Jones 1976a; Jones and Jones 1976b). These data were surprising since increased water retention associated with the premenstruum would be more likely to result in lower blood alcohol levels after a fixed alcohol dose than at other times during the menstrual cycle. The degree of water retention in relation to the total body water-lipid pool would determine alcohol dilution in body water compartments.

Recent clinical studies have not confirmed reports that blood alcohol levels vary with menstrual cycle phase. Peak blood alcohol levels did not differ at the premenstruum, menstruation, and cycle days 12 to 15 in 9 women given sufficient alcohol to produce peak blood alcohol levels of 103 mg/dl (Hay et al. 1984).

One limitation of these clinical studies was that menstrual cycle phase was defined by calendar estimates and subsequent verification of predicted cycle phase was not reported. Changes in pituitary and gonadal hormone levels that define each menstrual cycle phase were not measured. A number of variables which might influence alcohol absorption and metabolism, such as drinking frequency, recency of alcohol consumption, other drug use, nutritional status, and hours of fasting, usually were not reported, and only a relatively low dose of alcohol was studied.

We reexamined the question of whether or not blood alcohol levels after a standard dose of alcohol vary as a function of menstrual cycle phase in female macaque monkeys (Mello et al. 1984). Monkeys were studied at four phases of the menstrual cycle: the premenstruum, menstruation, the periovulatory phase, and the midluteal phase. Calendar estimates of menstrual cycle phase were confirmed by radioimmunoassay of LH and estradiol. Ascending and peak blood alcohol levels after low (1.5 g/kg), moderate (2.5 g/kg), and high (3.5 g/kg) doses of alcohol were measured. The average peak blood alcohol levels after nasogastric intubation of low, moderate, and high doses of alcohol averaged 139 mg/dl, 238 mg/dl, and 335 mg/dl. There were no differences in peak blood alcohol levels at the premenstruum, menstruation, the periovulatory phase, or the midluteal phase of the menstrual cycle after a standard dose of alcohol. The only difference as a function of menstrual cycle phase was the rate of increase in blood alcohol curve after a low dose of alcohol. Blood alcohol levels were significantly higher 30 minutes after alcohol administration during the premenstruum than during menstruation or the midluteal phase ($p<0.02$). However, at higher alcohol doses, no significant

differences were observed in the rate of increase in blood alcohol levels as a function of menstrual cycle phase (Mello et al. 1984).

Recent studies of the acute effects of marijuana on subjective mood reports and pulse rate also showed no differences as a function of menstrual cycle phase (Lex et al. 1984). Twenty-eight women volunteered to live on a clinical research ward for 4 consecutive days. On the second and fourth days following admission, women were given marijuana (one 1-gm cigarette containing approximately 1.8 percent delta-9-THC) or marijuana placebo under double-blind conditions. Ten women were studied during the follicular phase of the menstrual cycle and nine during the luteal phase. While five subjects were studied during the ovulatory phase of the menstrual cycle, the brief duration of the periovulatory phase precluded their serving as their own controls, so a separate control group of four women were compared. Marijuana produced significant increases in ratings of intoxication within 15 minutes after smoking, whereas placebo marijuana cigarettes did not. However, there were no significant differences as a function of menstrual cycle phase in subjective level of intoxication or the time course or degree of elevation in pulse rate following marijuana. Marijuana did not alter factor scores on the POMS (Profile of Mood States) for friendliness, anger, fatigue, depression, tension, vigor, or elation. However, the confusion score (which includes feeling more confused, unable to concentrate, muddled, bewildered, forgetful, uncertain about things, and unable to be efficient) did increase after marijuana but not after placebo smoking. Confusion was somewhat more pronounced in subjects studied during the follicular phase (Lex et al. 1984).

In contrast to the relative lack of effects of menstrual cycle phase on subjective and physiological reactions to marijuana, there was a significant influence of history of marijuana smoking. Intermittent marijuana smokers (five or less times each week) had significantly higher pulse rates, subjective levels of intoxication, and POMS confusion scores than subjects with a past history of regular marijuana use defined as six or more times each week. Marijuana-induced changes in pulse rate, intoxication, and confusion persisted longer in subjects with a history of intermittent marijuana smoking (Lex et al. 1984).

These studies suggest that the effects of alcohol and marijuana remain relatively constant across the menstrual cycle. Since there appears to be no compelling evidence that alcohol and drug effects become more salient at any particular menstrual cycle phase, any changes in drug use which are consistently correlated with a specific phase of the menstrual cycle probably cannot be attributed to cycle-related changes in drug effects.

SEX DIFFERENCES AND ALCOHOL EFFECTS

Alcohol is unique among abused drugs in that it is distributed throughout body water and its concentration is affected by body

habitus (Kalant 1971). Men and women differ in total body water, and there are reports that women develop higher blood alcohol levels than men after an equivalent dose of alcohol (Jones and Jones 1976a; Jones and Jones 1976b; Dubowski 1976). Acute alcohol doses of 0.33, 0.66, and 1.32 ml/kg each produced higher blood alcohol levels in women than in male controls (Jones and Jones 1976a; Jones and Jones 1976b). These findings were interpreted to indicate that since women have less water per body unit than males, and since alcohol is distributed throughout the body water, the same dose of alcohol should result in higher peak blood alcohol levels in females than in males. However, this view has recently been challenged in studies of the acute effects of alcohol in men and women when data were adjusted statistically for total body water, estimated anthropometrically, or measured directly by 3H-water dilution (Sutker et al. 1983; Marshall et al. 1983). The most recent data illustrate the differential effects of the method used to calculate the alcohol dose (Goist and Sutker 1985). Blood alcohol levels in 12 men and 12 women (tested at the premenstrual phase of the menstrual cycle) were compared following acute alcohol administration. When alcohol doses were equated for body weight, women reached significantly higher peak blood alcohol concentrations than men. However, when equivalent alcohol doses were based on total body water, there were no significant sex differences. Self-reported levels of intoxication at peak blood alcohol levels did not differ as a function of either alcohol dose determination or sex (Goist and Sutker 1985).

Detailed comparisons of the effects of other drugs as a function of sex are not currently available. However, it seems unlikely that the effects of drugs administered intravenously or via inhalation would differ appreciably as a function of sex.

CONCLUSIONS

The effects of drugs do not appear to differ as a function of phase of the menstrual cycle. In women who do not experience premenstrual dysphoria, there appears to be no consistent relationship between drug use and menstrual cycle phase. However, there is some evidence that women who do have premenstrual dysphoria may increase alcohol and/or marijuana use at the premenstruum. These data suggest that premenstrual dysphoria may be one proximal determinant of increased drug use by women. Insofar as the periodic recurrence of premenstrual dysphoria covaries with changes in drug use, this may be one factor that differentiates drug use patterns in men and women. Further studies will be necessary to evaluate this hypothesis and examine the generality of the apparent covariance between alcohol and drug use and premenstrual dysphoria.

REFERENCES

Abelson, H.I.; Fishburne, P.M.; and Cisin, I. National Survey on Drug Abuse 1977. Vol. I. Princeton, NJ: Response Analysis Corporation,1977.

Alcoholism and Alcohol Abuse Among Women: Research Issues. National Institute on Alcohol Abuse and Alcoholism Research Monograph 1. DHHS Pub. No. (ADM) 80-835. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1980.

AuBuchon, P.G., and Calhoun, K.S. Menstrual cycle symptomatology: The role of social expectancy and experimental demand characteristics. Psychosom Med 47(1)-35-45, 1985.

Bardwick, J.M. The sex hormones, the central nervous system and affect variability in humans. In: Franks, V., and Burtle, V., eds. Women in Therapy. New Psychotherapies for a Changing Society. New York: Brunner/Mazel Publishers, 1974. pp. 27-50.

Belfer, M.L., and Shader, R.I. Premenstrual factors as determinants of alcoholism in women. In: Greenblatt, M., and Schuckit, M.A., eds. Alcoholism Problems in Women and Children. New York: Grune & Stratton, Inc., 1976. pp. 97-102.

Belfer, M.L.; Shader, R.I.; Carroll, M.; and Hermatz, J.S. Alcoholism in women. Arch Gen Psychiatry 25:540-544 1971.

Braude, M.C., and Ludford, J.P., eds. Marijuana Effects on Endocrine and Reproductive Systems, A RAUS Review Report. National Institute on Drug Abuse Research Monograph 44. DHHS Pub. No. (ADM) 84-1278. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off.. 1984. 135 pp.

Clayton, R. Extent and consequences of drug abuse. In: Drug Abuse and Drug Abuse Research, DHHS Triannual Report to Congress. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off. (461-357-6027), 1984. pp. 13-34.

Dubowski, K.M. Human-pharmacokinetics of ethanol. 1. Peak blood concentrations and elimination in male and female subjects. Alcohol Tech Rep 5(4):55-72, 1976.

Eddy, C.C., and Ford, J.L. Alcoholism in Women. Dubuque, IA: Kendall/Hunt Publishing Company, 1980. 189 pp.

Fehr, K.O., and Kalant, H., eds. Cannabis and Health Hazards. Toronto, Canada: Addiction Research Foundation, 1983. 843 pp.

Goist, K.C., and Sutker, P.B. Acute alcohol intoxication and body composition in women and men. Pharmacol Biochem Behav 22:811-814, 1985.

Goldberg, S.R.; Hoffmeister, F.; and Schlichting, U.U. Morphine antagonists: Modification of behavioral effects by morphine dependence. In: Singh, J.H.; Miller, L.; and Lal, H., eds. Drug Addiction I. Experimental Pharmacology. Mt. Kisco, NY: Futura Publishing Company, 1972. pp. 31-48.

Griffin, M.; Mendelson, J.H.; Mello, N.K.; and Lex, B.W. Marijuana use across the menstrual cycle. Submitted for publication, 1985.

Halbreich, U.; Endicott, J.; Schacht, S.; and Nee, J. The diversity of premenstrual changes as reflected in the Premenstrual Assessment Form. Acta Psychiat 65:46-65, 1982.

Harding, W.M., and Zinberg, N.E. Occasional opiate use. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Vol. III. Greenwich: JAI Press, 1983. pp. 27-61.

Haskett, R.F.; Steiner, M.; Osmun, J.N.; and Carroll, B.J. Severe premenstrual tension: Delineation of the syndrome. Biol Psychiat 15(1):121-139, 1980.

Hay, W.M.; Heermans, H.W.; Nathan, P.E.; and Frankenstein, W. Menstrual cycle, tolerance and blood alcohol level discrimination ability. Addict Behav 9:66-77, 1984.

Jones, B.M., and Jones, M.K. Alcohol effects in women during the menstrual cycle. Ann NY Acad Sci 173:567-587, 1976a.

Jones. B.M.. and Jones. M.K. Women and alcohol: Intoxication. metabolism, and the menstrual cycle. In: Greenblatt, M., and Schuckit, M.A., eds. Alcoholism Problems in Women and Children. New York: Grune & Stratton. Inc.. 1976b. pp. 103-136.

Kalant, H. Absorption diffusion, distribution and elimination of ethanol: Effects on biological membranes. In: Kissin. B.. and Begleiter, H., eds. The Biology of Alcoholism. Vol. I: New York: Plenum Press, 1971. pp. 1-62.

Kalant, O.J., ed. Alcohol and Drug Problems in Women. Research Advances in Alcohol and Drug Problems. Vol. V. New York: Plenum Press, 1980. 762 pp.

Knobil, E. The neuroendocrine control of the menstrual cycle. Recent Prog Horm Res 36:53-88, 1980.

Lex, B.W.; Mendelson, J.H.; Bavli, S.; Harvey, K.; and Mello, N.K. Effects of acute marijuana smoking on pulse rate and mood states in women. Psychopharmacology 84(2):178-187, 1984.

Lex, B.W.; Griffin, M.; Mello, N.K.; and Mendelson, J.H. Concordant alcohol and marijuana use in women. Submitted for publication, 1985.

Marijuana and Health. Institute of Medicine. Washington, DC: National Academy Press. 1982. 188 pp.

Marlatt, G.A., and Rohsenow, D.J. Cognitive. processes in alcohol use: Expectancy and the balanced placebo design. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Vol. I. Greenwich: JAI Press, 1980. pp. 159-200.

Marshall, A.W.; Tingstone, D.; Boss, M.; and Morgan, M.Y. Ethanol elimination in males and females: Relationship to menstrual cycle and body composition. Hepatology 3:701-706, 1983.

McGuire, M.T.; Mendelson, J.H.; and Stein, S. Comparative psychosocial studies of alcoholic and non-alcoholic subjects undergoing experimentally induced ethanol intoxication. Psychosom Med 28:13-25, 1966.

Mello, N.K. Stimulus self-administration: Some implications for the prediction of drug abuse liability. In: Thompson, T., and Unna, K.R Predicting Dependence Liability of Stimulant and Depressant Drugs. Baltimore: University Park Press, 1977. pp. 243-260.

Mello, N.K. Some behavioral and biological aspects of alcohol problems in women. In: Kalant, O.J., ed. Alcohol and Drug Problems in Women Research Advances in Alcohol and Drug Problems. Vol. V. New York: Plenum Press, 1980. pp. 263-298.

Mello, N.K. Etiological theories of alcoholism. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Vol. III. Greenwich: JAI Press, 1983a. 330 pp.

Mello, N.K. A behavioral analysis of the reinforcing properties of alcohol and other drugs in man. In: Kissin, B., and Begleiter, H., eds. The Pathogenesis of Alcoholism, Biological Factors. Vol. VII. New York: Plenum Press, 1983b. pp. 133-198.

Mello, N.K.; Bree, M.P.; Skupny, A.S.T.; and Mendelson, J.H. Blood alcohol levels as a function of menstrual cycle phase in female Macaque monkeys. Alcohol 1(1):27-31, 1984.

Mello, N.K., and Mendelson, J.H. Drinking patterns during work-contingent and non-contingent alcohol acquisition. Psychosom Med 34(2):139-164, 1972.

Mello, N.K., and Mendelson, J.H. Alcohol and human behavior. In: Iversen, L.L.; Iversen, L.D.; and Snyder, S.H., eds. Handbook of Psychopharmacology. Vol. XII. New York: Plenum Press, 1978. pp. 235-317.

Mello, N.K., and Mendelson. J.H. Operant acquisition of marijuana by women. J Pharmacol Exp Ther 235(1):162:171, 1985.

Mendelson, J.H.; McGuire, M.; and Mello, N.K. A new device for administering placebo alcohol. Alcohol 1:417-419, 1984.

Moos, R.H. Typology of menstrual cycle symptoms. Am J Obstet Gynecol 103:390-402, 1969.

Morse, W.H., and Kelleher, R.T. Determinants of reinforcement and punishment. In: Honig, W.K., and Staddon, J.E.R., eds. Operant Behavior. Vol. II. Englewood Cliffs, NJ: Prentice Hall, 1977. pp. 174-200.

Morse, W.H.; McKearney, J.W.; and Kelleher, R.T. Control of behavior by noxious stimuli. In: Iversen, L.L.; Iversen. S.D.; and Snyder, S.H., eds. Handbook of Psychopharmacology. Vol. VII. New York: Plenum Press, 1977. pp. 151-180:

Podolsky, E. Women alcoholics and premenstrual tension. J Am Med Women's Assoc 18(10):816-818, 1963.

Reid, R.L., and Yen, S.S.C. Premenstrual syndrome. Am J Obstet Gynecol 139:85-104, 1981.

Report of the Public Health Service Task Force on Women's Health Issues. Public Health Report 100(1):73-106. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1985.

Rubinow, D.R., and Roy-Byrne, P. Premenstrual syndromes: Overview from a methodologic perspective. Am J Psychiatry 141:163-172. 1984.

Ruble; D.N. Premenstrual symptoms: A reinterpretation. Science 197:191-292. 1977.

Sanders, D.; Warner, P.; Backstrom, T.; and Bancroft, J. Mood, sexuality, hormones and the menstrual cycle. I. Changes in mood and physical state: Description of subjects and method. Psychosom Med 145(6):487-501 1983.

Sandmaier, M. The Invisible Alcoholic: Women and Alcohol Abuse in America. New York: McGraw Hill, 1980. 298 pp.

Smart, R.G. The epidemiology of cannabis use and its health consequences in western countries. In: Fehr, K.O., and Kalant, H ., eds. Cannabis and Health Hazards. Toronto, Canada: Addiction Research Foundation, 1983. pp. 723-761.

Smith, S.L. Mood and the menstrual cycle. In: Sachar, E.J., ed. Topics in Psychoendocrinology. New York: Grune & Stratton; Inc., 1975. pp. 19-58.

Steiner, M., and Carroll, B.J. The psychobiology of premenstrual dysphoria: Review of theories and treatments. Psychoneuroendocrinology 2:321-335, 1977.

Steiner, M.; Haskett, R.F.; and Carroll, B.J. Premenstrual tension syndrome: The development of research diagnostic criteria and new rating scales. Acta Psychiatr Scand 62:177-190, 1980.

Sutker, P.B.; Tabakoff, B.; Goist, K.C.; and Randall, C.L. Acute alcohol intoxication, mood states and alcohol metabolism in women and men. Pharmacol Biochem Behav 18:349-354, 1983.

Tamerin, J.S.; Weiner, S.; and Mendelson, J.H. Alcoholics' expectancies and recall-of experiences-during intoxication. Am J Psychiatry 226:1697-1704, 1970.

Vaitukaitis, J.L. Premenstrual Syndrome. N Engl J Med 311(21):1371-1373, 1984.

Wilcoxon, L.A.; Schrader, S.L.; and Sherif, C.W. Daily self-reports on activities, life events, moods, and somatic changes during the menstrual cycle. Psychosom Med 38:399-417, 1976.

Wilsnack, S.C., and Beckman, L.J., eds. Alcohol Problems in Women: Antecedents, Consequences, Intervention. New York: Guilford Press, 1984. 480 pp.

Wilson, J.D., and Foster, D.W., eds. Williams Textbook of Endocrinology. 7th Edition. Philadelphia: W.B.Saunders, 1985.

Winger, G.D., and Woods, J.H. The reinforcing property of ethanol in the rhesus monkey. I. Initiation, maintenance and termination of intravenous ethanol-reinforced responding. In: Seixas, F.A., and Eggleston, S., eds. Alcoholism and the Central Nervous System. Ann NY Acad Sci 215:162-175, 1973.

Woods, J.H.; Downs, D.A.; and Carney, J. Behavioral functions of narcotic antagonists: Response-drug contingencies. Fed Proc 34(9):1777-1784, 1975.

ACKNOWLEDGEMENTS

Preparation of this review was supported, in part, by Grant #DA00101 from the National Institute on Drug Abuse, and Grants AA04368 and AA06252 from the National Institute on Alcohol Abuse and Alcoholism, ADAMHA.

AUTHOR

Nancy K. Mello
Alcohol and Drug Abuse Research Center
Harvard Medical School-McLean Hospital
115 Mill Street
Belmont, MA (12178

Gender Dimorphism in Brain

Michael Baum

The classic research of Jost (1950) and, more recently, of Wilson et al. (1981) established that androgen, secreted by the mammalian testes during fetal development, plays a crucial role in organizing the internal and external genital structures that are characteristic of the male. In the absence of this androgenic stimulation, individuals of either genetic sex develop phenotypically feminine internal and external genitalia. Knowing these facts, Young and his coworkers (Phoenix et al. 1959) provided the first indirect evidence that perinatal exposure of the male to testicular hormones permanently alters the structure of the mammalian brain. Working with guinea pigs, these workers found that prenatal administration of testosterone (T) to pregnant animals caused two types of change in the reproductive behavior of the female offspring. First, it defeminized their behavior, i.e., reduced their capacity to display feminine coital behaviors after adult treatment with ovarian steroids. Second, it masculinized their behavior, i.e., augmented their ability to display masculine coital patterns of behavior after adult treatment with T. Subsequently, these findings were repeated and extended in a wide variety of mammalian species (Baum 1979).

Further research, carried out in several nonprimate mammalian species, showed that perinatal exposure to testicular androgens also defeminizes the ability of the hypothalamic-pituitary axis to mediate estrogen-induced surges in luteinizing hormone (LH), which is characteristic of females around the time of ovulation (Neill 1972).

Although most investigators assumed that both these behavioral and neuroendocrine consequences of perinatal androgen exposure reflected a permanent, structural change in the CNS, it was only in 1971 that the first direct demonstration of such a structural change was published. Raisman and Field (1971) used electron microscopy to analyze synaptic connectivity in the dorso-lateral portion of the rat preoptic area (POA). They reported that, in females, preoptic dendrites receive a higher proportion of affer-

ent inputs onto dendritic spines than in males. Furthermore, neonatal treatment with T created the male phenotype in genetic females (Raisman and Field 1973).

This first finding of a sex dimorphism in neural connectivitywas followed by a report (Nottebohm and Arnold 1976) that the forebrain nuclei that control singing in song birds are larger in males (which typically sing) than in females (which sing considerably less than males). These first efforts laid the groundwork for numerous subsequent studies that have firmly established that, in several vertebrate classes, testicular hormones act in the male during species-specific, critical periods of development to alter the morphology of certain brain regions.

Raisman and Field (1971; 1973) originally directed their attention to the rat preoptic area (POA) because earlier research had implicated this area in the control of both reproductive behavior and the estrogenic regulation of LH secretion, two functions that were known to be sexually dimorphic. These workers used a tedious, quantitative analysis of synaptic connectivity to demonstrate a neural dimorphism. More recent work with the rat (Gorski et al. 1978), and subsequently with the guinea pig (Hines et al. 1985), gerbil (Commins and Yahr 1984a), and human (Swaab and Fliers 1985) has shown that nuclei exist in the male POA that are significantly larger, i.e., contain more neurons, than in the female. Along a similar line, my coworkers and I (Tobet et al., in press) recently found that, in the male ferret, a bilateral nucleus exists in the dorsal portion of the POA/anterior hypothalamus (POA/AH) which is not present in females (figure 1). This dorsal nucleus (dn) of the POA/AH consists primarily of neurons with large cell bodies. The somal areas of these neurons increased significantly in response to adult exposure to T or either of the two primary neural metabolites of T, estradiol (E) and dihydrotestosterone (DHT), but not to progesterone (Tobet et al., in press).

Adult exposure of gonadectomized female ferrets to these gonadal steroids failed to organize a male-like dnPOA/AH, nor did these treatments affect somal areas in cells located in the dorsal portion of the female POA/AH. Whereas adult exposure to sex steroids failed to create a dnPOA/AH in female ferrets, prenatal exposure to T, achieved by administerin T pellets to pregnant ferrets over the last 11 days of gestation (total gestation is 42 days), created a male-like dnPOA/AH in genetic females. Neonatal castration of male ferrets failed to block the normal development of a dnPOA/AH.

Taken together, these data show that the final quarter of gestation constitutes the critical period for the formation of this sexually dimorphic structure in the male ferret diencephalon.

A large body of literature (Callard et al. 1984) shows that, during perinatal development, androgen is readily converted into estrogen in subcortical brain regions of all vertebrate species

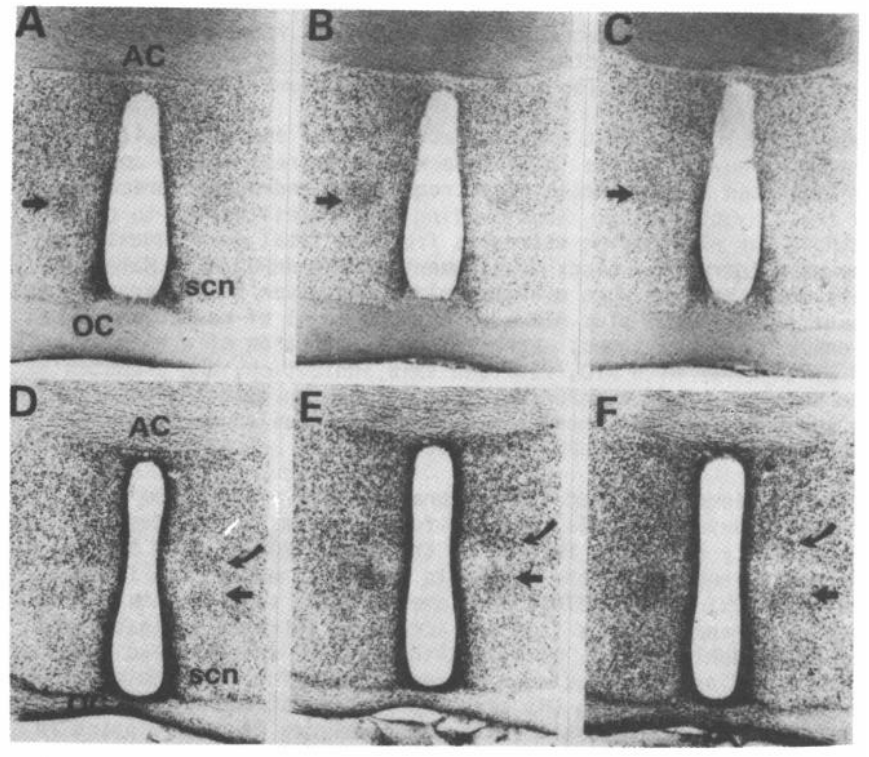

FIGURE 1. *Photomicrographs of sequential 60-micron-thick coronal sections through the preoptic/anterior hypothalamic area (POA/AH) of one gonadectomized adult female (A, B, and C) and one male (D, E, and F) ferret*

NOTE: Sections were stained with thionin. One bilateral nucleus can be seen in the ventral POA/AH of males and females (straight arrows), whereas in males a second more dorsal bilateral nucleus is also discernible (curved arrows). Magnification approx. 30x. AC- anterior commissure: OC- optic chiasm; V- third ventricle; acn- suprachiasmatic nucleus.

studied to date. The ferret is no exception to this rule. High levels of aromatase activity (the enzyme complex responsible for conversion of androgen to estrogen) are present in the AH/POA, hypothalamus, and temporal lobe of perinatal ferrets of both sexes (Tobet et al. 1985). Also, neural receptors for estrogen were isolated in these same brain regions 5 days prior to birth (earlier ages were not assessed), suggesting that the intraneuronal receptors for E are available prenatally to mediate biological actions of any estrogen present (Vito et al. 1985). These observations, together with the finding (Erskine and Baum 1982) that

plasma concentrations of T are significantly higher in males than in female ferrets prenatally, led us to ask whether the ability of T to create a dnPOA/AH in ferrets when given experimentally to fetal females, or when secreted endogenously in fetal males, depends on the formation and action of estrogenic metabolites of this testicular androgen. The answer is, quite unambiguously, yes.

Tobet (1985) found that administration of the steroid, 1,4,6-androstatriene-3,17-dione (ATD) to pregnant ferrets almost completely inhibited the synthesis of estrogen from androgenic precursor in fetal hypothalamus. Thus, adding ATD administration to other methods for eliminating estrogens from the fetal environment of the male ferret may block development of the dnPOA/AH. Male ferrets whose mothers were ovariectomized and given progesterone (to sustain pregnancy) plus ATD over days 30 to 41 of gestation lacked a dnPOA/AH in adulthood. Prenatal administration of a high dosage of E, together with ATD, reversed this inhibition, and promoted the development of a dnPOA/AH. Furthermore, prenatal exposure to an androgen receptor antagonist, flutamide, failed to attenuate the development of a dnPOA/AH in other males.

These findings show that local neural formation of E from T during embryonic development is required for the normal development of one sexually dimorphic feature of the dorsal POA/AH. In the rat the medial nucleus of the POA/AH is larger in males than in females (Gorski et al. 1978), and some evidence suggests that this size difference results from the action of estrogen perinatally in the male (Dohler et al. 1984). Although more species need to be studied, prior to proposing a universal role for estrogenic metabolites of T in creating CNS sex dimorphisms, strong data for two mammalian orders, rodentia (rat) and carnivora (ferret), point in this direction.

To date, there is only limited evidence linking the existence of morphologic dimorphisms of the POA/AH to sex differences in neuroendocrine or behavioral function. The best example of such a link exists in the gerbil, where lesions of the sexually dimorphic nucleus of the POA/AH in males caused severe deficits in scent marking and masculine coital behaviors (Commins and Yahr 1984b). To date, such studies have not been successful in the rat (Arendash and Gorski 1983). That is, although workers have long known that the rat POA contributes to the control of both masculine and feminine sexual behavior in males and females? respectively, and to the control of LH secretion in females, discrete manipulations of the sexually dimorphic area of the POA/AH have not caused consistent changes in any of these functions.

There is. however, suggestive evidence in the ferret that the estrogen-dependent dnPOA/AH may contribute to the normal process of coital masculinization in the male. Behavioral studies were carried out using the same ferrets that had been used in our anatomical study (Tobet 1985). All animals were castrated on postnatal day 5, and later in adulthood were given T propionate daily, prior

to being tested with sexually receptive females. Compared with a group of control males that were castrated on postnatal day 114, males that were castrated on postnatal day 5, and whose mothers were sham-operated (ovariectomized) and sham-implanted (progesterone plus ATD), displayed significantly lower levels of neck grip, mount, and pelvic thrusting behavior (coital behaviors displayed by the male ferret). However, males derived from mothers that had been ovariectomized and given progesterone plus ATD over gestational days 30 to 41 displayed even lower levels of these masculine coital behaviors than either control males or males whose mothers had received flutamide during gestation. Thus, we hypothesize that prenatal exposure to estrogenic metabolites of T leads to the development in males of a dnPOA/AH, which in turn promotes the sensitivity of the neonatal CNS to the behavioral, masculinizing action of T itself.

At present, no evidence exists showing whether, in humans, prenatal exposure of the developing male POA to estrogen promotes the development of the recently described sexual dimorphism of the POA/AH (Swaab and Fliers 1985). A recent study (Ehrhardt et al. 1985) has, however, shown that prenatal exposure of women to the synthetic estrogen, diethylstilbestrol (which in past years was given to pregnant mothers as an anti-abortion agent) did cause a small, yet statistically significant, increment in the incidence of homo- or bisexual orientation, as compared with either sibling or clinical control groups. Much more work remains to be carried out on both the behavioral and anatomical facets of human sexual differentiation. However, the available evidence is in general agreement with the results of experiments conducted using several different nonhuman mammalian species, including the ferret.

How do the above data concerning hormonally determined sex dimorphisms in brain morphology as well as in behavioral potential relate to the issue of gender and drug abuse? They may relate in at least two ways. First, the response of male and female patients to a therapeutic drug or to a drug of abuse may differ as a result of sexually dimorphic differences in brain structure. To date, most research along this line has been limited to elucidating sex differences that can be attributed to the action of sex steroids (ovarian steroids in the female/testicular steroids in the male) in either the liver (Gustafsson et al. 1980) or the brain (Decker et al. 1982). However, in neither animal models nor in man has much attention been paid to the possible contribution of sexually dimorphic neural structures or connectivity per se as keys to gender differences in drug action.

As more information becomes available concerning the existence of sex dimorphisms in brain structure, I expect more studies will be directed specifically to assessing possible consequences for drug action. A second possible interaction between drugs and gender dimorphisms in the brain concerns the possible effect of drugs consumed by the mother on the development of normal sex dimorphisms in brain structures. To my knowledge, nobody has shown di-

rectly that prenatal or perinatal exposure to any drug can influence the development of sexually dimorphic neuronal structures. However, much data concerning the effects of several drugs of abuse on neuroendocrine and behavioral parameters strongly suggests that perinatal drug exposure may ultimately affect behavior by altering the development of sexually dimorphic neural features.

A brief, selective review follows of studies in which perinatal exposure to drugs of abuse affected neuroendocrine function or behavioral development in animals. Administration of tetrahydrocannabinol to pregnant mice caused a significant reduction in plasma T in fetal male offspring; this deficit in T was associated with a long-term reduction in masculine coital ability (Dalterio and Bartke 1978; Dalterio and Bartke 1981). Similar reductions in fetal testicular secretion of T were observed in male rats born of mothers given phenobarbitol at the end of gestation (Gupta et al. 1982). Neonatal administration of pentobarbitol to male hamsters caused permanent deficits in masculine coital capacity (Clemens et al. 1979). Likewise, administration of morphine to pregnant rats late in gestation caused reductions in plasma T in fetal males that were associated with long-term deficits in masculine coital potential (Ward et al. 1983). By contrast, no such behavioral effect was obtained in male offspring derived from rats in which morphine treatment was stopped just prior to the onset of the gestational age of sexual differentiation, e.g., gestational day 18 (Vathy et al. 1985). In another study (Lumia et al. 1985) chronic ingestion of ethyl alcohol by pregnant rats caused significant increments in the ability of male offspring to display feminine sexual behavior in response to adult treatment with ovarian hormones (i.e., ethanol attenuated the normal process of coital defeminization) without affecting masculine coital potential. Similar effects were recently reported in the male offspring of pregnant rats treated with nicotine (Rodriguez-Sierra 1985).

None of these reported effects of various drugs of abuse on the reproductive behavioral capacity of offspring have as yet been linked directly to changes in the brain structure. In several instances, however, the effects of fetal exposure of drugs of abuse on later behavior have been linked, particularly in the male, to reductions in circulating levels of T. Such results, along with the knowledge that prenatal exposure either to T itself or to estrogenic metabolites of T may contribute importantly to brain sexual differentiation in males of several mammalian orders, raises the question of whether drug abuse in pregnant women may disrupt the normal course of brain sexual differentiation in their male fetuses. More basic studies on the hormonal regulation of brain and behavioral sex determination, coupled with studies on the possible effects of perinatal drug exposure on this process, are needed to answer this question.

REFERENCES

Arendash, G.W., and Gorski, R.A. Effects of discrete lesions of the sexually dimorphic nucleus of the preoptic area or other medial preoptic regions on the sexual behavior of male rats. Brain Res Bull 10:147-154, 1983.

Baum, M.J. Differentiation of coital behavior in mammals: A comparative analysis. Neurosci Biobehav Rev 3:265-284, 1979.

Becker, J.B.; Robinson, T.E.; and Lorenz, K.A. Sex differences and estrous cycle variations in amphetamine-elicited rotational behavior. Eur J Pharmacol 80:65-72, 1982.

Callard, G.V. Aromatization in brain and pituitary: An evolutionary perspective. In: Celotti, F.; Naftolin, F.; and Martini, L., eds. Metabolism of Hormonal Steroids in the Neuroendocrine Structures. New York: Raven Press, 1984. pp. 79-102.

Clemens, L.G.; Popham, T.V.; and Ruppert, P.H. Neonatal treatment of hamsters with barbiturate alters adult sexual behavior. Dev Psychobiol 12:49-59, 1979.

Commins, D., and Yahr, P. Adult testosterone levels influence the morphology of a sexually dimorphic area in the Mongolian gerbil. J Comp Neurol 224:132-140, 1984a.

Commins, D., and Yahr, P. Lesions of the sexually dimorphic area disrupt mating and marking in gerbils. Brain Res Bull 13:185-193, 1984b.

Dalterio, S., and Bartke, A. Perinatal exposure to cannabinoids alters male reproductive function in mice. Science 205:1420-1422, 1978.

Dalterio, S., and Bartke, A. Fetal testosterone in mice: Effect of gestational age and cannabinoid exposure. J Endocrinology 91:509-514, 1981.

Dohler, K.D.; Srivastava, S.S.; Shryne, L.E.; Jarzab, B.; Sipos, A.; and Gorski, R.A. Differentiation of the sexually dimorphic nucleus of the preoptic area of the rat brain is inhibited by postnatal treatment with an estrogen antagonist. Neuroendocrinology 38:297-301, 1984.

Ehrhardt, A.A.; Meyer-Bahlburg, H.F.L.; Rosen, L.R.; Feldman, J.F.; Veridiano, N.P; Zimmerman, I.; and McEwen, B.S. Sexual orientation after prenatal exposure to exogenous estrogen. Arch Sex Behav 14:57-78, 1985.

Erskine, M.S., and Baum, M.J. Plasma concentrations of testosterone and dihydrotestosterone during perinatal development in male and female ferrets. Endocrinology 111:767-772, 1982.

Gorski, R.A.; Gordon, J.H.; Shryne, J.E.; and Southam, A.M. Evidence for a morphological sex difference within the medial preoptic area of the rat brain. Brain Res 148:333-346, 1978.

Gupta, C.; Yaffe, S.J.; and Shapiro, B.H. Prenatal exposure to phenobarbitol permanently decreases testosterone and causes reproductive dysfunction. Science 216:640-642, 1982.

Gustaffson, J.A.; Mode, A.; Norstedt, G.; Hokfelt, T.; Sonnenschein, C.; Enroth, P.; and Skett, P. The hypothalamo-pituitarv-liver axis: A new system in control of hepatic steroid and drug metabolism. In: Litwack, G., ed. Biochemical Actions of Hormones. Vol. 7. New York: Academic Press, 1980. pp. 47-89

Hines, M.; Davis, F.C.; Coquelin, A.; Goy, R.W.; and Gorski, R.A. Sexually dimorphic regions in the medial preoptic area and the bed nucleus of the stria terminalis of the guinea pig brain: A description and an investigation of their relationship to gonadal steroids in adulthood. J Neurosci 5:40-47, 1985.

Jost, A. Recherches sur le controle de l'organogenese sexuelle du lapin et remarques sur certaines malformations de l'appareil genital humain. Gynec et Obstr (Paris) 49:44-60, 1950.

Lumia, A.; Kleber, P.; Van der Woude, S.; Flynn, J.; and Broide, J. Prenatal exposure to alcohol facilitates feminine sexual responsivity without disrupting masculine sexual behavior in male rats. Paper presented at the Conference of Reproductive Behavior, Asilomar, CA, June, 1985.

Neill, J.D. Sexual differences in the hypothalamic regulation of prolactin secretion. Endocrinology 90:1154-1159, 1972.

Nottebohm, F., and Arnold, A.P. Sexual dimorphism in vocal control areas of the songbird brain. Science 194:211-213, 1976.

Phoenix, C.H.; Goy, R.W.; Gerall, A.A.; and Young, W.C. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65: 369-382, 1959.

Raisman, G., and Field, P.M. Sexual dimorphism in the preoptic area of the rat. Science 173:731-733, 1971.

Raisman, G., and Field, P.M. Sexual dimorphism in the neuropil of the preoptic area of the rat and its dependence on neonatal androgen. Brain Res 54:1-29, 1973.

Rodriguez-Sierra, J. Prenatal nicotine exposure feminizes male rats at adulthood. Paper presented at the Conference on Reproductive Behavior, Asilomar, CA. June, 1985.

Swaab, D.F.; and Fliers, E. A sexually dimorphic nucleus in the human brain. Science 228:1112-1114, 1985.

Tobet, S.A. A sexual dimorphism in the preoptic/anterior hypothalamic area of ferrets: Hormonal determinants and functional correlates. Unpublished Ph.D. dissertation, M.I.T., 1985.

Tobet, S.A.; Shim, J.H.; Osiecki, S.T.; Baum, M.J.; and Canick, J.A. Androgen aromatization and 5-alpha reduction in ferret brain during perinatal development: Effects of sex and testosterone manipulation. Endocrinology 116:1869-1877, 1985.

Tobet, S.A.; Zahniser, D.J.; and Baum, M.J. Sexual dimorphism in the preoptic/anterior hypothalamic area of ferrets: Effects of adult exposure to sex steroids. Brain Res, in press.

Vathy, I.U.; Etgen, A.M.; and Barfield, R.J. Effects of prenatal exposure to morphine on the development of sexual behavior in rats. Pharmacol Biochem Behav 22:227-232, 1985.

Vito, C.C.; Baum, Bloom, C.; and Fox, T.O. Androgen and estrogen receptors in perinatal ferret brain. J Neurosci 5:268-274, 1985.

Ward, O.B., Jr.; Orth, J.M.; and Weisz, J. A possible role of opiates in modifying sexual differentiation. In: Schlumpf, M., and Lichtensteiger, W., eds. Drugs and Hormones in Brain Development. Basel: Karger, 1983. pp. 194-200.
Wilson, J.D.; George, F.W.; and Griffin, J.E. The hormonal control of sexual development. Science 211:1278-1284, 1981.

ACKNOWLEDGEMENTS

The author is the recipient of Research Scientist Development Award MH 000392. The author's research is supported by Grant HD 13634, awarded by the National Institutes of Health.

AUTHOR

Michael J. Baum, Ph.D.
Associate Professor
Department of Biology
Boston University
2 Cummington St.
Boston, MA 02215

Drugs and Drug Interactions in the Elderly Woman

Monique C. Braude

Although the elderly are commonly assumed not to be users of illicit drugs, they are generally recognized as having a high level of use of legal drugs. In fact, when speaking of the elderly, it seems more appropriate to speak of drug misuse than of drug abuse (Glantz 1982). To avoid confusion, definitions of the terms drug misuse and drug abuse will be those adopted by the Federal Strategy Council on Drug Abuse in 1979.

Drug abuse is the nontherapeutic use of any psychoactive substance, including alcohol, in such a manner as to adversely affect some aspects of the user's life. The substance may be obtained from any number of sources: by prescription, from a friend, over-the-counter, or through the illicit market. The use pattern may be occasional or habitual. Drug misuse is the inappropriate use of drugs intended for therapeutic purposes. This includes inappropriate prescribing or use of drugs resulting from inadequate knowledge of the drug's effects, by either the physician or the patient; it also includes self-medication by the patient in a manner inconsistent with the label information.

One difference between men's and women's use/misuse is owing to a higher proportion of women (60 percent) among the U.S. population aged 65 years and older. Because of the longer life expectancy of women, the problems of the elderly are increasingly those of women. Future growth of the older population is expected to be substantial and, by the year 2000, the Census Bureau projects a population of 19 million older women versus 12.7 million older men. In spite of this fact, research has failed to explore adequately the unique health problems of the older woman.

RISK OF ADVERSE EFFECTS DUE TO DRUG INTERACTIONS

Of major concern is the elderly woman at especially high risk for harmful effects from drug interactions. In Hecht's review of medicine and tie elderly (1983), the author pointed out the following facts. The elderly--those 65 and over--constitute at

present about 11 percent of the total population, yet they take about 25 percent of all drugs dispensed in the United States, both prescription and over-the-counter (OTC). It is the rare older patient who needs only one or two prescription drugs. For most, polypharmacy is the rule rather than the exception. A University of Florida College of Pharmacy survey reported, in 1980, that elderly patients took an average of eight different drugs a month. Other studies have shown that older patients may be getting as many as 14 to 18 different drugs in the course of a year. Nursing home patients have been reported to take as many as 20 to 30 drugs.

The reason the elderly take so many drugs is not hard to understand. They are more likely than other age groups to have one or more chronic illnesses, including heart disease, high blood pressure, diabetes and arthritis. Few such diseases can be treated with just one drug. Medication for chronic ills usually must be taken over long periods, frequently for the rest of the patient's life.

Elderly women have been prescribed drugs such as estrogens to replace diminished hormones after menopause and to prevent later years' osteoporosis. They also use sedatives, hypnotics, anti-anxiety drugs, antihypertensive medication, vitamins, analgesics, diuretics, laxatives, and tranquilizers at a rate of two and a half times that of elderly men.

The very fact that the elderly must take so many medications increases their chance of experiencing adverse reactions--a chance three times greater than that of the younger patient. Such reactions may be severe enough to require hospitalization. The reactions elderly patients may experience include stupor, confusion or paradoxical overstimulation from sedatives, intestinal bleeding from aspirin, lowered blood pressure from antipsychotics such as chlorpromazine, and fainting following use of antidepressants, diuretics, sedatives, tranquilizers, and some high blood pressure medications.

Taking so many drugs also increases the potential for harmful drug interactions. One drug can alter the effect of another, for instance, by speeding up or slowing down its metabolism in the liver, so that two similar drugs taken together may produce an effect that is greater than expected, or the drugs may counteract one another. Women, according to Hamilton and Parry (1983), and as supported by data from the Drug Abuse Warning Network (DAWN), have more adverse drug reactions than men and, especially after menopause, may be more vulnerable to tardive dyskinesia, a disorder associated with use of psychoactive drugs.

The young as well as the old patient can experience adverse drug reactions, but the problem is compounded in the elderly by the very process of growing old. With age, there are physiological changes that can affect the way in which drugs behave in the body

(Barry, this volume). In addition, such factors as diet, alcohol consumption, disease, weather conditions (such as high heat and humidity), malnutrition, and even bed rest can alter the movement of drugs through the body.

The potentiation of psychoactive drug effects by alcohol may represent an additional danger for older women. Although generally less recognized than for men, use of alcohol by older women to combat depression or feelings of inadequacy or loneliness exists, and can interfere with the drugs that they are taking for medical purposes. As the environmental stresses (such as loss of spouse, family and friends, income, employment, decreased physical beauty, mobility, health, stamina, valued roles at home and in the neighborhood, independence, self-esteem) increase in later years, women whose habitual coping responses to stress involved drinking or drug taking may be particularly vulnerable in old age. Most of the psychoactive drugs taken by the elderly woman to combat depression, for instance, are potentiated by alcohol, resulting in overdose incidents.

CHANGES IN DRUG DISPOSITION WITH AGE

The elderly woman may also be at risk due to changes in drug disposition, which may be the result of changes in absorption, distribution, metabolism, or elimination occurring with age. Drugs usually enter the body by mouth or by injection. How well drugs will produce their effect depends first on how well they are absorbed. While there is no clear evidence that age alone affects absorption, it has been suggested that decreased absorption might occur as a result of physiological changes such as decreased gastric acidity, or a reduction in peristaltic activity that changes the time it takes food to leave the stomach, or a decreased intestinal blood flow.

Where age does make a difference is in drug distribution, the process by which drugs are delivered to various sites in the body. Drug distribution in the elderly is altered in part because of changes in the body's composition. The total body water and lean body mass--essentially muscle and bone--decrease, while the proportion of fat increases, even though there is no increase in total weight. This means that drugs normally distributed in lean body tissue, such as digoxin, will end up at higher concentrations in the bloodstream. On the other hand, barbiturates (Nembutal and others), phenothiazines (Thorazine and others), and diazepam (Valium) are stored in fatty tissue. The increased fat in the elderly can serve as a reservoir for these drugs and prolong their "working" time.

Drug distribution can also be altered by age-related changes. Plasma proteins in the blood aid in transporting many drugs from the intestines throughout the body. A certain percentage of the drug is always bound to the protein. Only the unbound, or free, portion of the drug can work. Thus, binding is important in

determining how much drug will be available to produce the desired effect. With age, there is a decline in the amount of albumin, one of the blood proteins. Some drugs are highly bound to albumin, including the epilepsy drug Dilantin, Valium, and blood-thinning drugs (Dicumarol). A reduction in albumin will result in an increased amount of active drug, so what would normally be a therapeutic dose of the drug may prove to be a toxic one. Still other problems may develop because drugs compete for these binding sites. When one drug is blocked at the binding site by a second drug, the amount of the first drug that is freely circulating increases, as does the potential for toxicity. For example, phenylbutazone, salicylates, and sufonamides can displace tolbutamide (a drug for treating diabetes), leading to hypoglycemia.

Metabolism also changes with age. Drug metabolism rates in the elderly are one-half to two-thirds the rates of middle-aged and younger patients. Metabolism takes place primarily in the liver, where drugs are changed into water-soluble form so that they can be excreted. One drug may stimulate the metabolism of another, thus decreasing its effectiveness. Phenobarbital has this effect on anticlotting drugs. On the other hand, the antibiotic chloramphenicol slows the metabolism of these drugs, thereby increasing the magnitude and duration of their effects. The capability of the liver to perform this vital function depends on the blood flow to that organ. In the elderly, this blood flow is decreased. Drugs ingested orally, including beta blockers, narcotics, nitrates, hydralazine, and tricyclic antidepressants pass through the liver before they reach the general circulation. Because of the reduced blood flow, smaller amounts of these drugs are metabolized and excreted. Consequently, the amount that enters the elderly person's system is higher than it should be.

Finally, the body's processes for eliminating drugs can be impaired in the elderly because of changes that occur in the aging kidney, changes that are more dramatic than those in any other organ. The kidneys become smaller, as blood flow and filtering capacity decrease. Such kidney impairment retards the elimination of water-soluble drugs such as digoxin, certain antibiotics, chlorpropamide, and hypotensive agents, leaving the elderly patient more prone to adverse drug reactions.

INCREASED SENSITIVITY TO DRUGS IN THE ELDERLY

As if this weren't enough, the elderly appear to be more sensitive to certain drugs. For instance, they seem to be more affected by anticholinergic drugs. These drugs can cause confusion, disorientation, hallucinations, and delirium, as well as blurred vision, dry mouth, palpitations, and constipation in the elderly. Among anticholinergics are medications for spastic colon, drugs used for treatment of Parkinson's disease, some antihistamines, tricyclic antidepressants, and drugs to control irregular heartbeats. Older patients may experience fainting and dizzy spells from drugs such

as antidepressants, which don't usually produce such effects in younger patients. Older women also seem to be more sensitive to diazepam, thus requiring smaller doses than younger patients.

Nonprescription, or over-the-counter (OTC), drugs have a prominent place in the medicine cabinets of most elderly people. Analgesics (painkillers), antacids, cough and cold preparations, and laxatives are among the OTC drug products most frequently used by older people. While many people don't think of these as drugs, OTC drug products can be the cause of adverse side effects in older patients. Aspirin, for instance, can increase the effect of blood thinners, and decrease sodium and chloride excretion--a matter of concern to those with congestive heart failure. Chronic use of aspirin may lead to iron deficiency anemia. Antacids can interfere with the absorption of some drugs, such as the antibiotic tetracycline, while chronic use of laxatives can lead to electrolyte and water balance disturbances.

While many elderly people may have some vitamin deficiencies, treatment with megadoses of vitamins is generally not recommended. One reason for avoiding them is the side effects of such doses. Too much vitamin C may raise uric acid levels and trigger gout in those disposed to this painful disease. Vitamin C can also cause false readings on urine tests essential to control diabetes. Too much vitamin A can be the cause of fatigue, malaise and lethargy.

It would seem that the best way to avoid adverse reactions in older patients is simply to reduce the amount and number of drugs they take. However, prescribing for the elderly, like life itself, is not simple. The changes that come with age often are gradual, and patients, being individuals, do not necessarily age at the same rate. Drug manufacturers, for the most part, do not test their products in elderly patients, and there are no easy, clear guidelines to determine how much or little of a drug a particular patient will need. To solve some of these problems, the Food and Drug Administration, encouraged by the American Association of Retired Persons and the National Institute on Aging, is looking into the development of guidelines for geriatric testing of drugs.

One should not forget that, since older women suffer from multiple chronic illnesses and are users of multiple drugs, nutrition becomes a major health concern for this population, as these illnesses and concomitant drug use often interfere with the ability to eat and absorb foods needed for good nutrition.

CONCLUSIONS AND RECOMMENDATIONS

A comprehensive strategy will be necessary to respond to the growing crisis of resource shortages in the face of expanding numbers of older women, and a clear policy is needed regarding the health issues of older women. All relevant agencies at the State and Federal level should include this topic as a research priority.

The strategy needs to conceptualize aging women to include middle and later life, and needs to address the double jeopardy of agism and sexism. To be most effective, a strategy will require an integrated approach to the multiple factors influencing the health of elderly women and will respond to high-risk subgroups of older women. Solutions that strengthen informal caring are both cost-effective and practical; these can be integrated with formal resources.

The planning and implementation of a strategy to address the health issues of aging women will require research, education, resource coordination, legislation, advocacy, and insurance. The initiative now begun must continue to define areas of need and to distinguish the needs of the very elderly woman, whose risks are immediate and linked to long-term care, from those of the woman who is chronologically old but functioning at a high level, at least until she experiences health and economic deficits. It should also reflect the needs of the middle-aged woman dealing with life transitions and managing dependent people, and those of the younger woman with an old age to plan for.

A response to the health needs of older women requires continuity that incorporates a futuristic orientation with the imperatives of the present. To plan an effective current and future strategy, broad priorities must be matched with a comprehensive research agenda and educational efforts. A comprehensive research agenda would address the normal aging process as well as the pathological models. Furthermore, biomedical, applied health care, social science, and clinical intervention research are all part of this research agenda. To date, all types of research have neglected to design studies that compare older men with women, younger with older women, and subgroups of older women with each other. In studies where such data have been collected, information related to older women's concerns is either only partially analyzed or not readily accessible in published form.

The field is wide open to the creative investigator. New analytical procedures may need to be discovered and applied to produce reliable data about the interaction of age and gender variables. Health survey research, program design, and outcome studies need to be increased in number and scope.

Significant educational advances have been made in medical, nursing, social work, and other key professions as they shift toward more gerontological and geriatric content, but much of the curriculum is devoid of gender-related information. Clinical training often fails to reduce myths and stereotypes held by practitioners about older women. The focus of education can transcend the narrow pathological/disease perspective and move toward an understanding of function and dysfunction within an environmental perspective. With this understanding, economic resources in support of gerontological and geriatric education can be distributed effectively among the relevant disciplines, to

improve training and continuing education, so that the older woman is better served.

REFERENCES

Glantz, M. Predictions of elderly drug abuse. In: Peterson, D., and Whittington, F., eds. Drugs, Alcohol and Aging. Dubuque, Iowa: Kendall Hunt Publishing Co., 1982. pp. 117-126.

Hamilton, J., and Parry, B. Sex-related differences in clinical drug response: Implications for women's health. J Am Med Wom Assoc 38:126-132, 1983.

Hecht, A. Medicine and the elderly. FDA Consumer, September 1983. pp. 20-21.

AUTHOR

Monique C. Braude, Ph.D.
Senior Research Pharmacologist
Division of Preclinical Research
National Institute on Drug Abuse
Room 10A-31, Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Gender as a Factor in Treating the Elderly

Patricia P. Barry

THE ELDERLY

Chronologic age alone does not account for the increased incidence of drug toxicity with advancing years. Elderly persons have more disease, often severe and of long duration, requiring more medications. In addition, factors such as nutrition, mental status, functional capacity, and use of alcohol and cigarettes are important. In these respects, as in many others, the elderly comprise a heterogeneous group that must be carefully evaluated, on an individual basis, in the treatment of illness.

Several problems are common in the clinical practice of geriatrics. The elderly often are afflicted with multiple diseases. Heart disease. cancer, chronic lung disease, and Alzheimer's disease, which are major causes of death in the elderly, may also lead to chronic ill health. Additionally, functional impairment due to arthritis, impaired vision and hearing, and depression may limit the elderly person's ability to attend to personal needs, or to maintain mobility and adequate nutrition. The clinician must also consider the management of such common diseases as diabetes and hypertension in the treatment plan.

PHYSIOLOGIC CHANGES

Biological changes of aging have been recognized as important factors to be considered in planning drug therapy. Gastrointestinal changes, such as increased gastric pH, increased gastric emptying time (Stevenson et al. 1979). and decreased active transport (Bender 1968). have been noted in clinical studies. In the renal system, function declines in many elderly patients, even in the absence of renal disease. Such parameters as glomerular filtration, as well as tubular secretion and absorption, may be reduced as much as 35 percent (Rowe et al. 1976). Due to decreased endogenous production of creatinine (Vestal 1978). serum creatinine, which is a measure used to indicate kidney function, may not reflect the decrease in creatinine clearance, which may be as much

as 10 ml/min/decade (Kampmann et al. 1974). Cockcroft and Gault (1976) developed a useful formula for calculating estimated creatinine clearance in the elderly:

$$\text{Creatinine Clearance} = \frac{(140\text{-age}) \text{ body weight}}{72 \times \text{serum creatinine}}$$

The hepatic changes in the elderly are not usually reflected by abnormalities in the standard liver function tests. Not only can the production of albumin decrease, but reduced hepatic blood flow may be a major determinant of the prolonged metabolism of many drugs (Geokas and Haverbach 1969). Microsomal enzyme activity, especially hydroxylation (a Phase I reaction) is often reduced in the elderly (Greenblatt et al. 1982). Body composition alterations in the elderly include a reduction in lean body mass (Forbes and Reina 1970) and total body water (Novak 1972), and an increase in adipose tissue mass, which may be even more significant in elderly women than in elderly men (Greenblatt et al. 1982).

ALTERED PHARMACOKINETICS

The changes noted may affect the pharmacokinetics of many medications in the elderly patient. Absorption, reviewed by Stevenson et al. (1979), has not been shown to significantly decrease in most elderly persons. The drugs so far studied, however, are among those known to have good absorption properties in the general population, and it is possible that drugs known to be poorly absorbed will show decreased absorption by the elderly.

Drug distribution is influenced by the volume of distribution and the extent of protein binding. Drugs that are lipid soluble may have an increased volume of distribution in the elderly, due to the increased proportion of adipose tissue, especially in women. The volume of distribution for water-soluble drugs is contracted in many elderly, resulting in higher plasma levels. Finally, drugs that are extensively bound to albumin may have increased levels of unbound drug in the elderly, if the serum albumin is decreased.

Clearance is primarily a function of the liver and kidney, and is dependent upon blood flow to these organs. In elderly patients with diminished perfusion, therefore, clearance may be reduced due to decreased renal elimination and hepatic metabolism.

Both volume of distribution and clearance of a drug will affect the serum half life by the following relationship:

$$t\ 1/2 = \frac{0.693 \times \text{Volume of distribution}}{\text{clearance}}$$

Persons with increased volume of distribution or decreased clearance, or both, will have increased serum half life (t 1/2) and greater susceptibility to drug toxicity (Greenblatt et al. 1982).

DRUG PROBLEMS

In several studies of compliance reviewed by Vestal (1978), the elderly were found to have serious difficulties. Error frequencies ranged from 25 to 50 percent, and were often due to lack of understanding of drug regimens. Vestal also noted that the incidence of drug reactions is higher in the elderly, ranging from 15 to 24 percent in hospital settings. Drugs that may cause problems include digoxin, diuretics, antihypertensives, anticoagulants, bronchodilators, analgesics, sedative-hypnotics, antidepressants, and antipsychotics. Drug toxicity may be manifested by confusion, sedation, hypotension, fluid and/or electrolyte disturbances, cardiac arrhythmias, anorexia, urinary retention, and many other common complaints.

GENDER DIFFERENCES

Greenblatt et al. (1982) noted that the body proportion of adipose tissue increases with age, from 18 to 36 percent in men and from 33 to 48 percent in women. Women have a larger volume of distribution of lipid-soluble drugs, and a smaller volume of distribution for water soluble drugs. Decreased protein binding in women has been noted in some studies, but data are conflicting (Wilson 1984). However, diminished activity of hepatic oxidative enzymes, resulting in decreased drug clearance has been found to be more significant in elderly men than in elderly women (Greenblatt et al. 1982).

DRUG STUDIES

Sex-related differences have been studied by Greenblatt and coworkers, and reported for diazepam, desmethyldiazepam (an active metabolite), oxazepam, and temazepam; half-life of these drugs is consistently longer in women (Wilson 1984). Gender differences in oxidation are important in the metabolism of these drugs; for oxazepam and temazepam, the clearance rate is higher in men (Greenblatt et al. 1980a, Divoll et al. 1981); for diazepam and desmethyldiazepam it is lower in men (Greenblatt et al. 1980b; Ochs et al. 1981; Allen et al. 1980). The increased half-life of the latter drugs in women is apparently related to their greater volume of distribution for these lipid-soluble drugs.

Other drugs in which gender differences have been observed include heparin, which has greater adverse effects in women (Greenblatt et al. 1982), and imipramine, which is less protein-bound in women (Kristensen 1983). Goble (1975) has extensively reviewed a number of drugs for sex-related differences in response or side effects.

TREATMENT CONSIDERATIONS

Elderly women differ in other important respects from elderly men. They are more likely to be widowed, live alone, or reside in an institution; many have reduced income. (Elderly men more often

reside with their spouses, and often have the assistance of veterans' benefits.) Medical problems such as osteoporosis and urinary incontinence are more common in women, in addition to the obvious importance of medical problems specific to women, such as cancer of the breast, ovary, and uterus.

In the field of geriatric medicine, considerable attention has been directed to the problems associated with prescription drug use and misuse. Little attention has been directed to the specific considerations of elderly women, despite the fact that our population becomes increasingly female with age. Most drug studies comparing women with men have considered only younger women and have emphasized such factors as pregnancy, menstruation, and the use of oral contraceptives, despite the fact that women today live one-third of their lives after menopause. Future research must therefore address the physiologic, pharmacologic and socioeconomic factors that contribute to gender differences in our elderly population.

REFERENCES

Allen, M.D.; Greenblatt, D.J.; Harmatz, J.S.; and Shader, R.I. Desmethyl diazepam kinetics in the elderly after oral prazepam. Clin Pharmacol Ther 28:196-202. 1980.

Bender, A.D. Effect of age on intestinal absorption: Implications of drug absorption in the elderly. J Am Geriatr Soc 16:1331-1339, 1968

Cockcroft, D.W., and Gault, M.H. Prediction of creatinine clearnace from serum creatinine. Nephron 16:31-41, 1976.

Divoll, M.; Greenblatt. D.J.; Harmatz, J.S.; and Shader, R.I. Effect of age and gender on disposition of temazepam. J Pharm Sci 70:1104-1107, 1981.

Forbes, G.B., and Reina, J.C. Adult lean body mass declines with age: Some longitudinal observations. Metabolism 19:653-663, 1970.

Geokos, M.D., and Haverbach. B.J. The aging gastrointestinal tract. Am J Surg 117:881-892, 1969.

Goble, F.C. Sex as a factor in metabolism, toxicity and efficacy of pharmacodynamic and chemotherapeutic agents. In: Garattini et al., eds. Advances in Pharmacology and Chemotherapy Vol. 13. New York: Academic Press, 1975. pp. 174-252.

Greenblatt, D.J.; Allen, M.D.; Hirmatz; J.S.; and Shader, R.I. Diazepam disposition determinants. Clin Pharmacol Ther 27:301-302, 1980a.

Greenblatt, D.J.; Divoll, M.; Harmatz, J.S.; and Shader, R.I. Oxazepam kinetics: Effects of age and sex. J Pharmacol Exp Ther 215:86-91, 1980b.

Greenblatt, D.J.; Sellers, E.M.; and Shader, R.I. Drug disposition in old age. N Engl J Med 306:1081-1088, 1982.

Kampmann, J.; Siersbaek-Nielsen, K.; Kristensen, M.; and Molholm Hansen, J. Rapid evaluation of creatinine clearance. Acta Med Scand 196:517-520, 1974.

Kristensen, C.B. Imipramine serum protein binding in healthy subjects. Clin Pharmacol Ther 34:689-694, 1983.
Novak, L.P. Aging, total body potassium, fat free mass and cell mass in males and females between the ages of 18 and 85. J Geronotol 27:438-443, 1972.
Ochs, H.R.; Greenblatt, D.J.; Divoll, M.; Abernethy, D.R.; Feyerabend, H.; and Dingler, H.J. Diazepam kinetics in relation to age and sex. Pharmacology 23:24-30, 1981.
Rowe, J.W.; Andres, R.; Tobin, J.D.; Norris, A.H.; and Shock, N.W. The effect of age on creatinine clearance a man: A cross-sectional and longitudinal study. J Geronotol 31:155-163, 1976.
Stevenson, I.H.; Salem, S.A.M.; and Shepard, I.M.M. Studies on drug metabolism and absorption in the elderly. In: Crooks, J. and Stevenson, I.H., eds. Drugs and the Elderly. Baltimore: University Park Press, 1979. pp.51-63.
Vestal, R.E. Drug use in the elderly: A review of problems and special considerations. Drugs 16:358-382, 1978.
Wilson, K. Sex-related differences in drug disposition in man. Clin Pharmacokinet 9:189-202, 1984.

AUTHOR

Patricia P. Barry, M.D.
Geriatric Section
Department of Medicine and
Home Medical Service
Boston University Medical Center
Boston, Massachusetts

Gender and the Teenage Smoker

Ellen R. Gritz

INTRODUCTION

Cigarette smoking is no longer a behavior that is considered normative for men but socially disapproved for women, thus undertaken in secret, or openly as a symbol of risque or avante guarde feminism. As a result of sweeping changes in social forces during this century, cigarette smoking became an acceptable behavior for both males and females. We are thus witnessing the "disinhibition" of a problem, the emergence of a problem-in-waiting.

Women's smoking prevalence increased from 18.1 percent in 1935 to 33.3 percent in 1965 and has since decreased to 29.5 percent in 1983; in comparison, men's smoking prevalence decreased rather steadily from 52.5 percent in 1935 to 34.8 percent in 1983 (USDHHS 1980; NCHS, in press). The mean age of initiation of smoking among successive birth cohorts of women smokers from 1900 to 1960 has dropped to approximately the same mean age as men (USDHHS 1980). Interestingly, these great changes in women's smoking behavior have been paralleled by an unrivalled direct-appeal campaign by cigarette advertisers, which began in the mid- to late 1920's (Howe 1984).

The trend data describing women's smoking prevalence are not new, so why should it suddenly be considered the disinhibition of a problem? What is news in 1985 is the actualization of a National tragedy that was totally preventable--the emergence of lung cancer as the number one cause of cancer mortality among women, surpassing breast cancer (American Cancer Society 1985). In 1985, it is predicted that 38,600 women will die of lung cancer versus 38,400 of breast cancer. Lung cancer has become a major problem for women as a result of the dramatic increase in women's smoking just described. A disease that virtually did not exist in this country at the turn of the century is now killing more men and women annually than any other form of cancer (American Cancer Society 1985). The charge of this paper, however, is to concentrate on adolescent smoking and to speculate on some of the psychosocial factors which may promote smoking in teenage girls.

TRENDS IN CIGARETTE SMOKING AMONG ADOLESCENTS

Lagging behind, but paralleling changes in the smoking patterns of adult women, have been widespread changes in teenage smoking. However, "equality" in smoking behavior had been reached in adolescents prior to adults. National survey data show that gender differences in teenage cigarette smoking have virtually disappeared, and that female smoking now exceeds that of males for most analyses (Johnston et al. 1985; NIE 1979; Clayton, this volume). A series of cigarette smoking surveys among 12- to 18-year-olds was conducted by the National Clearinghouse for Smoking and Health and the National Institute of Education between 1968 and 1979 (NIE 1979). While a greater percentage of boys (14.7 percent) than girls (8.4 percent) smoked at the time of the 1968 survey, smoking prevalence increased steadily among girls until the 1979 survey, when the first evidence of a decline appeared. Smoking among boys began to decrease beginning with the 1972 survey. By 1979, the prevalence of smoking was higher among girls (12.7 percent) than among boys (10.7 percent). Although a National survey of smoking behavior in the 12- to 18-year-old age group has not been conducted since 1979, one is planned by the Office on Smoking and Health (Shopland, personal communication).

A second source of National data describing teenage smoking patterns comes from the Monitoring the Future project, a survey of drug use among high school seniors, conducted annually since 1975 by investigators at the University of Michigan Institute for Social Research and sponsored by the National Institute on Drug Abuse (Johnston et al. 1985). Between 1977 and 1980, the prevalence of cigarette smoking fell by nearly one-third and then leveled off for several years. The most recent survey showed the prevalence of daily use among high school seniors to be 18.7 percent in 1984--a reduction of 2.5 percent from the 21.2 percent prevalence in 1983 and a resumption of the downward trend (Johnston et al. 1985).

Gender-specific data revealed a higher prevalence of smoking among girls at levels of occasional smoking--one or more cigarettes per month (F=31.9 percent, M=25.9 percent) and one or more cigarettes per day (F=20.5 percent, M=16.0 percent). However, this gender difference decreased as consumption levels increased to one-half pack or more per day (F=12.8 percent, M=11.0 percent) and one pack or more per day (F=6.2 percent, M=6.6 percent), until approximate parity was reached at the latter consumption level, characteristic of adult smoking behavior. Figure 1 shows temporal trends by sex in daily cigarette smoking for any daily use and for one-half pack or more per day, and simultaneously displays temporal trends in daily use of marijuana and alcohol (Johnston et al. 1985). The trends for the three drugs are obviously quite different, with only cigarettes showing the reversal of the higher prevalence from males to females.

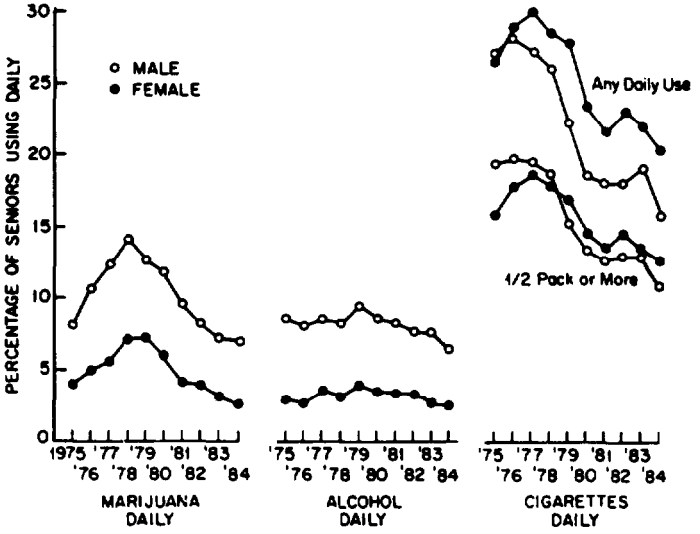

FIGURE 1. *Trends in 30-day prevalence of daily use of marijuana, alcohol, and cigarettes, by sex*

NOTE: Daily use for alcohol and marijuana is defined as use on 20 or more occasions In the past 30 days. Daily use of cigarettes is defined as smoking one or more cigarettes per day in the past 30 days.

SOURCE: Johnston e+ al. Use of licit and illicit drugs by America's high school students, 1975-1904. DHHS Pub. No. (ADM) 05-1394, 1985.

THE DEVELOPMENT OF SMOKING BEHAVIOR

Adolescent females have been characterized by cognitive and emotional immaturity, hypersensitivity to peer rejection, vulnerability to impulsive behavior, and difficulty in acquiring a positive body image (Freedman 1984). The combination of these four dimensions makes the teenage female exquisitely vulnerable to the seductive allure of smoking. Developmental models of the initiation of smoking behavior, such as that of Flay et al. (1983), set out factors predisposing to cigarette smoking; these may be biological, environmental, and/or psychological.

In the preparation or anticipation stage, family influences predominate. Thus, watching parents or older siblings smoke facilitates the development of a positive attitude toward smoking in the cognitively and emotionally immature girl and teaches her how, when, and where smoking is appropriate. The presence of smoking in the home will accustom her to the smell and sight of cigarettes and will also expose her passively to some of the health damaging effects of cigarette smoke, as well as teaching her to imitate the physical actions of smoking, if she is so inclined. As evidence

for this family influence, data show a fivefold increase in likelihood (20.3 percent versus 4.1 percent) that an adolescent girl will smoke if she is in a household in which one or both parents or an older sibling smoke compared to a household in which none of these persons smoke (NIE 1979).

During the period of initiation, trying the first cigarette, peers become most important. This is a period of social transition and of movement to a school more distant from home, a time where hypersensitivity to peer rejection may lead a young girl to accept the offer of a cigarette all too easily from a valued set of friends. Fifty percent of all first cigarettes are smoked with a friend (Bewley et al. 1974; Friedman et al. 1985; Palmer 1970), and almost 75 percent of all first cigarettes are smoked with another teenager (Biglan et al. 1983). Friedman et al. (1985) reported that 60 percent of all first-cigarette experiences or pressures to smoke occurred in the teenager's own home or in that of a friend, suggesting acceptance (or ease of sneak experimentation) in the two main social settings for this age group. Indeed, parents were even present in 7 percent of the first-cigarette incidents reported in that study. Teenage smokers stick together, as do nonsmokers, and initial experiences occur most frequently with persons of the same sex (Friedman et al. 1985; NIE 1979). Lifestyle choices are beginning to be made at this time, and may include a variety of behaviors and value orientations into which the image of a smoker fits (Wang-McCarthy and Gritz 1982).

The period of learning and becoming, experimental smoking, is operationally defined as smoking less than one cigarette per week. In this period of social reinforcement, the formation of a self-image is occurring. Thus, impulsive behaviors like smoking and experimentation with alcohol and sex may occur when socially prompted. The image of a smoker, described by both personality and physical attributes, can become highly valued and identified with; teenage girls may see smoking as a way to acquire such an image. McCarthy and Gritz (1984) demonstrated that the closer the ideal self-image of a smoker was to her/his description of a model in a cigarette advertisement, the more likely that adolescent intended to be a smoker (Barton et al. 1982; Chassin et al. 1981). In this stage of the model as well as in the following stage, the physical image of the female smoker portrayed in advertisements may wield substantial power. Also in this and the following stage, the smoker learns to regulate the nicotine dose of a cigarette, to become accustomed to its mood-altering and other pharmacologic effects, and to begin a pattern of conditioned reinforcement from smoking.

The final stage in the developmental model of smoking, habituation, is achieved when the adolescent is smoking at least one cigarette weekly. National surveys use this level to define regular smoking in the age group 12 to 18 years (NIE 1979). Dependence can begin to develop about this time. Skilled, by this stage, in techniques of inhalation and nicotine/dose regulation,

the teenage girl may especially learn to use cigarettes as a legal and sanctioned means of weight control, also highly valued during this period.

VULNERABILITIES FOR ADOLESCENT FEMALES: WEIGHT MD ADVERTISING

Using the developmental model for smoking for a teenage girl, it becomes easier to see how standards of slenderness and weight loss may be related to smoking and how cigarette advertising may capitalize on these and other descriptions of female beauty.

Feminine beauty has been equated with ultraslimness for a generation (Freedman 1984). Obsession with reducing body weight and the existence of serious eating disorders is increasingly prevalent among teenage girls and women today (Wooley and Wooley 1984; Yager 1985). Almost 20 years ago, Dwyer et al. (1967) reported that by the end of high school 60 percent of girls had already been on a serious diet and half that number were dieting at any one time (compared to 24 percent and 6 percent, respectively, for boys). Current data from the NIDA High School Senior Survey (Johnston et al. 1985) show an astounding use of nonprescription diet pills among female high school seniors: ever used, but not in past year--43 percent (versus 15 percent for boys); used in the past year, not in past month--27 percent (versus 9 percent for boys); used in past month, less than daily--14 percent (versus 5 percent for boys); and used daily in the past month--1.9 percent (versus 0.3 percent for boys). Interestingly, in the Glamour Magazine survey of 33,000 women, 50 percent of respondents reported using diet pills sometimes or often (Wooley and Wooley 1984). Analysis of the NIDA teenage data for concurrent use of reducing pills and cigarettes has not been reported, but an association might be predicted. Teenagers who smoke are more likely to have tried other substances such as alcohol and marijuana, and to engage in problem behaviors. The gateway theory of substance use predicts the order in which licit and illicit drugs are introduced, and analyses have been performed on continuation and discontinuation patterns (Jessor and Jessor 1977; Kandel 1978; Kandel and Logan 1984; O'Malley et al. 1984).

A recently published study (Charlton 1984) of smoking behaviors and beliefs conducted on 16,000 British children and adolescents revealed several fascinating relationships between beliefs about cigarette smoking and weight control:

- Across all respondents, the proportion agreeing that "smoking keeps your weight down" rose steadily from 16.6 percent in never smokers to 42.2 percent in the heaviest smokers (more than six cigarettes per week).

- This increase was more pronounced in girls than boys, and, among regular smokers (at least one cigarette per week) at all ages, girls were more likely than boys to agree that smoking controls weight.

- Concurrent with the advent of puberty, the belief among regular smokers that smoking controls weight takes a sharp increase, from 5.0 percent among 9- to 11-year-old girls to 35.7 percent in 12-year-old females. This belief rises steadily to a peak of 52.9 percent among 16-year-olds, the age at which a sharp drop in the percentage of males agreeing (29.0 percent) occurs. The authors note that among the various belief questions on the survey, only the question of weight control mirrors the post-pubertal rise in girls' smoking so closely. Comparable data for the United States are greatly needed, and could possibly be collected, along with the type of information in the NIDA High School Senior Surveys.

Cigarette smoking provides a lifestyle crutch with a physiological basis to facilitate weight control. Stimulation of the gastro-intestinal tract by nicotine results in increased tone and motor activity of the bowel (Gilman et al. 1980). Anecdotally, smoking a cigarette is said to suppress appetite; thus, smoking serves as a means of delaying eating or reducing consumption. Cigarettes are also often used to mark the end of a meal and frequently accompany coffee and alcohol consumption (McKennell and Thomas 1967). Thus, the ritual aspects of smoking and eating/drinking may come to represent social competence to an adolescent girl, along with an image of physical attractiveness.

This brings us to the putative role of cigarette advertising in female smoking, a highly debated influence with regard to the initiation of smoking. Pictorial advertising portrays smoking as fun, sophisticated, sexually adventurous, and involving risk taking (FTC 1981; FTC 1985; Yankelovich et al. 1977). At the very least, we can say that cigarette advertising provides an indirect Influence on smoking onset by supporting the image of smoking as a symbol of maturity, autonomy, and attractiveness.

These admired traits, and those mentioned above, form part of the myth surrounding the social benefits of smoking (Chapman and Fitzgerald 1982). Girls learn far earlier than puberty that beauty is a primary dimension of femininity; by adolescence, the cultivation of attractiveness has become a major task (Freedman 1984). Girls also grow up surrounded by omnipresent models of beautiful women on billboards, television, in movies and magazines, which are capable of influencing their evaluation of the importance of beauty for attaining popularity. Combined with the fact that early adolescence marks the highest degree of anxiety and greatest dissatisfaction with body image (Freedman 1984), the allure of cigarette ads targeted at women can be immense. Every psychosocial attribute and culturally relevant message valued in this age group can be found in cigarette ads which feature, in addition to those attributes mentioned earlier, athletics, dress, favorite activities, feminism, and very frequently, extreme slenderness.

The most recent Federal Trade Commission Report to Congress Pursuant to the Federal Cigarette Labeling and Advertising Act (Federal Trade Commission 1985) contains an analysis of cigarette advertising practices and expenditures for the years 1982-1983. In those years, ads directed primarily toward females featured glamorous and elegant women, and a "luxury brand" was introduced. The FTC Report summarizes the advertising approach as follows: "The cigarette marketers placed increasing emphasis on linking a particular brand with health, wealth, luxury, and achievement."

To note that cigarette manufacturers spent a total of $2.65 billion in 1983, compared to $1.2 billion in 1980, may serve to illustrate the degree of environmental flooding that is possible with a media campaign. The three forms of media on which the greatest amounts of money were spent for advertising in 1983 were magazines, newspapers, and outdoor displays, in decreasing order. Public entertainment or special events, including sports, musical, and other cultural events, received increased sponsorship. This included such sporting events as Team America Pro Soccer, the Western Rodeo series, Ski Days, the Virginia Slims Tennis Tournaments, and the Raleigh Children's Cancer Classic Celebrity golf Tournament. Cigarette advertising and giveaways, such as T-shirts with a brand logo, were frequently prominent at such events. Examples of cultural events sponsored in whole or part by the cigarette industry were the Kool Jazz Festival and the New York City Opera Company's National tour. Obviously, many of these events are attended by adolescents, who may even come to associate such attractions with particular brand images.

Recently, Warner (1985) has written convincingly regarding media self-censorship on the known relation between smoking and health. He cites several sources of self-censorship, the primary one being the fear of publishers that advertising will be withdrawn and thus substantial revenues lost if the health effects of smoking are openly addressed. Additionally, advertisements for antismoking products and services may be rejected by publishers for fear of offending the tobacco advertisers. Warner states, "Evidence... strongly suggests that the public is fed a media diet deficient in news, comment, and commercial promotion relating to the adverse consequences of smoking."

With specific regard to women's magazines, Whelan et al. (1981) reported that only eight feature articles on smoking or quitting were published in the 12 years between 1967 and 1979 in 10 leading magazines that carried cigarette advertising. Twice as many (16) such articles appeared during the same time period in two women's magazines that do not carry cigarette advertising. Compared to the dangers of smoking, far greater attention was given to other women's health issues, such as contraception, stress, mental health, and nutrition, in the magazines that accept cigarette advertising than in those that do not. Thus, there is a very clear source of bias in the amount of information about health issues, in general, and about smoking in particular, that an adolescent

female will encounter if she reads women's or other magazines which accept cigarette advertising. The female adolescent must somehow overcome this source of misinformation if she is to avoid habitual use of tobacco and increased risk of cancer.

DIRECTIONS FOR FUTURE HEALTH EDUCATION

To make nonsmoking appealing and counter the extremely sophisticated images presented by cigarette advertisers constitutes a major task for researchers and educators from the fields of school and public health, the medical professions, and health psychology (Gritz 1984; Howe 1984). Prevention programs often do not address the lifestyle choices and values of those adolescent girls most likely to take up smoking--those who are disinterested in school, not college-bound, who are precocious in social and sexual behaviors, and who may especially value the images peddled by advertisements (NIE 1979; Yankelovich et al. 1977). In addition, the health risks to fetus and mother associated with smoking in pregnancy, especially low birth weight, are important to remember since low birth weight is a major problem for teenage mothers (USDHHS 1980; USDHHS 1981). Parental smoking also elevates risk of respiratory disease in infants (USDHHS 1980). Thus, the teenage female smoker may be at risk for immediate as well as future health consequences. We need to learn to "market" nonsmoking to this population of young women in ways they will find attractive. using role models they adulate. In light of the worrisome prevalence trends of the mid-1980's. this may be our foremost undertaking in smoking prevention for women.

FOOTNOTES

1. Report to Congress: Pursuant to the Federal Cigarette Labeling and Advertising Act, for the Years 1982-1983. Washington DC: Federal Trade Commission, 1985. p. 7.

2. Warner, K.E. Cigarette advertising and media coverage of smoking and health. N Engl J Med 312(6):384-388, 1985. p. 387.

REFERENCES

Barton, J.; Chassin, L.; Presson, C.C.; and Sherman, S.J. Social image factors as motivators of smoking initiation in early and middle adolescence. Child Dev 53:1499-1511, 1982.

Better Health for Our Children: A National Strategy. Vol. IV. U.S. Department of Health and Human Services. Public Health Service, Office of the Assistant Secretary for Health and Surgeon General. DHHS Pub. No. (PHS) 79-55071. 1981. 931 pp.

Bewley, B.R.; Bland, J.M.; and Harris, R. Factors associated with the starting of cigarette smoking by primary school children. Br J Prev Soc Med 28:37-44, 1974.

Biglan, A.; Severson, H.; Bavry, J.; and McConnell, S. Social influence and adolescent smoking: A first look behind the barn. Health Educ 14:14-18, 1983.

Cancer Facts and Figures, 1985. New York: American Cancer Society, 1985. 31 pp.

Chapman, S., and Fitzgerald, B. Brand preference and advertising recall in adolescent smokers: Some implications for health promotion. Public Health 72(5):491-494, 1982.

Charlton, A. Smoking and weight control in teenagers. Public Health, (Lond) 98(5):277-281, 1984.

Chassin, L. Presson, C.C.; Sherman, S.J.; Corty, E.; and Olshavsky, R.W. Self-images and cigarette smoking in adolescence. Pers Soc Psychol Bull 7(4):670-676, 1981.

Dwyer, J.; Feldman, J.J.; and Mayer, J. Adolescent dieters: Who are they? Am J Clin Nutr 20:1045-1056, 1967.

Flay, B.R.; d'Avernas, J.R.; Best, J.A.; Kersall, M.W.; and Ryan, K.B. Cigarette smoking: Why young people do it and ways of preventing it. In: McGrath, P., and Firestone, P., eds. Pediatric and Behavioral Medicine: Treatment Issues. Volume of Behavior Therapy and Behavioral Medicine. New York: Springer, 1983. pp. 132-183.

Freedman, R.J. Reflections on beauty as it relates to health in adolescent females. Women Health 9(2/3):29-45, 1984.

Friedman, L.S.; Lichtenstein, E.; and Biglan, A. Smoking onset among teens: An empirical analysis of initial situations. Addict Behav 10(1):1-13, 1985.

Gilman, A.G.; Goodman, L.S.; and Gilman, A., eds. The Pharmacological Basis of Therapeutics. Sixth Edition. New York: Macmillan Publishing Co., Inc., 1980. 1843 pp.

Gritz, E.R. Cigarette smoking by adolescent females: Implications for health and behavior. Women Health 9(2/3):103-115, 1984.

Health, United States, 1985. National Center for Health Statistics, Public Health Service. Washington. DC: U.S. Govt. Print. Off., in press.

Howe, H. An historical view of women, smoking and advertising. Health Education 15(3):3-8, 1984.

Jessor, R., and Jessor, S.L. Problem Behavior and Psychosocial Development. A Longitudinal Study of Youth. New York: Academic Press, 1977. 281 pp.

Johnston, L.D.; O'Malley, P.M.; and Bachman, J.G. Use of licit and illicit drugs by America's high school students, 1975-1984, DHHS Pub. No. (ADM) 85-1394, 1985. 159 pp.

Kandel, D.B., ed. Longitudinal Research on Drug Use: Emperical Findings and Methodological Issues. Washington DC: Hemisphere-Wiley, 1978.

Kandel, D.B., and Logan, J.A. Patterns of drug use from adolescence to young adulthood: I. Periods of risk for initiation. continued use; and discontinuation. Am J Public Health 74:660-666. 1984.

McCarthy, W.J., and Gritz, E.R. Teenagers, cigarette smoking and reactions to selected cigarette ads. Paper presented at the Western Psychological Association. Los Angeles. April, 1984.

McKennell, A.C., and Thomas, R.K. Adults' and Adolescents' Smoking Habits and Attitudes. Government Social Survey. London: HMSO. 1967. 308 pp.
O'Malley, P.M.; Bachman, J.G.; and Johnston, L.D. Period, age and cohort effects on substance use among American youth, 1976-1982. Am J Pub Health 74:682-688, 1984.
Palmer, A.B. Some variables contributing to the onset of cigarette smoking in junior high school students. Soc Sci Med 4:359-366, 1970.
Report to Congress: Pursuant to the Federal Cigarette Labeling and Advertising Act, for the Years 1982-1983. Washington, DC: Federal Trade Commission, 1985. 50 pp.
Shopland, D. Personal communication. Acting Director, Office on Smoking and Health, June, 1985.
Staff Report on the Cigarette Advertising Investigation. Washington, DC: Federal Trade Commission, 1981. 210 pp.
Teenage Smoking, Immediate and Long-Term Patterns. Rockville, MD: Department of Health, Education, and Welfare, National Institute of Education, 1979. 259 pp.
The Health Consequences of Smoking for Women. A Report of the Surgeon General. Department of Health and Human Services, Public Health Service. Office of the Assistant Secretary for Health, Office on Smoking and Health. Rockville, MD: 1980. 359 pp.
Warner, K.E. Cigarette advertising and media coverage of smoking and health. N Engl J Med 312(6):384-388, 1985.
Whelan, E.M.; Sheridan, M.J.; Meister, K.A.; and Mosher, B.A. Analysis of coverage of tobacco hazards in women's magazines. J Public Health Policy 2:28-35, 1981.
Wong-McCarthy, W.J., and Gritz, E.R. Preventing regular teenage cigarette smoking. Pediatr Ann 11(8):683-689, 1982.
Wooley, W., and Wooley, S. Feeling fat in a thin society: 33,000 Women tell how they feel about their bodies. Glamour Magazine. February, 1984. pp. 198-252.
Yager, J. Introduction to section IV, eating disorders. Ann Rev Amer Psychiat Assn 4:401-405, 1985.
Yankelovich, Skelly, and White, Inc. A Study of Cigarette Smoking Among Teenage Girls and Young Women Summary of the Findings. DHEW Pub. No. (NIH) 77-1203, 1977. 31 pp.

ACKNOWLEDGEMENTS

This work was supported by PHS Grant No. 1-P50 CA36 409 awarded by the National Cancer Institute, DHHS.

AUTHOR

Ellen R. Gritz, Ph.D.
Director
Division of Cancer Control
Jonsson Comprehensive Cancer Center
10920 Wilshire Boulevard, Suite 1106
Los Angeles, CA 90024

Gender Differences in Drug Use: An Epidemiological Perspective

Richard R. Clayton, Harwin L. Voss, Cynthia Robbins, and William F. Skinner

The purpose of this paper is to provide a broad overview of gender differences in drug use. This is a formidable task because much of what is known about drug use is based on studies of males. Further, drug use is a heterogeneous phenomenon, involving a variety of drugs having effects that vary with circumstance. Specifically, this paper will examine:

- the prevalence of use of several drugs by men and women in different age groups (youth, 12 to 17 years old; young adults, 18 to 25 years old; mid-adults, 26 to 34 years old; and older adults, 35 years old or older);
- the use of psychotherapeutics medically and nonmedically, by sex and age group; and
- differences in age at onset of use of various drugs, by sex and age.

The findings are based on data obtained in the 1982 National Survey on Drug Abuse through personal interviews with 5,624 individuals 12 years old or older. Before examining these specific issues, however, we will review the broader societal context within which drug use and abuse by women has become a topic of major concern for public health professionals.

THE SOCIETAL CONTEXT OF PUBLIC HEALTH ISSUES

Some social issues are, by nature, temporary, being prominent for a period of time until the public turns its attention to other concerns. During the early 1960s, under the banner of civil rights, the twin issues of poverty and discrimination were prominent. During the late 1960s and early 1970s, the war in Vietnam was the major issue. As historians describe the past they often label eras by the issues that dominated the public's attention. Thus, references to the "civil rights" era and the "Vietnam' era invoke images that link us as individuals to forces at the societal level that influenced our lives.

Other social issues are, by nature, lingering or perhaps permanent, remaining prominent over longer periods of time and sustaining the public's attention. One such issue is drug abuse, which has been of growing public concern for almost two decades since the epidemic of marijuana use emerged in the mid-1960s (O'Donnell et al. 1976). One reason drug abuse has continued salience may be that the "drug scene" appears as constantly In flux. New drugs emerge, such as PCP and MDMA, or old drugs take fashion, such as cocaine, and a new epidemic threatens the public health.

Issues of public health and policy often link together, as new issues are seen in the context of matters already of public-policy concern. This has been the case for women's issues, ignored until quite recently. The existence of a conference focused on gender differences in drug use and abuse is one example of this linking of issues.

This linkage is timely. In the past, drug abuse research has focused too often exclusively on men, on only one class of drugs, such as opiates. or on one type of user, such as addicts. One cannot understand drug use and abuse in the United States by studying only male opiate addicts, just as one cannot understand alcohol abuse and problem drinking by studying only skid row alcoholics. In view of this, the mistakes of the past should not be continued by focusing exclusively on drug use and abuse among women, but rather both genders should be studied at the same time to reveal differences and similarities. More can be learned by studying gender as a variable, by comparing the patterns of drug use of men and women, than by studying either sex alone. While a few research questions are gender-unique in the drug field, for Instance, the influence of drugs on the neuronal and hormonal processes In the menstrual cycle (Mello, this volume), the majority of important questions about women's drug use and abuse are best addressed from a comparative perspective, using gender as an experimental variable.

BASIC ASSUMPTIONS

In addition to the assumption that a comparative approach offers a promising way to examine drug use and abuse by women, several additional assumptions underlie this paper.

First, production of knowledge takes time. The two national institutes dedicated to the study of substance abuse, alcohol and drug abuse, have been in existence for only 10 years. Instead of chastising ourselves for how little is known about gender differences in drug use, a more constructive approach would be to note how much has been learned in such a short time.

Second, while the differences between men and women have been of interest to poets, novelists, and philosophers for many years, only recently have social scientists devoted serious attention to

gender differences. The reason sex differences have been ignored is simple. For most of human history the lives of men and women were essentially on separate paths. There was a man's world and a woman's world. Obviously, this situation has changed markedly in the past 20 to 30 years. As options have expanded for both sexes, men and women are doing things now that never would have occurred in the past. There is considerable diversity in the behavioral options available for both sexes and considerable overlap in those options.

Finally, disciplinary disputes within the field of drug abuse appear to be dissipating, and the various disciplines now acknowledge the relevance of fields besides their own. Sociologists, for example, recognize that once the variables they consider to be relevant have been measured, a substantial amount of variance in drug use is left unexplained. The unexplained variance may be accounted for by independent variables favored by other disciplines. This recognition accounts, in part, for the ascendance of gender differences in drug use as important for public policy. By focusing exclusively on men or women, information is lost about gender as an independent variable affecting the dependent variable, drug use. Variance cannot be attributed to a constant.

EPIDEMIOLOGY AS AN ORGANIZING FRAMEWORK

The organizing conceptual framework for this paper is provided by epidemiology, of which there are at least three types: classical, psychiatric, and social. Classical epidemiology derives from a medical orientation and has usually been employed to trace the course of a disease through a population. Excellent examples of the application of classical epidemiology in the study of drug abuse are the investigations of De Alarcon (1969). Levengood et al. (1973), and Hughes et al. (1971) on the spread of heroin through communities.

Psychiatric epidemiology involves an application of classical (medical) techniques of tracing the spread of a phenomenon through a population, but adds diagnostic confirmational criteria to validate and further describe the particular phenomenon under study. For example, it may be important in studying drug use to confirm whether a drug was taken medically or illicitly. As Robins (1984) notes, what distinguishes drug abuse from infectious diseases as the focus of epidemiological research is "the willingness of the host to participate, at least at first."

Social epidemiology, in this paper, is the conceptual framework for examining gender differences in drug use. Social epidemiology is generally survey-based and is focused on a large geopolitical area rather than a single community. The principal functions of such studies are to provide a description. not only of the extent of the problem, but also its nature. The components as well as the size of the problem are measured to detect new aspects of the problem and to chart changes or trends. Social epidemiological

studies of drug use provide a picture of who is using what, at what frequency, and with what acute consequences. Social epidemiology is more useful for generating than testing hypotheses. One of the most useful functions of social epidemiological studies of drug use is to evaluate the accuracy of cornnonsense perceptions of the scope and nature of a social problem such as drug use.

LIFETIME PREVALENCE OF DRUG USE

Drug use is complex and difficult to study. The least precise, but most frequently measured dimension of drug involvement is lifetime prevalence, the use of one or more drugs over the course of a person's life. The data in table 1 are of this kind and show, by both gender and age group, the epidemic of drug use that occurred in the United States beginning in the mid-1960s, the epidemic related to the passage of the so-called "baby boom generation." Two of the age groups (18 to 25 and 26 to 34 years old) roughly correspond to the baby boom birth cohorts, or persons born in the years 1948 through 1964.

On the basis of earlier research, it would be hypothesized that the lifetime prevalence of use of illicit substances will be higher among males than females, while the prevalence of medical use of psychotherapeutics will be higher among females than males (Mellinger and Balter 1981; Yamaguchi and Kandel 1984).

Further, the prevalence rates for use of illicit drugs would be expected to be higher for individuals in the two baby boom age groups than for persons younger or older. Among youth, lower rates would be anticipated because initiation of drug use is developmental in character, building from one to several drugs and from infrequent to more frequent use. Lower rates would be expected among older individuals because they had entered adult roles when the drug epidemic of the 1960s and 1970s began. On the other hand, Mellinger and Balter (1981) suggest that the probability of using psychotherapeutic drugs increases with age, so that the prevalence rates for these drugs might be expected to be highest in the oldest age category.

Checking these assumptions against the 1982 survey data, we find agreement with expectations, with some exceptions. In table 1, 32 comparisons of males and females with respect to the use of illicit drugs can be made. The males, as expected, have the higher prevalence rate except for categories of prescribed drugs, regardless of age group. Furthermore, the rates for use of illicit drugs are higher in the two baby boom age groups, regardless of gender, also as expected.

The instances in which the hypotheses are not supported are in the use of prescription psychotherapeutics among youth, where in three of the four comparisons, males have slightly higher rates of use of prescription sedatives, stimulants, and analgesics. Females, however, show higher use of prescribed tranquilizers in most

TABLE 1. *Lifetime prevalence of various drugs by age group and gender: 1982 Rational Survey on Drug Abuse*

Drugs Used, Lifetime	Youth[a]		Young Adults[b]		Mid-Adults[c]		Older Adults[d]	
	M	F	M	F	M	F	M	F
	Percent							
Marijuana	27.5	24.4	67.6	59.6	64.8	46.6	17.0	7.3
Cocaine	6.5	6.4	34.5	22.3	25.7	17.9	6.6	1.9
Heroin	0.6	0.1	1.4	0.9	5.8	1.4	0.6	0.0
Hallucinogens	4.8	3.5	21.8	14.8	23.9	12.3	4.1	0.3
Sedatives-NM	4.6	4.0	20.5	13.5	15.8	8.4	3.5	0.3
Tranquilizers-NM	6.2	3.3	16.5	12.4	12.6	6.1	2.6	0.4
Stimulants-NM	5.9	5.7	16.8	12.2	16.4	9.3	3.5	1.1
Analgesics-NM	4.3	3.8	15.3	8.6	11.6	5.2	2.5	0.4
Sedatives-Rx	4.2	3.3	6.2	8.7	10.6	14.1	11.3	18.4
Tranquilizers-Rx	7.8	9.0	13.9	20.6	22.4	41.2	26.7	48.5
Stimulants-Rx	3.9	1.4	1.5	5.2	3.4	16.5	4.6	12.0
Analgesics-Rx	19.5	18.7	45.0	57.2	59.8	60.5	38.9	50.1

a. Youth, 12 to 17 years old in 1982, were born in 1965-70.
b. Young Adults, 18 to 25 years old in 1982, were born In 1957-64.
c. Mid-Adults, 26 to 34 years old in 1982, were born in 1948-56.
d. Older Adults, 35 years old or over in 1982, were born prior to 1948.

categories, as expected. If one allows for reasonable margins of error, male and female youth do not differ in terms of lifetime use of these four classes of drugs.

Contrary to expectations, the highest rates for psychotherapeutics are not uniformly found among the respondents in the oldest age group. It should be noted that the lifetime prevalence rates for some of the psychotherapeutics are quite high. For example, almost one-half of the females who are 35 or older have used tranquilizers medically, and 50 percent of these women have used analgesics medically. Further, the rates are somewhat higher among the women 18 to 25 and 26 to 34. While it would be inappropriate to interpret these data as evidence of abuse of these drugs, such high prevalence rates show that a substantial proportion of women age 35 and older are "at risk" for progression toward abusive patterns of use. It is, therefore, important to examine the frequency or extent to which these four classes of drugs are used by men and women, as well as how they are used (e.g., nonmedically only, medically only, both medically and nonmedically).

FREQUENCY OF USE

There is little consensus regarding what constitutes frequent or abusive use of drugs and, as one might expect, the criteria vary by class of drug. Because the literature offers few guidelines, an arbitrary decision was made to classify "more frequent" users according to the following definitions:

- for cigarettes, if they smoked a pack or more each day during the preceding 30 days;
- for marijuana, if they smoked during 10 or more days of the past 30 days;
- for alcohol, if they drank on 10 or more days of the past 30 days;
- for cocaine, if they used on 5 or more days of the past 30 days.

The data shown in table 2 reveal that patterned differences by sex exist when these criteria are applied. Almost three times as many adult men as women report using marijuana on 10 or more days during the preceding month. The ratio for alcohol use on 10 or more of the past 30 days is about 2.7 to 1. Thus, gender differences in drug use exist and are in the expected direction for this sample, whether the measure is lifetime prevalence or more frequent use of licit and illicit drugs.

MEDICAL AND NONMEDICAL USE OF PSYCHOTHERAPEUTICS

Some classes of drugs serve legitimate medical functions and are obtained primarily through prescriptions. These drugs can also be used nonmedically, or in ways inconsistent with the physician's instructions despite being obtained from a pharmacy. Persons who obtain drugs other than by means of a prescription are nonmedical users by definition, but it is also possible to misuse a properly prescribed drug, which is to use it nonmedically. In the 1982 National Survey, questions were posed that dealt with the medical and nonmedical use of sedatives, tranquilizers, stimulants, and analgesics.

The data shown in table 3 provide evidence concerning gender differences in the use of psychotherapeutic drugs by age group. A word of caution is necessary before these data are discussed. The figures are percentages of those who have "ever used" the particular substances, not percentages of the total sample. With this caveat in mind, the data in adjacent columns can be used to address important hypotheses about gender differences in drug use.

TABLE 2. *Recent, more frequent use of cigarettes, alcohol, marijuana, and cocaine, by age group and gender: 1982 National Survey on Drug Abuse*

Recent, More Frequent Use of Four Drugs	Youth[a]		Young Adults[b]		Mid-Adults[c]		Older Adults[d]	
	M	F	M	F	M	F	M	F
	Percent							
Cigarettes:								
Pack or more per day, past 30 days	5.0	2.3	19.1	18.0	31.2	22.4	25.2	15.1
Alcohol:								
Used 10 or more of past 30 days	4.2	0.7	27.2	10.4	28.3	13.1	27.6	12.2
Marijuana:								
Used 10 or more of past 30 days	7.4	3.8	23.1	8.7	11.3	7.1	2.2	0.2
Cocaine:								
Used 5 or more of past 30 days	0.5	0.5	2.7	0.3	0.8	0.2	0.1	0.0

a. Youth, 12 to 17 years old in 1982, were born in 1965-70.
b. Young Adults, 18 to 25 years old in 1982, were born in 1957-64.
c. Mid-Adults, 26 to 34 years old in 1982, were born In 1948-56.
d. Older Adults, 35 years old or over in 1982, were born prior to 1948.

As predicted, women are generally more likely than men to report medical use of psychotherapeutics except for youthful and older respondents, where the gender difference is reversed or smaller. Of the 16 comparisons, the only reversed gender difference is in use of stimulants by youth, 29 percent of males compared to 17 percent of females, but small or near zero gender differences appear for youth and older adults. It should be noted again that these percentages refer only to those who have ever used stimulants, not to all youth.

Forgetting prescribed medical use for now to look at gender differences in nonmedical use of psychotherapeutics (table 3), we

TABLE 3. *Percent of "ever users" of four classes of psychotherapeutics who report use nonmedically only, only by prescription, and both medically and nonmedically by age group and gender: 1982 National Survey on Drug Abuse*

Types of Usage of Four Classes of Psychotherapeutics	Youth[a]		Young Adults[b]		Mid-Adults[c]		Older Adults[d]	
	M	F	M	F	M	F	M	F
				Percent				
Sedatives:								
Nonmedical only	48	54	72	55	52	28	17	0.3
Rx-only	41	42	8	31	28	57	75	99
Both NonMed & Rx	10	4	20	14	20	15	8	1
Tranquilizers:								
Nonmedical only	39	24	46	29	23	6	5	0.4
Rx-only	52	71	36	58	57	86	91	99
Both NonMed & Rx	9	5	18	13	20	7	4	0.5
Stimulants:								
Nonmedical only	55	79	92	67	81	23	39	4
Rx-only	29	17	7	21	9	57	53	92
Both NonMed & Rx	16	4	1	12	10	20	8	4
Analgesics:								
Nonmedical only	8	13	10	3	4	1	2	0
Rx-only	81	83	69	85	81	93	94	99
Both NonMed & Rx	12	4	20	12	15	6	4	1

a. Youth, 12 to 17 years old in 1982, were born in 1965-70.
b. Young Adults, 18 to 25 years old in 1982, were born in 1957-64.
c. Mid-Adults, 26 to 34 years old in 1982, were born in 1948-56.
d. Older Adults, 35 years old or over in 1982, were born prior to 1948.

find males predominating, as expected, except in three instances--sedatives, stimulants, and analgesics among youth. but the significance of these exceptions has not been determined.

The expectation that males will be more likely than females to report using these drugs both medically and nonmedically is supported by the data. Of 16 possible comparisons, two are exceptions to this expectation. Both exceptions occur for stimulants

for young and mid-adults and involve substantial differences between males and females. Among young adults, only 1 percent of the males who have used stimulants report having used both medically and nonmedically in comparison with 12 percent of the females. Among mid-adults, 10 percent of males and 20 percent of females use stimulants both medically and nonmedically.

Overall, these data confirm expectations based on the existing literature concerning gender differences in the use of the psychotherapeutics. It is also apparent that persons in the older age groups, particularly the oldest group, are most likely to have used these drugs only in a medical context (see table 3). The exceptions to the expected patterns cluster in one class of drugs, the stimulants. There is evidence from the survey of high school seniors that the proportion of females using stimulants nonmedically for weight control has increased substantially during the past 10 years (Johnston et al. 1985). This may account, at least partially, for the high proportion of young females who report that they used stimulants only nonmedically.

CONSEQUENCES OF USE OF PSYCHOTHERAPEUTICS

There is a commonsense but untested assumption that use of psychotherapeutics by women is related to role-related stress. Stated differently, women are said to use these drugs in a quasi-medical way to cope with or to alleviate stress. In the 1982 National Survey on Drug Abuse, the respondents were asked if they had ever experienced the following consequences as a result of using the psychotherapeutic drugs: depression, argumentativeness, automobile accident, trouble at school, trouble at work, or a medical emergency. In analyzing these data, the psychotherapeutics were combined into three mutually exclusive categories: nonmedical use, medical use, and both medical and nonmedical use. The questions had been posed with respect to specific drugs, but our interest was in respondents experience of the consequence, regardless of the specific psychotherapeutic drug producing it. Age was ignored because the number of positive responses was too small for a meaningful analysis by age.

Looking at table 4, it is clear that respondents rarely attribute adverse consequences to the use of psychotherapeutics. The most prevalent consequence is depression, but it is reported by only 5.9 percent of the males and 7.1 percent of the females who had ever used the psychotherapeutics. Respondents who used psychotherapeutic drugs both medically and nonmedically were more likely to report depression and argumentativeness than subjects who used drugs only medically or only nonmedically. There do not seem to

TABLE 4. *Consequences attributed to use of psychotherapeutic drugs (sedatives, tranquilizers, stimulants, analgesics) by, type of use and gender: 1982 National Survey on Drug Abuse*

Gender and Problems Attributed to Use of Psycho-therapeutic Drugs	Types of Use (Percent)			
	Rx Only	Nonmedical Only	Both Nonmedical and Medical	Totals
MALES n=	[1,081]	[104]	[275]	[1,461]
Depression	3.4	7.9	15.0	5.9 [86]
Argumentative	1.4	7.1	15.5	4.6 [67]
Auto Accident	0.0	5.0	4.0	1.0 [16]
Trouble--School	.2	5.2	8.6	2.2 [32]
Trouble--Work	1.8	3.1	3.2	2.2 [32]
Medical Emergency	.2	0.0	2.3	.6 [9]
FEMALES n=	[1,743]	[49]	[218]	[2,009]
Depression	5.4	16.4	18.4	7.1 [142]
Argumentative	2.2	13.6	15.0	3.4 [78]
Auto Accident	.1	0.0	.9	.3 [5]
Trouble--School	.6	6.1	9.6	1.8 [36]
Trouble--Work	1.0	1.0	6.6	1.6 [32]
Medical Emergency	.1	0.0	3.2	.5 [9]

be differences between males and females, except for depression in respondents who report only nonmedical use of psychotherapeutics. Few people, however, reported any adverse consequences, and the sample is too small for reliably measuring small differences.

AGE AT INITIATION OF DRUG USE

Although concern has been expressed that children are initiating drug use at younger and younger ages, little research has focused directly on age at onset. Virtually nothing is known about gender difference in age at onset for abused drugs, including whether or not it has changed over the years.

In the 1982 National Survey, respondents were asked to specify the age of first use of various drugs. In presenting the data, a decision was made to exclude persons between the ages of 12 and 19 because the usual age at onset for the "gateway drugs"--cigarettes, alcohol, and marijuana--is presumed to occur during the teens. By starting with persons who have already passed

through the period during which they are "most at risk," we avoid the problem of confounding due to differential periods at risk.

Adjacent birth cohorts (e.g., 20 to 21, 22 to 23) were combined to avoid the problem of small sample size in certain cells of the table. It was decided not to present age at onset for age groups in which less than 10 percent of respondents used the drug.

Finally, medians rather than means are presented because they are less sensitive to outliers.

These data are relevant to important issues and questions of public policy:

- Is the age at onset of drug use decreasing? If so, for what drugs?
- Have the differences between males and females in age at onset of drug use changed?
- From an epidemiological perspective, is there evidence of an age, period, or cohort effect with regard to age at onset of drug use?

The data in tables 5 and 6 show, by gender, the median age at onset of use, both medical and nonmedical, of a number of drugs and drug classes--cigarettes, alcohol, marijuana, cocaine, sedatives, tranquilizers , stimulants, and analgesics. The ages shown in these tables reflect midpoints--one-half of the subjects who report use of that particular drug first used it earlier than the age shown, while the other half used it later.

Cigarette and Alcohol Use

In every comparison between men and women for cigarettes and alcohol, the median age at onset of use is higher for women than it is for men (figure 1). The median age at onset for cigarettes appears to be rising for males, the average median age being 13.6 for young respondents (12-19) compared to 12.8 for older respondents (58-65). The trend for women is the opposite, with the average median age being 14.5 for young respondents and 16.6 for older respondents. It is important to note that although a greater change occurred among women, the net result is a convergence in the median age at onset of cigarette use for males and females.

This convergence depends on both women and men changing age at first use (cigarettes) and in opposite directions.

TABLE 5. *Median age at first use of various drugs: 1982 National Survey on Drug Abuse (males)*

Age	Birth-Year	Cigs	Alco	Marij	Seds NM	Seds Rx	Tran NM	Tran Rx	Stim NM	Stim Rx	Anal NM	Anal Rx	Coca
20-21	1961/62	13.5	14.5	15.7	17.6	15.2	17.0	17.0	17.5	****	17.4	17.4	18.5
22-23	1959/60	13.7	14.7	15.5	18.1	14.8	16.9	17.7	18.2	****	18.9	18.7	18.5
24-25	1957/58	13.3	14.8	16.0	17.5	****	18.5	18.7	18.3	****	18.5	18.1	19.7
26-27	1955/56	14.1	15.5	16.9	17.2	18.0	17.2	19.0	17.1	****	****	19.8	22.1
28-29	1953/54	13.7	15.5	17.6	18.5	****	20.4	21.5	19.8	****	21.6	21.3	21.2
30-31	1951/52	13.6	16.0	18.5	18.2	****	18.3	24.1	19.0	****	18.3	22.7	23.4
32-33	1949/50	14.6	16.1	19.4	21.2	24.2	****	23.3	20.5	****	****	22.5	27.1
34-35	1947/48	13.7	15.4	20.9	22.7	24.0	22.8	27.7	20.4	****	25.3	23.5	30.0
36-37	1945/46	12.1	13.2	20.5	25.4	13.7	****	24.7	18.4	****	19.6	24.9	22.2
38-39	1943/44	13.9	16.0	21.8	****	****	****	33.3	****	****	****	27.7	32.8
40-41	1941/42	13.7	15.3	25.1	****	22.3	****	35.8	****	31.9	****	19.8	33.8
42-43	1939/40	15.4	17.4	30.0	40.0	29.0	35.0	30.4	35.0	****	****	20.2	41.0
44-45	1937/38	12.0	15.2	39.2	****	****	****	39.5	****	****	****	32.3	****
46-47	1935/36	12.1	12.4	35.0	****	****	****	36.8	****	****	****	31.6	****
48-49	1933/34	14.9	16.1	****	****	43.7	****	44.5	****	****	****	44.2	****
50-51	1931/32	12.2	16.4	40.0	****	****	****	36.2	****	****	****	44.4	****

****Less than 10 percent of respondents in this 2-year age group report use of the drug.

TABLE 5. *Median age at first use of various drugs: 1982 National Survey on Drug Abuse (females)*

Age	Birth-Year	Cigs	Alco	Marij	Seds NM	Seds Rx	Tran NM	Tran Rx	Stim NM	Stim Rx	Anal NM	Anal Rx	Coca
20-21	1961/62	14.2	15.7	16.2	17.3	****	17.6	17.5	17.6	****	****	17.7	18.0
22-23	1959/60	13.9	15.4	15.9	17.3	16.2	16.6	18.0	17.4	****	16.3	18.4	19.8
24-25	1957/58	14.4	16.3	16.4	17.3	****	17.1	20.7	16.8	****	****	19.6	20.6
26-27	1955/56	15.5	16.5	17.0	18.2	21.5	****	21.5	19.4	21.2	****	20.2	20.9
28-29	1953/54	15.3	16.7	18.2	20.2	20.4	****	21.7	18.6	20.2	****	21.3	23.6
30-31	1951/52	15.6	17.3	19.1	****	24.1	****	23.3	22.2	19.8	****	22.5	27.0
32-33	1949/50	15.7	17.5	20.3	****	24.6	****	24.9	****	24.1	****	23.9	28.1
34-35	1947/48	16.3	17.9	23.5	****	24.8	****	25.2	****	25.1	****	24.2	****
36-37	1945/46	16.2	17.0	24.8	****	23.4	****	28.9	****	26.0	****	26.5	32.2
38-39	1943/44	14.7	17.4	****	****	29.6	****	27.4	****	22.3	****	29.0	****
40-41	1941/42	15.8	18.5	34.9	****	28.9	****	30.3	20.0	24.3	****	27.9	38.2
42-43	1939/40	15.4	18.7	****	****	25.1	****	30.3	****	30.1	****	35.6	****
44-45	1937/38	15.6	17.6	31.1	****	33.7	****	37.2	****	36.6	****	33.8	****
46-47	1935/36	15.7	18.8	****	****	35.1	****	30.8	****	30.0	****	28.3	****
48-49	1933/34	18.4	18.2	****	****	33.0	****	40.2	****	35.1	****	35.7	****
50-51	1931/32	16.8	17.7	37.7	****	****	****	37.6	****	31.8	****	40.4	****

****Less than 10 percent of respondents in this 2-year age group report use of the drug.

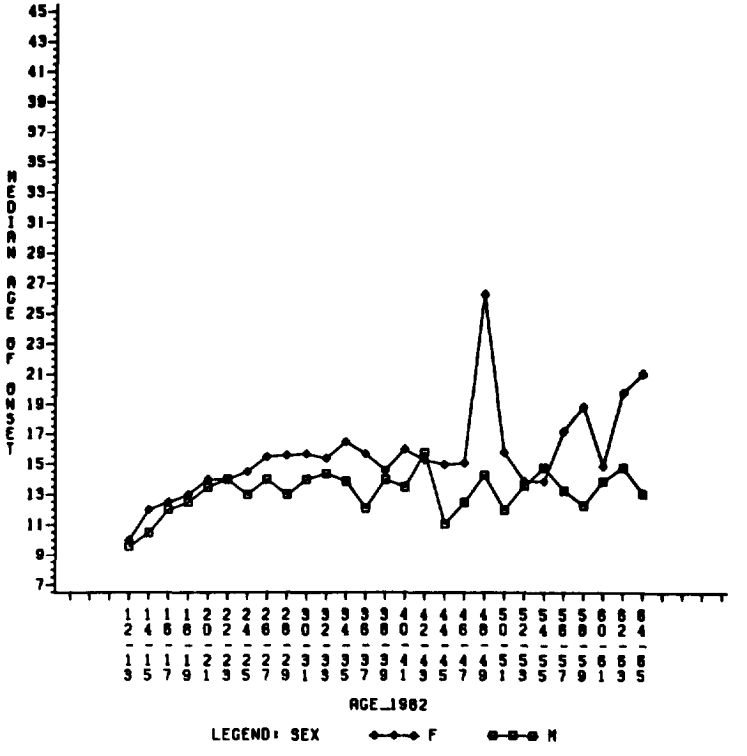

FIGURE 1. *Median age of onset of cigarettes for males and females*

For alcohol, males show no change in their age at first use (figure 2). For males, initial use of alcohol is a developmental or age-specific phenomenon. For women, median age at first use of alcohol has dropped an average of almost 2 years from the oldest to the youngest four age groups. This suggests an influence of era, a cohort effect, for females beginning to consume alcohol in this society.

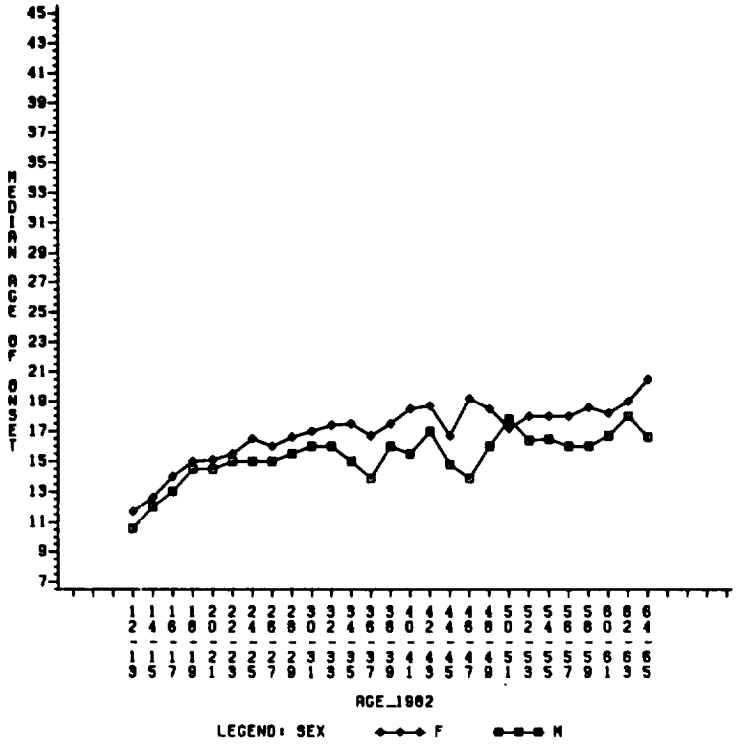

FIGURE 2. *Median age of onset of alcohol for males and females*

Marijuana and Cocaine

Three findings are apparent from examining the data for marijuana in tables 5 and 6. First, men in only one age group have less than 10 percent of respondents reporting marijuana use compared to four such age groups for women. Second, for both men and women, the median age at first use of marijuana is related to when the respondents were born, with younger age groups starting use earlier than older respondents. This suggests either a cohort or a period effect for marijuana use. Third, there is little difference by gender in the median age at onset of marijuana use. For example, for each of the cohorts born between 1949-50 and 1961-62, there Is less than a l-year difference between males and females in onset of marijuana use.

For cocaine, also, there is a cohort or a period effect, with the younger respondents using the drug earlier than the older age groups. For females there are seven age groups in which less than 10 percent of the respondents report use of cocaine, while for males there are four. The trend is toward younger men and women starting use of cocaine. A separate analysis of data from the 1982 National Survey focusing explicitly on cocaine suggests that an epidemic (i.e., period effect) of cocaine use occurred during the late 1970s and early 1980s. In fact, 47 percent of the respondents in the 1982 survey who had ever used cocaine used it first in 1979, 1980, or 1981 (Clayton 1985).

Nonmedical Use of the Psychotherapeutics

Psychotherapeutics can be used medically or nonmedically, and several conclusions may be drawn from the data regarding nonmedical use of these drugs. First, young females are the ones likely to use these drugs nonmedically, whereas older males use them nonmedically. For example, In only 1 of the 16 age groups (22 to 23) do more than 10 percent of the female respondents re port having used analgesics nonmedically. Only women in the five youngest age groups contain more than 10 percent of respondents reporting nonmedical use of sedatives and tranquilizers. For tranquilizers, more than 10 percent report use in the three youngest age groups. Among these age groups, the median ages at onset do not differ greatly. For stimulants, 9 of the 16 age groups contain 10 percent or more women reporting nonmedical use, and there is little difference in the age at onset in these groups.

Nonmedical use of the psychotherapeutics is more prevalent among men, and, for each of the four psychotherapeutics, the median age at onset is similar for the age groups of 20 to 21 through 30 to 31. It appears that age at onset of nonmedical use of psychotherapeutics represents a developmental phenomenon for males or a societal trend away from recreational use of psychotherapeutics. Among females, nonmedical use is not sufficiently prevalent to justify a generalization.

Medical Use of the Psychotherapeutics

The clearest gender difference in medical use of psychotherapeutics is for stimulants. Among males, only 1 of the 16 age groups has a prevalence above 10 percent. In contrast, females' medical use of the stimulants is not a rare occurrence. The median age at onset of stimulant prescriptions is essentially the same for every age group from 20 to 21 through 30 to 31. This finding is consistent with the notion that women in these age groups use stimulants for dieting purposes. The reasons for use of drugs are, however, not available from the 1982 survey data.

Looking now at medical use of sedatives, use is less prevalent among males than females, just as it is for stimulants. For both

males and females, the median age at onset is lower for younger age groups.

The same trend appears for medical use of tranquilizers and analgesics. Males and females show an earlier median age at onset for the younger age groups. The age at onset for medical use of all these drugs seems to be declining.

Onset of drug use is not exclusively an adolescent phenomenon, as can be seen from the data presented in tables 5 and 6. For example, a substantial proportion (21.9 percent) of persons ever using marijuana or cocaine first used after the age of 20. For males, the percent starting at age 20 or later is 21.5; for females, it is 22.8. Thus, the percentage of persons waiting until adulthood to try these drugs does not differ significantly by gender. These findings are not consistent with the widely held assumption that reaching the age of 20 without having used these drugs assures a future probability of initiation close to zero.

What accounts for this unexpected finding that runs counter to one of the most commonly held assumptions in the drug abuse field? Several possible answers exist. First, most data about when drug use begins comes from samples of adolescents. The annual surveys of high school seniors, for instance, is based on a sample aged 18 or under. To examine differences in age at onset, a full range of ages must be studied. To our knowledge, the data pertaining to age at onset gathered in the series of national surveys sponsored by NIDA have yet to be analyzed. Second, an era effect may be confused with a cohort effect. That is, a temporary epidemic of drug use, in which the median age at onset of drug use differs between age groups but is similar within age groups, can add to evidence for adult initiation of drug use. This is in contrast to a long-term cohort effect, whereby younger age groups show a long-term or permanent trend to use at an earlier age. One must examine the years in which new users appear in order to separate these possibilities. It is possible that women will lag behind men by an average of a year or more when the data are more closely analyzed.

DISCUSSION

Patterns of drug use by gender, as analyzed here, confirm some popular opinions. For example, measured in terms of lifetime prevalence, rates of drug use are higher among males than females. In addition, males report more frequent and extensive use of cigarettes, alcohol, marijuana, and cocaine than do females. For the psychotherapeutic drugs, men are more likely to obtain them nonmedically, while women are more likely to obtain these drugs through medical channels. Median age at onset for older women was at a later age than for men of comparable age.

Notable among the younger cohorts is an apparent convergence between the sexes in the age at initiation of drug use. Specifically, the median age at onset of cigarette use has Increased among men and decreased among women, eliminating any gender difference for respondents 33 or younger. For alcohol, males show a stable median age at onset across a wide range of birth years. Females, however, show a decreasing median age at onset that is almost 2 years lower in the youngest cohorts than in the oldest cohorts. The pattern of drug use of men and women is becoming more similar according to these results, which comes as no great surprise. The explanation of this convergence, however, remains to be found.

Disconfirming a widely held belief that a person who does not begin using marijuana during adolescence will not start after age 20, the data show that 22 percent of the respondents in the 1982 National Survey started using marijuana after age 20. No gender differences show in the percentage of respondents who started to use marijuana after 20, suggesting a period or era effect when using the drug may have been the fashion. Although lifetime prevalence of marijuana use is sufficiently high in persons under 20 that one might suspect the rate was approaching maximum, over 20 percent of males and females begin use at a later age. For cocaine, the figure is more striking, with almost 50 percent of lifetime users starting after age 20. As with marijuana, males and females show no differences in percent initiating cocaine use after age 20. The important implication of this finding is that prevention programs aimed only at the young miss a sizable portion of the population at risk.

From the perspective of public policy, gender differences exist for use of several drugs and should be considered in the development of prevention and treatment strategies. Treating the "drug abuser," with little effort to tailor the program to the characteristics of the clients, is known to be inefficient in treating patients with different psychiatric diagnoses. To the extent that the gender variable determines patterns of drug use and abuse, it is reasonable to expect that efficient treatment will attend to these differences. The data reported in this paper show that men and women do differ in both how they obtain and how they use psychotherapeutic drugs.

The Federal research agenda for studying gender as a variable affecting drug use and abuse can easily be accommodated and is an important topic for public policy. Some of the gender effects in substance abuse that require attention are:

- the use of stimulants by women, particularly younger women, to lose weight, and the relationship of such use to anorexia and bulemia;

- the near and long-term effects of drugs on the reproductive process, including male reproductive biology, and the implications for the public health of future generations;

- the factors that account for higher levels of physician visits and prescriptions for women compared to men;

- the effects of women's changing role and increasing presence in the labor force on "patterns" of drug use and abuse; and

- the possible link between divorce and substance use.

REFERENCES

Clayton, R.R. Cocaine use in the United States: In a blizzard or just being snowed? In: Kozel, N.J., and Adams, E.H., eds. Cocaine Use in America: Epidemiologic and Clinical Perspectives. National Institute on Drug Abuse Monograph 61 DHHS Pub. No. (ADM) 85-1414. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 8-34.

De Alarcon, R. The spread of heroin in a community. Bull Narcotics 21:17-21, 1969.

Hughes, P.H.; Crawford, G.A.; Barker, N.W.; Schumann, S.; and Jaffe, J.H. The social structure of a heroin copping community. Am J Psychiatry 128:43-50, 1971.

Johnston, L.D.; O'Malley, P.M.; and Bachman, J.G. Use of Licit and Illicit Drugs by America's High School Students 1975-1984. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., DHHS Pub. NO. (ADM) 85-1394. 1985. 159 pp.

Kandel, D.B.; Davies, M.; and Raveis, V.H. The stressfulness of daily social roles for women: Marital, occupational and household roles. Journal of Health and Social Behavior 26 (March):64-78, 1985.

Levengood, R.; Lowinger, P.; and Schoof. K. Heroin addiction in the suburbs--An epidemiological study. Am J Public Health 63:209-213. 1973.

Mellinger, G.D., and Balter, M.B. Prevalence and patterns of use of psychotherapeutic drugs: Results from a 1979 national survey of American adults. In: Tognoni, G.; Bellantuono, C.; and Lader, M., eds. Epidemiological Impact of Psychotropic Drugs. New York: Elsevier/North Holland Biomedical Press, 1981.

O'Donnell, J.A.; Voss. H.L.; Clayton, R.R.; Slatin, G.T.; and Room, R.G.W. Young Men and Drugs--A Nationwide Survey. National Institute on Drug Abuse Monograph 5. DHEW Pub. No. (ADM) 76-311. Washington, D.C.: Supt. of DOCS., U.S. Govt. Print. Off., 1976. 144 pp.

Robins, L.N. The natural history of adolescent drug use. Am J Public Health 74(7):656-657, 1984.

Yamaguchi, K., and Kandel, D.B. Patterns of drug use from adolescence to young adulthood: III. Predictors of progression. Am J Public Health 74(7):673-681, 1984.

ACKNOWLEDGEMENT

York on this paper was completed under the auspices of Contract No. 271-84-7301 from the National Institute on Drug Abuse.

AUTHORS

Richard R. Clayton, Ph.D.
Professor
Department of Sociology
University of Kentucky
Lexington, KY 40506

Harwin L. Voss, Ph.D.
Professor
Department of Sociology
University of Kentucky
Lexington, KY 40506

Cynthia Robbins, Ph.D.
Assistant Professor
Department of Sociology
University of Kentucky
Lexington, KY 40506

William F. Skinner, Ph.D.
Assistant Professor
Department of Sociology
University of Kentucky
Lexington, KY 40506

National Institute on Drug Abuse Research

monograph series

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Drug Abuse Information (NCDAI). Please contact NCDAI also for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. NTIS prices are for paper copy. Microfiche copies, at $6.50, are also available from NTIS. Prices from either source are subject to change.

Addresses are:

NCADI
National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, Maryland 20852

GPO
Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

NTIS
National Technical Information Service
U.S. Department of Commerce
Springfield, Virginia 22161

1 FINDINGS OF DRUG ABUSE RESEARCH.
Vol. 1: GPO out of stock — NCDAI out of stock
Vol. 2: GPO out of stock — NTIS PB #272 867/AS $36.95
NTIS PB #272 868/AS $30.95

2 OPERATIONAL DEFINITIONS IN SOCIO-BEHAVIORAL DRUG USE RESEARCH
1975. Jack Elinson, Ph.D., and David Nurco, Ph.D., eds.
NCDAI out of stock
GPO out of stock — NTIS PB #246 338/AS $18.95

3 AMINERGIC HYPOTHESES OF BEHAVIOR: REALITY OR CLICHE? Bruce J. Bernard, Ph.D., ed.
NCDAI out of stock
GPO out of stock — NTIS PE #246 687/AS $18.95

4 NARCOTIC ANTAGONISTS: THE SEARCH FOR LONG-ACTING PREPARATIONS.
Robert Willette, Ph.D., ed.
NCDAI out of stock
GPO out of stock — NTIS PB #247 096/AS $11.95

5 YOUNG MEN AND DRUGS: A NATIONWIDE SURVEY. John A. O'Donnell, Ph.D., et al.
NCDAI out of stock
GPO out of stock
NTIS PB #247 446/AS $18.95

6 EFFECTS OF LABELING THE "DRUG ABUSER": AN INQUIRY. Jay R. Williams, Ph.D.
NCDAI out of stock
GPO out of stock
NTIS PB #249 092/AS $11.95

7 CANNABINOID ASSAYS IN HUMANS. Robert Willette, Ph.D., ed.
GPO out of stock
NCDAI out of stock
NTIS PB #251 905/AS $18.95

8 Rx: 3x/WEEK LAAM - ALTERNATIVE TO METHADONE. Jack Blaine. M.D., and Pierre Renault, M.D., eds.
NCDAI out of stock
Not available from GPO
NTIS PB #253 763/AS $18.95

9 NARCOTIC ANTAGONISTS: NALTREXONE PROGRESS REPORT. Demetrios Julius, M.D., and Pierre Renault, M.D., eds.
GPO out of stock
NCDAI out of stock
NTIS PB #255 833/AS $18.95

10 EPIDEMIOLOGY OF DRUG ABUSE: CURRENT ISSUES. Louise G. Richards, Ph.D., and Louise B. Blevens, eds.
NCDAI out of stock
GPO out of stock
NTIS PB #266 691/AS $24.95

11 DRUGS AND DRIVING. Robert Willette, Ph.D., ed.
NCDAI out of stock
GPO Stock #017-024-00576-2 $5.50
NTIS PB #269 602/AS $18.95

12 PSYCHODYNAMICS OF DRUG DEPENDENCE. Jack D. Elaine, M.D., and Demetrios A. Julius, M.D., eds.
NCDAI out of stock
GPO out of stock
NTIS PB #276 084/AS $18.95

13 COCAINE: 1977. Robert C. Petersen, Ph.D., and Richard C. Stillman, M.D., eds.
NCDAI out of stock
GPO Stock #017-024-00592-4 $6
NTIS PB #269 175/AS $24.95

14 MARIHUANA RESEARCH FINDINGS: 1976. Robert C. Petersen, Ph.D., ed.
NCDAI out of stock
GPO out of stock
NTIS PB #271 279/AS $24.95

15 REVIEW OF INHALANTS: EUPHORIA TO DYSFUNCTION. Charles Wm. Sharp, Ph.D., and Mary Lee Brehm, Ph.D., eds.
NCDAI out of stock
GPO out of stock
NTIS PB #275 798/AS $30.95

16 THE EPIDEMIOLOGY OF HEROIN AND OTHER NARCOTICS. Joan Dunne Rittenhouse, Ph.D., ed.
NCDAI out of stock
GPO out of stock
NTIS PB #276 357/AS $24.95

17 RESEARCH ON SMOKING BEHAVIOR. Murray E. Jarvik. M.D., Ph.D., et al., eds.
NCDAI out of stock
GPO out of stock
NTIS PB #276 353/AS $30.95

18 BEHAVIORAL TOLERANCE: RESEARCH AND TREATMENT IMPLICATIONS.
Norman A. Krasneyor, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #276 337/AS $18.95

19 THE INTERNATIONAL CHALLENGE OF DRUG ABUSE. Robert C. Petersen, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #293 807/AS $30.95

20 SELF-ADMINISTRATION OF ABUSED SUBSTANCES: METHODS FOR STUDY.
Norman A. Krasnegor. Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #288 471/AS $24.95

21 PHENCYCLIDINE (PCP) ABUSE: AN APPRAISAL. Robert C. Petersen, Ph.D., and Richard C. Stillman, M.D., eds. NCDAI out of stock
GPO Stock #017-024-00785-4 $7 NTIS PB #288 472/AS $30.95

22 QUASAR: QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS OF ANALGESICS, NARCOTIC ANTAGONISTS, AND HALLUCINOGENS. Gene Barnett, Ph.D .; Milan Trsic, Ph.D .; and Robert Willette, Ph.D.; eds.
GPO out of stock NCDAI out of stock
NTIS PB #292 265/AS $36.95

23 CIGARETTE SMOKING AS A DEPENDENCE PROCESS. Norman A. Krasnegor, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-00895-B $6 NTIS PB #297 721/AS $24.95

24 SYNTHETIC ESTIMATES FOR SMALL AREAS: STATISTICAL WORKSHOP PAPERS AND DISCUSSION. Jos. Steinberg, ed. NCDAI out of stock
GPO out of stock NTIS PB #299 009/AS $24.95

25 BEHAVIORAL ANALYSIS AND TREATMENT OF SUBSTANCE ABUSE. Norman A. Krasnegor, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #80-112428 $24.95

26 THE BEHAVIORAL ASPECTS OF SMOKING. Norman A. Krasnegor, Ph.D., ed. (Reprint from 1979 Surgeon General's Report on Smoking and Health.)
GPO out of stock NTIS PB #80-118755 $18.95

27 PROBLEMS OF DRUG DEPENDENCE, 1979: PROCEEDINGS OF THE 41ST ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. L.S. Harris, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-00981-4 $9 NTIS PB #80-175482 $42.95

28 NARCOTIC ANTAGONISTS: NALTREXONE PHARMACOCHEMISTRY AND SUSTAINED-RELEASE PREPARATIONS. Robert Willette, Ph.D., and Gene Barnett, Ph.D., eds. NCDAI out of stock
GPO out of stock NTIS PB #81-238875 $24.95

29 DRUG ABUSE DEATHS IN NINE CITIES: A SURVEY REPORT. Louis A. Gottschalk. M.D., et al. NCDAI out of stock
GPO out of stock NTIS PB #80-178882 $18.95

30 THEORIES ON DRUG ABUSE: SELECTED CONTEMPORARY PERSPECTIVES. Dan J. Lettieri, Ph.D.; Mollie Sayers; and Helen W. Pearson, eds.
NCDAI out of stock
GPO Stock #017-024-00997-1 $10 Not available from NTIS

31 MARIJUANA RESEARCH FINDINGS: 1980. Robert C. Petersen, Ph.D., ed.
GPO out of stock NTIS PB #80-215171 $24.95

32 GC/MS ASSAYS FOR ABUSED DRUGS IN BODY FLUIDS. Rodger L. Foltz, Ph.D.; Allison F. Fentiman, Jr., Ph.D.; and Ruth B. Foltz.
GPO out of stock NTIS PB #81-133746 $24.95

33 BENZODIAZEPINES: A REVIEW OF RESEARCH RESULTS, 1980. Stephen I. Szara, M.D., D.Sc., and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01108-8 $5 NTIS PB #82-139106 $18.95

34 PROBLEMS OF DRUG DEPENDENCE. 1980: PROCEEDINGS OF THE 42ND ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-01061-8 $8 NTIS PB #81-194847 $36.95

35 DEMOGRAPHIC TRENDS AND DRUG ABUSE, 1980-1995. Louise G. Richards, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #82-103417 $18.95

36 NEW APPROACHES TO TREATMENT OF CHRONIC PAIN: A REVIEW OF MULTIDISCIPLINARY PAIN CLINICS AND PAIN CENTERS. Lorenz K.Y. Ng, M.D., ed.
GPO out of stock NTIS PB #81-240913 $24.95

37 BEHAVIORAL PHARMACOLOGY OF HUMAN DRUG DEPENDENCE. Travis Thompson, Ph.D., and Chris E. Johanson, Ph.D., eds.
NCDAI out of stock
GPO Stock #017-024-01109-6 $7 NTIS PB #82-136961 $30.95

38 DRUG ABUSE AND THE AMERICAN ADOLESCENT. Dan J. Lettieri, Ph.D.. and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO Stock #017-024-01107-0 $4.50 NCDAI out of stock
NTIS PB #82-148198 $18.95

39 YOUNG MEN AND DRUGS IN MANHATTAN: A CAUSAL ANALYSIS. Richard R. Clayton, Ph.D., and Harwin L. Voss, Ph.D.
GPO Stock #017-024-01097-9 $5.50 NCDAI out of stock
NTIS PB #82-147372 $24.95

40 ADOLESCENT MARIJUANA ABUSERS AND THEIR FAMILIES. Herbert Hendin, M.D., Ann Pollinger, Ph.D., Richard Ulman. Ph.D., and Arthur Carr, Ph.D. NCDAI out of stock
GPO out of stock NTIS PB #82-133117 $18.95

41 PROBLEMS OF DRUG DEPENDENCE, 1981: PROCEEDINGS OF THE 43RD ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
Not available from GPO NTIS PB #82-190760 $42.95

42 THE ANALYSIS OF CANNABINOIDS IN BIOLOGICAL FLUIDS. Richard L. Hawks, Ph.D., ed.
GPO Stock #017-024-01151-7 $5 NTIS PB #83-136044 $18.95

43 PROBLEMS OF DRUG DEPENDENCE, 1982: PROCEEDINGS OF THE 44TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #83-252-692/AS $42.95

44 MARIJUANA EFFECTS ON THE ENDOCRINE AND REPRODUCTIVE SYSTEMS. Monique C. Braude, Ph.D., and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report. NCDAI out of stock
GPO Stock #017-024-01202-5 $4 NTIS PB #85-150563/AS $18.95

45 CONTEMPORARY RESEARCH IN PAIN AND ANALGESIA, 1983. Roger M. Brown, Ph.D.; Theodore M. Pinkert, M.D., J.D.; and Jacqueline P. Ludford, M.S.. eds. A RAUS Review Report. NCDAI out of stock
GPO Stock #017-024-01191-6 $2.75 NTIS PB #84-184670/AS $13.95

46 BEHAVIORAL INTERVENTION TECHNIQUES IN DRUG ABUSE TREATMENT. John Grabowski. Ph.D.; Maxine L. Stitzer, Ph.D., and Jack E. Henningfield, Ph.D., eds.
GPO Stock #017-024-01192-4 $4.25 NTIS PB #84-184688/AS $18.95

47 PREVENTING ADOLESCENT DRUG ABUSE: INTERVENTION STRATEGIES. Thomas J. Glynn, Ph.D.; Carl G. Leukefeld, D.S.W.; and Jacqueline P. Ludford. M.S., eds. A RAUS Review Report.
GPO Stock #017-024-01180-1 $5.50 NTIS PB #85-159663/AS $24.95

48 MEASUREMENT IN THE ANALYSIS AND TREATMENT OF SMOKING BEHAVIOR. John Grabowski, Ph.D., and Catherine S. Bell, M.S., eds.
GPO Stock #017-024-01181-9 $4.50 NCDAI out of stock
NTIS PB 84-145-184 $18.95

49 PROBLEMS OF DRUG DEPENDENCE, 1983: PROCEEDINGS OF THE 45TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D.. ed. NCDAI out of stock
GPO Stock #017-024-01198-3 $12 NTIS PB 85-151553/AS $36.95

50 COCAINE: PHARMACOLOGY, EFFECTS, AND TREATMENT OF ABUSE. John Grabowski, Ph.D., ed.
GPO Stock #017-024-01214-9 $4.50 NTIS PB 85-150381/AS $18.95

51 DRUG ABUSE TREATMENT EVALUATION: STRATEGIES, PROGRESS, AND PROSPECTS. Frank M. Tims, Ph.D., ed.
GPO Stock #017-024-01218-1 $4.50 NTIS PB 85-150365/AS $18.95

52 TESTING DRUGS FOR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. Joseph V. Brady, Ph.D., and Scott E. Lukas. Ph.D., eds.
GPO Stock #017-024-0204-1 $4.25 NTIS PB 85-150373/AS $18.95

53 PHARMACOLOGICAL ADJUNCTS IN SMOKING CESSATION. John Grabowski, Ph.D., and Sharon M. Hall, Ph.D., eds.
GPO Stock #017-024-01266-1 $3.50 NCDAI out of stock

54 MECHANISMS OF TOLERANCE AND DEPENDENCE. Charles Wm. Sharp, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-01213-1 $8.50

55 PROBLEMS OF DRUG DEPENDENCE, 1984. PROCEEDINGS OF THE 46TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-01242-4 $9.50

56 ETIOLOGY OF DRUG ABUSE: IMPLICATIONS FOR PREVENTION. Coryl LaRue Jones, Ph.D., and Robert J. Battjes, D.S.W.. eds.
GPO Stock #017-024-01250-5 $6.50

57 SELF-REPORT METHODS OF ESTIMATING DRUG USE: MEETING CURRENT CHALLENGES TO VALIDITY. Beatrice A. Rouse, Ph.D.. Nicholas J. Kozel, M.S., and Louise G. Richards, Ph.D, eds.
GPO Stock #017-024-01246-7 $4.25 NCDAI out of stock

58 PROGRESS IN THE DEVELOPMENT OF COST-EFFECTIVE TREATMENT FOR DRUG ABUSERS. Rebecca S. Ashery, D.S.W., ed.
GPO Stock #017-024-01247-5 $4.25 NCDAI out of stock

59 CURRENT RESEARCH ON THE CONSEQUENCES OF MATERNAL DRUG ABUSE. Theodore M. Pinkert, M.D., J.D., ed.
GPO Stock #017-024-01249-1 $2.50

60 PRENATAL DRUG EXPOSURE: KINETICS AND DYNAMICS. C. Nora Chiang, Ph.D., and Charles C. Lee, Ph.D., eds.
GPO Stock #017-024-01257-2 $3.50

61 COCAINE USE IN AMERICA: EPIDEMIOLOGIC AND CLINICAL PERSPECTIVES. Nicholas J. Kozel, M.S., and Edgar H. Adams, M.S., eds.
GPO Stock #017-024-01258-1 $5

62 NEUROSCIENCE METHODS IN DRUG ABUSE RESEARCH. Roger M. Brown, Ph.D., and David P. Friedman, Ph.D., eds.
GPO Stock #017-024-01260-2 $3.50

63 PREVENTION RESEARCH: DETERRING DRUG ABUSE AMONG CHILDREN AND ADOLESCENTS. Catherine S. Bell, M.S., and Robert Battjes, D.S.W.. eds.
GPO Stock #017-024-01263-7 $5.50

64 PHENCYCLIDINE: AN UPDATE. Doris H. Clouet, Ph.D., ed.
GPO Stock #017-024-01281-5 $6.50

65 WOMEN AND DRUGS: A NEW ERA FOR RESEARCH. Barbara A. Ray, Ph.D., and Monique C. Braude, Ph.D., eds.
GPO Stock #017-024-01283-1 $3.25

66 GENETIC AND BIOLOGICAL MARKERS IN DRUG ABUSE AND ALCOHOLISM. Monique C. Braude. Ph.D., and Helen M. Chao, Ph.D. eds.
GPO Stock #017-024-01291-2 $3.50 NCDAI out of stock

67 PROBLEMS OF DRUG DEPENDENCE, 1985. PROCEEDINGS OF THE 47TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-01292-1 $18

68 STRATEGIES FOR RESEARCH ON THE INTERACTIONS OF DRUGS OF ABUSE. Monique C. Braude, Ph.D., and Harold M. Ginzburg, M.D..J.D.,M.P.H., eds.
GPO Stock #017-024-01296-3 $6.50 NCDAI out of stock

69 OPIOID PEPTIDES: MEDICINAL CHEMISTRY. Rao S. Rapaka, Ph.D.; Gene Barnett, Ph.D.; and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-1297-1 $11

70 OPIOID PEPTIDES: MOLECULAR PHARMACOLOGY, BIOSYNTHESIS, AND ANALYSIS. Rao S. Rapaka. Ph.D., and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-1298-O $12

71 OPIATE RECEPTOR SUBTYPES AND BRAIN FUNCTION. Roger M. Brown, Ph.D.; Doris H. Clouet, Ph.D.; and David P. Friedman, Ph.D., eds.
GPO Stock #017-024-01303-0 $6

72 RELAPSE AND RECOVERY IN DRUG ABUSE. Frank M. Tims, Ph.D., and Carl G. Leukefeld, D.S.W., eds.
GPO Stock #017-024-01302-1 $6

73 URINE TESTING FOR DRUGS OF ABUSE. Richard L. Hawks, Ph.D., and C. Nora Chiang, Ph.D.. eds.
GPO Stock #017-024-1313-7 3.75

74 NEUROBIOLOGY OF BEHAVIORAL CONTROL IN DRUG ABUSE. Stephen I. Szara, M.D., D.Sc.. ed.
GPO Stock #017-024-1314-5 $3.75

75 PROGRESS IN OPIOID RESEARCH. PROCEEDINGS OF THE 1986 INTERNATIONAL NARCOTICS RESEARCH CONFERENCE. John W. Holaday, Ph.D.; Ping-Yee Law, Ph.D.; and Albert Her-z. M.D., eds.
GPO Stock #017-024-01315-3 $21

76 PROBLEMS OF DRUG DEPENDENCE, 1986. PROCEEDINGS OF THE 48TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-1316-1 $16

IN PRESS

77 ADOLESCENT DRUG ABUSE: ANALYSES OF TREATMENT RESEARCH. Elizabeth R. Rahdert, Ph.D. and John Grabowski, Ph.D., eds.

☆U.S. GOVERNMENT PRINTING OFFICE: 1990-276-211/21013

DHHS Publication No. (ADM)90-1447
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1986. Reprinted 1987, 1990