

# **Medications Development Research for Treatment of Amphetamine and Methamphetamine Addiction**

Report to Congress

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## **I. Introduction**

In compliance with Section 3633 of the Children's Health Act of 2000, Public Law 106-310, as amended by section 2502 of the 21<sup>st</sup> Century Department of Justice Appropriations Authorization Act, Public Law 107-273, this report presents an update on the development of medications for the treatment of addiction to amphetamine and methamphetamine.

### **What are Amphetamines and Methamphetamine?**

Amphetamines are part of a class of drugs called stimulants, which can profoundly alter brain and body functions. They can produce feelings of euphoria, increase alertness and arousal as well as blood pressure and heart rate, and they decrease appetite. They are Schedule II medications, which means they have a high potential for abuse and are available only through a prescription. There are only a few accepted medical indications for their use, such as the treatment of attention deficit hyperactivity disorder and narcolepsy (a sleep disorder). Methamphetamine is a form of amphetamine that is structurally and functionally similar; and once in the brain, methamphetamine and amphetamine are indistinguishable. However, methamphetamine differs from amphetamine in that, at comparable doses, much higher levels of methamphetamine get into the brain, making it a more potent stimulant than amphetamine. In addition, methamphetamine has a longer duration of action. Compared to amphetamine, methamphetamine has greater effects on the central nervous system (which leads to euphoria, motor stimulation, and anorexia) than on the sympathetic nervous system (which controls blood pressure and heart rate). This leads to a greater potential for harm to the brain. Nevertheless, both stimulants are highly addictive and have similar health liabilities. Because of their common mechanisms of action, research focusing on medications development for methamphetamine also encompasses amphetamine.

Methamphetamine is a white odorless bitter-tasting crystalline powder that dissolves easily in water or alcohol. Street names for methamphetamine include speed, meth, chalk, crystal, and glass. Methamphetamine comes in many forms and can be snorted, swallowed, injected, or smoked. In the 1980s, "ice," a smokable form of methamphetamine, came into use. Ice is a large, usually clear crystal of high purity that is smoked in a glass pipe like crack cocaine, and leaves a residue that can be re-smoked. The preferred method of methamphetamine abuse varies by geographical region and has changed over time. The routes of administration that lead to very fast uptake of the drug in brain, such as smoking and injecting, are the most dangerous since they have a greater addictive potential as well as more severe medical consequences.

Immediately after smoking or intravenously injecting amphetamine or methamphetamine, the user experiences an intense rush or "flash" that lasts a few minutes and is described as extremely pleasurable. Snorting or oral ingestion produces euphoria--a high, but not an intense rush. As with similar stimulants, amphetamines most often are used in a "binge and crash" pattern. Because rapid tolerance to the pleasurable effects of these drugs occurs, the high can disappear in minutes, even before the drug concentration in the blood falls significantly. This leads to a bingeing pattern of drug use in order to try to maintain the high.

Amphetamines affect many brain structures but predominantly those that contain the neurotransmitter (chemical messenger) dopamine, due to similarities in their chemical structures. Dopamine is involved in motivation, the experience of pleasure, motor function, and is a

common mechanism of action for most drugs of abuse including amphetamine, cocaine, nicotine, marijuana and alcohol. Drugs of abuse produce a sense of euphoria by increasing dopamine neurotransmission in a variety of ways. Amphetamines are the most potent of the stimulant drugs in increasing dopamine levels, more than three times that of cocaine. This extra sense of pleasure is followed by a “crash” or depression that often leads to increased abuse of these drugs and eventually to difficulty in feeling any pleasure.

As the primary Institute within the National Institutes of Health dealing with drugs of abuse, the National Institute on Drug Abuse (NIDA) is tracking the use of amphetamine and methamphetamine and is encouraging and supporting multifaceted research on their abuse, including prevention, epidemiology, basic and clinical neurobiology, and behavioral and pharmacological treatment. The establishment of a Medications Development Program at NIDA by Congress in 1992 (Section 464P of the Public Health Service Act, 42 USC 285o-4) has greatly facilitated NIDA’s efforts to develop treatments for drug addiction, including addiction to methamphetamine.

### **The Extent of the Problem**

According to NIDA’s 2004 Monitoring the Future Survey of drug use and related attitudes of America’s adolescents, 15 percent of 12<sup>th</sup> graders, 11.9 percent of 10<sup>th</sup> graders, and 7.5 percent of 8<sup>th</sup> graders reported having used *amphetamine* at least once in their lifetime, and 6.2 percent of 12<sup>th</sup> graders, 5.3 percent of 10<sup>th</sup> graders and 2.5 percent of 8<sup>th</sup> graders have reported using *methamphetamine* at least once in their lifetime. These numbers, while disturbing, *do not* represent an increase over previous years.

Particularly concerning are findings from NIDA’s Community Epidemiology Work Group (CEWG), which monitors drug abuse problems (mostly in adults) in 21 sentinel areas across the Nation, documenting increases in methamphetamine abuse in various regions across the United States and continued spread into rural communities. Long reported as a predominant drug problem in the Western United States, methamphetamine abuse has now become a substantial drug problem in other areas of the Country as well. Traditionally associated with white, male, blue-collar workers, methamphetamine is now being used by more diverse population groups that change over time and differ by geographic area.

The extent of methamphetamine abuse varies greatly by geographical region, but reports indicate that methamphetamine is available in all CEWG areas, and patterns in several areas appear to be in transition. In January 2005, CEWG reported that indicators of methamphetamine abuse have persisted at high levels in the Western United States including Honolulu, Seattle, San Francisco, Los Angeles, and San Diego, and have increased in several areas through 2003-2004, including Colorado, Phoenix, Atlanta, and Minneapolis/St. Paul.

In Minneapolis/St. Paul, primary treatment admissions for methamphetamine as a percent of illicit drug treatment admissions increased from 10.6 to 18.7 percent from 2001 to 2004. In Atlanta, primary methamphetamine admissions represented nearly 11 percent of the illicit drug treatment admissions in the first half of 2004 compared to 6.7 and 6.9 percent in 2002 and 2003, respectively. Indicators of methamphetamine abuse have raised concern not only in metropolitan Atlanta, but also in suburban communities neighboring Atlanta and in rural Georgia.

With the exception of Atlanta, methamphetamine treatment admissions in eastern CEWG areas remain low, at less than 1 percent of total substance abuse treatment admissions. However, there are increased reports of clandestine lab seizures in more rural areas of Eastern States, including Georgia, New York, and Maryland. Reports of the popularity of methamphetamine in some club contexts and within specific groups of users in eastern CEWG areas such as New York, Philadelphia, Washington DC, and Miami, underscore the potential threat of spread in areas where most indicators are still low. The clear availability of methamphetamine in these metropolitan areas warrants vigilance in monitoring indicators to track whether methamphetamine diffuses to a broader population of users or becomes popular in a wider range of contexts.

One of the contributors to the spread of methamphetamine is that it is relatively easy to manufacture. It can be synthesized with minimal equipment and the precursors are easily accessible in many areas of the United States. The widespread availability and longer duration of its effects have made methamphetamine a more desirable drug than cocaine for many drug abusers.

### **Health Hazards of Amphetamine/Methamphetamine Abuse**

**Medical and Psychiatric Complications.** NIDA-supported research has yielded many insights into how all drugs of abuse, including amphetamines, affect the human body. Amphetamines can cause a variety of cardiovascular problems, including rapid heart rate, irregular heartbeat, increased blood pressure, and irreversible, stroke-producing damage to small blood vessels in the brain. Chronic methamphetamine abuse can result in inflammation of the heart lining and, among users who inject the drug, damaged blood vessels and skin abscesses. Acute lead poisoning is another potential risk for methamphetamine abusers. A common method of illegal methamphetamine production uses lead acetate as a reagent, and production errors may therefore result in methamphetamine contaminated with lead. Documented cases of acute lead poisoning have been reported in intravenous methamphetamine abusers.

Hyperthermia (elevated body temperature), convulsions and coma can occur with methamphetamine overdoses and, if not treated immediately, can result in death. In fact the Drug Abuse Warning Network, maintained by the Substance Abuse and Mental Health Services Administration (SAMHSA), reported that mentions of amphetamine in drug abuse related cases in hospital emergency departments increased 125.9 percent from 1995 to 2002 (from 9,581 to 21,644) and reports of methamphetamine mentions remained stable, but high during this timeframe, at 17,696 in 2002.

Long-term amphetamine/methamphetamine abuse can result in many serious health consequences, including addiction. Research shows that addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use despite adverse consequences, which is accompanied by functional and molecular changes in the brain. In addition to being addicted to the drug, chronic abusers may experience withdrawal when use is stopped, which can include symptoms of depression, anxiety, fatigue, and an intense craving for the drug.

Chronic methamphetamine abusers also exhibit symptoms during intoxication that include violent behavior, anxiety, depression, confusion, and insomnia; and heavy users may show progressive social and occupational deterioration. Methamphetamine abusers can also display a number of psychotic features, including paranoia, auditory hallucinations and delusions.

Psychotic symptoms can sometimes last for months or years after methamphetamine abuse has ceased and stress has been shown to precipitate spontaneous recurrence of methamphetamine psychosis in formerly psychotic methamphetamine abusers.

**Prenatal Effects.** Because these drugs are abused by women of childbearing age, fetal exposure to amphetamines could potentially cause significant problems. Unfortunately, our knowledge of the effects of prenatal exposure is limited. The few human studies that exist have shown increased rates of premature delivery, placental abruption, fetal growth retardation, and cardiac and brain abnormalities. A recent NIDA-funded study showed that prenatal exposure to methamphetamine resulted in smaller subcortical brain volumes, which was associated with poorer performance on tests of attention and memory conducted at about 7 years of age. However, most of these studies in humans are confounded by methodological problems, such as small sample sizes and maternal use of other drugs. Thus, it is important that caution is exercised in interpreting the findings thus far.

To increase our knowledge in this area, NIDA launched the first large-scale study of the developmental consequences of prenatal methamphetamine exposure in 2001, which includes seven hospitals in Iowa, Oklahoma, California, and Hawaii, states where methamphetamine abuse is prevalent. This study is evaluating developmental outcomes such as cognition, social relationships, motor skills and medical status, and comparing outcomes to well-matched controls for socioeconomic status and other variables.

**HIV/AIDS.** Drug abuse remains one of the primary vectors for HIV, hepatitis B, and hepatitis C transmission. The recent case of an HIV-infected methamphetamine abuser in New York City with a particularly virulent strain of HIV is a sobering reminder of the link between drug abuse and HIV. Methamphetamine abuse increases the risk of contracting HIV not only due to the use of contaminated injection equipment, but also due to increased risky sexual behaviors as well as physiological changes that may favor HIV transmission.

Preliminary studies also suggest that methamphetamine use may affect HIV disease progression. For example, animal studies suggest that methamphetamine abuse may result in a more rapid and increased brain HIV viral load. Moreover, in a study of HIV-positive individuals being treated with highly active anti-retroviral therapy (HAART), current methamphetamine abusers had higher plasma viral loads than those who did not, suggesting that HIV-positive methamphetamine abusers on HAART therapy may be at greater risk of developing AIDS. These differences could be due to poor medication adherence or to interactions between methamphetamine and HIV medications. Similarly, preliminary studies suggest that interactions between methamphetamine and HIV itself may lead to more severe consequences for methamphetamine abusing, HIV-positive patients, including greater neuronal injury and neuropsychological impairment. More research is needed to better understand these interactions.

## **Effects of Amphetamine/Methamphetamine Abuse on the Brain**

**Basic Research Findings.** NIDA has been conducting basic research on amphetamines for more than 20 years. As the abuse of methamphetamine has increased, NIDA's research efforts in this area have also increased. Basic animal (preclinical) research studies are critically important to the understanding of drug effects, and have provided important information that is now facilitating the development of effective medications for treating problems associated with drug abuse.

Scientific studies examining the consequences of amphetamine exposure in animals have demonstrated its toxic effects on the brain. In animals, high doses of amphetamines cause damage to nerve endings of brain cells that produce the neurotransmitters dopamine and serotonin. In rats, one high dose is enough to cause damage, and prolonged exposure seems to make it worse. Researchers have reported that as much as 50 percent of the dopamine-producing cells in the brain can be affected after prolonged exposure to methamphetamine. Researchers have also found that serotonin-containing nerve cells may be damaged even more extensively. However, some of methamphetamine's effects on the dopamine and serotonin systems have also been shown to be reversible suggesting that these cells may be capable of some degree of recovery.

**Clinical Research Findings.** Brain imaging technologies allow researchers to look into the brains of living drug abusers. This provides important information on how drugs of abuse change the structure and functioning of specific brain regions. However, the limitations of brain imaging in humans make it difficult to determine conclusively that brain cells are damaged or destroyed. Nevertheless, using sensitive neuropsychological and cognitive testing, it is possible to gain insight into how brain changes may be affecting behavior and function, and also determine whether these changes can be reversed.

Studies of methamphetamine abusers have demonstrated significant alterations in the activity of the dopamine system that are associated with reduced motor speed and impaired verbal learning. Moreover, recent studies in chronic methamphetamine abusers have revealed severe structural alterations and functional deficits in areas of the brain associated with emotion as well as memory. These findings may help account for many of the emotional and cognitive problems observed in chronic methamphetamine abusers.

Fortunately, some of the effects of chronic methamphetamine abuse appear to be, at least partially, reversible. A recent neuroimaging study showed recovery in some brain regions following protracted abstinence (2 years, but not 6 months). This was associated with improved performance on motor and verbal memory tests. The results of this study may be highly significant for the development of treatments to reverse the harmful effects of methamphetamine abuse on the brain. However, function in other brain regions did not display recovery even after 2 years of abstinence, indicating that some methamphetamine-induced changes are very long lasting if not permanent. Moreover, the increased risk of cerebrovascular accidents from the abuse of methamphetamine can lead to irreversible damage to the brain.

## **Current Treatments**

At this time, the most effective treatments for methamphetamine addiction are behavioral interventions. These approaches are designed to help modify the patient's expectancies and behaviors related to drug use, and to increase skills in coping with various life stressors.

Emergency room physicians who treat individuals exhibiting methamphetamine intoxication and overdose have also established some useful protocols. For example, acute methamphetamine intoxication can often be handled by observation in a safe, quiet environment. In cases of extreme excitement or panic, treatment with anti-anxiety agents such as benzodiazepines has been helpful, and in cases of methamphetamine-induced psychoses, short-term use of antipsychotic medications has been reported to successfully manage this syndrome. Antidepressant medications may also be helpful in combating the depressive symptoms frequently seen in methamphetamine withdrawal, although most antidepressants are not effective for several weeks, diminishing their utility for treating an acute depressive response. Also, to combat hyperthermia and convulsions, which can be fatal complications of methamphetamine overdose, patients are cooled off in ice baths and anticonvulsant drugs may be administered.

There are, however, no specific medications that counteract the effects of methamphetamine or that prolong abstinence from and reduce the abuse of methamphetamine by an individual addicted to the drug. Thus, there remains a significant unmet need in addressing an urgent National priority.

Efforts by NIDA to date to enlist the private sector in its program to identify, develop, and commercialize effective medications for the treatment of methamphetamine addiction have been only partially successful. The pharmaceutical industry continues to be reluctant to become involved in the development of anti-addiction medications. This is due largely to the existence of a number of disincentives, which are primarily financial in nature. The costs of bringing a new medication to market are in the range of \$500 million to \$1 billion and require at least a 10-year commitment. Such a commitment by private industry is unlikely to provide a profitable return on the investment for developing and bringing to market an anti-addiction medication. In order to stimulate private sector involvement in development of anti-addiction medications, strong market incentives are needed. This has been underscored by both the Institute of Medicine in its 1995 report "Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector" and by a 1997 NIH Consensus Development Conference on the Effective Medical Treatment of Heroin Addiction.

## **II. NIDA's Current Methamphetamine Treatment Development Efforts**

### **Overview**

NIDA recognizes the multi-faceted problems posed by methamphetamine abuse and addiction and has increased its research efforts accordingly, but much remains to be accomplished.

Research has confirmed that addiction is a treatable, though chronic and relapsing, disease of the brain. NIDA research shows that comprehensive treatments that focus on the whole individual, and not just on drug abuse, have the highest success rates. These programs typically include a combination of behavioral treatments, medications (if available), and other services (e.g., job training and referral to medical, psychological, and social services) that are tailored to the needs

of the individual patient. Science-based treatments benefit not only the patient, but can also be cost effective for society, by saving money that would have been spent on the public health and safety consequences of drug abuse and addiction.

### **Methamphetamine Addiction Treatment Think Tank**

In early 2000, NIDA's Division of Treatment Research and Development (DTR&D), now known as NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), convened a Methamphetamine Addiction Treatment Think Tank that brought together preclinical and clinical experts to provide NIDA with expert guidance on the establishment and research focus of NIDA's program for the development of medications for treating methamphetamine addiction and related problems. This panel of experts made several recommendations that NIDA is using to guide research on treatments for methamphetamine addiction.

**Recommendation 1:** The establishment of a Methamphetamine Clinical Trials Group (MCTG) that would conduct clinical trials of medications for methamphetamine.

**NIDA Action:** Sites in which methamphetamine abuse is prevalent were selected to conduct clinical pharmacology and outpatient studies of medications proposed to treat different aspects of methamphetamine abuse.

**Recommendation 2:** The primary focus of NIDA's program should be on the development of medications for treating methamphetamine addiction.

**NIDA Action:** This is the major focus of the MCTG described above. More details on medications development for methamphetamine addiction are discussed below.

**Recommendation 3:** NIDA should consider focusing on treatments for methamphetamine overdose.

**NIDA Action:** At present there are no specific pharmacological treatments available for treating methamphetamine overdose. NIDA is currently funding projects for the development of monoclonal antibody-based medications for treating methamphetamine overdose. These medications bind to the drug in the bloodstream thereby preventing its action to provide a rapid reversal of drug effects in an emergency room setting.

**Recommendation 4:** Several additional areas of research are needed; including treatments for other problems caused by methamphetamine abuse, such as possible neurodegeneration, cognitive impairment, and psychoses.

A first step in treating drug addiction is the treatment of the addiction itself. But many abused drugs can cause a multitude of other problems related to their profound effects in the brain. The panel of experts emphasized that the treatment of these other problems is necessary if a person is to recover and return to a normal and productive life. Thus, the panel agreed that medications development efforts should be broadened. For example, medications to improve cognitive skills or reverse the impairments produced by methamphetamine could facilitate treatment success, while at the same time allowing a recovering addict to function normally in work and home settings. Likewise, medications that address the resultant psychosis should also dramatically improve the success rate of treatment of methamphetamine addiction.

**NIDA Action:** Establish the Methamphetamine Treatment Discovery Program.

## **Methamphetamine Treatment Discovery Program (MTDP)**

Continuing to capitalize on the input of its experts, NIDA's DPMCDAs Medications Discovery and Toxicology Branch established the MTDP. Its mission is to identify, evaluate, and recommend potential treatments for the medical management of methamphetamine addiction and its effects using a preclinical (animal/cellular) approach. The program focuses on discovering medications to reduce or eliminate drug-seeking behaviors. In addition, the MTDP is developing the capability to evaluate, in animals, medications to reverse methamphetamine neurotoxicity and cognitive impairment.

The MTDP solicits and tests compounds submitted to the program by scientists funded through NIDA grants and contracts, by domestic and foreign pharmaceutical companies and by MTDP team members. The tests are conducted under blinded conditions; that is, the testers do not know the identity of the compound they are testing. In this manner, proprietary information is protected and potential experimental bias is eliminated.

The MTDP uses a number of approaches to choose specific compounds or classes of compounds to test. A "bottom-up" approach focuses on compounds with a compelling rationale based on findings in animals. A "top-down" approach identifies and tests approved therapeutic drugs already available to clinicians for treating indications other than drug abuse (e.g., anxiety, depression, or Parkinson's disease) for their potential as methamphetamine abuse therapeutics. In addition, since methamphetamine shares some of the same properties as cocaine, the MTDP is also testing compounds with preliminary data that suggest usefulness in treating cocaine addiction.

Once potential compounds are identified, they are first screened using a series of tests performed using tissues and cells. Next, they are tested in experimental animal models. As test results are returned to the MTDP, the members of the MTDP team analyze the data and, based on the test results, determine which compounds look most promising for further evaluation. Promising compounds can undergo further laboratory tests and computer modeling studies designed to predict whether they will be safe in humans. These tests search for side effects, determine if the drugs are toxic or carcinogenic, and evaluate whether there are interactions with other drugs (including drugs of abuse). In addition, duration of therapeutic effects and how long the compound remains in the body are determined.

After these tests, if a compound still looks promising, all the data are consolidated and presented to an independent group of outside consultants from the pharmaceutical industry and academia for review. This expert group is tasked with recommending whether a compound should be advanced to clinical trials in humans or if additional animal tests are required.

## **Animal Models Relevant to Medications Development**

Animal models of drug abuse and addiction as well as models for the different consequences of drug abuse, including overdose, neurotoxicity and damage to the developing fetus of pregnant drug abusers, can be useful tools for understanding mechanisms of drug action. They not only provide valuable information on the specific sites in the brain where drugs act and the changes in neuronal function that they cause, but they provide a means of developing medications that target specific brain changes caused by drug abuse and testing possible pharmacotherapies for safety and efficacy before these therapies are tested in humans.

For example, animals can be trained to self-administer a drug, that is, they learn to press a lever to receive a dose of a particular drug. Because these drugs activate reward centers of the brain, these animals will continue to press the lever to obtain more of the drug. Potential pharmacotherapies can be tested to see if they interfere with this behavior. For example, the compound baclofen, which acts on the GABA neurotransmitter system of the brain, which is known to modulate dopamine neurotransmission, has been shown to decrease both methamphetamine and amphetamine self-administration in rats. This compound, as well as others initially tested using this model (e.g., lobeline) are now being tested in clinical trials (as discussed below).

Once an animal has been trained to self-administer a drug, this behavior can also be diminished by not providing the drug in response to the lever press. However, similar to what has been observed in human addicts, rats will resume lever pressing when re-exposed to the drug or after encountering a stressful event. Potential therapies can be tested in these models to see if they can prevent such reinstatement or relapse. For example, medications which block activity at a specific brain receptor (known as alpha-2 adrenoceptor) have been shown to induce relapse in an animal model of reinstatement, similar to when these animals are exposed to a stressful stimulus. For this reason, medications that may act to enhance activity at this receptor may prevent reinstatement due to stress. Clonidine is an already approved medication that acts at this site, and is currently being tested in clinical trials (as discussed below).

Another characteristic of repeated exposure to stimulants, which can be studied using animal models, is “sensitization”, that is when some of the drug effects actually increase over time. For example, repeated administration of methamphetamine in rodents leads to an enhanced locomotor response (running or circling), which gradually can become stereotypic (repetitive and fixed) in nature depending upon the drug dosage, number of drug exposures, and individual vulnerability factors. It is thought that the sensitization model may be related to a number of characteristics of addiction in humans, including the intensification of craving that accompanies drug addiction, especially when one is presented with cues or reminders of their previous drug experiences; and the development of psychotic behaviors, including paranoid thinking, hallucinations and delusions. The neural circuitry underlying this behavior has been elucidated and important roles for the neurotransmitters glutamate and dopamine, among others, have been revealed. This information is being used in the development of novel approaches to counter some of the various aspects of addiction. For example, the medication valproate used to treat epilepsy has been shown to prevent behavioral sensitization when co-administered with methamphetamine and to affect the expression of sensitization when administered after its development. Similar medications such as topiramate are currently being tested in clinical trials (as discussed below).

Animal models are also currently being used to identify possible treatment approaches for repairing the damage to the brain following methamphetamine abuse. For example, these animal models are being used to assess the influence of neurotrophic factors, chemicals that are involved in cell survival and growth, which may someday be useful in reversing methamphetamine’s harmful effects on the brain and the associated functional deficits (such as cognitive and motor deficits). In one study, nonhuman primates were injected with a substance known as glial cell-line derived neurotrophic factor (GDNF) in brain areas that are susceptible to the damaging

effects of methamphetamine. In this study, monkeys who were given GDNF showed less neurotoxicity from methamphetamine than animals that did not receive GDNF. These results suggest that GDNF might be useful for mitigating some of the harmful effects of methamphetamine.

Animal models are providing valuable information that can be used to understand all aspects of methamphetamine abuse and addiction, which in turn forms a foundation for the development of pharmacotherapies that can treat addiction to methamphetamine as well as the harmful consequences of its use.

### **Methamphetamine Clinical Trials Group (MCTG)**

In addition to NIDA's preclinical efforts and following recommendations from the Methamphetamine Treatment Think Tank, NIDA established the MCTG to conduct clinical (human) trials of medications for methamphetamine addiction. This group is capable of conducting both phase I (safety) and phase II (efficacy) clinical studies. It has sites in geographic areas in which methamphetamine abuse is particularly high: San Diego, Kansas City, Des Moines, Costa Mesa, San Antonio, Los Angeles, and Honolulu.

Some of the medications NIDA currently has under development for treating methamphetamine abuse are:

- **Bupropion** -- an antidepressant that inhibits the uptake of the neurotransmitter dopamine in the brain. This property may make bupropion useful for treating methamphetamine addiction as well as the depression that is exhibited by many drug abusers.
- **Sertraline** -- an antidepressant that blocks uptake of the neurotransmitter serotonin, which is also affected by methamphetamine. This property may make sertraline potentially useful for treating methamphetamine addiction as well as the depression that is exhibited by many drug abusers.
- **Lobeline** -- a compound that affects the dopamine and nicotine systems in brain neurons and reduces methamphetamine self-administration in rats.
- **Aripiprazole** -- a medication recently approved by the Food and Drug Administration (FDA) for treating schizophrenia, which acts on dopamine receptors and may help reducing the stimulant effects of methamphetamine as well as being useful for relapse prevention. Aripiprazole has also been shown to improve cognition in patients with schizophrenia, suggesting another potential benefit of the drug.
- **Carvediol, Clonidine, Atomoxetine, and Prazosin** -- medications that affect the neurotransmitters epinephrine and norepinephrine, which also have a role in the euphoric, motor activating, and rewarding effects of stimulants. These medications are already approved for clinical use, have generally well-understood mechanisms of action, are safe, and have been the subject of animal or clinical studies that suggest their potential for use in treating addiction to amphetamine/methamphetamine.

- **Modafinil** -- a novel non-amphetamine stimulant medication approved by the FDA for treating narcolepsy and currently under study for treating attention deficit hyperactivity disorder (ADHD), cognitive deficits in Alzheimer's disease and negative symptoms in schizophrenia. Modafinil is being considered for treating methamphetamine addiction and its consequences because: 1) its actions as a stimulant may decrease craving and methamphetamine seeking; 2) it has low abuse potential and does not seem to produce addiction; 3) it may improve concentration, daytime alertness and cognitive functions; 4) it may have antidepressant properties; and 5) the effects of modafinil are long-lasting and persist for as long as 4 months after treatment.
- **Perindopril** -- a medication currently used to treat hypertension. In animals, perindopril has been shown to increase dopamine levels in the brain and reduce neurotoxicity to the dopamine system. NIDA is conducting a human laboratory study to determine whether oral perindopril can be safely administered to patients taking methamphetamine to prepare for an outpatient-based clinical trial that would assess the ability of perindopril to prevent relapse to drug use in treatment-seeking methamphetamine addicted individuals.
- **Rivastigmine** -- a medication approved by the FDA to treat Alzheimer's dementia due to its cognitive enhancing properties. Amphetamine and methamphetamine addiction have been associated with neurocognitive deficits, both immediately after withdrawal and after long-term abstinence. A medication that is effective at reducing these neurocognitive deficits may assist individuals in recovery to obtain more benefit from counseling strategies and facilitate behavioral change.
- **Topiramate** -- a medication that acts on the neurotransmitter systems GABA and glutamate and is currently used to treat epilepsy. It has been hypothesized that topiramate will be associated with decreased dopamine release via its actions on the GABA and glutamate systems.
- **Baclofen** -- a compound that reduces the release of a variety of neurotransmitters in the central nervous system through its actions on the GABA neurotransmitter system and has been shown to decrease self-administration of cocaine and methamphetamine in animals.

### **Medications Development Working Group**

In May 2004, the Director of NIDA convened a Medications Development Program (MDP) Subcommittee, composed of members from the National Advisory Council on Drug Abuse and distinguished leaders from the drug abuse and addiction field. The Subcommittee's objectives were to comprehensively review NIDA's current medications development programs and provide recommendations for ongoing and future research objectives on pharmacotherapies for treating drugs of addiction. As a result of this review, an external Medications Development Work Group was established to define and review decisions regarding the identification, advancement and discontinuation of addiction treatment compounds under development, including those to treat methamphetamine abuse. This Work Group met for the first time in March 2005 and plans to meet biannually to review NIDA's ongoing and proposed medications development efforts.

## **Clinical Behavioral Therapies Program**

Research has clearly shown that behavioral therapies are an integral part of effective treatment programs. Consequently, and following the advice of the Methamphetamine Treatment Think Tank, NIDA is also conducting research on behavioral therapies that might be effective for treating methamphetamine addiction.

Studies have now shown that a program known as the Matrix Model can be used successfully for the treatment of methamphetamine addiction. The Matrix Model was developed in the 1980s for treating cocaine addiction. It consists of a 16-week program that includes group and individual therapy and components that address relapse prevention, behavioral changes needed to remain off drugs, communication among family members, establishment of new environments unrelated to drugs, and other relevant topics. When applied to methamphetamine abusers, the Matrix Model has been found to be an effective treatment approach.

Another promising behavioral therapy, Motivational Incentives for Enhanced Drug Abuse Recovery (MIEDAR), is a cost-effective, incentive method for cocaine and methamphetamine abstinence. A recent study showed that the incentive condition had approximately twice as many participants with at least 8 weeks of documented sustained abstinence compared to treatment as usual.

Because no single behavioral treatment will be effective for everyone, research into behavioral approaches for treating methamphetamine addiction is ongoing. It is expected that, as with other types of addiction, combining pharmacotherapies with behavioral therapies will be the most effective way to treat methamphetamine addiction.

## **Other Research Gaps to be Addressed**

Although research has provided considerable insight into the mechanisms by which methamphetamine exerts its effects, gaps continue to exist in the scientific knowledge about the basic pharmacology, toxicity, and treatment of methamphetamine abuse. Some of these knowledge gaps include:

**Identification of biomarkers.** NIDA will also be conducting research aimed at identifying biomarkers or indicators that can be used to predict how individuals will respond to medications and behavioral therapies. These can include physiological, genetic, or hormonal markers as well as those that can be detected using neuroimaging techniques. This knowledge should increase dramatically the success rate of treatment for methamphetamine and other addictions.

**Relapse prevention.** Two of the major causes of relapse to drug abuse are craving and exposure to stressful situations. NIDA will be conducting human laboratory studies to screen medications that are effective in suppressing craving. These studies will target systems known to be involved in drug craving (glutamate and a specific brain dopamine receptor). Similarly, stress reduction using a combination of behavioral and pharmacological approaches, will be studied as an approach for preventing relapse. Novel medications are in development that act on brain chemicals involved in the stress response.

**Cognitive impairment.** Research has clearly established that methamphetamine causes impairments in certain cognitive functions, such as memory. An important area of research that NIDA will continue to pursue is the development of medications that can improve cognitive functions that have been altered by methamphetamine. These medications should not only improve treatment outcomes but also facilitate the return of methamphetamine abusers as functional members of society.

**Associated psychoses.** Finally, NIDA plans to conduct research to better characterize antipsychotic medications that may be useful for treating symptoms often found in methamphetamine abusers. This research will involve studies of the natural history of methamphetamine abuse and associated psychoses and the neurobiology and pharmacology of psychosis in methamphetamine patients.

### **III. Conclusion**

Methamphetamine abuse and addiction in the United States are major problems that are spreading to new geographic areas and populations. The devastating consequences of abuse of this drug translate into an increasing burden on the Nation's public health and public safety systems.

Preclinical and clinical research regarding the effects of methamphetamine abuse and treatments for methamphetamine addiction has revealed much, but knowledge gaps exist that still need to be filled. Research findings to date show a direct relationship between changes in brain structure and function in methamphetamine abusers and changes in behavior, cognition, and mood. The results underscore the serious nature of methamphetamine abuse and emphasize the need to alert users and potential users to the long-lasting, profound effects of this drug. And, for those instances when information dissemination and prevention efforts are not successful, ongoing treatment research, supported by NIDA, will bear fruit in helping to treat the addiction and other health ramifications of methamphetamine abuse.

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