

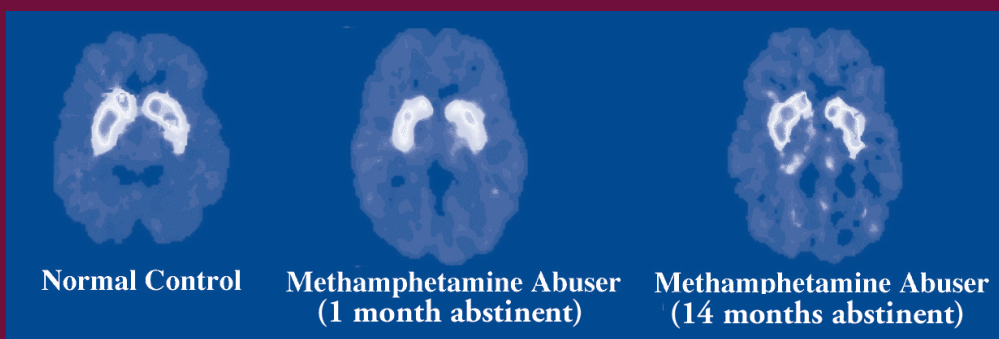
*A Collection of*

# NIDA NOTES

NATIONAL INSTITUTE  
ON DRUG ABUSE

*Articles That Address*

## RESEARCH ON METHAMPHETAMINE



U.S. Department of Health and Human Services  
National Institutes of Health  
National Institute on Drug Abuse

NN0060

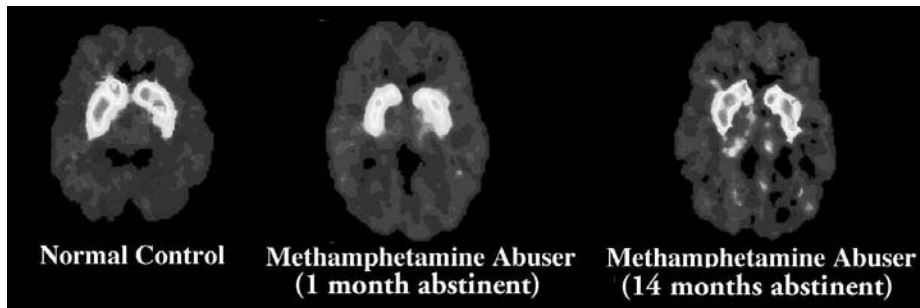
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**U.S. Department of Health and Human Services  
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## Introduction

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at [www.drugabuse.gov](http://www.drugabuse.gov).

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## Low-Cost Incentives Improve Outcomes in Stimulant Abuse Treatment

In community-based treatment programs, the intervention added \$2.42 per patient per day to counseling costs.

By Lori Whitten, *NIDA Notes* Staff Writer

The opportunity to win rewards worth as little as \$1 for abstinence can help motivate outpatients to stay in behavioral therapy and remain drug-free, according to a NIDA Clinical Trials Network (CTN) study. At eight community-based addiction treatment programs across the United States, stimulant abusers who could earn a chance to win a prize by providing drug-free urine samples were four times as likely as peers who were not offered this incentive to attain 12 weeks of continuous abstinence. Prizes for the incentive intervention cost the programs about \$200, or \$2.42 a day per participant.

“Many addiction treatment clinics face the challenge of high patient dropout rates. Reinforcing abstinence helps keep patients interested in attending treatment for longer periods, which can facilitate behavioral changes to keep them off drugs for the long haul,” says Dr. Nancy Petry of the University of Connecticut School of Medicine, coleader of the study. Prior research has found that, no matter how it is achieved, duration of abstinence during treatment is one of the best predictors of abstinence 1 year later. “More patients achieve this therapeutic milestone with a boost from incentive programs,” says the study’s other coleader, Dr. Maxine Stitzer of The Johns Hopkins University School of Medicine.

The CTN investigators randomly assigned 415 treatment-seeking stimulant abusers (see chart) to one of two conditions: usual care or usual care plus abstinence-based incentives for 12 weeks. Usual care typically consisted of group counseling, although some patients received individual and family therapy. Patients gave urine and breath samples twice weekly. Research assistants tested the urine samples for stimulants, opiates, and marijuana, and tested the breath samples for alcohol.

Each participant in the incentive condition received immediate feedback on his or her samples. After submitting stimulant- and alcohol-negative samples, the patient could draw from an opaque container with 500 chips, each with words of encouragement or an assigned value: Half of the chips simply said, “good job;” 209 could be traded for \$1 prizes, 40 for \$20 prizes, and 1 for a \$100 prize. Prizes were conferred immediately and included many options, ranging from toiletries, snacks, and bus

### CHARACTERISTICS OF STUDY PARTICIPANTS

Patients at eight community-based clinics across the country were ethnically diverse and generally reflected the national population of treatment-seeking stimulant abusers.

Characteristic	%
<b>Ethnicity</b>	
White	42
African-American	35
Hispanic	12
Other	9
Male	44
Unemployed	65
On parole or probation	35
<b>Abuse of other drugs</b>	
Alcohol	42
Marijuana	20
Opioids	9

tokens to kitchen items, telephones, and retail store certificates for televisions, music players, and DVD players. The number of draws earned increased by one each week in which all the patient’s samples were stimulant- and alcohol-negative, but fell back to one following a positive sample or an unexcused absence. When a participant first achieved two consecutive weeks of abstinence, he or she received a \$20 prize. Participants who submitted stimulant- and alcohol-negative samples could earn two bonus draws a week if their urine samples were also opioid- and marijuana-negative.

More patients in the incentive program (49 percent) than in usual care (35 percent) completed 12 weeks of counseling. Patients in the incentive group achieved an average duration of sustained abstinence of 4.4 consecutive weeks, compared with only 2.6 weeks among counseling-only patients. Nineteen percent of patients receiving the incentive intervention attained 12 weeks of continuous abstinence compared with 5 percent of those in usual care. Intervention patients also attended more counseling sessions (19 versus 16) and submitted more stimulant-negative urine samples during treatment than patients in usual care (48 versus 36 percent).

## Incentives Accentuate the Positive

“Incentive programs, including low-cost ones, add excitement and additional reasons to attend substance abuse treatment. Many substance abusers are ambivalent about treatment, and rewards may help them stay involved in counseling,” says Dr. Petry. Extending retention in treatment may prolong abstinence, in part, because it gives counselors more time to help patients re-engage in a drug-free lifestyle, says Dr. Stitzer. Helping patients sustain abstinence once they leave therapy is a challenge for all treatments, including incentive programs.

Some previous clinical trials of voucher-based incentive programs showed benefits of the treatment persisting for 1 to 2 years, but others found no added value over the long term compared with usual care. Further research will focus on followup with patients to determine the conditions under which incentive interventions, particularly as applied by community-based treatment programs, support extended abstinence.

Other relatively small, often single-site NIDA-funded clinical trials over the past 15 years have demonstrated that motivational incentives are an effective adjunct to standard therapy for opiate-, marijuana-, alcohol-, and cocaine-addicted patients. Patients in most of those early studies always received vouchers exchangeable for goods or services, rather than chances to win prizes, for positive behaviors; costs typically ran to about \$1,000 per patient over 3 months, with the result that few community programs adopted the motivational incentive approach. Dr. Petry developed her prize-drawing system to make incentives affordable for community programs. She has tested it successfully in several Connecticut treatment programs, and now its effectiveness is confirmed by the CTN trial. NIDA is collaborating with the Substance Abuse and Mental Health Services Administration’s Addiction Technology Transfer Center to promote awareness of the low-cost motivational incentive technique (see text box).

The CTN researchers note that some community-based treatment providers resist the idea of motivational incentives based on a belief that clinicians should not reward patients for behaviors “that they are supposed to do anyway.” In response, the researchers point out that groups

## Blending Initiative Disseminates Information on Low-Cost Incentives

Clinicians and administrators who wish to learn more about using low-cost incentives to motivate patients to stay off drugs can get information through the Blending Initiative, a program established by NIDA and the Substance Abuse and Mental Health Services Administration to speed the adoption of scientific findings into drug abuse treatment. The Blending Initiative has developed an awareness program that disseminates practical information on low-cost incentive programs and a summary of research evidence that supports their use as an adjunct to addiction treatment.


A DVD/CD-ROM describes the principles underlying incentive programs, the range of behaviors that clinics can target, and findings from studies of the intervention with a variety of patient populations. In the video component, clinicians, patients, and managers describe their experiences with the use of low-cost incentives in Manhattan and Connecticut outpatient methadone treatment programs. Viewers observe a group of Connecticut clients participating in a prize draw and a panel of directors and clinical managers discussing implementation challenges, ways to overcome problems, and the reasons they think the low-cost incentive program is effective. The CD-ROM component includes a flexible PowerPoint presentation suited for executive briefings or a 3-hour workshop. The Blending Initiative expects to release the information package in fall 2006, and it will be posted on NIDA’s Web site, [www.drugabuse.gov](http://www.drugabuse.gov) and on the Addiction Technology Transfer Center (ATTC) Web site, [www.nattc.org](http://www.nattc.org).

“We anticipate that the awareness campaign will leave the addiction treatment community wanting more, for example, Web-based training and workshops on how to implement low-cost incentive programs,” says Ms. Lonnetta Albright, director of the Great Lakes ATTC and leader of the Promoting Awareness of Motivational Incentives Blending Team.

The 2006 Blending Initiative program, “Bridges to the Future,” was held October 16 and 17, 2006 in Seattle, Washington (see [www.sei2003.com/blendingseattle](http://www.sei2003.com/blendingseattle)).

and individuals often use external incentives to motivate others—from employees’ bonuses to children’s allowances for household chores. Dr. Stitzer advocates a shift in perspective from punishing lapses to celebrating successes. She observes that counselors have often changed their views when they have seen incentives help revolving-door patients stay in therapy. “Incentive programs—the idea of catching people being good and rewarding the behavior—can infuse addiction treatment with a positive outlook and reinvigorate patients and counselors,” says Dr. Stitzer.

### Source

- Petry, N.M., et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: A National Drug Abuse Treatment Clinical Trials Network Study. *Archives of General Psychiatry* 62(10):1148-1156, 2005. 

## Methamphetamine Evokes and Subverts Brain Protective Responses

Two new studies appear to highlight the role of glial cells—the nervous system’s equivalents to the body’s immune cells—in methamphetamine abuse.

By Patrick Zickler, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have produced brain images demonstrating that structures in an area called the striatum expand in volume during early methamphetamine abuse, then regress toward normal. The investigators believe their findings likely are attributable to neuroprotective cells in the brain mounting an initial attempt to counteract the drug’s toxic effects, which continued exposure subsequently overwhelms. In a related result, scientists working with mice have produced evidence that methamphetamine may prompt cells that normally serve neuroprotective functions to instead attack healthy brain cells.

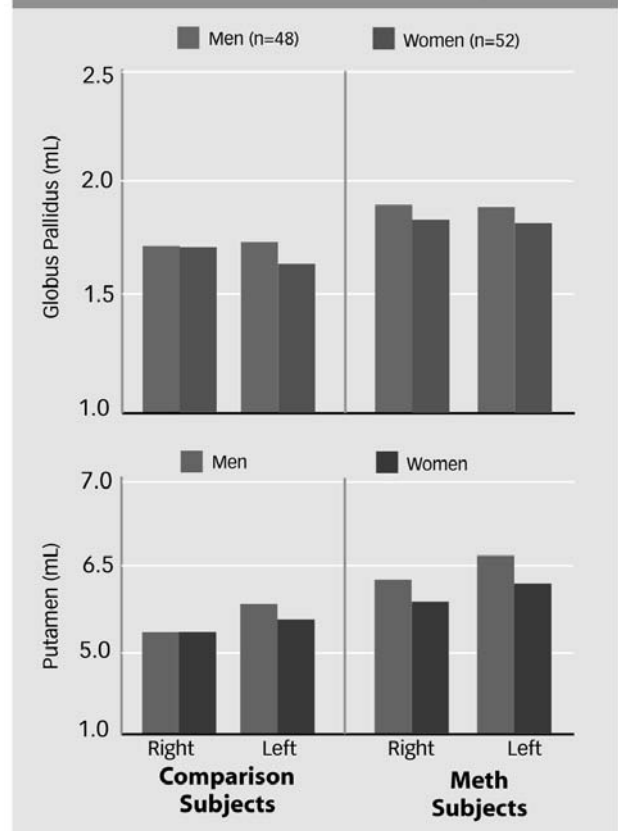
### Structural Fluctuation Suggests Glial Activation

Dr. Linda Chang (now at the University of Hawaii) and colleagues at the University of California, Los Angeles, used magnetic resonance imaging to measure the volumes of striatal brain structures, including the putamen and globus pallidus, in a group of methamphetamine abusers. The studied individuals, 26 women and 24 men (average age 31 years), had abused methamphetamine (average 1.6 g/day on 6.3 days/week) for periods ranging from 4 to 15 years. All had been abstinent for periods ranging from 1 week to 4 years at the time of the study; 44 also took tests of verbal memory and intelligence, gross and fine motor function, mood, executive function, and other capacities likely to be affected by striatal damage.

The researchers expected to find that the methamphetamine abusers’ striatal regions were smaller than those of a comparison group of age- and gender-matched individuals with no history of methamphetamine abuse. Such a finding would be consistent with previous research showing that methamphetamine reduces the density of striatal dopamine terminals. Instead, says Dr. Chang, “Contrary to our hypothesis, striatal volumes were larger in the methamphetamine abusers as a group.” The size difference was greatest among individuals with less cumulative exposure to the drug, and smaller among those with more. Those with the most exposure also performed slightly worse on neuropsychological tests of verbal fluency and visual-motor coordination.

#### STRUCTURES IN THE BRAIN’S STRIATAL REGION ARE ENLARGED IN METHAMPHETAMINE ABUSERS

Average volumes of the globus pallidus and putamen—structures in the brain’s striatal region—are larger in men and women with a history of methamphetamine abuse than in men and women with no exposure to the drug.



Dr. Chang believes the surprising increase in striatal volumes of methamphetamine abusers may reflect the activity of glia—cells that provide protective and reparative functions for the brain’s main functional cells, the neurons. When molecules potentially harmful to neurons penetrate the brain, glia mount a response resembling the inflammation and scar tissue formation associated with immune responses in other parts of the body. Possibly, Dr. Chang suggests, methamphetamine provokes glia to react in this way, leading to an increase in regional volume analogous

to the swelling seen in bodily immune responses. Subsequently, she speculates, the glial response may taper off as cumulative exposure to the drug—and neuron damage—mount. Continued abuse results in damage that is manifested in decreased cognitive performance.

“This work is consistent with an increasing body of research that shows a relationship between methamphetamine exposure and structural changes in the brain,” says Dr. Steven Grant of NIDA’s Division of Clinical Neuroscience and Behavioral Research. “It links methamphetamine abuse, structural change, and functional deficits and suggests that the magnitude of these effects is related to the degree of abuse. We don’t understand what is happening at deeper levels, but the observations made in this study suggest that the volume changes are related to methamphetamine’s direct or indirect effect on glial cells. We still need to understand how structural changes result in functional deficits; how much, if any, of this damage can be reversed; and how methamphetamine acts at the cellular level.”

### In Mice, Methamphetamine Misdirects Glia To Attack Brain Cells

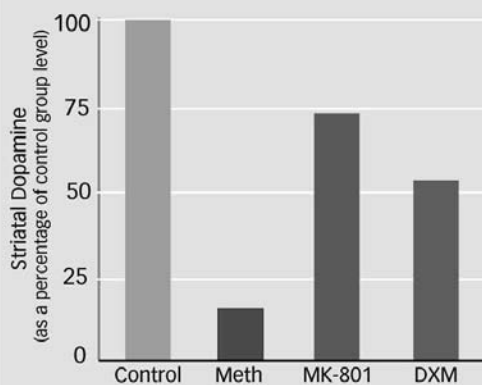
A study by Drs. Donald Kuhn and David Thomas and colleagues at Wayne State University School of Medicine indicates that methamphetamine’s toxic effects may include subverting some glial cells to attack rather than preserve neurons. Specifically, their results indicate that the drug incites a subset of glia called microglia to mount an immune response against dopamine neurons.

Normally, microglia protect neurons against toxic injury by several mechanisms. They detect and bind to invading molecules, including viruses or bacteria, making them easily accessible to destructive immune system cells such as lymphocytes. As well, they produce compounds, some toxic, to help contain or eliminate the danger. Methamphetamine, the new study suggests, causes dopamine neurons to release a signal that decoys the microglia into turning these normally protective responses against the neurons themselves. When that happens, Dr. Kuhn says, “The microglia aren’t reacting to methamphetamine’s neural damage. Instead, they are active participants in the drug’s neurotoxicity.”

To begin their experiments, the researchers reasoned that if microglia contribute to methamphetamine toxicity to dopamine terminals, compounds that protect against such toxicity might do so, at least in part, by inhibiting microglial activation. Their first hypothesis, accordingly, was that the compound MK-801, which is known to be protective, blunts microglial activation. The team showed this to be the case by exposing cell cultures of mouse microglia to two proteins known to precipitate damaging

#### COMPOUNDS THAT BLOCK THE ACTION OF MICROGLIA COUNTER A TOXIC EFFECT OF METHAMPHETAMINE

Striatal regions of mice exposed to methamphetamine contain decreased dopamine content, compared with those of unexposed controls. Treatment with MK-801 or dextromethorphan (DXM) prior to methamphetamine injection reduced the extent of depletion, suggesting that microglia play a role in methamphetamine’s toxic effect on the brain’s dopamine system.



microglial responses: lipopolysaccharide (LPS) and HIV Tat, a derivative of the human immunodeficiency virus. Compared with LPS and HIV Tat exposure without pretreatment, exposure following pretreatment with MK-801 significantly reduced the amount of two protein products of microglial activation, called cyclooxygenase-2 (Cox-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Dextromethorphan (DXM), a compound biochemically similar to MK-801, had the same effect.

“These results suggested that both MK-801 and dextromethorphan exert direct action on the microglial cells in culture to block the activation process,” Dr. Kuhn says. Having determined that the two compounds block microglial activation in vitro, the researchers next hypothesized that they would also do so in living animals.

Drs. Kuhn and Thomas injected mice with either MK-801 or DXM and then methamphetamine (5 mg/kg of body weight) 15 minutes later, repeating this sequence four times at 2-hour intervals. A control group of mice received the same regimen, but with saline substituted for methamphetamine. Forty-eight hours after the last injection, the researchers assayed the brains of the mice for Cox-2 and TNF- $\alpha$ , the indicators of microglia activation, and for striatal dopamine levels, a widely used index of damage to dopamine neurons. Dr. Kuhn says, “We found that both DXM and MK-801 significantly reduced the markers of striatal microglial activation associated with methamphetamine exposure and protected against



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dopamine nerve terminal damage in the striatum. The close association between the ability of MK-801 and DXM to significantly lower both microglial activation and neuronal damage suggests a causal link between the two. It looks as though the damage associated with methamphetamine abuse is the result of microglial action.”

The apparent association of microglia and damage to dopamine neurons has implications beyond what it may reveal about methamphetamine abuse, says Dr. Jerry Frankenheim of NIDA’s Division of Basic Neuroscience and Behavioral Research. “Microglia are the primary immune defense cells in the brain. They safeguard neural functions, yet excessive activation can cause microglia to harm neurons. Other research implicates microglial involvement in a wide range of neurodegenerative disor-

ders, including Alzheimer’s disease, Parkinson’s disease, and stroke. Understanding how methamphetamine is able to decoy microglia into a destructive rather than reparative role could also help explain the processes involved in these other disorders.”

#### Sources

- Chang, L., et al. Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biological Psychiatry* 57(9):967–974, 2005.
- Thomas, D.M., and Kuhn, D.M. MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. *Brain Research* 1050(1-2):190–198, 2005. **NN**

## Methamphetamine Increases, and HIV Decreases, Brain Volumes

HIV infection and methamphetamine addiction produce distinct, partly overlapping effects on brain structures.

By John S. DeMott, *NIDA NOTES* Contributing Writer

In a study that confirmed the association between HIV infection and loss of brain volume, NIDA-funded investigators also found an association between methamphetamine addiction and increased regional brain volume. Each type of volume change was associated with neurocognitive impairments, but it was unclear whether the two together caused any cognitive effects beyond the sum of what each produced individually.

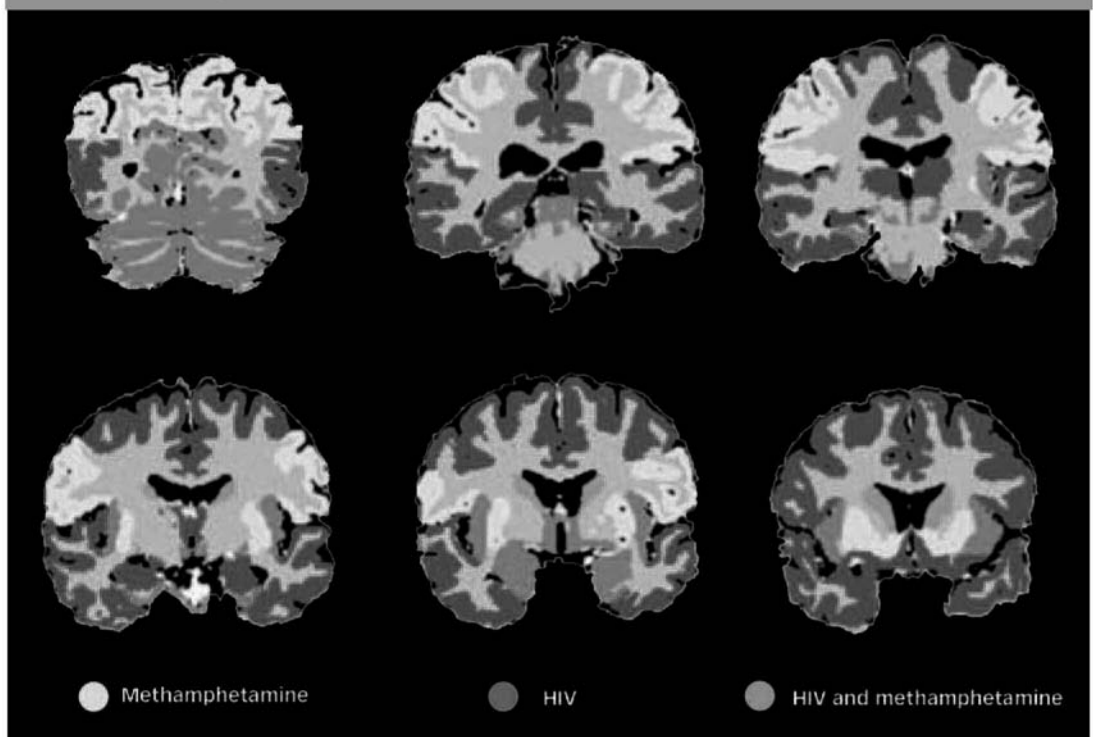
Using structural magnetic resonance imaging (MRI), Drs. Terry L. Jernigan, Anthony C. Gamst, and colleagues at the University of California, San Diego (UCSD) mapped the major gray-matter brain structures of 103 people in four age- and education-matched groups: HIV-infected; methamphetamine-addicted; having both conditions; and having neither. The methamphetamine-addicted individuals were in recovery at UCSD's HIV Neurobehavioral Research Center.

After accounting for normal age-related reductions in brain volume, the participants with HIV had smaller volumes of cortical, limbic, and striatal structures, with the associations being most pronounced in the frontal and temporal lobes. Methamphetamine addiction was linked with increased volume in the parietal cortex and in all three segments of the basal ganglia—caudate nucleus, lenticular nucleus, and nucleus accumbens (NAc). In the caudate,

volume reductions related to HIV and increases related to methamphetamine overlapped, producing a net volume approximating normal.

A further analysis of the volume data may reinforce existing evidence that drug abuse is especially damaging during adolescence and young adulthood, when the brain is still developing. The results showed that addicted individuals who were younger had greater NAc volume differentials compared with their non-drug-abusing age mates than did older addicted individuals. One possible explanation for this is that the drug interfered with the pruning of some NAc connecting fibers that normally occurs in the transition to adulthood, producing a small but measurable

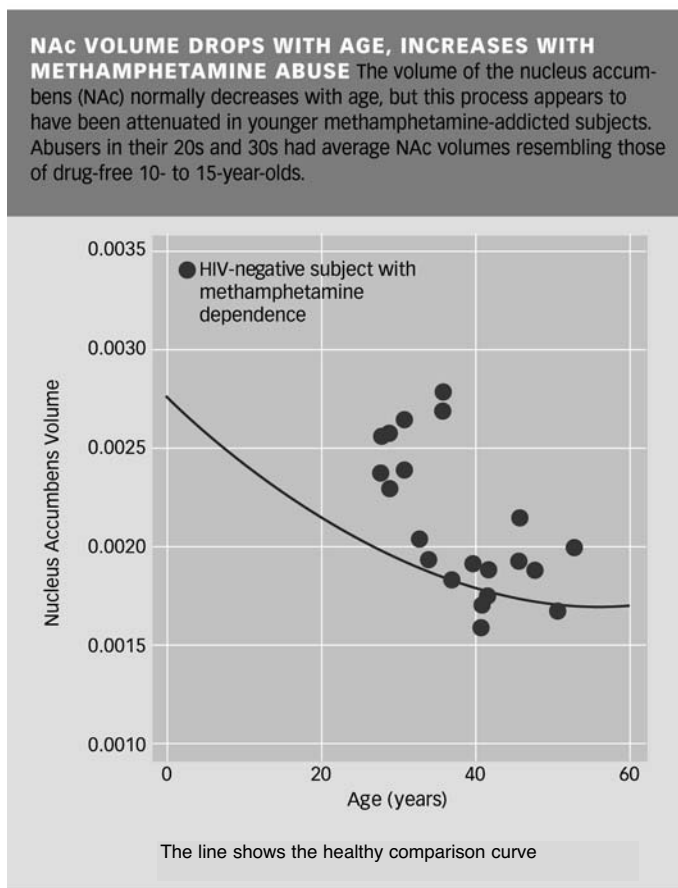
**HIV SHRINKS BRAIN VOLUME, METHAMPHETAMINE ABUSE INCREASES IT** Composite magnetic resonance imaging (MRI) scans of brain cross-sections show the effects of methamphetamine abuse and HIV infection on brain architecture. Volumes of regions shown in yellow were larger in methamphetamine-addicted individuals than in unexposed controls. Volumes of regions shown in red were smaller in HIV-positive than in noninfected individuals. The volume in the caudate nucleus, shown in orange, illustrates the superimposed effects of both conditions, which had an offsetting effect on volume. The offsetting volume effect did not cancel the functional brain damage associated with HIV infection and methamphetamine abuse.



Reprinted from *American Journal of Psychiatry*, Vol. 162(8):1461-1472, Jernigan, T.L., et al.: "Effects of methamphetamine dependence and HIV infection on cerebral morphology." © 2005, with permission from the American Psychiatric Association.

(See [www.nida.gov/NIDA\\_notes/NNVol20N6/Increases.html](http://www.nida.gov/NIDA_notes/NNVol20N6/Increases.html) for color image)

reduction in NAc volume. “While we can’t be certain of the explanation, this finding highlights the concern that exposure during adolescence may alter the course of ongoing brain maturation,” says Dr. Jernigan (see chart).



Reprinted from *American Journal of Psychiatry*, Vol. 162(8): 1461-1472, Jernigan, T.L., et al.: “Effects of methamphetamine dependence and HIV infection on cerebral morphology,” © 2005, with permission from the American Psychiatric Association.

Although the study results provided little information about specific drug mechanisms, the investigators note that animal studies have shown methamphetamine can incite inflammatory responses and abnormal growth of nerve fibers, each of which can increase tissue volume. “These findings emphasize that the brain’s response to stimulant exposure, and indeed to HIV as well, is probably quite dynamic, characterized by overlapping responses in different glial, as well as neuronal, cell populations,” says Dr. Jernigan. “The findings raise interesting questions for multiple-modality imaging studies, and underscore the degree of neural plasticity, and thus the potential for targeted intervention.”

Dr. Jernigan says a finding of extensive change in the parietal cortex of methamphetamine abusers “helps to confirm the importance of parietal lobe involvement and may help correct a tendency in the field to neglect this region.”

**“The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals.”**

### Implications for Brain Function

The researchers looked for correlations between the brain volume abnormalities and ratings of neuropsychological impairment. At the outset of the study, all other groups were significantly impaired relative to the HIV-negative and methamphetamine-negative group, which had a rating of 2.9 compared with 4.7 for those with both conditions, 4.2 for methamphetamine-addicted participants and 4.1 for HIV-positive individuals. Brain impairment was most pronounced in the HIV-positive participants with the most extensive loss of cortical volume and in the methamphetamine-addicted participants with the highest increase in cortical volume. The investigators found only one significant correlation between brain volumes and impairment in addicted individuals with HIV, a finding they believe probably reflects confounding by the opposed volume impacts of the two pathologies. The correlation was between hippocampal volume—a structure that both factors may damage—and severity of cognitive impairment in the dually diagnosed group.

“The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals,” Dr. Jernigan says. “This is very exciting, because our results raise a number of specific questions that may not have been posed without these findings.”

Dr. Ro Nemeth-Coslett, a NIDA psychologist, agrees. “As often happens in research, these results raise more questions than they answer. Dr. Jernigan’s findings of structural inconsistencies in pathology are unaccounted for. Now we need mechanistic studies to provide a clearer understanding of what aspects of microscopic cellular organization actually drive the MRI measures.”

### Source

- Jernigan, T. L., et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry* 162(8):1461-1472, 2005. [NN](#)

## Brain Activity Patterns Signal Risk Of Relapse to Methamphetamine

Methamphetamine abusers who relapse after treatment appear to make decisions using different brain regions than do those who remain abstinent.

BY Patrick Zickler, *NIDA NOTES* Contributing Writer

NIDA-supported investigators have found that functional magnetic resonance imaging (fMRI) of the brain, performed during a psychological test, can predict with high accuracy whether an individual will relapse following treatment for methamphetamine abuse. Their study revealed a characteristic pattern of brain activity in methamphetamine-abusing men who relapsed within 1 to 3 years after completing treatment and a different pattern in men who did not.

Dr. Martin Paulus and colleagues at the University of California, San Diego, took the point of departure for their work from previous research that showed methamphetamine abusers and nonabusers activating different brain areas during psychological tests of decisionmaking.

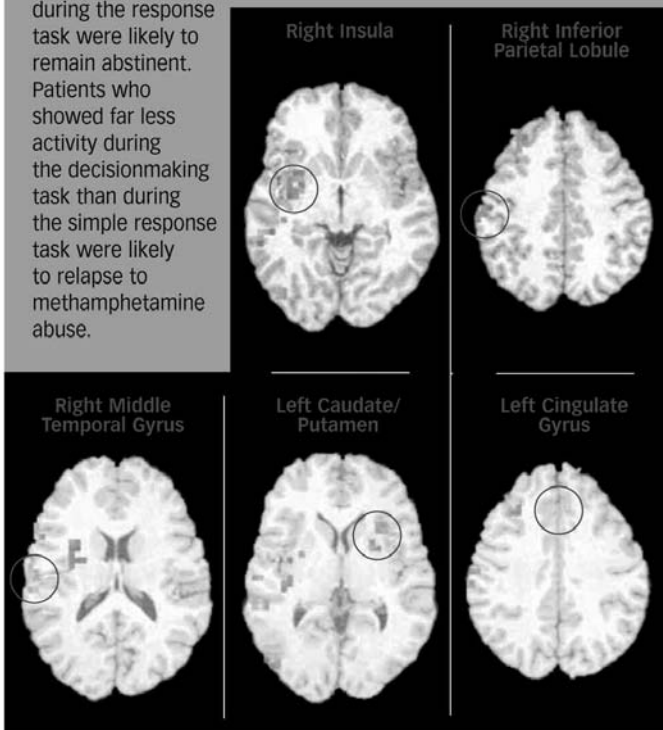
These earlier studies showed that poor choices made by drug abusers correlate to distinctive patterns of activity in some areas of the brain. Dr. Paulus's team hypothesized that activity patterns in those regions might also be associated with relapse to drug abuse, which involves similarly destructive decisions.

To test their hypothesis, the researchers recruited 46 men who had voluntarily entered and completed a 28-day inpatient drug treatment program after abusing methamphetamine for periods ranging from 3 to 34 years. When each man had been abstinent for about 4 weeks, he participated in two psychological tests. During one, he was asked to watch a computer screen and press a button every time a symbol appeared. In the other, he was asked to try to predict whether a flashing symbol would next occur on the left side or right side of the computer screen. The difference between the two tasks was that, in the first, the test-taker needed only to react upon seeing the symbol, while in the second, he needed to decide which side to choose. The researchers recorded the men's brain activity with fMRI throughout the tests.

A year or more (360 to 967 days) after the imaging sessions, Dr. Paulus's team was able to locate and contact 40 of the 46 patients. Of these, 18 had relapsed to methamphetamine abuse (median time to relapse, 279 days; range, 36 to 820 days). Comparing their fMRI results with those of the 22 nonrelapsers, the researchers noted nine regions where the groups' brain activity had differed during decisionmaking. The relapse group showed less activation of the dorsolateral, prefrontal, parietal, and temporal cortices and the insula—regions associated with evaluation and choice among actions that may lead to either beneficial or harmful outcomes. The patterns of brain activation predicted relapse in 17 of the 18 men who had resumed methamphetamine abuse and predicted successful abstinence in 20 of the 22 patients who had not relapsed, Dr. Paulus says.

"The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome," Dr. Paulus says. "The differences in brain activity are pronounced, with little overlap." Differences in the right insula, right posterior cingulate, and right middle temporal gyrus differentiated relapsers from nonrelapsers. Other brain regions predicted the timing of relapse.

**DRUG ABUSE AND DECISIONMAKING** Researchers used functional magnetic resonance imaging (fMRI) to measure patterns of regional brain activity while abstinent methamphetamine abusers performed two tasks, one that required decisionmaking and one that required only a simple response. Participants who showed greater activity in selected brain regions (circled and highlighted in the brain images shown below) during the decisionmaking task than during the response task were likely to remain abstinent. Patients who showed far less activity during the decisionmaking task than during the simple response task were likely to relapse to methamphetamine abuse.

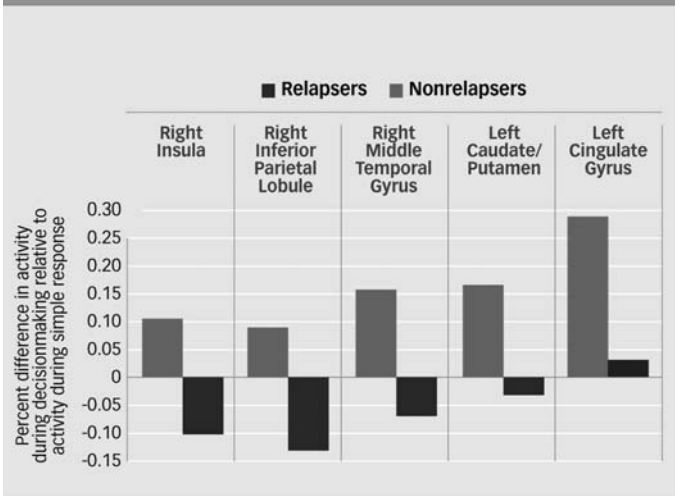


**“The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome. The differences in brain activity are pronounced, with little overlap.”**

“Some of these predictive areas have not previously been strongly associated with drug abuse,” observes Dr. Steven Grant of NIDA’s Division of Clinical Neurosciences and Behavioral Research. “For example, while other investigators have reported alterations in the parietal lobe related to drug abuse, this is the first study to show the parietal cortex playing an important role. However, because so many brain regions were related to relapse, we still do not have a full understanding of what specific process might be dysfunctional in the relapse group.”

The potential clinical implications of the new finding are promising, but uncertain. For example, no women were included among the participants, who were enrolled from treatment programs. “It’s important to confirm the findings in women, for whom social, demographic, and other factors associated with relapse may differ,” Dr. Paulus points out. Nonetheless, he says that, in principle, programs treating methamphetamine abuse might use the fMRI protocol to assess patients, then assign those likelier to relapse to higher levels of care. Dr. Paulus believes such an approach might prove cost-effective, even with typical fMRI charges of up to \$700 per hour in academic imaging centers. “The human and social costs of relapse are high,” Dr. Paulus says. “Using this imaging technique to

**RELAPERS, NONRELAPERS MAKE DECISIONS DIFFERENTLY**  
 During a decisionmaking exercise, nonrelapsers activated five brain regions that relapsers did not.



precisely allocate care to the patients who need it most might well produce enough savings elsewhere to more than offset its expense. An alternative, more practical course of action might be to use these fMRI results as a benchmark for development of other assessments that are less costly, but have the same predictive strength.”

**Source**

- Paulus, M.P.; Tapert, S.F.; and Schuckit, M.A. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry* 62(7):761-768, 2005. **NN**

## Community-Based Treatment Benefits Methamphetamine Abusers

A large California study finds favorable effects for inpatients and outpatients; women's gains are larger.

By Lori Whitten, *NIDA NOTES* Staff Writer

Methamphetamine abusers can achieve long-term abstinence with the help of standard community-based drug abuse treatment. Nine months after beginning therapy, 87 percent of patients treated for heavy or long-term methamphetamine abuse in California outpatient and residential programs were abstinent from all drugs, according to a NIDA-supported analysis. "In the public dialogue, and even among professionals in the field, one sometimes hears that meth abuse is 'not treatable.' But that view is not borne out by recent clinical trials or our study, which shows that community-based treatment reduces drug abuse and other problems," says lead investigator Dr. Yih-Ing Hser.

Dr. Hser and colleagues at the University of California, Los Angeles analyzed data from the California Treatment Outcome Project (CalTOP), an ongoing study that has followed the progress of adult substance abusers treated at 43 outpatient and residential programs throughout the State since April 2000. The researchers focused on 1,073 patients who reported that methamphetamine abuse was their primary drug problem (572) or that they had abused the stimulant regularly for at least 1 year before beginning treatment (501). Most were in their 30s or younger, White or Latino, unemployed, and on public assistance; most had an arrest history. They had abused methamphetamine for about 9 years, on average, and nearly one-quarter (22 percent) reported injecting drugs at least once. Although 64 percent had children aged 18 or younger, one-third of parents did not live with their children in the month before beginning treatment. One parent in five reported that a child protection court had ordered that his or her children live with someone else, and 6.3 percent had their parental rights terminated by the State.

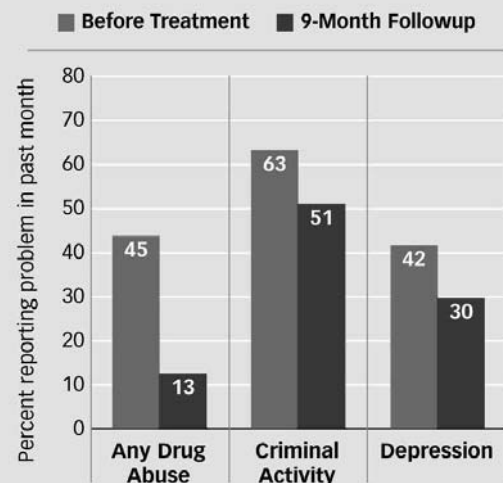
The patients received the addiction treatment services routinely provided by each program. These usually included group therapy, with an average of 69 drug-related and 51 alcohol-related sessions during the first 3 months of treatment. On average, the patients also received 22 sessions on dealing with mental health symptoms and 13 addressing psychosocial problems, including family, parenting, and employment.

More than 60 percent of the patients completed 3 months of treatment. Among all the patients in the study—those who finished 3 months and those who did not—the average reported frequency of methamphetamine abuse fell from 2.7 to 0.5 days per month from the start of treatment to 9 months later. The portion who were abstinent from all drugs rose from 55 percent to 87 percent

***"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure."***

in the same interval, and 68 percent were abstinent and also not incarcerated. Patients improved in all areas—drug and alcohol abuse; mental health symptoms; and employment, family, and legal problems—except one: men's medical problems.

**ABUSERS ACHIEVE GAINS WITH TREATMENT** Nine months after methamphetamine abusers began addiction treatment, they had reduced past-month drug abuse and criminal activity, and fewer reported depression.



Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research says these findings should reassure professionals working in the addiction, social services, and criminal justice fields that current therapies work for these troubled patients. "Dr. Hser's findings suggest that treatments available in the community help meth abusers reduce drug abuse and start to get their lives back on track, echoing prior research," he says.

### Women's Experiences

Dr. Hser's findings confirm gender differences seen in other studies: Women began treatment with more severe psychosocial problems than men (see chart, right) and benefited more. Although treatment retention levels were similar for the two sexes, the women made greater gains in the areas of family relationships and medical problems, while achieving similar improvements in all other areas at the 9-month followup. The women's better outcomes may have resulted in part from more intensive services (see chart below); as well, Dr. Hser says that many women in the study had a powerful motivator—family. "Many were trying to maintain or regain custody of their children by demonstrating improvement during treatment. Others had 'hit bottom,' saw how drug abuse was hurting their families, and decided to make a change," she says.

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they

**MEN, WOMEN EXPERIENCE DIFFERENT PROBLEMS** Women beginning treatment for methamphetamine abuse reported more psychosocial problems, while men reported more crime and criminal justice involvement.

	Women, % (n=567)	Men, % (n=506)	Total, % (N=1,073)
<b>Family and Social Circumstances</b>			
Children living with someone else by court order	29.3	9.9	20.1
Parental rights terminated	10.1	2.2	6.3
Family abused substances	21.7	10.5	16.4
Physically abused (past month)	5.5	1.8	3.7
Sexually abused (past month)	2.5	0.6	1.6
Employed	23.8	43.9	33.3
On public assistance	63.1	37.0	50.8
<b>Criminal Justice System Involvement</b>			
On parole	4.4	12.7	8.3
On probation	32.3	37.6	34.8
Ever arrested	76.7	88.3	82.2
Arrest in past year	36.7	45.1	40.6
Criminal activity (past month)	55.2	71.7	63.0
<b>Psychiatric Symptoms (Past Month)</b>			
Serious depression	38.8	29.8	34.6
Difficulties with understanding, concentrating, remembering	36.2	26.5	31.6
Suicidal thoughts	11.3	6.3	9.0
Prescribed psychiatric medicine	21.3	15.4	18.6

**WOMEN RECEIVE MORE SERVICES IN SOME AREAS** For some problems, women received more services than men during the first 3 months of treatment.

Services	Women (No. of interventions <sup>†</sup> )	Men (No. of interventions <sup>†</sup> )
Employment*	4.6	2.3
Family <sup>†</sup>	6.5	4.6
Mental Health <sup>‡</sup>	23.6	19.9
Parenting*	4.2	1.7

<sup>\*</sup> Includes counseling sessions, medical appointments, and prescriptions. <sup>\*</sup> Outpatients. <sup>†</sup> Outpatient and residential.

may bear to the consequences of prenatal drug exposure," says Dr. Hser.

Dr. Hser and her colleagues continue to analyze CaTOP data, aiming to determine the longer-term impact of therapy and identify ways programs can

improve outcomes. "Enhancing psychiatric, parenting, and employment services would better match patients' needs, and my team plans to study the relationship between help for these problems and longer-term outcomes," says Dr. Hser. They also plan to investigate whether women-only treatment is more effective for pregnant methamphetamine abusers than mixed-gender programs.

"The field needs more research following meth abusers over time to get a picture of the long-term outcomes of treatment, relapse episodes, and whether these patients require additional support to sustain gains made during therapy," says Dr. Hilton. "Because the availability of community health and social services varies across States, we cannot generalize the findings from one State, such as California. We need data from across the country," he adds.

### Source

- Hser, Y.-I.; Evans, E.; and Huang, Y.-C. Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment* 28(1):77-85, 2005. **NN**

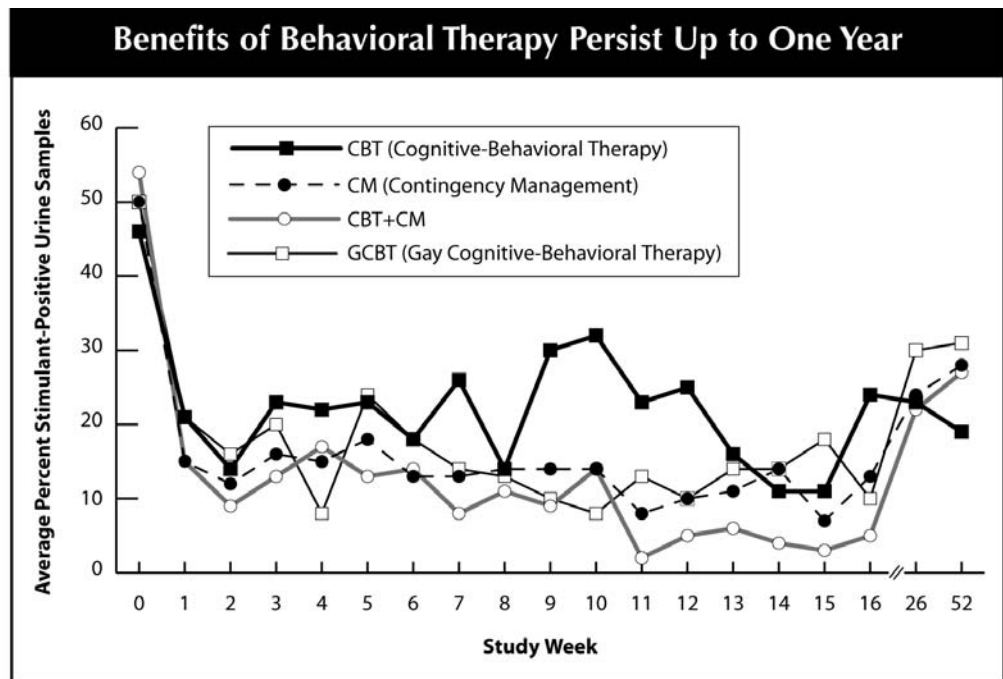
## Treatment Curbs Methamphetamine Abuse Among Gay and Bisexual Men

By Lori Whitten, *NIDA NOTES* Staff Writer

Behavioral therapy can help gay and bisexual men (GBM) reduce methamphetamine abuse and risky sexual behaviors and sustain these gains for 1 year, NIDA-funded researchers report. By the end of a 16-week trial of four different behavioral therapies, study participants' stimulant-positive urine samples fell 31 percent, and their number of past-month sexual partners fell more than 50 percent—outcomes that regressed little at the followup visits. Symptoms of depression also improved.

Dr. Steven Shoptaw and colleagues at the University of California, Los Angeles and the Friends Research Institute recruited 263 methamphetamine-addicted GBM throughout Los Angeles County, particularly in Hollywood, where HIV prevalence is especially high. Of these, 162 completed the requirements for entering the treatment phase of the study, which were to attend six assessments and participate in at least two of four group sessions on abstinence skills during a 2-week "baseline period." Men who met the requirements reported less severity and shorter duration of methamphetamine abuse than those who did not, despite having abused methamphetamine for 5 years and having spent \$293 on the drug in the past month, on average. Half had engaged in unprotected anal intercourse (UAI) with someone other than their primary partner in the past month, and 84 percent of these men linked the behavior to methamphetamine abuse. Most participants (73 percent) reported symptoms of depression, with about 30 percent describing these as moderate to severe.

The researchers randomly assigned each patient to one of four behavioral therapies: cognitive-behavioral therapy (CBT), contingency management (CM), CBT+CM, or



*Although all interventions were effective, participants who received contingency management (CM), cognitive-behavioral therapy (CBT) and CM, or culturally tailored Gay CBT (GCBT) submitted fewer stimulant-positive urine samples during treatment, compared with those in standard CBT.*

Gay CBT (GCBT). In CBT, participants analyzed situations and emotions linked with relapse, practiced ways to manage craving and thoughts about drug abuse, and discussed healthy behaviors in group sessions. In CM, participants received vouchers redeemable for groceries, transportation, and clothing if they submitted stimulant-negative urine samples. GCBT addressed standard CBT issues—including relapse, craving, and healthy behaviors—using specific examples from gay cultural events and environments. For example, they compared the experience of owning up to a drug problem with the experience of acknowledging sexual orientation by “coming out.” All four interventions were offered three times a week for 4 months.

### Multiple, Lasting Benefits

Participants reduced methamphetamine abuse and risky sexual behaviors and experienced fewer depression symp-



toms in the last month of treatment compared with the month before therapy, regardless of the therapeutic approach. Overall, they decreased methamphetamine abuse from 9.6 to 2.4 days a month and reduced the number of past-month sexual partners from 9.8 to 4.3, on average. The percentage who reported unprotected insertive anal intercourse—a risk factor for HIV-infected individuals to transmit the virus to partners—fell from 36.9 percent to 16.7 percent by the end of treatment. Beck Depression Inventory (BDI) scores improved from 14.3 (in the “mild to moderate” range) at baseline to 5.4 (“minimal”) in the last week of treatment.

Although all therapies benefited participants, response to the treatments differed. During the treatment period, participants in GCBT and the combined treatments attended more weeks of therapy and submitted fewer stimulant-positive urine samples than those who received standard CBT during treatment. Participants receiving GCBT showed a faster decrease in unprotected receptive anal intercourse—a risk factor for acquiring the virus from a partner—compared with those in standard CBT. Most participants (80 percent) took part in the 1-year followup. Generally, they sustained the lower levels of methamphetamine abuse, risky sexual behaviors, and depression observed at the end of treatment (see page 12, “Benefits of Behavioral Therapy Persist Up to One Year”).

“It is encouraging that several types of behavioral treatment reduced both drug abuse and risky sexual behaviors among gay and bisexual men at high risk for contracting

or transmitting HIV,” says Ms. Debra Grossman of NIDA’s Division of Neuroscience and Behavioral Research. However, more studies are needed to determine the components of treatment that affect risky sexual behaviors and the link between methamphetamine abuse and such behaviors in other populations, she adds.

### Methamphetamine Treatment as HIV Prevention

For about a decade in California, the drug most tightly linked with HIV infection in GBM has been methamphetamine. The drug conveys a sense of heightened sexuality in the short term and is associated with risky sexual behaviors and extremely high rates of HIV infection in those seeking treatment. Sixty percent of the participants in Dr. Shoptaw’s study reported HIV-positive status, a prevalence much higher than his group has observed among GBM seeking treatment for cocaine (30 percent), alcohol (15 percent), or heroin (5 percent) abuse.

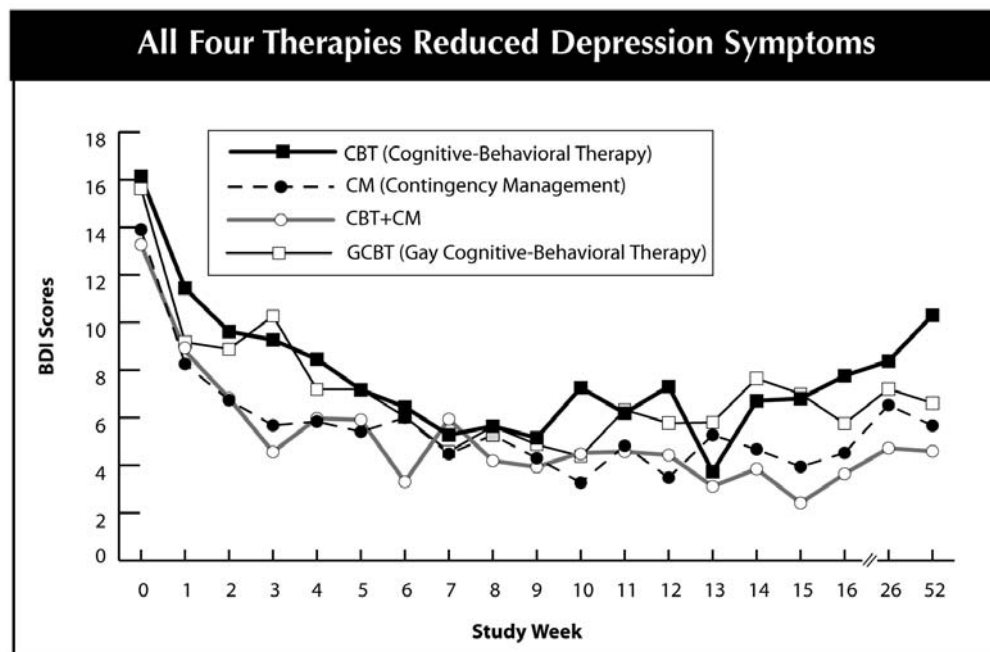
“The reductions in risky sexual behavior in this study exceeded those observed in HIV prevention trials among GBM. We conclude that treatment for meth abuse fits into a comprehensive HIV prevention strategy,” says Dr. Shoptaw. The findings have already made an impact: These data helped policymakers at the California Office of AIDS decide to allocate \$3 million for programs that address methamphetamine abuse among GBM.

### Methamphetamine and the Blues

The researchers were not surprised by the high percentage of their study participants who reported depression symptoms at the beginning of the study. GBM are three times as likely as heterosexual men to have clinical depression.

Methamphetamine abusers often say they take the drug to kick the blues, but results from the current study suggest that continuing abuse may serve to relieve low moods related to stimulant withdrawal rather than alleviate underlying chronic depression.

When they analyzed the temporal link between metham-



Participants demonstrated improvement in Beck Depression Inventory (BDI) scores, which dropped sharply the first week of treatment and leveled off at week 4.

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phetamine abuse and depression, Dr. Shoptaw and his colleagues found that a urine sample indicating abuse of the drug within the past 5 days strongly predicted high BDI scores and abstinence strongly predicted low scores. In contrast, BDI scores did not predict episodes of future methamphetamine abuse, which is what would be expected if the men were abusing the drug to alleviate depression. “Meth abusers probably remember feeling better after taking the drug, but this perception may not match the physiology of long-term stimulant abuse,” says Dr. James Peck, a member of the research team who led the analysis of the depression data.

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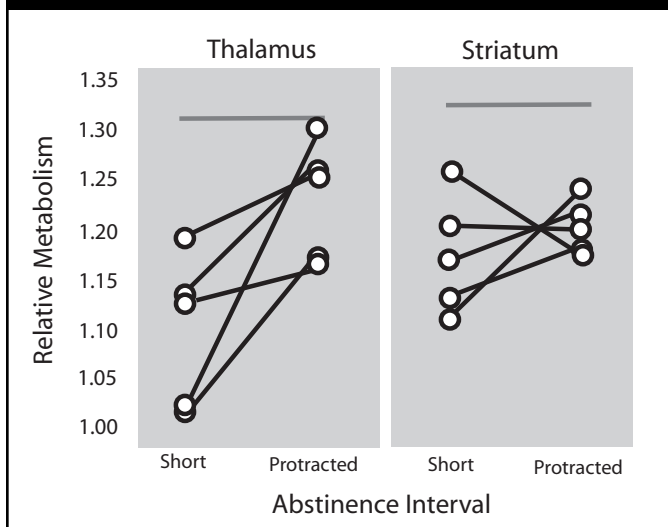
- Shoptaw, S., et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug and Alcohol Dependence* 78(2):125-134, 2005.
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## Long-Term Abstinence Brings Partial Recovery From Methamphetamine Damage

By Patrick Zickler, NIDA NOTES Staff Writer

### Some Methamphetamine-Related Deficits Recover After Protracted Abstinence



Relative metabolic activity (regional metabolic rate compared with rate for entire brain) was reduced in the striatum and thalamus of five methamphetamine abusers, compared with nonusers, after short abstinence. After protracted (more than 9 months) abstinence, thalamic metabolism returned to normal levels (blue line indicates median level for healthy comparison subjects). Striatal metabolism showed no recovery after abstinence.

Methamphetamine abusers who remain abstinent for 9 months or longer show modest improvement in performance on some tests of motor skill and memory. They also appear to recover from some of the drug's damaging effects on metabolism in the thalamus, a brain region involved in relaying and filtering sensory, motor, and emotional signals between the cerebral cortex and other brain structures. Drug-related deficits appear to persist longer, however, in another brain region, the striatum, which plays a role in reward-linked motivation, planning, and impulse control.

Dr. Gene-Jack Wang and colleagues at the Brookhaven National Laboratory in Upton, New York, evaluated metabolism and neuropsychological function in a small group of methamphetamine abusers (three women and

two men; average age, 29) who entered treatment as part of a California drug court rehabilitation program. In tests following an abstinence of 2 months or less, the methamphetamine abusers scored lower than nonabusers, though within normal ranges, on tests of gross motor function (timed while walking in a straight line for a defined distance), fine motor coordination (inserting pegs into small angled holes), memory (learning and recalling lists of unrelated words immediately, after a delay, and after a distraction), and attention (identifying numbers previously associated with symbols). When tested again after an additional 9 months of abstinence (average total abstinence was 17 months), these methamphetamine abusers had improved performance on three of five neuropsychological measures: the timed gait test, symbol-digit association, and delayed word recall. The changes in test scores correlated with improvement in thalamic metabolism.

The researchers used positron emission tomography (PET) to evaluate methamphetamine's effect on metabolism in the thalamus and striatum. This technique involves injection of a radioactively labeled form of glucose, the body's basic metabolic fuel. Differences in activity among brain regions are reflected by different rates of glucose consumption. PET imaging captures the signals emitted by the radioactive glucose molecules; the strength of the signal indicates the intensity of metabolic activity. The methamphetamine abusers had lower metabolism in the thalamus than did nonabusers when evaluated after the short abstinence. However, the abusers' thalamic metabolism was not significantly different from the nonabusers' after the longer drug-free period, suggesting that drug damage in this brain region is reversed with abstinence. "The correlation between increased thalamic metabolism and the tendency to better scores on some tasks suggests that the thalamic changes are functionally significant," Dr. Wang says.

After a short abstinence, metabolism in another brain region, the striatum, also was lower in methamphetamine abusers than in participants who had never used the drug. In contrast to the findings with thalamic metabolism, however, abusers did not show recovery of striatal metabolism after the longer abstinence.

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***The emerging pattern of these studies offers encouraging evidence that some of the destructive effects of methamphetamine abuse may be reversible.***

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methamphetamine causes damage to brain circuits that rely on the neurotransmitter dopamine. “Recovery of thalamic metabolism could indicate in part a compensatory adaptation to the loss of these dopamine cells by increased activity in other brain cells that extend from the striatum into the thalamus,” says Dr. Joseph Frascella of NIDA’s Division of Clinical Neuroscience, Development, and Behavioral Treatments. “But there is a troubling indication that some of the drug’s damage is longer lasting. The

The emerging pattern of these studies offers encouraging evidence that some of the destructive effects of methamphetamine abuse may be reversible. The brain may respond to damage by rerouting some connections. Earlier work made it clear that

persistent reduction in striatal metabolism seems to reflect the drug’s toxicity to dopamine terminals in that region.”

This lasting deficit in striatal metabolism may hold a clue to the cause of other methamphetamine-related effects. In some followup studies, methamphetamine abusers report lack of motivation and anhedonia—an absence of pleasure in response to acts that had previously been pleasurable—as long as 2 years after their last use of methamphetamine. Motivation and pleasurable response are both governed in part by activities in one specific region of the striatum, the nucleus accumbens, Dr. Wang explains.

“The anhedonia and decreased motivation reported by some abstinent abusers may be the result of reduced activity—indicated in this study by reduced metabolism—in the nucleus accumbens, which has a high density of dopamine cells,” says Dr. Wang.

**Source**

Wang, G.-J., et al. Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *American Journal of Psychiatry* 161(2):242-248, 2004. **NN**

## Mood Disorders in Methamphetamine Abusers Linked to Changes in Brain Metabolism

Impaired metabolism in one part of the brain, the striatum, may be the culprit in methamphetamine-linked mood disturbances. In a study similar to the one reported in the accompanying article (see page 15, “Long-Term Abstinence Brings Partial Recovery From Methamphetamine Damage”), 17 chronic abusers of methamphetamine underwent positron emission tomography (PET) brain scans in the first week of rehabilitative treatment, a time when many patients report high levels of depression and anxiety. The scans revealed that metabolic activity in the striatum varied with the severity of the patients’ affective symptoms.

The patients in the study (11 men and 6 women, with an average age of 34.5 years) had used methamphetamine, on average, for about 10 years. PET studies also were conducted on a comparison group of 18 volunteers who had never taken the drug but had comparable histories of marijuana and alcohol abuse. The lead investigator on the NIDA-funded study was Dr. Edythe London of the University of California, Los Angeles.

All participants completed research questionnaires designed to assess levels of depression and of generalized (trait) and transitory (state) anxiety. For methamphetamine abusers, the average depression inventory score was 9.8 (scores between 9 and 15 are considered minimal to mild depression) compared with an average score of 1.1 for the comparison group. On a 1-to-4 scale of anxiety, abusers scored an average 1.9 for state anxiety and 2.2 for trait anxiety (compared with 1.4 and 1.5, respectively, for

the comparison group). The higher measures of mood disturbances among methamphetamine abusers corresponded to differences, relative to the comparison group, in regional brain metabolism.

“It appears that, at least in early abstinence, methamphetamine abusers who report negative mood states have dysfunctions in these brain regions,” says Dr. London. “The abnormalities in metabolism that we see involve brain regions that other investigations have implicated in mood regulation.”

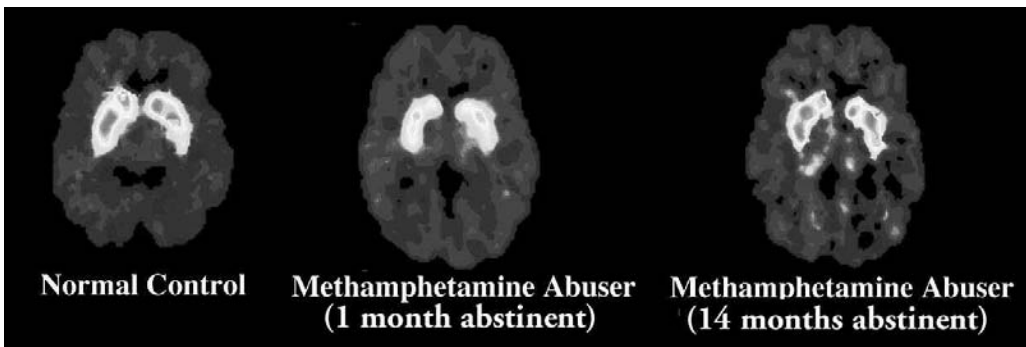
There is no pharmacological treatment for methamphetamine abuse, and negative moods can hinder behavioral therapy, which relies on patients’ voluntary participation. “Early abstinence is the toughest stage of treatment for methamphetamine abuse,” says Dr. Joseph Frascella of NIDA’s Division of Clinical Neuroscience, Development, and Behavioral Treatments. “It’s in the early stage that mood disturbances may derail or complicate the most effective treatment, cognitive behavioral therapy. Methamphetamine abuse and addiction do not exist in isolation, and this study suggests that associated depression and anxiety also must be addressed in treatment.”

### Source

London, E.D., et al. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Archives of General Psychiatry* 61(1):73-84, 2004. **NN**

## Methamphetamine Abuse Linked to Impaired Cognitive and Motor Skills Despite Recovery of Dopamine Transporters

By Patrick Zickler, NIDA NOTES Staff Writer



*Brain images of a person who has never used methamphetamine (left) and of a methamphetamine user after 1 month of abstinence (center). Lighter colors show distribution of dopamine transporters (DAT) in the striatum. DAT distribution is reduced in striatum of methamphetamine user. Brain image of a methamphetamine user after 14 months' abstinence (right) shows substantial recovery of DAT in striatum. Low levels of DAT in methamphetamine users were associated with poorer performance on tests of memory and motor skills, which did not improve with DAT after lengthy abstinence.*

Animal studies have demonstrated that methamphetamine, a highly addictive stimulant, damages brain cells involved in transport of the chemical messenger dopamine. Now, NIDA-supported researchers have found that long-term methamphetamine abuse by humans is associated with a reduction in dopamine transporters after 2 months' abstinence from methamphetamine and that this damage appears to be linked to slowed motor skills and weakened memory. Methamphetamine abusers who were retested after remaining abstinent for at least 9 months showed substantial recovery from damage to the dopamine transporters but not from impairments in motor skills and memory.

### Dopamine Transporter Damage After Brief Abstinence

Dr. Nora Volkow and colleagues at the Brookhaven National Laboratory in Upton, New York, and at the University of California, Los Angeles, used brain imaging studies and tests of motor skills and memory to investigate the effects of methamphetamine in 15 former methamphetamine abusers. The participants (nine women and six men, average age 32 years) had used the drug at least 5 days per week for at least 2 years, and had been abstinent from methamphetamine for at least 2 months.

The researchers used positron emission tomography (PET) to measure levels of dopamine transporters in the brain. PET imaging detects signals from chemical "tracers" that are injected into the bloodstream and carried to the brain, where they bind to dopamine transporters. The strength of the signals indicates the number of transporters. Compared with participants who never used the drug, methamphetamine abusers had an average reduction of 24 percent in levels of dopamine transporters

(DAT) in the striatum, a part of the brain associated with control of movement, attention, motivation, and reward.

Participants also took a series of tests to assess brain functions associated with the striatum: fine motor skills (inserting pegs into angled holes as quickly as possible), gross motor skills (walking as rapidly as possible in a straight line), and memory (learning and recalling a list of unrelated words immediately, after a delay, and after a distraction). "The abstinent methamphetamine abusers showed impaired memory and slowed motor skills that were directly proportional to the deficits in DAT. The lower the levels of DAT, the worse their performance," Dr. Volkow says.

"The reduction of dopamine transporters was seen in all of the abusers," Dr. Volkow says. "DAT loss also occurs with age at a rate of 6 to 7 percent per decade, so the DAT losses in methamphetamine abusers are roughly equivalent to 40 years of aging." Furthermore, she says, DAT reduction in the range of 40 to 90 percent is one characteristic of Parkinson's disease, a progressive neurodegenerative disorder that causes tremor, weakness, and—in some patients—cognitive impairment. "There is a concern that methamphetamine abusers may be at increased risk for neurodegenerative disease as they age. This will depend

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in part on the reversibility of DAT losses induced by methamphetamine abuse.”

### **Dopamine Transporter Recovery**

To assess the persistence of methamphetamine-related DAT loss and impairments, the researchers reevaluated five study participants (three women and two men, average age 29 years) after they had abstained from taking the drug for at least 9 months. While these participants’ DAT levels had increased to roughly equal those of never-users of methamphetamine, they performed no better than

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### ***Methamphetamine abusers may be at increased risk for neurodegenerative disease as they age.***

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before on tests of gross and fine motor skills and memory. Additional evaluations of five other former methamphetamine abusers with 9 months or more of abstinence (four women and one man, average age 35 years) produced similar findings: normal DAT levels but reduced motor and cognitive skills.

“This study documents significant recovery of DAT with protracted abstinence from methamphetamine,” Dr. Volkow says. “Moreover, for those evaluated twice, the longer the interval between the first and second evalua-

tions, the larger the increases in DAT. This suggests that recovery is related to the length of time that methamphetamine abusers can stay off the drug. But, although there is a recovery in DAT levels, there is no parallel improvement in function.”

The relationship between impaired function and DAT loss and recovery is unclear. It is possible that the DAT recovery is due to increased branching of dopamine terminals rather than increased numbers of terminals, Dr. Volkow says. “This may be insufficient to compensate for lost terminals. It is also possible that the neuropsychological functions require other brain systems that recover slowly or not at all from the effects of methamphetamine. Or the failure to find an unambiguous association between DAT recovery and improved function might reflect the small number of participants who were able to stay drug free. We will need longer term studies to see if increases in DAT over longer periods of time are sufficient for complete recovery of function.”

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## Methamphetamine, Cocaine Abusers Have Different Patterns of Drug Use, Suffer Different Cognitive Impairments

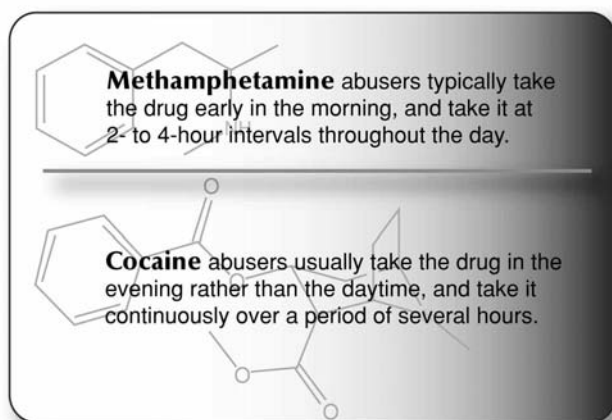
By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported research has found that methamphetamine abusers typically use the drug throughout the day in a pattern that resembles taking medication, while cocaine abusers often exhibit a binge pattern, using the drug continuously over a period of several evening and nighttime hours. And, according to the researchers at the University of California, Los Angeles (UCLA), the drugs appear to cause different types of deficits in reasoning and concentration.

### Patterns of Use

Dr. Sara Simon and her UCLA colleagues interviewed 120 methamphetamine abusers and 63 cocaine abusers to determine patterns of drug use. Ninety-seven of the methamphetamine abusers and 56 cocaine abusers were recruited from treatment programs; the others were currently using the drug and not seeking treatment.

Continuous use—more than 20 times per month—was more common for both cocaine abusers (52 percent) and methamphetamine abusers (70 percent) than was any other pattern of drug use. Among those who used either drug fewer than 20 times per month, methamphetamine abusers were 4 times as likely as cocaine abusers (48 percent compared with 12 percent) to use the drug at least once per week in a regular cycle.



“The typical methamphetamine abuser reported using the drug when he or she first got up in the morning, then using approximately every 2 to 4 hours during their waking day. Most of the descriptions of use more closely

resembled taking a medication than using a drug for pleasure,” Dr. Simon says. “Cocaine abusers reported patterns that fit a picture of recreational use: They began in the evening and continued until all the cocaine on hand had been used.”

The different patterns of use may in part be a result of the drugs’ different effects in the body, the researchers say: Methamphetamine triggers the release of large amounts of the neurotransmitter dopamine into areas of the brain that regulate feelings of pleasure, whereas cocaine blocks the removal of dopamine, resulting in an accumulation that causes continuous pleasurable stimulation of brain cells. The effects of methamphetamine typically last more than 10 hours, and the half-life (the time it takes for the body to remove 50 percent of the drug) of methamphetamine is 12 hours. Cocaine’s half-life is roughly 1 hour, and the drug’s high lasts about 20 to 30 minutes.

Understanding the patterns of use for methamphetamine and cocaine will help treatment providers and drug users identify circumstances that may lead to relapse to drug use. “Differences in use patterns indicate different triggers and different times and places when the recovering abuser is particularly vulnerable,” says Dr. Simon.

### Effects on Reasoning and Memory

In another study, Dr. Simon and her colleagues evaluated the effects of methamphetamine and cocaine on learning and memory in 40 methamphetamine abusers and 40 cocaine abusers who were not in treatment and 80 individuals who had never used either stimulant drug. The researchers administered tests to evaluate memory, perceptual speed and ability to manipulate information, ability to ignore irrelevant information, general intelligence, verbal fluency, and executive function (abstract reasoning, reactive flexibility, and ability to use feedback).

Methamphetamine abusers performed more poorly than nonusers of stimulants in tests of word recall, perceptual speed, ability to manipulate information, and abstract thinking. Cocaine abusers scored more poorly than nonusers of stimulants in tests measuring ability to recall words and pictures and working memory.

“Methamphetamine abusers displayed impairments on the tests of perceptual speed and manipulation of information



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that were not seen in the cocaine group. Moreover, in tests that require both speed and manipulation, there was even more difference between the groups than on tests of either skill separately,” Dr. Simon says.

“Overall, both drugs are associated with similar cognitive deficits,” Dr. Simon says. “The most striking difference is that methamphetamine abusers have more trouble than cocaine abusers at tasks requiring attention and the ability to organize information.”

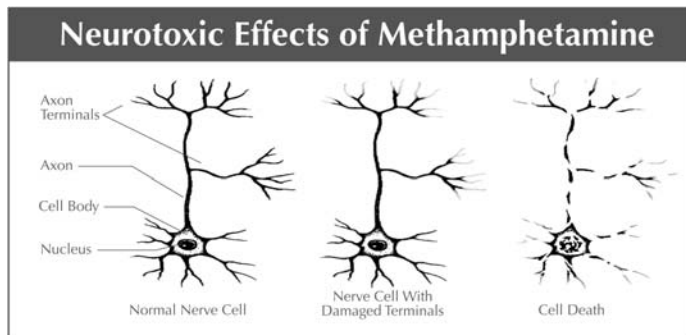
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## Methamphetamine Brain Damage in Mice More Extensive Than Previously Thought

By Robert Mathias, NIDA NOTES Staff Writer

NIDA researchers have found that, when it comes to brain cells, “speed” actually does kill. “Speed” is a street name for methamphetamine, a powerfully addictive stimulant. Previous research had shown that methamphetamine damages but does not kill certain nerve cells in brain structures that control movement. The new research, conducted in mice, indicates that methamphetamine-induced damage prompts other nerve cells in brain regions involved in cognition as well as movement to self-destruct. The new findings raise concerns that methamphetamine may have significantly more harmful long-term consequences than previously thought, the researchers say.

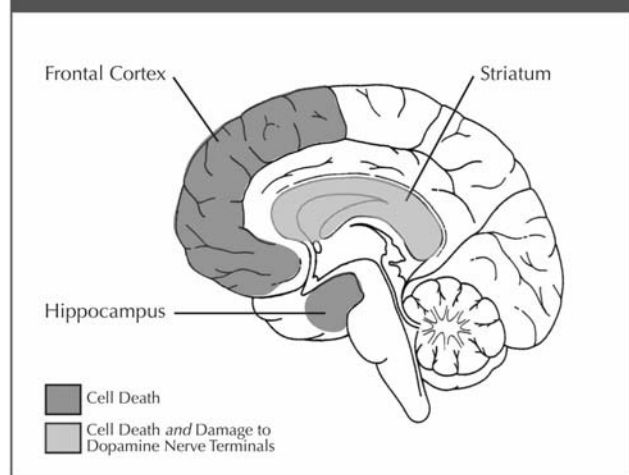


Previous research showed that methamphetamine damages the nerve terminals of dopamine-producing brain cells. The new research shows methamphetamine also triggers a natural mechanism called apoptosis that prompts the complete disintegration and death of additional nerve cells in other brain regions.

Previous research showed that methamphetamine damages the nerve endings of brain cells containing dopamine, a chemical messenger that plays a role in movement and pleasure. Animal studies indicate that a gradual, partial recovery occurs in the dopamine system when methamphetamine exposure is stopped. For example, a recent imaging and postmortem study of the brains of monkeys found substantial recovery in dopamine function over an 18-month period following the animals' last exposure to the drug. However, human brain imaging studies suggest that significant damage to nerve endings of dopamine-containing cells persists in the brains of chronic methamphetamine abusers for at least 3 years after they have stopped using the drug. The damage, which affects dopamine nerve endings located in the brain structures

that make up the striatum, is similar to but less extensive than that caused by Parkinson's disease.

### Human Brain Areas Corresponding to the Mouse Brain Areas Damaged by Methamphetamine



Methamphetamine-induced damage to nerve terminals of dopamine-producing cells occurs primarily in a brain region called the striatum. Methamphetamine-induced apoptosis killed off different types of nerve cells in the frontal cortex, the hippocampus, and the striatum in mice.

“People used to think that the most serious methamphetamine-induced damage was to dopamine nerve terminals because it put people at risk for developing Parkinson's disease as they got older,” says Dr. Jean Lud Cadet, clinical director of NIDA's Intramural Research Program (IRP). “We've now shown in our lab that methamphetamine is much more toxic than previously thought. It does not just destroy the endings of dopamine-containing nerve cells, it also kills other nerve cells that produce other neurotransmitters in additional brain pathways,” he says.

IRP researchers led by Dr. Cadet first linked this widespread loss of brain cells to a natural mechanism called apoptosis, through which the body programs unhealthy cells to kill themselves. In a study in cell cultures, they showed that treating rat brain cells with methamphetamine caused cell death marked by apoptotic patterns, such as DNA fragmentation and disintegration of cell bodies.

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Subsequent studies in genetically engineered mice that lacked specific genes known to promote or suppress programmed cell death suggested that at least part of the nerve damage caused by methamphetamine may result from activation of the molecular machinery that is involved in apoptosis. The strongest evidence that methamphetamine unleashes widespread apoptosis in animals came in a recent study that showed the drug caused DNA fragmentation and loss of nerve cell bodies in the striatum, the hippocampus, and the frontal cortex of mice brains.

“Although these findings are in mice, if methamphetamine kills nerve cells in the same brain regions of humans who abuse the drug, the functional consequences could be significant,” Dr. Cadet says. Loss of cells in the hippocampus and cortex could damage memory, cognitive function, and decision-making capacity, he says. Loss of striatal cells could lead to serious movement disorders that resemble tardive dyskinesia and Huntington’s chorea.

Recent brain imaging studies in former methamphetamine abusers conducted by Dr. Richard Ernst and Dr. Linda Chang at the Harbor-UCLA Medical Center in Torrance, California, provide additional support for the finding that methamphetamine abuse causes brain cell death, says Dr. Cadet. The California researchers found alterations in brain chemistry in long-term methamphetamine abusers indicative of nerve cell loss or damage similar to that found in people suffering from strokes or Alzheimer’s disease (see page 27, “Brain Imaging Studies Show Long-Term Damage From Methamphetamine Abuse”).

If methamphetamine kills brain cells in humans, it may cause cognitive impairments that will have to be addressed when treating methamphetamine abusers, Dr. Cadet says. Although impaired people can do well in treatment, it is possible that developing medications to repair the brain could help such patients to do even better, he says (See page 24, “NIDA Pursues Many Approaches to Reversing Methamphetamine’s Neurotoxic Effects”).

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## NIDA Pursues Many Approaches to Reversing Methamphetamine's Neurotoxic Effects

By Robert Mathias, NIDA NOTES Staff Writer

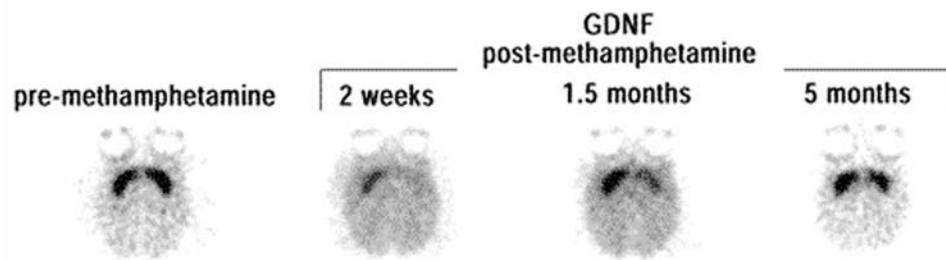
NIDA-supported scientists are pursuing a number of promising approaches to blocking or reversing some of the brain damage wreaked by chronic abuse of methamphetamine. Research has shown that methamphetamine can damage blood vessels and nerve endings in the brain and cause changes in brain chemicals. These effects put chronic methamphetamine abusers at risk for cognitive impairment and early onset of movement disorders associated with aging. (See page 22, "Methamphetamine Brain Damage in Mice More Extensive Than Previously Thought".)

In January, NIDA's Division of Treatment Research and Development (DTR&D) convened a "Methamphetamine Addiction Treatment Think Tank." The meeting brought together preclinical and clinical researchers to set up a new program within NIDA's Medications Development Program to develop methamphetamine medications. The program now is selecting and setting up five sites to conduct clinical pharmacology and outpatient studies of medications proposed to treat different aspects of methamphetamine abuse, beginning with methamphetamine

methamphetamine addiction," says Dr. Ahmed Elkashef of DTR&D, who heads the program. Such medications are aimed at stopping or reducing methamphetamine abuse and not at directly reversing cognitive impairment or other clinical manifestations of methamphetamine's neurotoxic effects when they already have occurred in drug abuse treatment patients, Dr. Elkashef says. However, by reducing drug use, this approach could stop additional neurotoxic damage that might occur with continuing drug use, he says.

In addition to preventing new brain damage, addiction treatment medications may also help treat some of the clinical manifestations of methamphetamine neurotoxicity. "We will assess cognitively impaired patients to see if medications that stop or reduce methamphetamine abuse also improve cognitive functioning," Dr. Elkashef says. Program scientists also plan to test a long list of promising medications that may be able to reverse cognitive impairment caused by methamphetamine abuse, Dr. Elkashef says.

One of the first compounds the program will test—selegiline—is a medication that has the potential to treat both methamphetamine addiction and its associated cognitive impairment. NIDA has been testing selegiline, an approved treatment for some symptoms of Parkinson's disease, as a cocaine treatment medication. Selegiline's neuroprotective effects counter several possible mechanisms of methamphetamine neurotoxicity, Dr. Elkashef says. "This medication has been shown to reduce cognitive impairments among HIV-positive patients, and we expect it to help treat that aspect of methamphetamine abuse," he says.



*These PET images show brain activity of a chemical messenger called dopamine (shown by dark color) in a monkey that was pretreated with glial-derived neurotrophic factor (GDNF) 1 week before being administered a neurotoxic dose of methamphetamine. Later images showed that the treated monkey had significantly greater recovery of dopamine function than an untreated monkey, at all time points following methamphetamine administration. (Brain images by Dr. William P. Melega.)*

addiction. Overdose, neurodegeneration and cognitive impairment, psychoses, and movement disorders will be secondary targets.

"The first priority of the methamphetamine medications development program is to develop medications to treat

Methamphetamine may damage the brain in many ways, including impairment of blood flow, production of harmful free radicals, and killing of brain cells. Thus, the methamphetamine medications development program also is considering using medications that have the potential to improve cognitive function by countering these effects.

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Potential cognitive enhancers, such as Hydergine, are thought to improve overall brain function by increasing blood flow and brain metabolism. Free radical scavengers, such as vitamin E, boost natural protective chemicals and processes that reduce brain damage caused by free radicals. Hydergine has shown modest success in improving alertness and short-term memory in stroke patients and individuals with Alzheimer's disease. Vitamin E administered with selegiline has slowed progression of Parkinson's disease and reduced severity of abnormal movements in tardive dyskinesia patients.

One possible strategy to address cognitive impairment in methamphetamine-addicted patients would be to add potential cognitive enhancers to drug addiction treatment medications, Dr. Elkashef says. However, the first step with each potential medication will be to assess whether clinical pharmacology interaction studies are needed to make sure it is safe to give it to outpatients who may continue to abuse methamphetamine, he stresses.

### **Developing Future Treatments**

At a much earlier stage of treatment development, NIDA-supported researchers are conducting preclinical studies that could lead to the development of more sophisticated approaches to repairing methamphetamine-induced brain damage. Among the approaches that have shown promising results in animal studies are:

- DADLE ([D-Ala<sup>2</sup>,D-Leu<sup>5</sup>] enkephalin), a synthetic brain chemical and known tissue-protective agent. DADLE has been shown to block and reverse one type of methamphetamine-induced brain damage in mice;
- Neurotrophic factors, proteins produced by the body that nourish and maintain nerve cells. One of these factors, glial-derived neurotrophic factor, has been shown to reduce methamphetamine's neurotoxic effects in monkeys;
- Genetic factors and natural anti-oxidants that promote cell survival. Boosting production of these genes and antioxidants in the brains of mice has been shown to prevent or moderate methamphetamine's neurotoxic effects.

Much additional research is needed to design safe and effective formulations of these treatments and ways to get them into the brain before researchers can begin testing in humans. However, these basic studies are increasing understanding of toxic reactions and protective mechanisms in the brain. This understanding should lead to the development of new medications that advance the goals of enabling patients to stop abusing methamphetamine and recover from at least some of the brain damage caused by the drug. **NN**

## Cocaine, Marijuana, and Heroin Abuse Up, Methamphetamine Abuse Down

By Robert Mathias, NIDA NOTES Staff Writer

Cocaine abuse indicators increased in many U.S. metropolitan areas during 1998 and the first half of 1999, according to a NIDA-supported network of drug abuse researchers who regularly report data on drug abuse in the United States. The rise follows several years of stable or declining use, the researchers reported at the December 1999 meeting of the Community Epidemiology Work Group (CEWG).

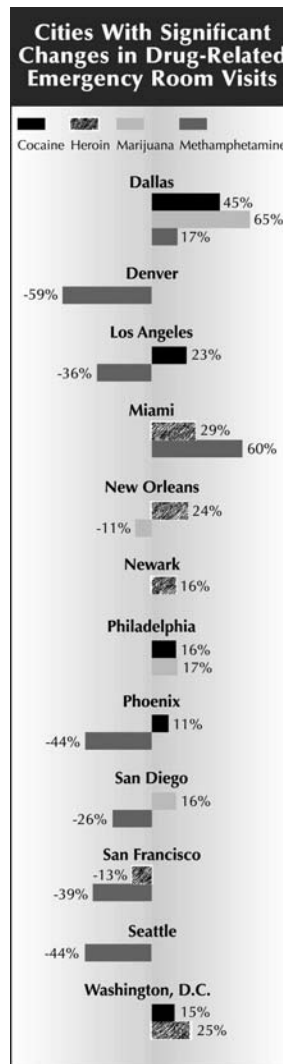
CEWG researchers meet twice a year to report on such drug abuse indicators as drug-related deaths, hospital emergency department (ED) visits, and treatment admissions. Data from 20 cities presented at the December meeting indicate that marijuana and heroin abuse also continued to increase in most areas of the country. However, methamphetamine abuse declined in most cities, including some areas that have been hardest hit by the problem. Highlights from the meeting's advance report are:

**Cocaine.** Indicators of cocaine abuse increased in half of the 20 CEWG cities, remained stable or mixed in 8, and decreased in 2. Five cities reported significant increases in cocaine-related ED incidents and 9 cities reported large increases in the number of cocaine-related deaths.

**Heroin.** Heroin abuse indicators increased in 10 CEWG cities, were stable or mixed in 9, and decreased in 1. Heroin abuse and snorting of the drug continued to increase among younger populations, such as college students. These trends were particularly apparent in East Coast cities where pure forms of white powder heroin, which can be snorted, are most available. Heroin-related deaths also increased in many areas of the country.

**Marijuana.** Seventeen CEWG cities reported increases in problems associated with marijuana abuse. The percentage of drug abusers whose primary drug of abuse was marijuana continued to increase in many cities. Rates of marijuana-related ED visits also continued the consistent, often dramatic, increases shown over the last 6 years. Increases in marijuana-related problems may be tied to increased availability, higher potency, and lower prices for the drug along with perceptions that marijuana abuse is less risky than abuse of other drugs, the report indicates.

**Methamphetamine.** Indicators of methamphetamine abuse decreased in West Coast and Southwest areas where abuse of the drug has been a major problem for years.



Many CEWG cities reported statistically significant increases from 1997 to 1998 in hospital emergency department (ED) visits due to cocaine, heroin, and marijuana use. However, methamphetamine-related ED visits declined sharply in most cities where rates had previously been highest. Source: Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 1998 (July 1999 Update).

Sharp declines in methamphetamine-related ED visits were reported in 1998 in six CEWG areas. Several areas also reported that methamphetamine treatment admissions, hospital mentions, and deaths continued to decline in the first half of 1999. Researchers cited several possible reasons for these decreases, including initiation of national and community methamphetamine abuse prevention programs and enactment of laws that make it more difficult to obtain the chemicals needed to produce the drug.

**Club Drugs.** Thirteen cities reported problems with MDMA (ecstasy) abuse. The drug is available at raves and nightclubs in most areas. Ecstasy abuse also is increasing in other settings, such as college campuses. Nine areas reported GHB (gamma-hydroxybutyrate) abuse at raves and clubs. Numerous medical emergencies and several deaths were associated with GHB abuse.

### For More Information

The CEWG "Advance Report, Epidemiologic Trends in Drug Abuse, December 1999," is available from NIDA's Web site, [www.drugabuse.gov](http://www.drugabuse.gov). **NN**

## Brain Imaging Studies Show Long-Term Damage From Methamphetamine Abuse

By Patrick Zickler, NIDA NOTES Staff Writer

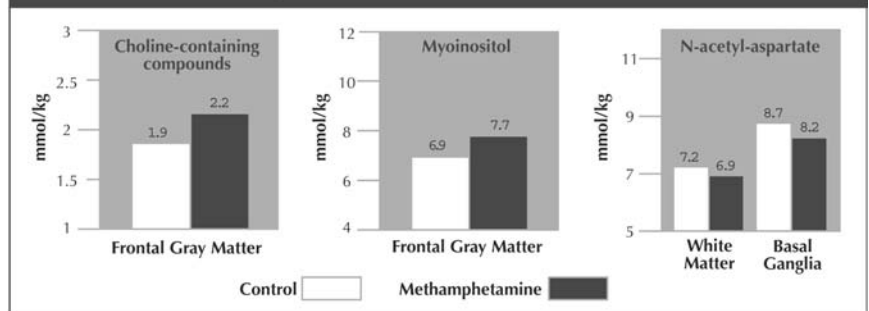
Methamphetamine—commonly known as “speed,” “meth,” “ice,” or “crystal”—is a powerfully addictive stimulant that acts on the central nervous system to produce increased wakefulness and physical activity as well as irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, and aggressiveness. The drug increases heart rate and blood pressure and can irreversibly damage blood vessels in the brain. Now, NIDA-supported research has demonstrated that methamphetamine abusers risk long-term brain damage.

Dr. Thomas Ernst and Dr. Linda Chang at the Harbor-UCLA Medical Center in Torrance, California, used a noninvasive brain imaging technique called magnetic resonance spectroscopy (MRS) to measure levels of brain chemicals that indicate whether brain cells are healthy or are diseased or damaged. “We found abnormal brain chemistry in methamphetamine users in all the brain regions we studied. In one of the regions, the amount of damage was also related to the history of drug use—those abusers who had the greatest cumulative lifetime methamphetamine use had the strongest indications of cell damage,” Dr. Chang says.

In each of the participants, the researchers examined a midfrontal region consisting largely of “gray matter”—nerve cell bodies and short extensions called dendrites that communicate with neighboring neurons—and an area in the basal ganglia, a neuron-dense region at the top of the brain stem. They also examined a right frontal area composed largely of “white matter,” or long nerve cell extensions called axons that communicate with more distant regions of the brain. These brain regions were selected because they are areas of high activity of dopamine, a neurotransmitter involved in the “rush” and pleasure associated with addictive drugs.

The researchers measured levels of N-acetyl-aspartate (NAA), a metabolite produced only in neurons. “NAA levels are a measure of the viability and density of neurons,” Dr. Ernst says. “Many diseases associated with brain

### Effects of Methamphetamine on Levels of Brain Chemicals



*Neurons in three areas of the brain show changes in levels of brain chemicals that serve as indicators of health of brain cells. Levels of choline-containing compounds and myoinositol are elevated and levels of N-acetyl-aspartate are reduced in methamphetamine abusers who have not used the drug for at least 2 weeks and up to 21 months. The changes in concentrations of these chemical markers suggest that methamphetamine use may result in long-term damage to brain cells used in thinking.*

cell loss or damage, such as Alzheimer’s disease, stroke, and epilepsy, are also associated with reduced NAA.”

The scientists also measured levels of two other chemical markers—choline-containing compounds and myoinositol (MI)—associated mostly with specialized cells called glial cells. “The primary role of glial cells is to maintain normal function of neurons, including repair of injury to the cells. Increases in glial markers suggest proliferation of these support cells in response to neuronal damage,” Dr. Ernst explains.

Dr. Chang and Dr. Ernst measured levels of the chemical markers in 26 participants who had a history of methamphetamine abuse but had not used the drug for periods ranging from 2 weeks to 21 months with a median of 4.25 months since last use. They compared the results to measurements of 24 participants who had no history of methamphetamine use.


Among the methamphetamine abusers, NAA levels were reduced by 5 percent in the frontal white matter and 6 percent in the basal ganglia compared with levels among nonusers. “The reduced concentrations of NAA in the drug users’ brains suggest that long-term methamphetamine abuse results in loss of or damage to neurons,” Dr. Ernst says. Methamphetamine abusers also showed

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increases of 11 percent in levels of MI and 13 percent in levels of choline-containing compounds in the frontal gray matter compared with nonusers. “This suggests an increased number or size of glial cells as a reaction to the injurious effects of the drug,” he adds.

“Methamphetamine may be substantially toxic to the cells we use in thinking,” Dr. Ernst says. “This long-term, and perhaps permanent, alteration in basic brain chemistry is additional evidence that methamphetamine abuse, like abuse of other drugs, should be considered a brain disease and treated accordingly.”

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## Methamphetamine Abuse Alert

In response to indicators that show methamphetamine abuse increasing across the Nation, NIDA sent a bulletin containing current, science-based information on methamphetamine to more than 200,000 drug abuse treatment providers, hospital emergency room workers, and other health services practitioners.

The four-page Community Drug Alert Bulletin on Methamphetamine arms health care providers with important information they can use to mount effective prevention and treatment responses to methamphetamine's threat to the public health. Highlights are below.

### What Methamphetamine Is

Methamphetamine is a powerfully addictive stimulant that dramatically affects many areas of the central nervous system. The drug has a high potential for widespread abuse because it can easily be made in clandestine laboratories from relatively inexpensive over-the-counter ingredients.

Methamphetamine can be purchased at a low cost, is available in many forms, and can be smoked, snorted, injected, or orally ingested.

Methamphetamine is sometimes called "speed," "meth," and "chalk." In its smoked form, the drug is often called "ice," "crystal," "crank," "fire," and "glass."

### Who Uses Methamphetamine

Traditionally associated with white male blue-collar workers, methamphetamine reportedly is being used by diverse groups in all regions of the country.

Use is increasing among men who have sex with men and use other drugs; young adults who attend "raves" or go to private clubs; homeless and runaway youth; commercial sex workers; members of motorcycle gangs; and people in occupations that demand long hours, mental alertness, and physical endurance.

### New Trends and Patterns of Use

Emerging evidence indicates that users increasingly are administering methamphetamine intravenously. Injecting the drug puts the user at increased risk of contracting HIV/AIDS, hepatitis, and other infectious diseases.

Often, methamphetamine is used in dangerous combination with other substances, including cocaine and "crack" cocaine, marijuana, heroin, and alcohol.

Methamphetamine is not usually sold and bought on the street. Users report that they obtain the drug from friends and acquaintances.

Methamphetamine, used primarily in urban areas of California, has become a substantial drug problem in other sections of the West and Southwest as well as rural and urban areas of the South and Midwest. Its use also is emerging in urban areas in the East.

### Signs of Methamphetamine Use

Some common signs of methamphetamine use include:

- agitation, excited speech, decreased appetite, increased physical activity, dilated pupils, and nausea and vomiting;
- occasional episodes of sudden and violent behavior, intense paranoia, visual and auditory hallucinations, and bouts of insomnia; and
- a tendency to compulsively clean and groom and repetitively disassemble and sort objects.

### Guidelines for Preventing Methamphetamine Use

Effective prevention of drug use begins with assessing the specific nature of the drug problem within the local community and adapting prevention programs accordingly. Prevention programs should start early, be comprehensive, and stress key points repeatedly. Family-focused prevention efforts have a greater impact than strategies that focus on parents only or children and adolescents only.

### Guidelines for Treating Methamphetamine Addiction


Cognitive behavioral interventions that help modify a patient's thinking and harmful behaviors and teach skills to cope with stressful situations have been effective.

Currently no medications are available to treat methamphetamine addiction or overdose. However, antidepressant medications can be prescribed which can serve to combat the depressive symptoms frequently experienced during methamphetamine withdrawal.

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**For More Information**

NIDA's Community Drug Alert Bulletin on Methamphetamine and the NIDA Research Report, Methamphetamine Abuse and Addiction (NCADI publication #PHD756) can be obtained from the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847, 1-800-729-6686. These

publications and additional information about methamphetamine can be found on the NIDA home page on the World Wide Web at [www.nida.nih.gov](http://www.nida.nih.gov). Fact sheets and recorded messages about methamphetamine abuse and addiction can also be found on Infobox, NIDA's automated information retrieval system, at (888) 644-6432. 

## NIDA Initiative Tackles Methamphetamine Use

By Robert Mathias, NIDA NOTES Staff Writer

In response to an upsurge in heroin use among America's young people in recent years, NIDA convened a national research-based conference on Heroin Use and Addiction in Washington, D.C., this past September. The well-attended conference drew more than 600 participants who examined all aspects of the changing nature of heroin use in the United States and shared scientific information and approaches to preventing and treating heroin abuse and addiction. Representatives of national drug abuse organizations, scientists, prevention and treatment practitioners, and criminal justice personnel took part in the conference.



*The numbers on the map represent the number of patients in these metropolitan areas who sought hospital emergency department treatment due to methamphetamine use.*

*Source: Year-End Preliminary Estimates from the 1996 Drug Abuse Warning Network, Substance Abuse and Mental Health Services Administration.*

NIDA has launched an Institute-wide initiative to expand scientific research on methamphetamine and apply the findings to the prevention and treatment of methamphetamine abuse. The Methamphetamine Initiative is aimed at increasing scientific knowledge about methamphetamine and providing the public and health care practitioners with the latest available information about the drug's use, consequences, prevention, and treatment.

Methamphetamine, also called "meth," is a potent, highly addictive form of amphetamine. Use of the drug has been a major problem in western areas of the United States

since the mid- to late 1980s and has been increasing in other areas of the country, such as the South and Midwest, since the early 1990s, according to reports from NIDA's Community Epidemiology Work Group (CEWG). Traditionally, methamphetamine use has been centered among white working class males and men who have sex with men. However, recent CEWG reports and drug use surveys indicate that use of the drug also may be increasing among other groups such as Hispanics in Los Angeles and adolescents in rural areas.

"We know from research that methamphetamine is a powerfully addictive stimulant associated with serious health conditions including brain damage, memory loss, psychotic-like behavior, heart damage, hepatitis, and HIV transmission," NIDA Director Dr. Alan I. Leshner said in discussing the Initiative's opening thrust—a NIDA-sponsored western regional methamphetamine symposium held in San Francisco in December 1996.

At that meeting, scientists, civic leaders, policymakers, public officials, and drug abuse prevention and treatment professionals discussed ways to improve State and local prevention and treatment responses to methamphetamine abuse.

Last year, NIDA received \$4.2 million in supplemental funding from the White House Office of National Drug Control Policy to expand the Institute's program of methamphetamine research. This year, the Director's Office of the National Institutes of Health awarded an additional \$2 million in special funds to NIDA for methamphetamine research. NIDA is using these monies to broaden the Initiative's methamphetamine research in the following areas: basic and clinical neurobiology, long-term effects of abuse, epidemiology and prevention, drug abuse treatment and health services, and medications development.

The Initiative's basic and clinical neurobiology research is aimed at better understanding the mechanisms that underlie methamphetamine's addictive potential and the adverse consequences of its chronic abuse. Previous research has shown that methamphetamine, like cocaine, achieves its euphoric effect by increasing the extracellular concentration of the neurotransmitter dopamine in the brain. However, methamphetamine and cocaine achieve their dopamine-enhancing effects through different cellular mechanisms. In addition, methamphetamine remains

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in the brain much longer than cocaine does and damages brain cells of animals that have been chronically exposed to the drug.

Researchers supported by NIDA's Division of Basic Research (DBR) under the Initiative, such as Dr. Paul Vezina at the University of Chicago, now are trying to unravel the underlying mechanisms through which animals chronically exposed to methamphetamine become more sensitive, or respond more strongly, to the drug. "The hypothesis in the field is that sensitization is linked to addiction," explains DBR's Dr. Jerry Frankenheim. Therefore, another basic research study, by Dr. Stephen Strakowski of the University of Cincinnati College of Medicine, is studying the process of stimulant sensitization in humans using amphetamine, which is closely related chemically to methamphetamine. The study is examining whether there is a link between stimulant sensitization in humans and their liking the drug and craving it later on. In other research, Dr. William Melega at the University of California at Los Angeles is examining how methamphetamine-induced neurotoxicity affects the behavior of animals.

"This basic research is key to understanding the differences between cocaine and methamphetamine," says Dr. Frankenheim. "The results of this research will help us determine if we need somewhat different approaches to preventing and treating methamphetamine and cocaine abuse," he says.

The Initiative also is trying to determine whether the methamphetamine-induced neurotoxicity that studies have shown in animals also occurs in humans. For example, Dr. George A. Ricaurte of The Johns Hopkins Medical Institutions in Baltimore is conducting brain imaging studies with long-term methamphetamine users to assess how chronic methamphetamine use affects the human brain, cognition, and other physiological functions. In addition, postmortem studies of the brains of chronic methamphetamine abusers are being conducted by Dr. Stephen Kish of the Clarke Institute of Psychiatry in Toronto, Canada. The studies will provide additional information about the long-term effects of methamphetamine abuse on human brain structure. In living humans, these effects on brain structure could affect brain function.

The Methamphetamine Initiative also is expanding NIDA's research on preventing methamphetamine abuse and addiction. For example, Dr. Steve Sussman of the University of Southern California has been developing a promising drug abuse prevention intervention for students in continuation or alternative public high schools in southern California. More than 10 percent of students participating in Dr. Sussman's ongoing prevention study are known to have used methamphetamine in the past.

Now, Dr. Sussman is expanding his research to examine current methamphetamine use among these youths and to assess whether the two experimental drug abuse prevention programs he has been developing can prevent methamphetamine use in this population. (For more information on Dr. Sussman's research, see "Specialized High School Prevention Programs Target At-Risk Adolescents," *NIDA NOTES*, May/June 1997)

The Initiative also is aiming to resolve puzzling patterns of methamphetamine abuse in the United States. "Why has methamphetamine use occurred predominantly in the western United States and Hawaii?" asks Dr. Zili Sloboda, who directs NIDA's Division of Epidemiology and Prevention Research (DEPR). To answer this and other questions about shifting patterns of methamphetamine use, DEPR is launching a study in five cities where methamphetamine use is high or where a methamphetamine problem may be emerging. This study will identify characteristics of methamphetamine users, patterns of initiation and use, and consequences of use, says Dr. Sloboda. Ultimately, the findings of this research will be used to develop more effective methamphetamine prevention programs, she says.

Development of behavioral treatments tailored to the specific needs of methamphetamine-abusing populations also is being emphasized under the Initiative. For example, men who have sex with men represent a significant target group for methamphetamine treatment interventions. Previous research shows that methamphetamine use is high in this population and is linked to high-risk sexual behaviors and the transmission of HIV. NIDA's Division of Clinical and Services Research (DCSR) has funded a new behavioral treatment research study among gay and bisexual male methamphetamine users in Los Angeles. This study, which is being conducted by Dr. Steven Shoptaw of the Los Angeles Treatment Research Center, will compare the relative effectiveness of contingency management, relapse prevention, and enhanced HIV counseling methods in reducing methamphetamine use and related high-HIV-risk sexual behaviors. DCSR also is expanding several studies that have been testing other promising behavioral treatments with cocaine-abusing populations. The goal is to see whether these treatments are appropriate and can be adapted to treat methamphetamine abuse and associated behaviors effectively, says the Division's Dr. Dorynne Czechowicz.

The development of medications to reduce methamphetamine abuse and craving and to repair brain systems damaged by chronic methamphetamine use is another major Initiative priority. In seeking potential treatment compounds to reduce methamphetamine abuse, NIDA's Medications Development Division (MDD) is capitalizing on the substantial research that has been done to develop

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cocaine treatment medications. Though the initial mechanisms of action for cocaine and methamphetamine differ, ultimately they both greatly increase the levels of dopamine between brain cells, points out Dr. Betty Tai of MDD. “From that point, the cascade of events from the

cellular all the way to behavioral is quite similar,” she says. Therefore, any compound that has shown promise for treating cocaine abuse by producing a milder dopamine effect could be tested as a potential methamphetamine treatment medication, Dr. Tai says. **NN**

## Response to Escalating Methamphetamine Abuse Builds on NIDA-Funded Research

By Neil Swan, *NIDA NOTES* Staff Writer

NIDA-funded scientists are providing research crucial to the Nation's response to increasing methamphetamine abuse and addiction. Methamphetamine, also called "meth," is a potent form of amphetamine. It is a synthetic, highly addictive stimulant that is cheaper and longer lasting than cocaine.

Methamphetamine comes in many forms and can be smoked, snorted, orally ingested, or injected. The drug is a white, odorless, bitter-tasting crystalline powder that can be dissolved in water or alcohol. When made in clandestine labs, it is often in the form of a coarse powder or chunks that are off-white to yellow. Other nicknames include "speed," "crank," and "zip." The smokable form of the drug may be called "ice" or "crystal." The drug is addictive, and users can escalate quickly to larger and more frequent doses. Chronic abuse can lead to violent behavior. (For more information, see page 37, "Facts About Methamphetamine.")

The growing abuse of the drug is linked to its increasing availability and the fact that it can be easily manufactured from readily available chemical ingredients. Congress last summer passed the Comprehensive Methamphetamine Control Act establishing new controls over volume sales of the chemical ingredients used to produce the drug.

NIDA's Community Epidemiology Work Group (CEWG), a network of epidemiologists and researchers from 20 major U.S. metropolitan areas that provides frontline surveillance of the nature and extent of drug abuse, confirms that methamphetamine use has been prevalent in west coast cities and in western and southwestern communities, including many rural areas. Abuse of the drug now is being reported in urban settings in widening areas of the West, Midwest, and elsewhere. Methamphetamine is the dominant illicit drug problem in San Diego, according to CEWG data that include records of hospital emergency room admissions, drug-related deaths, and police drug seizures; and local observations of street buys and drug-trafficking patterns. Honolulu and San Francisco also have substantial methamphetamine-using populations, according to CEWG data. Recent reports indicate increasing patterns of methamphetamine use in Denver, Los Angeles, Minneapolis, Phoenix, Seattle, and Tucson as well.

Until recently, the drug's manufacture generally was dispersed so that small quantities were produced in rural areas. There are indications that methamphetamine now is being manufactured on a larger scale by organized groups operating out of Mexico and southern California.

Methamphetamine of Mexican origin is now found along newly extended trafficking routes in several States, including Arizona, Colorado, Iowa, Missouri, Nebraska, and Texas, according to CEWG. Clandestine labs have produced the drug in rural and desert areas where the telltale odors of the production process are less likely to be detected. Mobile labs in campers and vans have been reported in Washington.

A NIDA-funded study in Seattle confirmed that methamphetamine use was widespread among the city's homosexual and bisexual populations. Members of these groups using methamphetamine reported they practice sexual and needle-use behaviors that place them at heightened risk of contracting and transmitting HIV, the virus that causes AIDS. NIDA also supports basic research examining the neurobiological mechanisms involved in methamphetamine's action in the brain, seeking knowledge necessary for long-term solutions to abuse of the drug. Research has shown that methamphetamine releases high levels of the neurotransmitter dopamine, which stimulates brain cells, causing enhanced mood and increased body movement.

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***Animal studies show that high doses of methamphetamine damage nerve cells. In rats, one high dose of methamphetamine is enough to cause damage. Prolonged dosage seems to make it worse.***

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Another major research focus is on methamphetamine's neurotoxicity, specifically its action in damaging brain cells that contain dopamine and serotonin, another neurotransmitter. Scientists think that methamphetamine abuse over time may cause reduced levels of dopamine, which can cause symptoms like those of Parkinson's disease, a severe movement disorder.

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Animal studies going back more than 20 years show that high doses of methamphetamine damage neuron cell-endings, says Dr. Lewis S. Seiden of the University of Chicago, a NIDA-funded researcher who has studied methamphetamine for many years. "The damage is essentially permanent, although there may be some regrowth. The damage occurs in rats, guinea pigs, pigs, cats, and nonhuman primates. In rats, one high dose of methamphetamine is enough to cause damage. Prolonged dosage seems to make it worse," he says. Recent NIDA-funded studies by Dr. George A. Ricaurte at Johns Hopkins Medical Institutions in Baltimore and by other scientists indicate that neurotoxic effects are more pronounced in nonhuman primates than in rodents.

Dopamine- and serotonin-containing neurons do not die after methamphetamine use, but their nerve endings or terminals are cut back or "pruned" by use of the drug, Dr. Ricaurte says. "The question is, does the same thing occur in humans?" he asks. "To answer that question we have recently developed brain imaging techniques to study these effects in humans who have previously used methamphetamine." (See "NIDA-Supported Researchers Use Brain Imaging to Deepen Understanding of Addiction," *NIDA Notes*, November/December 1996, Vol. 11, No.5)

Another NIDA-funded researcher, Dr. Glen R. Hanson at the University of Utah, found evidence that dopamine-generated compounds called free radicals that appear following methamphetamine use can affect serotonin production in contrasting ways. He also reports that several neuropeptide systems linked to dopamine brain pathways are profoundly altered by administration of low to high doses of methamphetamine.

"Our results suggest that high and low doses of methamphetamine affect a peptide called neurotensin in very different ways," says Dr. Hanson. High doses of methamphetamine limit neurotensin's function, perhaps resulting in exaggerated dopamine responses to the stimulant. Low doses of methamphetamine increase neurotensin levels and function, which in turn appear to counteract behavioral response to the drug. These findings suggest that neurotensin perhaps could be used to prevent excessive and damaging dopamine responses to methamphetamine, he adds.

NIDA is also supporting research into treatment for methamphetamine abuse. Dr. Richard A. Rawson of the Matrix Institute in Beverly Hills, California, is conducting two outpatient studies with patients using both cocaine and methamphetamine.

One study concerns a small group of gay, methamphetamine-using males in Hollywood, California, where use of the drug is closely related to high-risk sexual behavior. Methamphetamine is the "drug of choice" among these homosexual men whether it is snorted, injected, or smoked, says Dr. Rawson. "They all talk about the inter-

connectedness of their sexual behavior and methamphetamine use."

Another study concerns 600 heterosexual methamphetamine abusers seeking treatment at a facility in a rural area of San Bernardino County, California. Methamphetamine abuse has been a problem in this area since the late 1980s. Users typically have also used cocaine but find methamphetamine longer lasting and more easily available; many of those in treatment say they can readily get the drug, even at their work sites or public places like truck stops, says Dr. Rawson.

"Treatment response was somewhat poorer among methamphetamine abusers than among cocaine abusers—fewer meth abusers could remain drug-free," he says. "The methamphetamine abusers are twice as likely as cocaine abusers to require some kind of medical treatment," he says. "Methamphetamine abusers are more debilitated and show paranoia and hallucinations. There is more violence associated with methamphetamine abuse, according to the treatment staff."

Concern that methamphetamine abuse is a growing problem affecting many population groups has prompted the White House to launch a policy and planning approach called the President's National Strategy for Combating Methamphetamine Abuse. The White House Office of National Drug Control Policy sponsored a Western Regional Methamphetamine Conference last January in San Francisco and will sponsor a national methamphetamine conference in May in Omaha, Nebraska.

The Substance Abuse and Mental Health Services Administration, in collaboration with NIDA, in June sponsored a satellite meeting on methamphetamine abuse at the annual meeting of the College on Problems of Drug Dependence in Puerto Rico. This meeting involved more than 30 experts, many of them NIDA staffers and NIDA-funded researchers. (See "Recommendations to Advance Understanding of Methamphetamine," *NIDA Notes*, November/December 1996, Vol 11, No 5 for a report on the meeting's recommendations.)

NIDA also sponsored a symposium, "Methamphetamine Abuse, Treatment, and Prevention," in San Francisco in December 1996 focusing on national and regional issues relating to methamphetamine abuse.

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## Facts About Methamphetamine

Methamphetamine is a central nervous system stimulant with a high potential abuse and dependence. A synthetic drug, methamphetamine is closely related chemically to amphetamine, but produces greater effects on the central nervous system. The drug's euphoric effects are similar to but longer lasting than those of cocaine.

Methamphetamine takes the form of a white, odorless, and bitter-tasting crystalline powder, readily soluble in water or alcohol. Street methamphetamine is referred to by many names including "meth," "speed," "zip," "go-fast," "cristy," "chalk," and "crank." Pure methamphetamine hydrochloride, the smokable form of the drug, is called "L.A." or—because of its clear, chunky crystals—"ice" "crystal," "glass," or "quartz."

### Methods and Effects of Use

Methamphetamine can be smoked, injected intravenously, snorted, or ingested orally. The drug alters mood in different ways, depending on how it is taken. Immediately after smoking or intravenous injection, the user experiences an intense "rush" or "flash" that lasts only a few minutes and is described as extremely pleasurable. Smoking or injecting produces effects fastest, within 5 to 10 seconds. Snorting or ingesting orally produces euphoria—a high but not an intense rush. Snorting produces effects within 3 to 5 minutes, and ingesting orally produces effects within 15 to 20 minutes.

Even small amounts of methamphetamine can produce euphoria, enhanced wakefulness, increased physical activity, decreased appetite, and increased respiration. Other central nervous system effects include athetosis (writhing, jerky, or flailing movements), irritability, insomnia, confusion, tremors, anxiety, aggression, hyperthermia, and convulsions. Hyperthermia and convulsions sometimes can result in death.

Cardiovascular side effects include chest pain and hypertension and sometimes can result in cardiovascular collapse and death. In addition, methamphetamine causes increased heart rate and blood pressure and sometimes can cause irreversible damage to blood vessels in the brain,

producing strokes. Methamphetamine abuse during pregnancy may result in prenatal complications, increased rates of premature delivery, and altered neonatal behavioral patterns.

Psychological symptoms of prolonged methamphetamine abuse can resemble those of schizophrenia and are characterized by paranoia, hallucinations, repetitive behavior patterns, and formication (delusions of parasites or insects on the skin). Methamphetamine-induced paranoia can result in homicidal or suicidal thoughts. Although no characteristic physical signs of withdrawal are associated with methamphetamine abuse, users report drug craving, depressed mood, sleepiness, and hunger.


### Extent of Use

NIDA's 1996 Monitoring the Future study, which assessed the extent of drug use among 8th-, 10th-, and 12th-graders across the country, reports that:

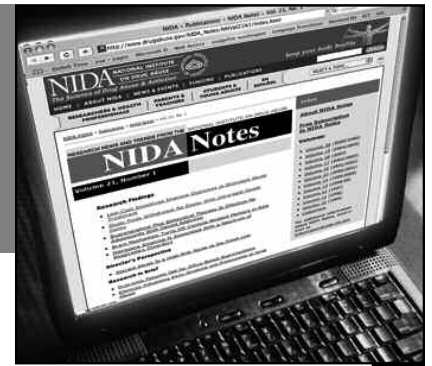
- When high school seniors were asked if they had used crystal methamphetamine at least once in their lifetimes, 4.4 percent said they had—an increase from 2.7 percent in 1990;
- In that same year, when high school seniors were asked if they had used crystal methamphetamine in the 12 months prior to the survey, 2.8 percent said they had—an increase from 1.3 percent in 1990.

The Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network reports that from 1991 to 1994, the number of methamphetamine-related visits to hospital emergency departments more than tripled, from 4,887 to 17,397.

### More Information

For more information about methamphetamine, contact the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847, at 1-800-729-6686. Information is also available at the NCADI Web site at <http://www.health.org> or at the NIDA Web site at <http://www.nida.nih.gov/> 

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Revised April 2008  
Printed September 2005