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Long-Term Abstinence Brings Partial Recovery From Methamphetamine Damage

By Patrick Zickler, *NIDA NOTES* Staff Writer

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.

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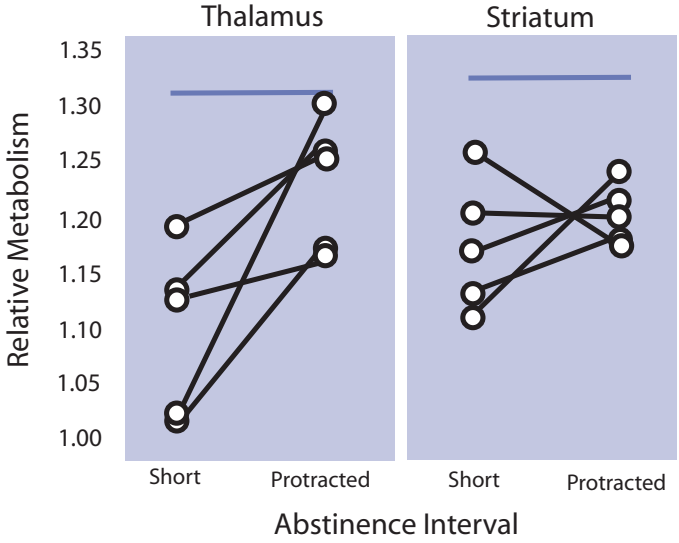
Some Methamphetamine-Related Deficits Recover After Protracted Abstinence



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.

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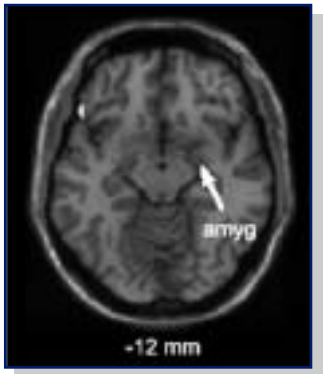
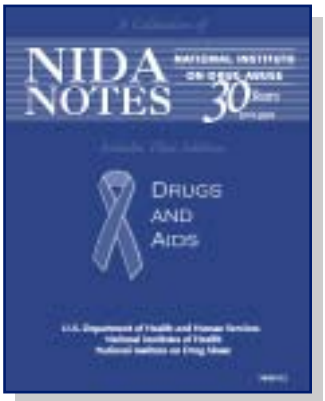


PET scans show differences in brain during cue-induced cocaine craving, p. 4



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Drug-Related Damage That Begins Before Birth

By NIDA Director Nora D. Volkow, M.D.

NIDA has long been concerned about the damaging effects of maternal drug abuse on unborn children. Our investigations began more than three decades ago, and the continued research commitment is providing an increasingly detailed picture of the scope and sequence of damage done by prenatal exposure to drugs of abuse. The effects are seen in reduced weight in newborns, behavioral disorders in toddlers, cognitive deficits in young schoolchildren, and increased vulnerability to drugs in adolescents.

Recently, NIDA, along with the National Institute of Child Health and Human Development and the National Institute of Health's Office of Research on Women's Health, sponsored a conference ("Long-Term Follow-Up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities," held March 23 and 24 in Bethesda, Maryland) where more than 100 researchers gathered to discuss the findings and future direction of more than 20 NIDA-supported investigations into the consequences of maternal drug abuse on child development. The largest of these research studies evaluates cocaine's impact on more than 1,300 children now entering adolescence. The longest ongoing study is investigating the effects of nicotine exposure from birth into early adulthood. The newest study will investigate possible effects of MDMA ("Ecstasy"). Research presented at the conference shows that prenatal exposure produces developmental damage that can be measured in day-old infants, school-age children, and young adults. The studies also establish that some of the damage can be overcome.

NIDA's long-term research on tobacco use provides convincing documentation of the harm done by maternal smoking during pregnancy. It is seen in 1- to 2-day-old infants, who scored higher than unexposed newborns on measures of stress and excitability. These symptoms are dose dependent: Children whose mothers were heavier smokers exhibit more pronounced effects (see "The Neurobehavioral Legacy of Prenatal Tobacco Exposure," *NIDA NOTES*, Vol. 18, No. 6, p. 8). Nicotine's effects persist. Teenagers whose mothers smoked during pregnancy perform more poorly on tasks requiring auditory memory than do teens who were not exposed. On tests of general intelligence, on which "normal" scores range from 99 to 109, children of nonsmoking mothers scored an average of 113.4, children of light smokers 109.8, and children of heavy smokers 105.2 (see "Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers," *NIDA NOTES*, Vol. 18, No. 6, p. 9). In some measures of cognitive function, however, the gap between exposed and unexposed children narrows with age, and the pattern of improvement suggests that environment helps. Exposed children show improved achievement as they grow older, and their better performance is associated most strongly with the educational level of the parents: Home and family factors that support learning appear to help overcome the damage of exposure.

NIDA's research shows that maternal cocaine use has multiple effects on mental development. Though small, these effects are measurable and have the potential to influence experience, ability, and achievement in childhood and later in life. Cocaine-exposed children, compared with children whose mothers did not use the drug, are more likely to score nearer the lower end of a normal range in tests of alertness and attention. Exposed children have also a downward shift averaging 3.26 points in scores on IQ tests where 100 is average. As is the case with nicotine, some of cocaine's damage can be overcome. Recently, NIDA-supported scientists at Case Western Reserve University in Cleveland, Ohio, reported that exposed children raised in stimulating and enriching environments had IQ scores similar to those of unexposed children when tested at age 4.

Human studies that span decades allow us to monitor the long-term developmental effects of prenatal drug exposure. Animal studies can more quickly provide important clues to the effects of drugs on fetal development. For example, our research on possible developmental effects of MDMA shows that in rats, prenatal exposure to the drug alters brain development and appears to cause damage that remains after the rats mature. Animals exposed to MDMA during a crucial prenatal developmental period late in pregnancy take significantly longer than unexposed animals to learn and remember, when fully grown, the strategies for escaping a maze (see "Prenatal Exposure to Ecstasy May Impair Memory and Cognition," *NIDA NOTES*, Vol. 17, No. 3, p. 8). Other research reveals damage done by MDMA exposure in the earliest period of brain development. When tested 3 weeks after birth, rats with early prenatal exposure took significantly longer than did unexposed animals to become accustomed to a new environment (see "Animal Study Finds Effects on Behavior, Brain Chemistry of Prenatal MDMA Exposure," *NIDA NOTES*, Vol. 19, No. 2, p. 13).

The results of our animal studies of MDMA will help guide research, now under way, on the effects of prenatal exposure of humans to MDMA. NIDA has initiated similar studies to assess the effects of methamphetamine. This research is in its earliest stages, but, like our investigations of nicotine and cocaine, will track the progress of prenatally exposed children as they grow through adolescence into adulthood. Through short-term animal research and decades-long longitudinal studies, NIDA is committed to providing the scientific foundation necessary for the development of social and clinical programs to prevent and treat the life-shaping prenatal damage associated with drug abuse. NN

Men and Women May Process Cocaine Cues Differently

By Lori Whitten, *NIDA NOTES* Staff Writer

Some aspects of cocaine addiction and recovery are different for men and women—including the reasons for seeking drug rehabilitation, response to treatment, and vulnerability to relapse. Women are more likely to seek cocaine abuse treatment in response to co-occurring depression, remain abstinent after treatment, and relapse in response to interpersonal problems and negative feelings. Cocaine-addicted women also demonstrate greater craving than men in response to drug cues. In the first brain imaging study of cocaine craving by cocaine-addicted women, NIDA-funded researchers have made observations that, if borne out in larger studies, may point to neurological sources of these differences.

Dr. Clinton Kilts and colleagues at the Emory School of Medicine in Atlanta used positron emission tomography (PET) to measure drug-craving-related changes in regional cerebral blood flow—a correlate of neural activity—in eight cocaine-addicted African-American women aged 35 to 46. The women had abstained from cocaine use for 1 to 14 days and reported frequent periods of cocaine craving in the 30 days preceding the study. While lying in the PET scanner, each woman listened to a 1-minute recording of a script describing her personal experiences of acquiring the drug and anticipating sensations associated with taking cocaine. Each patient's script was derived from her own answers to an autobiographical questionnaire and narrated in the first person:

"…I start thinking about how good it's going to feel to take that first hit…with my eyes wide open I take my lighter out of my pocket, put it to the stem, and get ready to take that first, good blast…."

Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People
(Cocaine-use imagery compared with neutral imagery)

Brain Region	Putative Role in Behavior	Activity Changes During Cocaine Craving	
		Men	Women
Right nucleus accumbens	Processes anticipated and attained rewards—probably contributes to the expectation of pleasure during craving	Increased activity	Increased activity
Amygdala	Generates and regulates emotional responses; assesses the positive or negative value of experiences and forms associations between experiences and emotional consequences	Increased activity	Decreased activity
Dorsal anterior cingulate cortex	Monitors competing options, inhibits goal-inappropriate behavior, and plans movements related to obtaining rewards; activity influenced by past experiences—possibly provides cognitive control of drug-seeking behavior	Increased activity	Increased activity, greater than that of men
Ventral anterior cingulate cortex	Regulates emotional response to cocaine cues; activation may precede craving onset	Increased activity	Increased activity, less than that of men
Frontal cortex	Monitors relationship of drug cue to drug availability; provides inhibition or control over actions; activity influenced by past experiences—possibly counter-regulates emotional input	Increased activity	Increased activity, greater than that of men

The researchers injected each woman with a radiotracer and took pictures of the blood flow in her brain as she listened to the script and relived the scene in her mind. After each brain scan, the women rated the urge to use cocaine, vividness of the mental image, and their emotions. They repeated this process twice.

The women also underwent imaging in three control situations: resting, listening to a script of a personal experience in nature, and listening to a script designed to provoke anger. The researchers verified that the mental imagery of the cocaine-related script induced a greater urge to use cocaine than the nature or anger script. By comparing the brain scans produced in response to the different scripts, the researchers were able to evaluate cerebral blood flow while the women were craving cocaine versus when they were relaxed and not thinking of the drug. The procedure also distinguished changes related to craving from those that might simply reflect strong general emotional reactions (as in the anger-inducing script). To examine possible sex differences

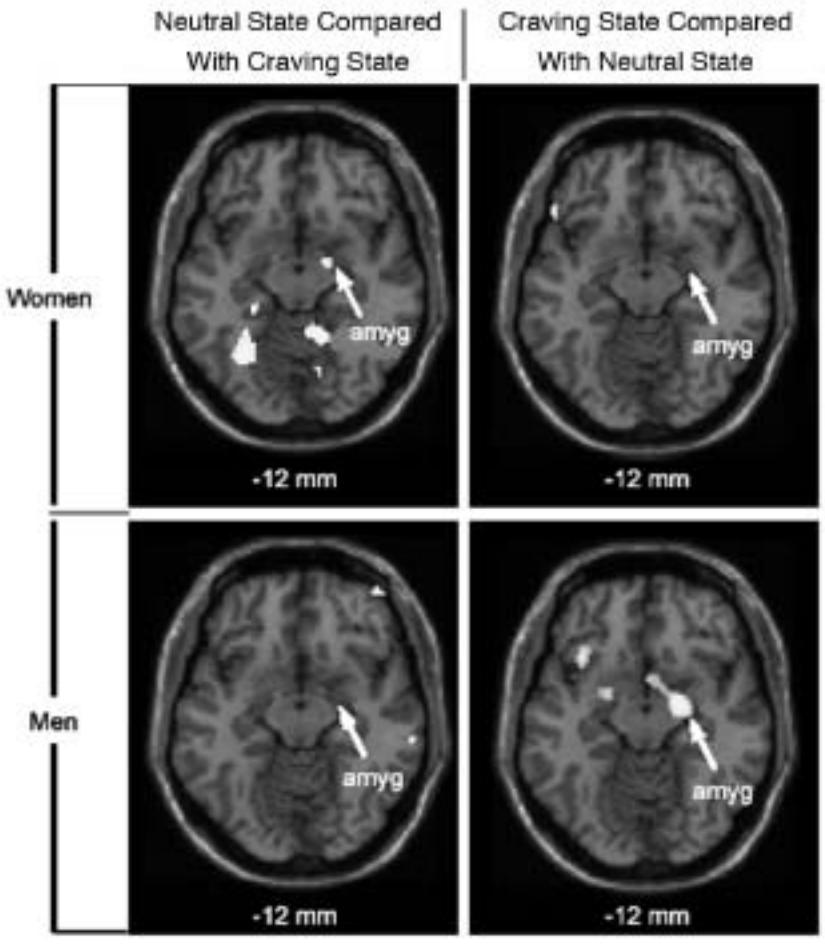
in the neural representation of cocaine craving, the investigators compared the findings in women with results from eight cocaine-addicted men of similar ages and backgrounds who experienced the same process.

In both men and women, cue-induced cocaine craving activated several brain areas involved in determining a cue's reward value and controlling reward-related behaviors, including the right nucleus accumbens—a structure that seems to produce the expectation of pleasure during drug craving (see table on preceding page, "Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People"). "These common activations suggest that both sexes may process cocaine-use memories—mental images that are associated with strong emotions—as cues that guide reward-based decisionmaking," says Dr. Kilts. However, men and women also showed some dissimilar neural responses to cocaine cues. Most notably, activity of the amygdala—a structure that assesses whether an experience is pleasurable or aversive and connects the experience with its consequences—fell in women during cocaine craving. "This finding is notable because our study and others have shown cue-induced amygdala activation in men," says Dr. Kilts. "Reduced neural responses in the amygdala may result from greater activation of the frontal cortex in women. The frontal cortex inhibits the activity of structures involved in emotional responding to drug cues, and our observations were consistent with previously reported sex differences in frontal cortical areas."

"As a field, we need more and better controlled studies of sex differences in factors that cause relapse," says Dr. Kilts. Combining imaging technologies in the same study—for example, PET with magnetoencephalography—would improve the localization of neural activity. "We could better define the neural responses that occur before, during, and after drug cues—illuminating the temporal sequence of the craving experience in men and women," he says.

"This research reveals that men and women differ in a critical brain area in their responses to cocaine craving," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience, Development, and Behavioral Treatments. "Differences in the amygdala may indicate that male and female abusers crave the drug for different reasons or hope to achieve different results from taking the drug. Imaging studies that examine gender differences in specific behavioral aspects of drug craving will provide insight on how to tailor treatment programs to meet the needs of men and women."

Brain Response Differs in Men and Women During Cue-Induced Craving



Source: Kilts, C.D.; Gross, R.E.; Ely, T.D.; and Drexler, K.P.G. (2004).

These PET scans show differences in blood flow between a neutral state and a cocaine-craving state. White areas indicate an increase in blood flow. Most notable is the decrease in blood flow in the women's amygdala (top right panel) during craving; men show an increase in blood flow during craving (bottom right panel).

Source

• Kilts, C.D.; Gross, R.E.; Ely, T.D.; and Drexler, K.P.G. The neural correlates of cue-induced craving in cocaine-dependent women. *American Journal of Psychiatry* 161(2):223-241, 2004.

Long-Term Abstinence Brings Partial Recovery from Methamphetamine Damage

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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.

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

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.

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 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 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

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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, 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

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

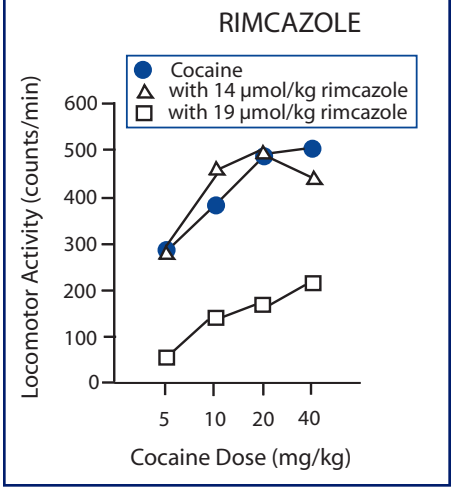
Sigma Antagonists: Potential Cocaine Medications With Novel Activity

By Patrick Zickler, *NIDA NOTES* Staff Writer

Investigators in NIDA's Intramural Research Program (IRP) have confirmed and extended previous findings that rimcazole, a medication developed in the 1980s to treat schizophrenia, weakens some of cocaine's effects in rodents. The new findings strengthen speculation that drugs like rimcazole that act at sigma receptors might help recovering individuals avoid temptations to relapse to cocaine. Rimcazole and related compounds share a novel mechanism of action, a sigma receptor blockade, that appears to have significant potential for loosening cocaine's hold on addicted individuals.

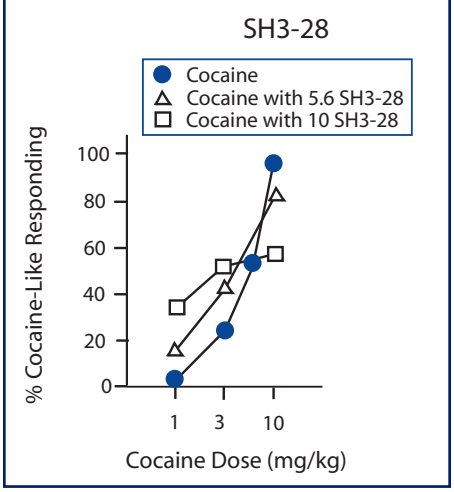
Drs. Jonathan Katz and Amy Newman and IRP colleagues showed that pretreating mice with rimcazole reduced one of cocaine's signature effects on rodent behavior: increases in locomotor activity—more running around. The impact on movement varied with the dosages of rimcazole and cocaine: At the maximum, a 73 µmol/kg dose of rimcazole reduced by 57% the amount of locomotor activity rats exhibited following administration of cocaine (40 mg/kg). Other rimcazole-like compounds reduced locomotor activity following cocaine exposure by up to 47%, also depending on dosages.

Coadministration of Rimcazole With Cocaine Blocks Locomotor Stimulation in Mice



When administered with cocaine, rimcazole blocked the stimulant effects of cocaine on locomotor activity.

Pretreatment With Rimcazole Analog SH3-28 Decreases Subjective Effects of Cocaine in Rats



In rats conditioned to press a lever in response to cocaine injection, SH3-28 pretreatment reduced the accuracy of the animals' responses to cocaine.

The demonstration that rimcazole attenuates locomotor stimulation by cocaine confirms previous similar findings by other researchers. The IRP team established for the first time an additional potentially important effect of rimcazole-like compounds: In rats, a closely related compound called SH3-28 weakens the subjective sensations that distinguish the cocaine experience. Rats pretreated with SH3-28 lost some of their ability to tell the difference between injections of cocaine and injections of saline—plain salt water.

In this experiment, the researchers first taught rats they could obtain food by choosing the correct lever between two options: To be rewarded, the animals needed to push one lever after receiving a cocaine injection and the other lever after receiving a saline injection. Once trained, rats pressed the cocaine-associated lever nearly 100% of the time after an injection of cocaine; however, when pretreated with 19 µmol/kg of SH3-28 prior to receiving cocaine, they pushed the correct lever only about 60% of the time. Should these results carry over to people, rimcazole or a rimcazole-like medication might be used in treatment of cocaine abuse. Recovering individuals who abused cocaine while taking the medication would learn that the drug did not produce the desired stimulant sensations, reducing their motivation for future use.

"This area of research is still in the early stages of effectiveness testing, but if the present results prove reliable and can be extended to humans, it would appear that rimcazole and its analogs may have promise in further drug discovery efforts

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Smoking Exposure *In Utero* Increases Risk of Later Addiction

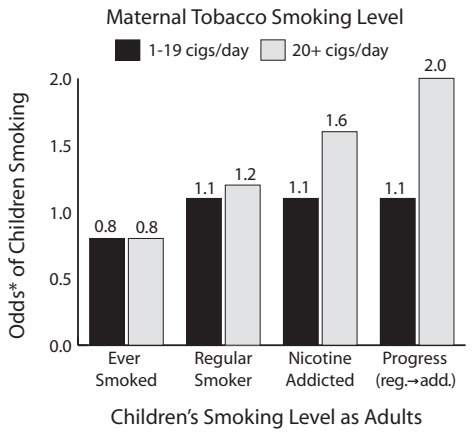
By Arnold Mann, *NIDA NOTES* Contributing Writer

An expectant mother's smoking during pregnancy does not increase the likelihood that her child will later try smoking or become a regular smoker. Her pack-a-day smoking, however, doubles the risk that if her child does become a smoker, he or she will become addicted to tobacco, according to the first study to examine rates of tobacco addiction in adults who were prenatally exposed.

The study was led by Dr. Stephen L. Buka of the Harvard School of Public Health in Boston and cosponsored by the National Cancer Institute, the National Institute of Mental Health, the Robert Wood Johnson Foundation, and NIDA. Dr. Buka, together with Drs. Edmond D. Shenassa and Raymond Niaura, both of Brown Medical School in Providence, Rhode Island, collected data from 1,248 individuals aged 17 to 39. All the study subjects' mothers had participated in the Providence cohort of the National Collaborative Perinatal Project (NCPP) between 1959 and 1966. As part of the NCPP, pregnant women provided information about their smoking and gave blood samples for measuring nicotine levels.

Among the men and women in the new study, 62 percent had smoked regularly and 45 percent met the medical criteria for tobacco dependence at some time in their lives. The criteria, as defined by DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Revision III), include persistent, unsuccessful attempts to quit or control smoking, continued use despite smoking-related problems, and smoking to reduce withdrawal symptoms. Thirty-eight percent were born to mothers who did not smoke, 25.6 percent to mothers who smoked less than a pack a day, and 36.4 percent to mothers who smoked a pack or more per day at some point during pregnancy.

Heavier Maternal Smoking During Pregnancy Increased Children's Odds of Nicotine Addiction as Adults



Children of women who smoked at least 20 cigarettes a day during pregnancy were more likely to become addicted to nicotine or progress from regular smoking to nicotine addiction as adults compared with children of women who smoked fewer than 20 cigarettes a day. Children of heavier smokers were no more likely to try smoking or to smoke regularly than children of lighter smokers.

Among children who had smoked at least once, those whose mothers smoked up to a pack a day during pregnancy had a 20 percent higher, and those whose mothers smoked a pack a day or more had a 60 percent higher odds of having at some time been addicted to tobacco, compared with those whose mothers had not smoked. Among children who had at some time in their lives smoked daily for a month or more, those exposed *in utero* to a mother's pack-a-day smoking had double the odds of progressing to addiction.

"The evidence from this study, which reinforces the findings of experimental research with animals, is compelling," says Dr. Buka. "Early exposure to tobacco during pregnancy apparently affects the individual's response to cigarettes in later adolescence and adulthood."

The researchers' statistical analyses indicated that the associations between maternal smoking during pregnancy and offspring's future smoking were independent of socioeconomic status, maternal age at pregnancy, offspring sex, and offspring age at the time of the interview. What's left, then, is a biological factor. "The most likely hypothesis is that the toxins in cigarettes cross the placental barrier and interact with the genes that control cell differentiation, permanently altering cells' responsiveness in ways that increase vulnerability to tobacco addiction," Dr. Buka says.

The cross-generational impetus to tobacco addiction documented by the study is a serious national health concern. Almost half of women who smoke continue to do so when they become pregnant, says Dr. Buka. The smoking mothers-to-be constitute about 12 percent of women who give birth—a national potential for 500,000 prenatal exposures every year.

The researchers also collected information about the study participants' marijuana abuse and found no tie to prenatal nicotine exposure. This

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toward the treatment of cocaine abuse," says Dr. Frank Vocci, director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse.

The Mechanisms of Action

Rimcazole achieves its cocaine-suppressing effects at least in part by binding to and blocking the sigma receptor. This is a protein on the surface of some brain cells that receives chemical messages and relays them to the interior of the cells, stimulating or inhibiting some cellular activities. Compounds that block the sigma receptor inhibit cells from responding to dopamine, a chemical messenger that contributes to many of the addictive effects of cocaine as well as of other addictive drugs.

Rimcazole also binds to another protein on the cell surface, called the dopamine transporter. Most chemicals that attach here mimic the effects of cocaine, which itself is a potent dopamine transporter blocker. The IRP researchers are currently investigating whether rimcazole and rimcazole-like compounds produce an effect opposite to cocaine's because their sigma blockade overrides their dopamine transporter effect, or whether some more complicated interaction between the two comes into play. So far, the evidence seems to point to the latter possibility.

"Our findings suggest that the interaction of sigma receptor ligands and cocaine is complex and appreciably different from competitive antagonism—that is, rimcazole and its analogs do not appear to physically block cocaine from its binding site," says Dr. Katz. "It is possible that the effects of these compounds are due to the particular balance of dopamine transporter and sigma receptor actions they produce."

The IRP team's research constitutes the initial studies in a program of drug discovery. Future investigations will examine whether rimcazole and related compounds block other stimulant-induced effects of cocaine, attempt to isolate the exact nature of their effects at the sigma receptor and dopamine transporter, and—if the compounds continue to show promise—evaluate their safety and efficacy in animals and people.

Source

• Katz, J.L., et al. Behavioral effects of rimcazole analogs alone and in combination with cocaine. *European Journal of Pharmacology* 468(2):109-119, 2003. NN

Smoking Exposure *In Utero* Increases Risk of Later Addiction

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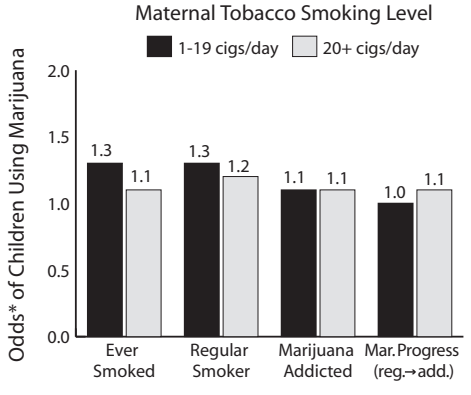
suggests, the investigators say, that the "pathophysiological pathway" that promotes vulnerability to tobacco addiction among offspring differs from the pathway that leads to marijuana addiction.

The study confirms the need for energetic efforts to deter women from smoking, especially during pregnancy, says Dr. Kevin Conway, deputy chief of NIDA's Epidemiology Research Branch. Preventing smoking by pregnant women will improve nicotine addiction rates of the next generation. "This study highlights opportunities for physicians to intervene with mothers who smoke, for the health of themselves and their children," says Dr. Conway.

"Healthy-baby prenatal visits, labor and delivery, and postnatal-care visits are golden opportunities for providers to offer assistance to quit smoking and prevent relapse, thereby reducing the risk of children's progression to nicotine addiction," says study coauthor Dr. Niaura. "Health care providers must take advantage of every opportunity to ask, advise, and assist patients in efforts to quit smoking."

Maternal Tobacco Smoking During Pregnancy Did Not Affect Children's Odds of Marijuana Use as Adults



The finding that in utero *exposure to tobacco did not affect later marijuana use indicates that the two drugs have different physiological pathways.*

Source

• Buka, S.L.; Shenassa, E.D.; and Niaura, R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: A 30-year prospective study. *American Journal of Psychiatry* 160(11):1978-1984, 2003. NN

CTN Update: Teamwork Develops Treatment Concept Into Study Protocol

By Barbara Shine, *NIDA NOTES* Contributing Writer

In NIDA's Clinical Trials Network (CTN), researchers and practitioners collaborate in the design as well as the execution of drug abuse treatment studies. Continuous collaboration with treatment providers, a distinguishing feature of the network, ensures a research focus on practical questions that arise in typical patient populations and community treatment settings.

A new study begins when a researcher or treatment provider identifies a clinical need and formulates a solution or intervention to meet it. Research ideas are accepted only if they coincide with public health priorities and meet two standards—feasibility and sustainability. A feasible research concept is one that can be tested in established, community-based treatment programs with varied patient populations. To meet the sustainability standard, the proposed intervention should be possible to continue in community treatment programs equipped with a realistic complement of resources after study completion. The concept proposal also must stand on a foundation of previous supporting research. Once it meets these criteria and gains approval within CTN and by NIDA, the proposal is ready to move on to protocol development and final NIDA approval and funding.

An example of the pragmatic approach to research design is the recently completed CTN-sponsored study "Motivational Incentives for Enhanced Drug Abuse Recovery." This work is based on the general idea that rewards—including supportive words, praise, money, or desirable objects—for a particular behavior promote like behavior in the future. Two protocols emerged: one for implementation in methadone maintenance clinics and another for study in clinics using treatments other than methadone maintenance.

"There were two key points to negotiate in designing these trials," says Dr. Maxine Stitzer of Johns Hopkins University School of Medicine in Baltimore, the principal investigator for both motivational incentive protocols. "The first was selection of the drug target. Previous incentive studies had targeted only one drug, but we targeted both cocaine and methamphetamine to address regional differences in stimulant abuse. We added alcohol as a primary target and opiates and marijuana as secondary drug targets to emphasize the importance of giving up all drugs, not just the particular one that brought the patients into treatment. Patients could draw chances to win prizes when their breath and urine samples were negative for target drugs."

"The second big issue was how much the prizes should be worth," says Dr. Stitzer. "Early studies in research centers cost upwards of a thousand dollars per patient for prizes; community treatment providers made it clear they needed an effective motivational approach that would not exhaust their much smaller budgets. People in our study drew chances to win a range of prizes—from bus tokens, to $20 grocery vouchers, to compact disc players—that were more realistic for community treatment centers."

Members of the protocol development group benefited from meeting with Dr. Nancy Petry, an investigator who conducted similar studies at the University of Connecticut in Farmington, and with several of her clinical staff and patients. "We really gained valuable insights and heard firsthand how the patients' motivations changed over the course of their treatment, from working for prizes to working for their own good," says Dr. Stitzer.

Once NIDA approved the motivational incentives protocol, investigators implemented the study in 14 treatment programs with a total of about 800 patients. Preliminary analysis of the data suggests that the addition of reward systems to standard therapy will improve outcomes for drug abuse patients. Once Dr. Stitzer and her team analyze and publish the results, clinicians will know whether motivational incentives are truly an effective adjunct to current therapies. NN

For More Information...

To learn more about CTN protocols, including studies that are now recruiting patients, visit the NIDA Clinical Trials Network Web site, *www.drugabuse.gov/CTN*. Both English and Spanish brochures for patients and physicians are available for download, and the site lists contact information for all regional research and training centers and clinical trials.

Dr. Petry's research is highlighted in "Fishbowls and Candybars: Using Low-Cost Incentives To Increase Treatment Retention" (*NIDA Science & Practice Perspectives*, Vol. 2, No. 1, p. 55), which is also available on NIDA's Web site.

"No Wrong Door" for People with Co-Occurring Disorders

By Lori Whitten, *NIDA NOTES* Staff Writer

More than 450 behavioral health professionals have committed to creating a system in which people with coexisting mental health and substance abuse problems as well as physical disorders find "no wrong door" when they seek help. Participants at the "Complexities of Co-Occurring Conditions: Harnessing Services Research To Improve Care for Mental, Substance Use, and Medical/Physical Disorders" conference, which was sponsored by NIDA and five Federal partners, acknowledged that system reform is challenging but necessary to ensure appropriate care. Achieving a service delivery system that addresses the complex needs of people with co-occurring disorders requires significant changes at the conceptual, organizational, and provider levels. One meeting cannot achieve such a major reform, but the conference brought together diverse professionals in a first step toward the goal.

"Co-occurring disorders challenge traditional care, which addresses one disease and immediately apparent symptoms even though most patients have multiple, chronic, and compounding problems that often relapse," explained Dr. Jack Stein, chief of NIDA's Services Research Branch, in welcoming the participants to the conference held June 23 through 25 in Washington, D.C.

Conference participants—researchers, clinicians, treatment evaluation experts, advocates and policymakers, service coordinators, and representatives from Federal health agencies.

The group overwhelmingly agreed that individuals with co-occurring disorders are the "expectation rather than the exception" across all service delivery systems. Acknowledging the high prevalence and severe consequences of co-occurring conditions, the participants advocated treatment that cuts across multiple systems of care. Reshaping treatment must involve the criminal justice system—often the point of first contact for people with co-occurring disorders—and address the higher probability of homelessness, HIV, and domestic violence in this population. Coordinating or integrating care is a major challenge, however, because parallel service systems have different funding, rules, policies, and traditions. Professionals increasingly acknowledge that integrated care for co-occurring disorders is appropriate, but they need guidance on the most effective forms of integrated treatment and how to bring them to communities with limited resources.

"It is imperative that we break through the 'translational bottleneck' to get evidence-based practices in prevention, treatment, and aftercare services for coexisting disorders into the community," said NIDA Director Dr. Nora D. Volkow. "NIDA and its partners are developing standards for evidence-based practice, which is an essential step toward a goal we must achieve—ensuring reimbursement for addiction treatment services," she said, drawing applause.

"The Department organized this collaborative conference to accelerate the translation of research into practice and build the knowledge base in the area of co-occurring disorders," Dr. Stein explained. Plenary session speakers discussed the role of health services research in the effort to improve access, quality, and cost-effectiveness of prevention and treatment.

Attendees participated in small-group panel sessions on specific topics, including research on particular co-occurring conditions, diagnostic tools, and integrated treatment strategies and outcomes. Interactive poster sessions encouraged collaborations and development of a research agenda.

In the panel discussions, behavioral health professionals agreed that substance abuse and mental health services are at a critical juncture, facing pressure from limited resources, changing infrastructure, rapid scientific advancements, and political and

cultural shifts. In such a dynamic and complex environment, reforming systems of care to ensure "no wrong door" for people with co-occurring disorders will be challenging. Participants called on professional societies to guide clinicians on simultaneous treatment and to recognize the inappropriateness of excluding people with co-occurring conditions from treatment (see "Adults with Co-Occurring Depression and Substance Abuse Benefit from Treatment of Depression," below). They called on professional groups and educational institutions to promote integrated, comprehensive services by reforming curricula, licensure and certification, and facility accreditation. Participants encouraged the Federal agencies sponsoring the conference to continue collaborative initiatives that support appropriate care for people with co-occurring disorders. NN

Adults With Co-Occurring Depression and Substance Abuse Benefit From Treatment of Depression

New evidence is overturning the long-held view that patients with co-occurring mental health and substance use disorders must achieve abstinence from drugs before treatment for depression can begin. There were sound reasons for adhering to this view, including clinician concern about drug interactions and recognition that depressive symptoms brought on by substance abuse are difficult to separate from clinical depression itself. As the field continues to refine screening tools that distinguish the disorders, however, new treatment approaches are being developed and assessed.

In a study that reinforces the need to revisit traditional management of these conditions, NIDA-funded researchers Drs. Edward Nunes and Frances Levin of Columbia University in New York City reviewed 33 years of published literature on the treatment of depression in the context of ongoing substance abuse. They found that antidepressant treatment is not sufficient for these patients, and they emphasize the need to integrate the treatment of depression and substance abuse. The investigators examined 44 placebo-controlled clinical trials published from 1970 to December 2003; 14 followed a rigorous methodology and were included in the study. Drs. Nunes and Levin used meta-analysis—a technique that synthesizes data from similar studies and determines how much particular factors affect outcomes—to examine the effects of antidepressant medication in approximately 850 patients with co-occurring substance abuse. They found that treating the depression of patients with co-occurring substance abuse conveys moderate benefit. Patients who responded to the antidepressant treatment also showed a reduction in substance abuse. However, cessation rates were generally low, even among studies demonstrating positive effects of antidepressants. Drs. Nunes and Levin suggest that clinicians first treat the depression with an evidence-based psychosocial intervention, followed by antidepressant medication if the depression does not improve.

"The study provides quantitative evidence on the benefit of treating depression in those with co-occurring substance abuse and supports integrated treatment of both disorders. Cognitive behavioral therapy is a good first approach for treating these patients, but the findings show the efficacy of antidepressant medications for patients with coexisting depression and substance abuse," says Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. Some clinicians worry that treating a patient's depression distracts attention from treating their co-occurring substance abuse. But Dr. Montoya says, "Patients may attach less stigma to seeking treatment for depression than substance abuse. Clinicians are increasingly finding that they have an opportunity to treat substance abuse in patients who present with depression; now, they have quantitative evidence to support the decision of concurrent treatment."

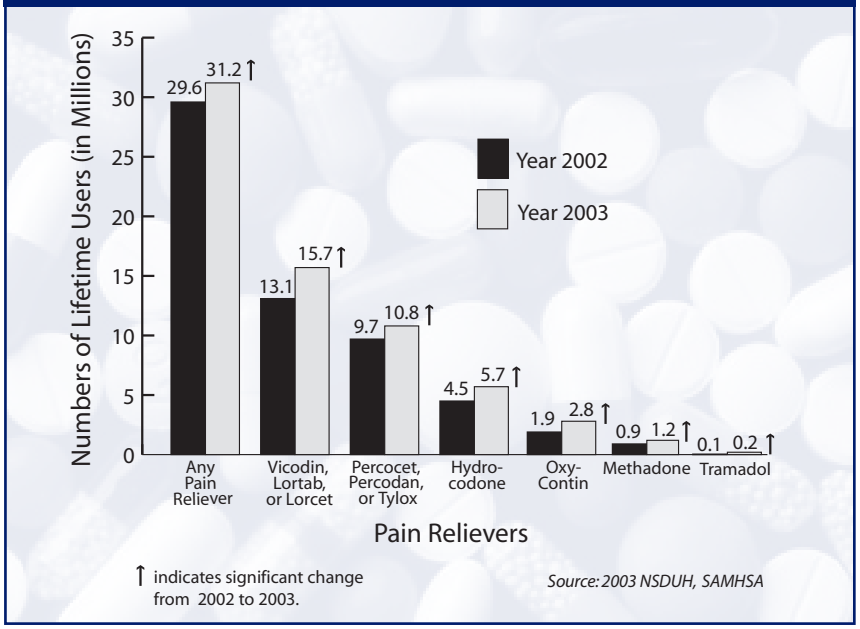
Source

• Nunes, E.V., and Levin, F.R. Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *JAMA* 291(15):1887-1896, 2004. NN

2003 Survey Reveals Increase in Prescription Drug Abuse, Sharp Drop in Abuse of Hallucinogens

The annual National Survey on Drug Abuse and Health (NSDUH), released in September 2004, indicates that in 2003 more than 19 million Americans—8.2 percent of the population aged 12 and older—were abusing illegal drugs each month. Overall, this represents no significant change from 2002, but the new data reveal significant changes for some drugs. For example, among youth aged 12 through 17, past-year abuse of MDMA ("Ecstasy") and LSD fell sharply—by 41 percent for MDMA and 54 percent for LSD. On a less encouraging note, lifetime abuse of prescription pain medications increased in all age groups and for all painkillers in the survey. Key findings from the 2003 NSDUH:

Lifetime Nonmedical Users of Selected Pain Relievers Among Persons Aged 12 or Older: 2002 and 2003



- **Tobacco.** An estimated 70.8 million Americans reported current (past-month) use of a tobacco product in 2003. This is 29.8 percent of the population aged 12 or older, similar to the rate in 2002 (30.4 percent). The highest rate of past-month cigarette smoking was among young adults aged 18 to 25 (40.2 percent). Among all smokers aged 12 or older, a higher proportion of males than females smoked cigarettes in 2003 (28.1 v. 23.0 percent), but among 12- to 17-year-olds, girls (12.5 percent) were as likely as boys (11.9 percent) to smoke. Among girls in this age group, the 2003 figures represent a significant decrease from last year's rate of 13.6 percent.
- **Marijuana.** Marijuana is the most commonly abused illicit drug, with 14.6 million (6.2 percent of the population) persons currently abusing the drug. There were an estimated 2.6 million new marijuana users in 2002, roughly two-thirds of whom were younger than age 18; half of the new abusers were female. The 2003 data reveal a drop of 20 percent in the number of youth who reported heavy (either daily or 20 or more days per month) use of marijuana. Significantly higher numbers of youth and young adults said they believe there is a significant health risk associated with smoking marijuana.
- **Hallucinogens.** The number of current abusers of MDMA decreased between 2002 and 2003, from 676,000 (0.3 percent) to 470,000 (0.2 percent). Past-year abuse of Ecstasy declined (from 3.2 million to 2.1 million abusers), as did past-year abuse of LSD (from 1 million to 558,000 abusers) between 2002 and 2003.
- **Prescription Drug Abuse.** An estimated 6.3 million persons (2.7 percent) aged 12 or over engaged in current nonmedical use of psychoactive therapeutic drugs. Of these, 4.7 million abused pain relievers, 1.8 million abused tranquilizers, 1.2 million abused stimulants, and 0.3 million abused sedatives. There was a significant increase in lifetime nonmedical use of pain relievers between 2002 and 2003 among persons aged 12 or older, with young adults (18-25) reporting a 15 percent increase in lifetime and current (past-month) use.

The 2003 survey report is based on interviews concerning use of alcohol, tobacco, and drugs with 67,784 respondents aged 12 and older. Lifetime use is defined as having ever used a substance in one's lifetime. Past-year use is having used the substance at least once in the past 12 months. Current use is use in the past 30 days. The full 2003 NSDUH is available at *http://www.oas.samhsa.gov/nhsda.htm*. NN

New Avenues for Sharing NIDA's Research News

In support of the Institute's mission to lead the Nation in bringing the power of science to bear on drug abuse and addiction, NIDA shares the results of the research it funds in print and on the Web. The new communication products include *NIDA NOTES* collections and science meeting summaries and special reports.

New *NIDA NOTES* Collections

NIDA will soon offer a rich compilation of past *NIDA NOTES* articles on cocaine abuse and addiction. This new collection provides a snapshot of research findings and news that seeks to improve understanding of topics ranging from how cocaine works in the brains of abusers to treatments that offer hope for recovery. Capturing the past 10 years of cocaine research as presented in *NIDA NOTES*, *A Collection of NIDA NOTES Articles That Address Research on Cocaine* is available in print and online. For access to this and other NIDA communication products noted, see "For More Information."

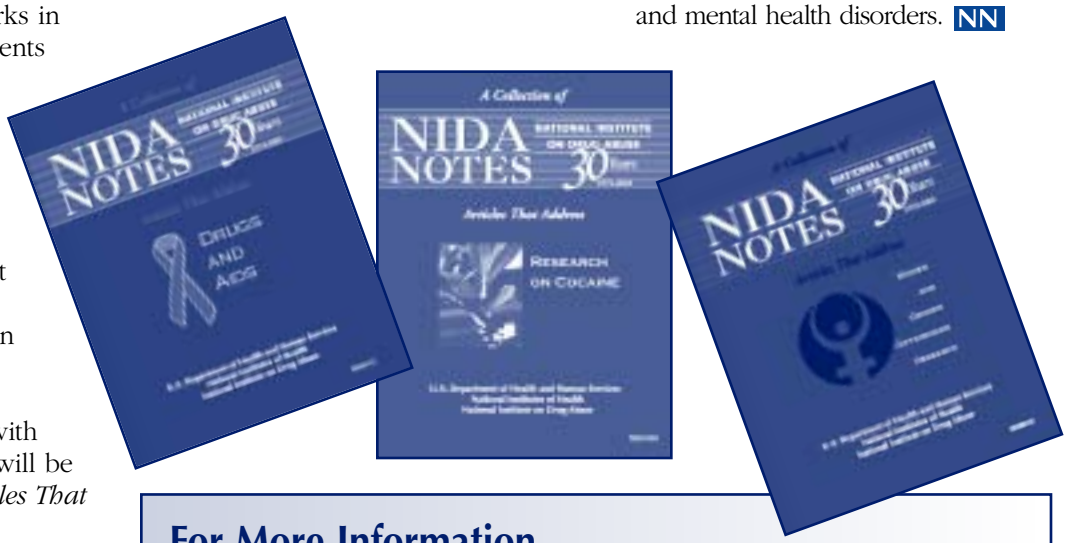
Also rolling off the press with the cocaine articles collection will be revisions of *NIDA NOTES Articles That Address Women and Gender Differences Research* and *NIDA NOTES Articles That Address Drugs and AIDS*. Both collections are highly popular at conferences and other NIDA events and are much requested through the National Clearinghouse for Alcohol and Drug Information (NCADI). These publications join the ranks of equally popular *NIDA NOTES* collections on heroin, nicotine, marijuana, club drugs, prevention, and treatment.

NIDA Science Meeting Summaries and Special Reports

"Advancing Research to Reduce Drug Abuse and HIV/AIDS Disparities: Methodological Considerations" is one of the latest in a new series of meeting summaries and special reports featured on NIDA's Web site. Each document will summarize the major topics discussed at a recent NIDA meeting, provide relevant and engaging graphics, and offer PowerPoint presentations from the meeting.

The new Science Meeting Summaries and Special Reports will offer synopses of key meeting points and PowerPoint presentations from meeting sessions.

NIDA plans to share many online summaries of future meetings. Upcoming meeting topics range from prenatal imaging to co-occurring substance abuse and mental health disorders. NN



For More Information . . .

Materials discussed in this article are just a mouseclick or phone call away.

NIDA NOTES Collections online: go to *www.drugabuse.gov/PubCat/PubsIndex.html* and select "NIDA NOTES." Visitors to this Web page can view and download each collection or use the National Clearinghouse for Alcohol and Drug Information (NCADI) publications number to order a print copy.

NIDA NOTES Collections in print: e-mail (info@health.org) or phone (1-800-729-6686) NCADI to order your print copy of each collection. Please refer to the NCADI publication number when ordering.

NIDA Science Meeting Summaries: visit *www.drugabuse.gov/whatsnew/meetings* for past meeting summaries and special reports.

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Editor: David Anderson, *Public Health Advisor, Public Information and Liaison Branch, Office of Science Policy and Communications*

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Staff Writers: Lori Whitten, Ph.D., and Patrick Zickler, *MasiMax Resources, Inc.*

Contributing Writers: Arnold Mann and Barbara Shine

Design/Layout: Maggie Bray, *MasiMax Resources, Inc.*

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