RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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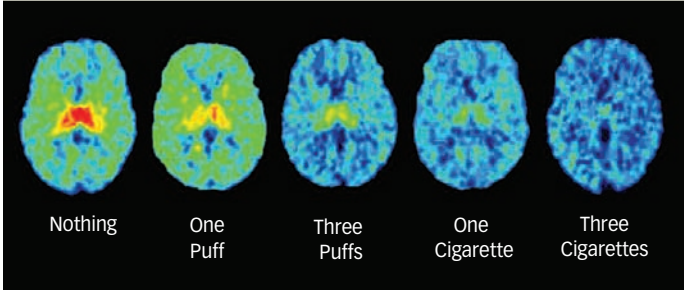
Imaging Studies Elucidate Neurobiology of Cigarette Craving

Researchers observe brain circuit activation, rapid receptor occupation.

BY LORI WHITTEN,
NIDA Notes Staff Writer

One difference between a smoker and an ex-smoker is that the latter has successfully overcome cravings for tobacco. To learn how people achieve this feat, NIDA-funded researcher Dr. Arthur Brody has been looking inside the brains of would-be quitters. His findings, based on three separate imaging studies, indicate that when smokers actively resist cravings, they engage brain areas that focus attention and regulate emotion; that heavy smokers can stave off craving only by keeping virtually all nicotinic receptors in the brain filled; and that nicotine is the only component of cigarette smoke that occupies these receptors.

SMOKING SATURATES RECEPTORS As nicotine from a cigarette attaches to the $\alpha_4\beta_2$*-nACh nicotinic receptors in the brain, it displaces a radiolabeled tracer (red and yellow indicate high levels of the tracer, green indicates intermediate levels, and blue indicates low levels). The nicotine from three puffs displaced 75 percent of the tracer from study participants' receptors, and the nicotine from three cigarettes, nearly all.



PATTERNS OF RESISTANCE

In one study, Dr. Brody and his colleagues at the University of California, Los Angeles charted the changes in cerebral activity that accompanied willful resistance to videotaped smoking cues. One of the changes, intensification of activity in a specific brain area, parallels the effects of bupropion, suggesting that the anti-smoking medication may reinforce cognitive strategies that people naturally implement when they try to quit. Other specific brain activity changes identified in the study may provide leads for developing new medications and behavioral treatments for smokers.

Dr. Brody enlisted 42 men and women from the community at the Greater Los Angeles Veterans Affairs Healthcare System. On the morning of the study, each participant smoked a final cigarette and, 25 minutes later, put on a pair of special goggles to watch short video clips during brain scanning. The clips introduced the viewer to everyday situations—driving, writing a letter, standing outside a building. Two of every three clips also featured images that commonly incite nicotine craving, such as a view of someone taking out a lighter, preparing to light a cigarette, or actually smoking a cigarette. The researchers asked the participant to record the intensity of his or her craving, while

[*Continued on page 11*]

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

New Vaccines Are Being Developed Against Addiction and Relapse

Since the first vaccine, for smallpox, was developed more than 200 years ago, immunization has proven to be a powerful weapon in the fight against infectious disease. Today, NIDA-supported researchers are using modern molecular biology to create vaccines against another deadly disease—addiction to drugs such as cocaine, nicotine, phencyclidine (PCP), and methamphetamine.

Immunization against drugs provides a different sort of protection than do the shots routinely given to prevent measles, hepatitis, and the flu. Those vaccines stimulate the immune system to produce antibodies that destroy or deactivate viruses or bacteria. Anti-drug vaccines also stimulate the immune system to produce antibodies, but these antibodies do not destroy drug molecules. Instead, they attach to drug molecules, forming a compound molecule that is too big to cross the blood-brain barrier easily. By slowing drugs' entry into the brain, the vaccines reduce or prevent the euphoria that promotes addiction. The higher the level of antibodies in the body, the more effective the vaccine in preventing euphoria.

Preliminary research on anti-drug vaccines is encouraging. NicVAX is a nicotine vaccine being developed, with NIDA support, by Nabi Biopharmaceuticals of Rockville, Maryland. In early studies, antibody levels rose with vaccine dose, and smokers receiving the vaccine did not smoke more to compensate for the reduced nicotine levels. In a 12-month trial, 16 percent of the NicVAX recipients quit smoking and remained abstinent, compared with 6 percent of recipients of an inactive substance.

In tests of TA-CD, a cocaine vaccine produced by Bermuda-based Celtic Pharma, investigators found that cocaine-dependent users who received high doses produced more antibodies against the drug than did those who were given less. High-dose recipients were also more likely to abstain from cocaine during the 12-week study.

To counter methamphetamine and PCP, researchers are exploring an approach called passive immunization. Injections of antibodies specifically targeted to these drugs quickly reduced the drug concentrations in the brains of laboratory animals. If this approach proves to be safe and effective for people, it could be a lifesaving treatment for overdose. Periodic antibody injections might also serve as a treatment for addiction to these and other drugs.

As drug vaccines emerge, researchers will need to learn the most effective ways to use them, perhaps combining them with behavioral therapy. Just as protection against infectious illness often requires "booster shots," drug vaccines will probably need to be administered more than once to have a long-term effect. ■

NIDA Notes

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Selenium Shows Promise as an Adjunct Therapy for HIV

Daily selenium supplements could serve as a useful adjunct therapy for HIV infection by holding HIV-1 viral load in check and elevating levels of infection-fighting CD4 cells. A randomized controlled trial, led by Dr. Barry Hurwitz of the University of Miami, included 262 HIV-infected men and women. After 9 months of treatment, greater increases of serum selenium predicted lower HIV viral load and greater CD4 cell count. Notably, of the 141 selenium-treated participants, the 50 whose selenium levels increased by 26.1 µg/L or more displayed no increase in HIV viral load, and their concentrations of CD4 cells increased by 24.2 percent. In contrast, the 121 placebo-treated participants averaged an increase of 20.2 percent in HIV viral load, which researchers consider large enough to affect the course of the disease. The selenium-treatment advantage, which was gained only by participants who took the supplement as scheduled, held when the researchers accounted for factors that affect immune responses, including antiretroviral therapy. No side effects were observed.

> Archives of Internal Medicine 167(2):148–154, 2007.

Brain Proteins Differ in Cocaine-Overdose Victims

Scientists have found differences in protein concentrations in the brain pleasure centers of 10 people who died from cocaine overdose as compared with 10 people who did not abuse the drug. Dr. Scott Hemby and colleagues at Wake Forest University and the University of Miami Schools of Medicine used mass spectrometry to measure more than 1,400 proteins in post-mortem tissue samples from the nucleus accumbens. Levels of roughly 50 proteins were found to be either higher or lower in the cocaine abusers. These proteins participate in basic neurobiological processes such as forming cellular structures, strengthening neuronal connections, sending chemical messages between cells, deriving energy from glucose, and protecting cells from injury. Such information may point scientists toward new insights into the molecular mechanisms and consequences of cocaine addiction.

> Molecular Psychiatry 12(1):55–73, 2007.

Reducing Postpartum Drug Use

In a recent clinical trial, a 20-minute computerized intervention reduced new mothers' drug abuse in the first 4 months postpartum. The computer software program, which was developed by Dr. Steven J. Ondersma and colleagues at Wayne State University in Detroit and Virginia Commonwealth University in Richmond, was administered in an urban obstetric hospital soon after each woman gave birth. The program features an animated narrator who asks questions, addresses ambivalence, provides feedback, and offers options. The intervention also included vouchers for an initial session of drug treatment and an easy-to-read brochure,

mailed to the women after they took their babies home, that discussed infant and maternal health and briefly addressed drug abuse. The researchers estimated that the intervention had a "small to moderate" beneficial effect in their study population—107 mostly poor women who abused drugs. At a 4-month followup, those who received the intervention reported using cocaine, amphetamine, and opiates less frequently than before the birth, while the comparison group reported slightly increased abuse of these drugs. No definitive differences were observed between the two groups regarding marijuana use.

> American Journal of Preventive Medicine 32(3):231–238, 2007.

Lofexidine May Enhance Naltrexone Efficacy

The anti-hypertensive medication lofexidine is used commonly in the United Kingdom and less often in the United States to alleviate symptoms of opiate withdrawal. Now, a pilot study by Dr. Rajita Sinha and colleagues at Yale University School of Medicine suggests that lofexidine can enhance success rates among patients taking maintenance naltrexone to avoid relapse to opioids. The researchers stabilized 18 opioid-detoxified men and women on naltrexone (50 mg) and lofexidine (2.4 mg) daily for 1 month. They then retained all the patients on naltrexone for 4 more weeks, but kept 8 on lofexidine and gave 10 others identical-looking pills containing lofexidine doses that—unbeknownst to the patients—tapered to zero over several days. Of the 13 patients who completed the study, 80 percent of those who continued to receive combination therapy submitted opiate-free urine samples throughout the 4-week period, compared with 25 percent of those tapered to placebo. A followup laboratory session that exposed 10 of the patients to stressful and opiate-related stimuli showed that lofexidine—but not placebo—reduced the patients' reaction to stress, stress-induced opiate craving, and negative emotions (such as anger), all of which can trigger relapse.

> Psychopharmacology 190(4):569–574, 2007.

Aripiprazole Prevents Rats From Resuming Cocaine Seeking

A medication prescribed for schizophrenia and manic phases of bipolar disorder shows promise as a cocaine addiction treatment.

BY LORI WHITTEN,
NIDA Notes Staff Writer

The antipsychotic medication aripiprazole appears to reduce cocaine craving in small studies of addicted individuals with schizophrenia and bipolar disorder. A recent NIDA-funded experiment suggests that aripiprazole may help not only those very-difficult-to-treat individuals, but others as well, to maintain abstinence from the stimulant.

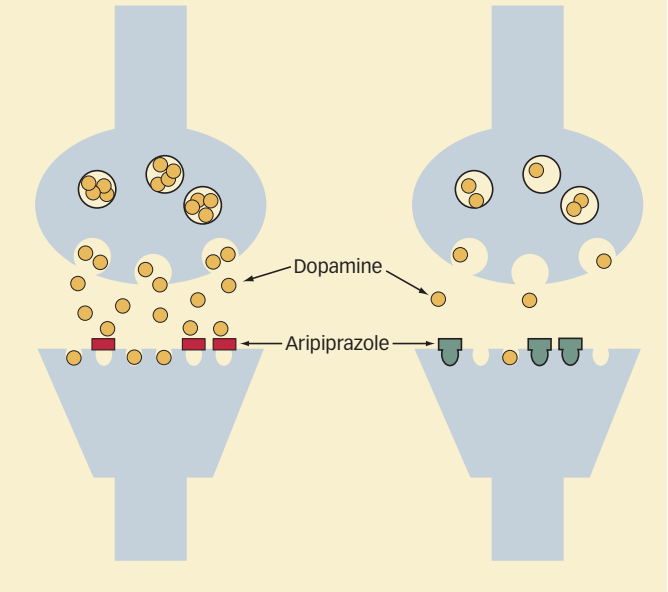
Drs. Ronald See and Matthew Feltenstein of the Medical University of South Carolina found that rats treated with aripiprazole were less likely than untreated rats to resume cocaine self-administration after a period of abstinence. The finding indicates that the medication reduces cocaine seeking directly rather than as a byproduct of altering psychotic symptoms or processes. Therefore, the researchers speculate, cocaine abusers who do not have concurrent psychotic illness may also benefit from aripiprazole.

INDIFFERENCE TO COCAINE WITH FEW SIDE EFFECTS

The researchers subjected rats to a protocol that simulates drug use, followed by the establishment of stable abstinence, and finally a test of the animals' vulnerability to relapse. Animals that are vulnerable respond to a relapse trigger—a cocaine-associated cue or a priming dose of the drug—by pressing a lever they previously used to self-administer the drug. The more vulnerable an animal is, the more often it will press the lever.

Rats given the lowest effective dose of aripiprazole (0.25 mg/kg) before the priming dose of cocaine pressed the lever associated with cocaine 50 percent as often as control rats did. The greater the dose of aripiprazole, the less the rats responded to the relapse triggers. For example, after the drug trigger, rats given the highest dose of aripiprazole (15 mg/kg) pressed the lever associated with cocaine only 9 percent as often as the rats receiving no aripiprazole.

ARIPIPRAZOLE ALLEVIATES DOPAMINE IMBALANCE THAT PROMOTES RELAPSE According to researchers, cocaine relapse may be fostered by high dopamine concentrations in the nucleus accumbens, one of the brain's reward centers, and low concentrations in the prefrontal cortex. Aripiprazole simultaneously blocks dopamine receptors (left) in brain regions with high concentrations of the neurochemical and stimulates receptors (right) in regions where concentrations are low.



To rule out the possibility that aripiprazole reduced the rats' cocaine seeking through general effects—such as sedation or lethargy—that would be undesirable in a medication, the investigators conducted further trials that showed:

- *Aripiprazole does not sedate animals to the point where they are too tired to approach and press levers for rewards.* During the protocol that mimicked relapse, the lowest medication doses that attenuated lever pressing did not suppress locomotor activity. Higher doses (1 mg/kg and 5 mg/kg) reduced spontaneous and cocaine-induced locomotor activity only modestly. Furthermore, while aripiprazole-treated rats pressed the drug-linked lever less often, they continued to press another lever, which delivered nothing at all, as often as before.
- *Aripiprazole does not make rats indifferent to rewards from all activities, including natural, healthy ones.* Aripiprazole did not reduce the enthusiasm with which rats pressed levers to obtain food, so it did not seem to blunt their natural pleasure responses. In addition, when the researchers put animals through a protocol that simulates ongoing drug use,

rather than recovery from an addiction, the animals pressed levers to obtain cocaine infusions just as avidly after receiving aripiprazole as after saline. This result indicates that while the medication may help individuals maintain abstinence, it is unlikely to diminish ongoing binge cocaine abuse.

"Aripiprazole's minimal effect on rats' motor activity and other behaviors is consistent with its good safety profile and general acceptance among patients as a psychiatric medication," says Dr. See. "We find it encouraging that low doses block drug seeking and seem to have no other discernible effects on the animals. Taken together, our findings suggest that aripiprazole may selectively reduce drug-seeking behavior and is a promising candidate medication for preventing cocaine relapse."

A SELECTIVE STABILIZER

Dr. See and colleagues focused on aripiprazole for practical reasons: It is generally safe, it is already on the market, and its pharmacological action suggests the potential to reduce relapse. Aripiprazole preferentially binds to dopamine receptors D_2 and D_3, which are proteins on brain cell surfaces that mediate dopamine's effects on cellular activity. The drug has different effects, depending on the amount of dopamine present. The overall effect is neurochemical modulation: Aripiprazole quiets hyperactive neurons and stimulates sluggish ones through both presynaptic and postsynaptic mechanisms, according to Dr. See. Such stabilization seems to account for the efficacy of aripiprazole as a psychiatric medication and may also underlie its benefit as a relapse-prevention agent.

"As a neurochemical stabilizer, aripiprazole most likely reduces excess dopamine activity in the mesolimbic reward circuit brought about by drug abuse," says Dr. See. "The medication also may simultaneously boost dopamine in the cortex, particularly the prefrontal circuits, thereby enhancing the ability to suppress the desire for drugs." Although aripiprazole also acts at serotonin receptors, pharmacologists currently consider dopamine stabilization to be its main therapeutic action.

To evaluate the full extent of aripiprazole's promise, it must still be determined whether the medication could be used to treat addiction to other psychostimulants besides cocaine, notes Dr. Cora Lee Wetherington of NIDA's Division of Basic Neuroscience and Behavioral Research. Dr. See notes that his team plans to perform animal tests of the drug's effect on methamphetamine.

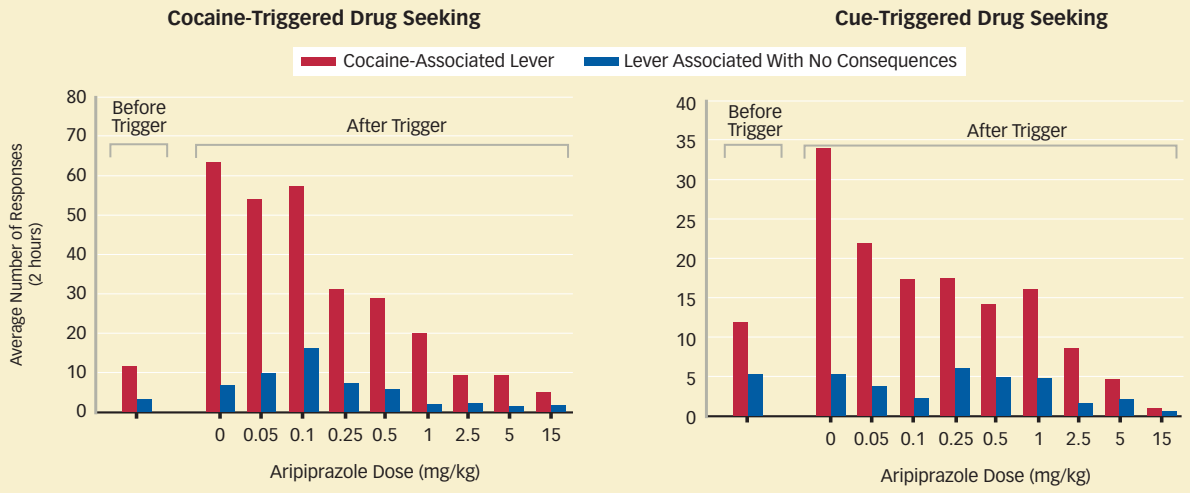
With regard to cocaine, Dr. Wetherington says, "the results of Dr. See's animal study suggest that aripiprazole may help prevent relapse in cocaine abusers both with and without psychiatric conditions. The work lays the groundwork for future clinical research."

Says Dr. See, "We hope to use brain imaging to examine aripiprazole's effects on cocaine abusers' responses to drug cues—to find out whether it dampens brain activity related to such cues. If so, that would also support the idea that the medication helps prevent relapse." ■

SOURCE

Feltenstein, M.W., Altar, C.A., and See, R.E. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. *Biological Psychiatry* 61(5):582-590, 2007.

ARIPIPRAZOLE ATTENUATES RETURN TO COCAINE SEEKING To induce renewed drug seeking, rats were given either a small amount of cocaine or a cue of a light and sound they had previously learned to associate with the drug. The higher the dose of aripiprazole a rat received, the less often it pressed a lever that had delivered cocaine during training. Each test group contained 11 to 15 animals.



Long-Term Cocaine Self-Administration Depresses Brain Activity

Neural activity of monkeys diminishes in regions linked with cognition and emotion.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Chronic exposure to cocaine depresses neural activity. Initially, the effect shows up mostly in the brain's reward areas. With longer exposure, however, neural depression spreads to circuits that form cognitive and emotional memories and associations, according to NIDA-funded research by Drs. Thomas J.R. Beveridge and Linda J. Porrino and colleagues at the Wake Forest University School of Medicine.

WIDER EFFECTS WITH LONGER EXPOSURE

The researchers trained 14 male monkeys to press a lever for a reward. Six monkeys received banana-flavored food morsels, and eight received an infusion of cocaine (either 0.03 mg/kg or 0.3 mg/kg). Each monkey received up to 30 portions of food or infusions of cocaine daily for either 5 or 100 days. The 100-day trial, much longer than most other studies of drug use in primates, closely mimicked chronic cocaine abuse among people. For monkeys in the high-dose group, each session ended when they self-administered a dose equivalent to a person taking roughly 0.5-1.0 grams of cocaine per day. The researchers estimate that their experiment models a person heavily abusing cocaine daily for roughly 1 year.

After each monkey's final session, Dr. Porrino's team mapped its rate of cerebral glucose metabolism—the primary indicator of cerebral energy expenditure. The researchers injected a radiolabeled form of glucose (2-[^{14}C]deoxyglucose; 2-DG) and, using autoradiography, obtained images that showed how much fuel different brain areas were utilizing (see image). Greater glucose metabolism indicates greater neural activity.

All the monkeys that had self-administered cocaine showed some localized depression of glucose metabolism. In the monkeys that self-administered cocaine daily for just 5 days, neural depression was largely restricted to pleasure and motivation areas, especially the reward circuit and areas that process expectations of rewards.

In the 100-day test, animals that had received the high dose of the drug revealed less neural activity in 40 of the 77 brain regions analyzed as compared with animals that had received only food morsels (see table, page 13). The high-dose monkeys incurred a 16 percent drop, on average, in overall cerebral glucose metabolism. The low dose of cocaine depressed metabolism in 14 of the regions, but not overall.

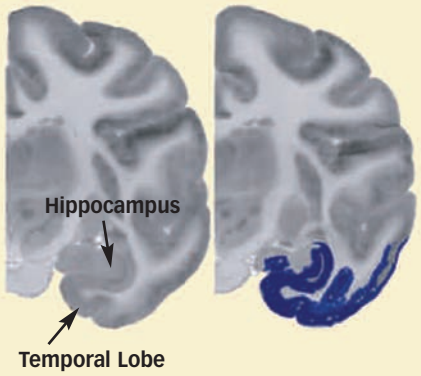
The tests suggest that with longer exposure to cocaine, reductions in neural activity expand within and beyond the pleasure and motivation centers, says Dr. Porrino. "Within the structure called the striatum, the blunting of activity spreads from the nucleus accumbens, a reward area, to the caudate-putamen, which controls behavior based on repetitive action," she says. Long-term cocaine use also depressed memory and information-processing areas.

The findings accord well with those of human imaging studies, which have found general depression in cerebral blood flow among chronic cocaine abusers compared with nonabusers. By using animals, however, Dr. Porrino eliminated two sources of uncertainty in those clinical studies: differences in metabolic rates that may have predated cocaine abuse and abuse of drugs other than cocaine. "My team can directly attribute to cocaine the depressed brain metabolism observed in the study," says Dr. Porrino.

"Our 100-day experimental protocol for rhesus monkeys gives a good picture of what might happen in the brains of cocaine abusers," she says. "Some addiction researchers believe that the shift in activity within the striatum may, in part, underlie the progression from voluntary drug taking to addiction. Moreover, human imaging research has linked drug craving with the amygdala and insula, temporal lobe areas depressed by cocaine in our study."

[*Continued on page 13*]

LONG-TERM COCAINE EXPOSURE BLUNTS TEMPORAL LOBE AREAS IN MONKEYS Blue coloring in these images represents areas of the temporal lobe that are less active after cocaine self-administration than after food self-administration. After 5 days of cocaine self-administration (left image), a monkey still shows normal activity in the temporal lobe area. In contrast, a monkey that self-administered cocaine for 100 days (right image) demonstrates lowered activity.



Methadone Reduces Rats' Cocaine Seeking

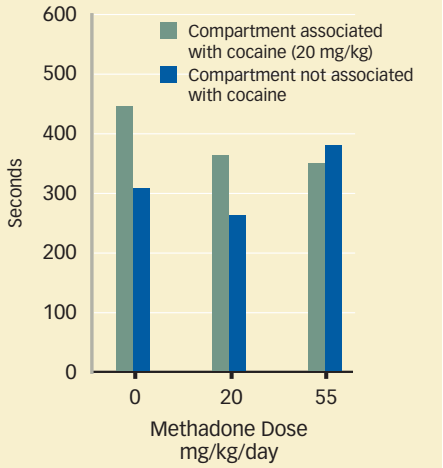
Continuously administered, high-dose methadone undermined animals' motivation to acquire cocaine.

BY NIDA NOTES STAFF

Methadone may prove to be an effective treatment for cocaine as well as opioid abuse, if the results of a recent study with rats, funded by NIDA and the Canadian Institutes of Health Research, can be replicated and applied to people. The animals' cocaine seeking dropped in response to methadone given in doses that produce blood levels equivalent to those therapeutically effective for opioid addiction. Methadone at more than twice that dose abolished cocaine seeking.

"Methadone is the primary drug used to treat opiate dependence worldwide, yet there is still so much to find out about it," says Dr. Francesco Leri of the University of Guelph in Ontario, Canada. "My colleagues and I are exploring the effects of maintaining relatively stable doses of methadone over time in rats to discover all of the benefits and properties of this valuable medication."

COCAINE SEEKING DIMINISHED
In the absence of methadone, each rat in a group of eight spent, on average, more time in a compartment that it associated with cocaine than in one not associated with the drug. When implanted mini-pumps delivered high-dose methadone to the rats, there was no significant difference between the times spent in the two compartments.



EXTINGUISHING RATS' MOTIVATION

Clinical trials have shown that people who take high-dose methadone for heroin addiction and who are also addicted to cocaine decrease their abuse of both drugs. To Dr. Leri, that observation suggested that methadone might have unexploited potential as a medication to treat cocaine abuse in patients both with and without histories of opioid abuse. Accordingly, with colleagues at Concordia University in Montreal and Rockefeller University in New York, Dr. Leri set out to better understand methadone's effect on cocaine seeking.

The team first tested whether methadone would suppress the normal tendency of rats to seek cocaine once they have been repeatedly exposed to the stimulant. To prepare their animals for the test, the researchers put some on methadone (20 or 55 mg/kg/day) via implanted mini-pumps and gave others saline by the same route. During these regimens, for 2 weeks, the researchers trained the animals to associate one designated chamber with cocaine injections and another with saline injections. Daily for 3 days, they injected each animal once with cocaine (1, 5, or 20 mg/kg) and once with saline. Immediately after each cocaine injection, they placed the animal in the first chamber; after each saline injection, they placed it in the second chamber.

On the day of the test, the researchers placed each rat between the two chambers without giving it any cocaine or saline, and monitored where it went. Among the animals given the highest dose of cocaine, those that received no methadone showed a strong preference for the cocaine-associated chamber; those that received the lower methadone dose showed less preference; and those maintained on the higher methadone dose, no preference at all, indicating a total loss of motivation to seek cocaine (see graph at left).

"Overall, our results support the usefulness of high-dose methadone as a pharmacological tool to reduce severe cocaine abuse in opioid-dependent individuals."
–Dr. Francesco Leri

Another experiment by Dr. Leri's team assessed methadone's impact on cocaine seeking by measuring how hard rats will work to obtain the drug intravenously. They first trained rats to press a lever for cocaine, then implanted mini-pumps: Eight animals received 30 mg/kg/day of methadone, while another six received only saline. The rats were allowed to self-administer cocaine, but the system was programmed to require progressively more presses before it would release each

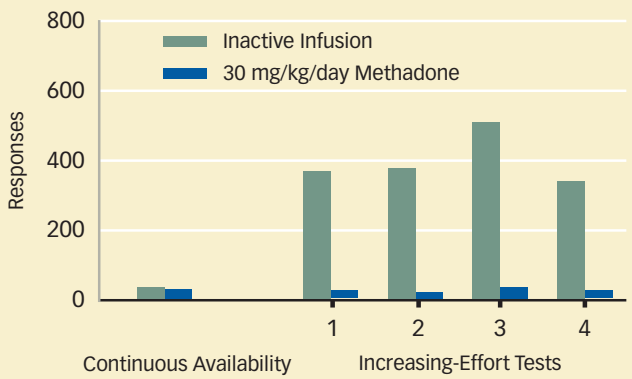
successive infusion. The eight methadone-treated animals gave up pressing the cocaine lever after six presses, on average, whereas the rats that did not receive methadone continued to press it more than 30 times to receive a single dose (see graph at right).

Some scientists have suggested that methadone-induced sluggishness saps individuals' initiative to seek cocaine. But Dr. Leri asserts that other behavioral tests by his team rule out this explanation. For example, methadone did not alter the animals' general activity, food consumption, or response to heat-generated pain.

"Overall, our results support the usefulness of high-dose methadone as a pharmacological tool to reduce severe cocaine abuse in opioid-dependent individuals and possibly in the management of addiction to only cocaine," Dr. Leri says.

Although the study found high-dose methadone to be effective in this regard, the highest doses of methadone tested in rats produced blood concentrations of the drug more than twice as high as those achieved in people undergoing standard methadone therapy. "To determine whether higher levels of methadone can be efficacious without producing adverse effects, we need clinical research on doses that are higher than customarily used in drug abusers," says Dr. Nancy Pilotte, of NIDA's Division of Basic Neuroscience and Behavioral Research.

RATS RECEIVING METHADONE EXPEND LITTLE EFFORT TO GAIN COCAINE When rats were required to respond with more and more lever presses to receive cocaine, the six animals infused with an inactive substance dramatically increased their average number of responses, while the eight animals infused with methadone kept their responses at the same level as their earlier responses to continuously available cocaine.



BRAIN CORRELATES

Methadone helps heroin abusers abstain from opioids by partially stimulating the brain's mu-opioid receptors, an effect that keeps the symptoms of withdrawal at bay and also blocks the rewarding effects of other opioids. But it is not clear how methadone suppresses cocaine seeking. Methadone does not, for example, directly interact with the dopamine transporter, the brain protein that is primarily responsible for the cocaine high.

Dr. Leri suspects that the mu-opioid receptor, which is the site where methadone exerts its primary activity against opioid addiction, also plays a role in the medication's potentially therapeutic effect on cocaine addiction. In support of this idea, he and collaborators at Rockefeller University in New York City showed that cocaine increases production of the mu-opioid receptor in the nucleus accumbens, a key brain area involved in reward and addiction. Methadone, they also found, counteracts these increases.

In the experiments, rats exposed to three injections of 5 or 20 mg/kg doses of cocaine were found to have more mu-opioid receptor messenger RNA (mRNA)—an indicator of receptor production rates—than animals exposed to three injected doses of the drug at 1 mg/kg. These elevations were less pronounced, however, in rats that were being maintained on 20 mg/day of methadone at the time of the cocaine exposures. Moreover, rats exposed to cocaine while being maintained on 55 mg/kg/day of methadone had mu opioid mRNA levels that were indistinguishable from those of rats that received no cocaine.

From these results, the researchers hypothesize that methadone probably blocks cocaine seeking by inhibiting cocaine-induced enhancement of mu-opioid receptor production. Other explanations may be possible, however, as enhancing receptor production is not methadone's only effect on brain chemistry. Among its other influences, it boosts the body's natural opioids, the endorphins. Dr. Mary Jeanne Kreek of Rockefeller University says, "We wonder whether people who are dependent on both heroin and cocaine respond well to methadone because methadone reduces the number of mu-opioid receptors in the reward system of their brains or whether they respond because cocaine depletes endorphins and methadone brings the endorphins back."

"Methadone and the mu-opioid antagonist, naltrexone, which blocks the mu receptor and its associated responses, can both be considered as treatments for cocaine abuse, as both decrease the availability of the mu-opiate receptor," says Dr. Pilotte. "Methadone may even be the better treatment as it does not force the client into an uncomfortable state of withdrawal as it decreases the incentive to take cocaine." ■

SOURCES

Leri, F., et al. High-dose methadone maintenance in rats: Effects on cocaine self-administration and behavioral side effects. *Neuropsychopharmacology* 32(11):2290-2300, 2007.

Leri, F., et al. Effects of high-dose methadone maintenance on cocaine place conditioning, cocaine self-administration, and mu-opioid receptor mRNA expression in the rat brain. *Neuropsychopharmacology* 31(7):1462-1474, 2006.

High-Risk Drug Offenders Do Better With Close Judicial Supervision

But frequency of drug court attendance does not affect treatment outcomes for people at low risk of relapse.

BY NIDA NOTES STAFF

Adjusting the frequency of mandatory drug court monitoring sessions according to offenders' risk of lapsing into criminal activity, including drug abuse, can enhance program success rates while conserving resources, according to a recent NIDA-supported study. Researchers found that high-risk drug offenders—those with antisocial personality disorder or prior histories of drug abuse treatment—achieved better outcomes when ordered to attend a judicial status hearing every 2 weeks, rather than at the 4- to 6-week intervals that drug courts typically impose. In contrast, lower risk offenders' treatment success was not compromised when courts required them to appear only if they committed serious or repeated infractions of program rules.

"Our research represents a first step in tailoring adaptive supervision interventions to drug-abusing offenders," says Dr. Douglas Marlowe of the Treatment Research Institute and the University of Pennsylvania, Philadelphia. Dr. Marlowe, Dr. David Festinger, and colleagues conducted the study as part of a broader effort to improve the efficacy and cost-effectiveness of drug court interventions by identifying which components of the model work best for various groups of drug offenders.

CUSTOM TAILORING COURT SUPERVISION

Drug courts are intensive, community-based programs that substitute judicially supervised treatment and case management for prosecution or incarceration. Defendants who complete the drug court program and remain arrest-free for 6 months after graduation have their charges dropped and their arrest records expunged. The judicial status hearing, during which a judge rewards achievements and punishes infractions with sanctions that progressively increase in severity, is among the costliest components of drug court programs.

MORE-FREQUENT COURT APPEARANCES IMPROVE OUTCOMES FOR HIGH-RISK OFFENDERS

	HIGH RISK*		LOW RISK	
	Biweekly Schedule	Standard Schedule	Standard Schedule	As Needed**
Rate of Graduation from Treatment Program	75%	56%	75%	72%
Average Days of Drug Use in Past 30 Days	8.00	9.51	3.50	4.32
Average Days of Alcohol Intoxication in Past 30 Days	1.40	2.67	2.02	1.30

Graduation rate assessed 12 months after beginning of treatment program; other data collected at 6-month followup.

*Participants were considered high-risk if they had antisocial personality disorder or previous treatment for drug addiction.

**Only scheduled to address serious or repeated infractions of treatment rules.

Drs. Marlowe and Festinger designed their study to answer two questions: Would high-risk drug offenders benefit from hearings held more frequently than usual, and would low-risk drug offenders still experience treatment gains if their hearings were held less often than the norm? The researchers had reason to predict the answers would be "yes" to both questions because of observations they had made in a previous study. That study's design and small participant population, however, had not allowed definitive findings on these issues.

Participants in the new study were recruited from a misdemeanor drug court in Wilmington, Delaware. Among the drugs that they reported abusing at the time of their assignment to drug court, cannabis was the most common, followed by alcohol, stimulants or cocaine, opiates, sedatives, and hallucinogens. Each participant was assigned to a clinical case manager who coordinated treatment referrals, submitted monthly reports to the judge, and appeared at the participant's judicial status hearings.

Ninety-two of the 279 participants were classified as high-risk because they had an antisocial personality disorder or had relapsed after previous treatment for drug abuse. Within the high-risk group, 42 were assigned to report to drug court biweekly, and 50 reported every 4 to 6 weeks. In the low-risk group, 92 were put on the 4- to 6-week schedule, and 95 were told to appear in court only after serious rule infringements—most commonly failure to attend counseling appointments or provide drug-free urine specimens.

Within a year, 75 percent of the high-risk participants who attended hearings every 2

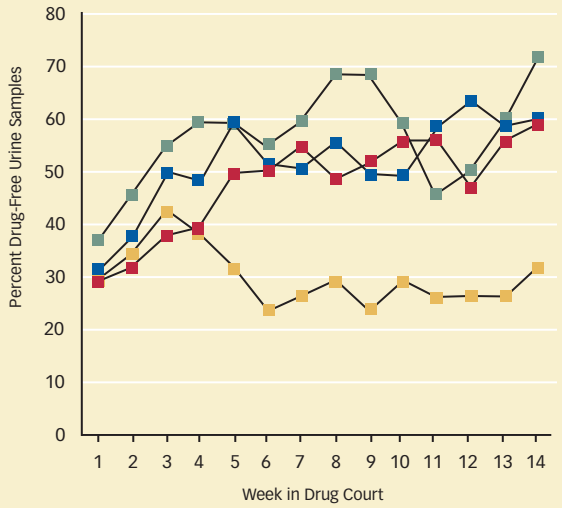
weeks graduated from the program, compared with 56 percent of high-risk participants assigned to follow the standard schedule. The former group also provided more drug-free urine samples and reported less alcohol intoxication (see table, page 9), as well as less criminal activity.

Among the low-risk participants, outcomes were similar regardless of how often hearings took place. For example, program graduation rates were 75 percent among the offenders who appeared in drug court every 4 to 6 weeks and 72 percent among those who appeared in court only when a problem arose, averaging less than two hearings during the study year. "Reducing the number of court hearings for these individuals could permit a program to conserve costly resources without sacrificing client outcomes or public safety," Dr. Marlowe says.

ROOM FOR IMPROVEMENT

"Adjusting the frequency of court hearings to participants' risk status will make a difference, but there still will be considerable room for improvement in drug court outcomes," Dr. Marlowe notes. For high-risk participants who continue to have drug or alcohol problems, the program needs further tailoring, he explains. Those who are not compliant with the program—for example, those who fail to attend counseling sessions or to deliver urine specimens—might respond to more frequent judicial supervision or to sanctions such as home curfews. In contrast, increasing the scope of treatment services might be more effective with high-risk participants who are compliant with program rules but fail to achieve abstinence because of the severity of their drug addiction or a related difficulty, such as a co-occurring mental disorder, family problems, unemployment, or homelessness. Dr. Marlowe notes that even low-risk drug offenders need more effective interventions.

DRUG COURT FREQUENCY CAN AFFECT TREATMENT OUTCOME Participants who were considered high-risk provided more drug-free urine samples when they were required to appear in drug court every 2 weeks (gray-green) rather than according to the standard schedule of every 4 to 6 weeks (gold). In contrast, participants who were at lower risk of relapse did comparably well on the standard schedule (blue) and when court appearances were scheduled only in response to treatment-rule infractions (red).



SOURCE: Marlowe, D.B., et al. Matching judicial supervision to clients' risk status in drug court. *Crime & Delinquency* 52, 52–76, 2006.

"Dr. Marlowe is helping us fill our knowledge gap about drug courts by identifying the elements that make them effective," says Dr. Redonna K. Chandler, chief of NIDA's Services Research Branch. "We may eventually be able to match criminal justice supervision and treatment services to the needs of individual offenders, making drug courts both more effective and more cost-effective."

Dr. Marlowe says, "We hope that drug court programs eventually become flexible enough to allow participants doing poorly to be switched to a more intensive track and allow those doing well in an intensive program to move to a lower supervision regimen." ■

SOURCE

Marlowe, D.B., et al. Adapting judicial supervision to the risk level of drug offenders: Discharge and 6-month outcomes from a prospective matching study. *Drug and Alcohol Dependence* 88(Suppl. 2):S4-13, 2007.

Drug Courts Add Value

Studies have shown that drug courts significantly increase the time drug abusers stay in treatment. An average of 60 percent of drug court clients complete at least 12 months of treatment, whereas only 10 percent of probationers and parolees typically remain for a year in community-based drug treatment programs, says Dr. Douglas Marlowe of the University of Pennsylvania, summarizing several research reports. A 1998 review of 13 drug court studies found that drug court clients abuse substances less frequently than comparable probationers (10 percent of urine tests were positive, compared with 31 percent). What's more, drug courts reduce re-arrest rates by 8 to 24 percent, according to five meta-analyses in 2005 and 2006. Although drug courts tend to be more expensive than other programs, the reduction in recidivism decreases later judicial costs and financial loss to crime victims, according to a U.S. Government Accountability Office report published in 2005.* It cited net predicted benefits of $1,000 to $15,000 per participant.

**Adult Drug Court: Evidence Indicates Recidivism Reduction and Mixed Results for Other Outcomes*, GAO-05-219, February 2005.

IMAGING STUDIES

[*Continued from page 1*]

either passively experiencing it or actively resisting it. The participants said that they usually resisted smoking cues by trying to distract themselves or ignore thoughts of smoking.

In the absence of smoking cues, the participants reported an average craving intensity of 2.4 out of a possible 5. The intensity rose to 3.0 when they saw a smoking cue. The intensity of the craving was similar whether or not the participants resisted the urge to smoke.

The researchers collected functional magnetic resonance images (fMRI) of the participants' brains while they were watching the videos. During efforts to resist smoking, activity increased in the dorsal anterior cingulate cortex (DACC) region, which participates in focusing attention and controlling emotions, as well as decisionmaking and planning, conflict avoidance, and error detection. Dr. Brody suggests that this DACC activation may reflect the participants' struggles to direct their attention away from cigarettes. Other researchers have noted intensified DACC activity when individuals employ specific trains of thought to try to control their emotional responses to anxiety-provoking stimuli. Engaging this area repeatedly may strengthen the neural circuit and bolster smokers' ability to resist cigarettes.

Dr. Brody and colleagues were intrigued by other changes in brain activity that occurred when their study participants resisted smoking cues. Among these were increased activity in the posterior cingulate cortex (PCC), which processes emotions and related sensory information, and in the precuneus, which has been related to consciousness of self.

Simultaneously, the team observed decreased activity in the lateral occipital and right postcentral gyri (LOG and RPG); the LOG deals with visual input and the RPG modulates movement. Changes in these areas had not been previously observed in the context of smoking cessation and so may provide new clues to the cognitive and emotional dynamics that accompany that effort.

Taken together, these findings suggest that actively resisting the urge to smoke involves a redistribution of neural activity from sensory and motor areas of the brain to those that mediate rewards and emotions.

SMOKING'S DRAMATIC EFFECTS ON RECEPTORS

In another study that underscores the challenge of quitting, Dr. Brody's team charted relationships between smoking, craving, and nicotinic receptors. They found that heavy smokers crave nicotine whenever the drug occupies less than 95 percent of the most common nicotinic receptors, the $\alpha_4\beta_2$*-nACh subset, in the brain. Smoking just a few puffs goes a long way toward saturating these receptors, which are the primary sites where nicotine attaches to brain neurons and exerts its psychoactive and physiological effects.

Although scientists have known that stimulation of these receptors underlies nicotine addiction, newly developed radiotracers have helped them measure receptor occupancy much more accurately and connect it to craving and other symptoms of withdrawal.

The 11 volunteers who took part in this study had smoked for 18 years, on average, and were currently smoking a pack a day. On the day of the study, following 2 days of abstinence, the participants smoked and reported their intensity of craving as the researchers used positron emission tomography (PET) imaging to observe $\alpha_4\beta_2$*-nACh receptors.

The images revealed that smoking occupied $\alpha_4\beta_2$*-nACh receptors throughout the brain with striking completeness, and for several hours. After the first puff, nicotine occupied one-third of the receptors; after the third puff, 75 percent; and after a full cigarette, 88 percent. As receptor occupancy increased, the participants' craving decreased, until—generally after 2.5 to 3 cigarettes—they achieved complete relief at about 95 percent occupancy.

"Our findings show how many receptors are taken up by nicotine," says Dr. Brody. "My colleagues and I were surprised that just one puff started to fill the receptors so substantially."

The team's findings suggest that some of the behaviors that characterize nicotine addiction may be explained by smokers' need to maintain receptor saturation. "Many smokers say they must have a cigarette to get their day going, which makes sense because receptor occupancy would be quite low after waking," says Dr. Brody.

Although near saturation of nicotinic receptors relieves craving, nicotine-dependent people smoke beyond this point. Moreover, Dr. Brody notes that "blood levels of nicotine that accompany replacement therapies, such as the patch or gum, would likely saturate the receptors, yet only 20 to 25 percent of smokers on this treatment stay abstinent for a year." These observations suggest that other factors also drive smoking.

EVIDENCE OF OTHER FACTORS

To separate the impact of nicotine from other aspects of smoking—including the more than 4,000 chemicals other than nicotine in cigarette smoke—Dr. Brody and colleagues conducted a third study. The investigators followed a procedure that paralleled the one they had used to track the impact of smoking on $\alpha_4\beta_2$*-nACh receptors. Again, they charted the relationships between smoking, craving, and nicotinic receptors—this time in response to cigarettes with only a trace amount of nicotine.

The 15 volunteers who took part in this study had smoked for 14 years and were cur-

rently smoking 19 cigarettes a day, on average. In two sessions, each after 2 days of abstinence and separated by at least a week, they participated in PET imaging scans and reported their intensity of craving. On one study day, the participants smoked a denicotinized cigarette. On the other study day, seven participants did not smoke, and eight smoked a low-nicotine cigarette.

The images revealed that smoking a denicotinized cigarette, which contains only about 4 percent of the nicotine in a regular cigarette, resulted in a 26 percent occupancy of nicotinic receptors, compared with 79 percent after a low-nicotine cigarette (half the nicotine content of a regular cigarette), and no occupancy among those not given any cigarette. The 26 percent occupancy by smoking a denicotinized cigarette was predicted based on the amount of nicotine present.

This study demonstrates that of all the chemicals found in cigarette smoke, nicotine is responsible for virtually all $\alpha_4\beta_2$*-nACh receptor occupation, the researchers note. These findings also demonstrate that smoking a cigarette with only a trace amount of nicotine leads to substantial receptor occupancy in the brain.

Although smoking a denicotinized cigarette had a smaller impact on nicotinic receptors compared with the effects of a low-nicotine or regular cigarette, it did lessen craving. Before they smoked, the participants reported an average craving intensity of about 5 (on a scale of 0 to 6); these reports fell to 3.6 and 2.4 for those smoking a denicotinized and low-nicotine cigarette, respectively. This accords well with findings of prior studies indicating that denicotinized cigarettes reduce the urge to smoke. The taste, smell, and feel of cigarette smoke in the mouth contribute to smoking's appeal, Dr. Brody says, and denicotinized cigarettes do provide these sensory experiences. Additional factors, such as stress and the perceived pleasure of smoking, also may play a role.

These findings elucidate why it is so difficult to give up cigarettes, according to Dr. Brody. "The many effects of smoking, including elevated mood and alleviation of anxiety, suggest that a long-term smoker may face considerable biochemical, cognitive, and emotional readjustments when he or she quits," says Dr. Brody.

Dr. Ro Nemeth of NIDA's Division of Clinical Neuroscience and Behavioral Research adds that inhalation is the fastest way for any drug to reach the brain. "The connection between a puff on a cigarette and the positive feelings it quickly generates helps maintain smoking, even when people know its negative consequences and want to quit," Dr. Nemeth says. ■

SOURCES

Brody, A.L., et al. Brain nicotinic acetylcholine receptor occupancy: Effect of smoking a denicotinized cigarette. *International Journal of Neuropsychopharmacology*, published online 2008.

Brody A.L., et al. Neural substrates of resisting craving during cigarette cue exposure. *Biological Psychiatry* 62(6):642-651, 2007.

Brody, A.L., et al. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. *Archives of General Psychiatry* 63(8): 907-915, 2006.

[*Continued from page 6*]

COCAINE SELF-ADMINISTERED BY MONKEYS FOR 100 DAYS DEPRESSES NEURAL ACTIVITY IN SPECIFIC BRAIN AREAS.

Name of area	Selected roles in behavior	Depression of metabolic activity* (percentage)
Nucleus accumbens (ventral striatum)	Processes reward and motivation	16–31
Caudate-putamen (dorsal striatum)	Controls behaviors based on repetitive action	10–23
Hypothalamus	Controls eating, fighting, mating, and sleep	18–22
Insula	Translates body signals into subjective feelings	17–19
Hippocampus	Consolidates memories and influences mood	15–23
Amygdala	Forms emotional and motivational memories, e.g., linking a cue and a drug to produce craving	13–19
Temporal cortex areas	Process emotional and cognitive information, e.g., recognition and short-term memory	17–22

* Animals self-administering cocaine at either dose were compared with animals self-administering food.

"The reduced activity of the temporal lobe indicates that this structure is somehow compromised," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. "Some of these regions mediate the ability to connect emotionally, and cocaine's blunting of them may induce a flattened affect similar to depression symptoms that are common among chronic cocaine abusers."

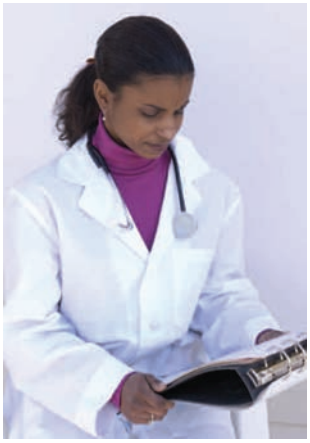
"Dr. Porrino and her colleagues have identified key brain structures affected by long-term cocaine exposure and have provided a valuable set of observations that could serve as a basis for future research," Dr. Pilotte says. For example, she adds, researchers might now focus on those regions when gauging the effectiveness of potential medications for cocaine addiction or when measuring recovery after abstinence. ■

SOURCES

Beveridge, T.J.R., et al. Chronic cocaine self-administration is associated with altered functional activity in the temporal lobes of nonhuman primates. *European Journal of Neuroscience* 23(11):3109-3118, 2006.

Porrino, L.J., et al. The effects of cocaine: A shifting target over the course of addiction. *Progress in Neuropsychopharmacology and Biological Psychiatry* 31(8):1593-1600, 2007.

NIDA Centers Raise Physicians' Awareness of Drug Abuse Issues



NIDA has established four Centers of Excellence for Physician Information to increase physicians' awareness of NIDA-funded research on the medical consequences of drug abuse and addiction and to provide the information and resources that doctors need to incorporate research findings into clinical practice.

The Centers are also developing standards for physician competencies as well as training curricula to prepare medical students and residents to assess patients' drug abuse issues in their eventual practice settings. Pilot testing of several curricula is scheduled to begin this fall.

The Centers were established in collaboration with the American Medical Association's consortium on education research. They are based at:

NIDA CoE drugabuse.gov
Centers of Excellence for Physician Information
A Program of the National Institute on Drug Abuse
National Institutes of Health • U.S. Dept. of Health & Human Services

- Creighton University School of Medicine, Omaha, Nebraska;
- the University of Pennsylvania School of Medicine in collaboration with Drexel University School of Medicine, both in Philadelphia;
- the University of North Dakota School of Medicine and Health Sciences in Grand Forks; and
- the Massachusetts Consortium of Medical Schools, which includes the University of Massachusetts Medical School in Worcester and Boston University School of Medicine, Harvard Medical School/Cambridge Health Alliance, and Tufts University School of Medicine in Boston.

"This has been an ambitious and challenging effort," says NIDA Director Dr. Nora D. Volkow. "Yet the NIDA Centers have made meaningful strides in identifying how and where medical students and resident physicians obtain information about medical drug abuse issues and also in identifying misperceptions and knowledge gaps that may hinder the effective care of patients who abuse prescription and illicit drugs."

Networking Web site: A Bridge to Transdisciplinary Research

NIDA Networking Project

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The NIDA Networking Project (NNP) Web site connects scientists, clinicians, addiction specialists, and policymakers to research-based information and resources.

The NNP Web site features 14 networks and almost 300 sites sponsored by NIDA or in partnership with other Federal agencies. The Web site includes:

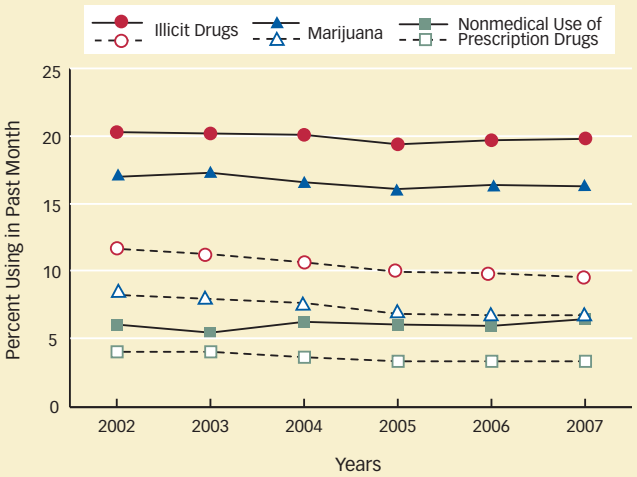
- AN INTERACTIVE MAP
- NETWORK DESCRIPTIONS
- LINKS TO NETWORK WEB SITES
- NETWORK COLLEAGUES DIRECTORY
- NEWS AND EVENTS

http://nnp.drugabuse.gov

For more information on the NNP Web site, please contact Susan David, NNP Coordinator (E-mail: davids2@nida.nih.gov; Telephone: 301-435-0640).

Fewer Young Adults Abuse Cocaine and Methamphetamine, National Survey Finds

ILLICIT DRUG USE AMONG YOUTHS AND YOUNG ADULTS
Youths (age 12 to 17) have lower rates of drug use than young adults (age 18 to 25). Youth rates (open symbols, broken lines) have fallen gradually, while the young adult (filled symbols, solid lines) rates have remained level.



The percentage of young adults who said they were abusing cocaine or methamphetamine dropped substantially from 2006 to 2007, according to the 2007 National Survey on Drug Use and Health (NSDUH), published in September 2008. Overall drug abuse, however, remained constant: According to the survey, an estimated 19.9 million Americans age 12 and over used an illicit drug in the previous month. That rate has held steady since 2002.

As in past years, young adults (aged 18-25) reported the highest rates of substance abuse. About 20 percent said they abused one or more illicit drugs; 16.4 percent said they abused marijuana, which topped the list of abused drugs in this cohort. Abuse rates for marijuana and most of the other drugs have changed little in the past 6 years. However, the decline in abuse of the stimulants cocaine and methamphetamine in this group runs counter to that pattern. In 2007, for example, 1.7 percent of the young adults reported cocaine abuse, a 23 percent decline from the previous year. Methamphetamine abuse in this age group dropped by a third, to 0.4 percent.

By contrast, 12- to 17-year-olds have reported a steady decline in overall illicit drug use, from 11.6 percent in 2002 to 9.5 percent in 2007. Driving the decline in this cohort has been an 18 percent drop in marijuana use, from 8.2 percent in 2002 to 6.7 percent in 2007. Inhalants are the only drug category that showed no decline among adolescents over that 6-year period, although rates for some drugs have leveled off since 2005.

Rates of drug abuse tend to decline steadily after the age of 25. However, as more baby boomers (people born between 1946 and 1964) enter the 50–59 age range, illicit drug use in that group has risen, jumping from 2.7 percent in 2002 to 5 percent in 2007. "Illicit drug use has historically been more prevalent in the baby boomer cohort. As its members age into the 50-59 age category, the prevalence increases relative to prior cohorts in this age group," says Dr. Marsha Lopez of NIDA's Division of Epidemiology, Services and Prevention Research.

Marijuana remains the most commonly used illicit drug across the survey, with an estimated 14.4 million past-month users. In 2007, roughly 2.1 million people smoked marijuana for the first time, and a similar number started using prescription painkillers for nonmedical purposes; these drugs drew more initiates last year than any other. Of the estimated 6.9 million people who used prescription psychotherapeutic drugs nonmedically, 5.2 million chose painkillers, representing a 16 percent rise in nonmedical use of these drugs since 2004. On a positive note, the 2007 survey found a significant 1-year decline in the nonmedical use of prescribed stimulants.

In 2007, as in previous years, men reported higher rates of past-month illicit drug use than women (10.4 percent versus 5.8 percent). Among ethnic groups, American Indians/Alaska natives had the highest rate of illicit drug use (12.6 percent) of any racial/ethnic group, followed by multiracial individuals (11.8 percent), African-Americans (9.5 percent), whites (8.2 percent), Hispanics (6.6 percent), and Asians (4.2 percent). No group had a significant change from the previous year.

The trends determined by NSDUH for adolescents and young adults are generally consistent with those reported by the NIDA-funded Monitoring the Future survey. (For more information, see *NIDA Notes*, Volume 21, Number 5, March 2008, page 15).

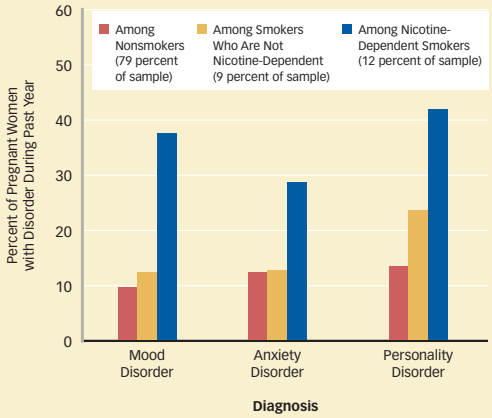
The survey, based on the responses of 67,500 participants, is available online at *www.oas.samhsa.gov/NSDUHlatest.htm*. Hard copies can be ordered free from *ncadistore.samhsa.gov/catalog/productDetails.aspx?ProductID=17911* or by calling (800) 729-6686. ■

SOURCE

Substance Abuse and Mental Health Services Administration, 2008. Results from the 2007 *National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, DHHS Publication No. SMA 08-4343). Rockville, MD: SAMHSA.

WHAT THE NUMBERS SAY

Nicotine Dependence Is Linked With Mental Disorders in Pregnant Women



The link between mental disorders and nicotine dependence that had been previously observed in the general population also pertains to pregnant women, according to a U.S. survey that included 1,516 pregnant women. Taking into account important characteristics—including age, education, income, and marital status—associations appeared between nicotine dependence and having a mood, anxiety, or personality disorder. The presence of mental disorders may make smoking cessation particularly difficult. Smoking during pregnancy is of special concern because, according to prior research, it increases the risk of women having infants with low birth weight; such children subsequently face an elevated risk of health consequences and of learning and behavior problems.

SOURCE: An analysis of data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions reported in Goodwin, R.D., Keyes, K., and Simuro, N. Mental disorders and nicotine dependence among pregnant women in the United States. *Obstetrics and Gynecology* 109(4):875-883, 2007.

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