RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Combination Treatment Extends Marijuana Abstinence

Vouchers provide a strong incentive for abstinence during treatment, and cognitive-behavioral therapy helps patients maintain abstinence after treatment ends.

BY DEBRA P. DAVIS,
NIDA Notes Senior Editor

Treatment that combines vouchers and cognitive-behavioral therapy (CBT) may be more effective in keeping marijuana abusers abstinent in the longer term than vouchers-only and CBT-only programs. In a study by Dr. Alan Budney and colleagues at the University of Vermont, vouchers alone generated the longest periods of abstinence during 14 weeks of treatment, while vouchers and CBT in combination yielded superior abstinence during a 12-month posttreatment period.

"This is our second study demonstrating that an abstinence-based voucher program can increase positive outcomes for folks seeking treatment for marijuana dependence," says Dr. Budney, who is now at the University of Arkansas for Medical Sciences. "It provides evidence that vouchers used as adjuncts to traditional behavioral therapy can improve outcomes."

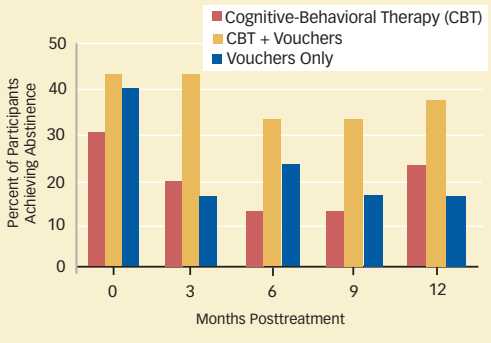
The current study extended the earlier one by including posttreatment assessments. Vouchers provided a strong incentive for abstinence during treatment, as they did in the earlier study, but the effect of vouchers alone did not hold up as well as the combined treatment once the program ended. The higher posttreatment abstinence rates for the combined treatment relative to the vouchers-only treatment suggest that the behavioral therapy helped to maintain the effect of the vouchers, Dr. Budney says. He attributes this maintenance effect to the coping skills and motivational training provided by the CBT.

For the study, 90 adults (69 men, 21 women) seeking treatment for marijuana dependence at a university-based outpatient clinic in Burlington, Vermont, were randomly assigned to treatment with vouchers (30), CBT (30), or both (30). Most were smoking marijuana daily and presenting themselves for treatment for the first time; their average length of marijuana abuse was 14 years.

Each time a participant in the vouchers-only or combination treatment submitted a marijuana-negative urine sample, he or she received a voucher worth $1.50; a second consecutive negative sample earned $3.00, a third $4.50, and so on. In addition, each consecutive pair of negative samples netted a

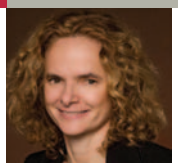
[*Continued on page 6*]

COMBINED TREATMENT HELPS MAINTAIN ABSTINENCE Over the 12 months following treatment, abstinence levels for all treatment conditions tended to decline, but levels for the combined treatment remained consistently higher than those for CBT or vouchers only.



ALSO IN THIS ISSUE

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



Epigenetics: The Promise of a New Science

Recently, scientists have developed a more sophisticated understanding of the ways in which genetics influences a person's health. The complement of genes a person inherits at birth is, of course, essential. But all genes are not created equal; only some genes are "expressed"—that is, actively participate in protein production. Today, a new field of scientific inquiry, called epigenetics, investigates the cellular mechanisms that control gene expression and its impacts on health and behavior.

Epigenetic processes allow experience to influence cellular processes. For example, epigenetic alterations that accumulate during a person's lifetime can contribute to aging, the development of cancer, obesity, and other health conditions.

NIDA is funding studies to learn how epigenetic mechanisms figure in the neurobiology of drug abuse and addiction. In a dozen projects, researchers are elucidating the links between exposure to drugs of abuse, epigenetic processes, gene function, and neurobiological and behavioral changes in animal models of addiction. A recent study, for example, showed that cocaine triggers an epigenetic process called chromatin remodeling and that this contributes to rats' behavioral responses to the drug ("Gene Experiment Confirms a Suspected Cocaine Action," *NIDA Notes*, Vol. 21, No. 4). Cocaine-induced epigenetic changes may increase the number of neural connections between the reward pathway and other brain regions that regulate emotions and memories to drive craving. We see every reason to hope that increased understanding of drugs' effects on epigenetic processes in the brain will open the door to analogous new addiction therapies.

National Institutes of Health (NIH) Director Dr. Elias Zerhouni has charged NIDA with a key role in developing a program within the NIH Roadmap Initiative on epigenomics—the analysis of epigenetic changes across a species' entire genetic blueprint. This agency-wide effort aims to provide researchers with standard tools and technologies to develop comprehensive epigenome maps that potentially will point the way to more effective responses to a wide range of health problems. To learn more about the Roadmap Epigenomics Program, visit nihroadmap.nih.gov/epigenomics/index.asp. ■

NIDA Notes

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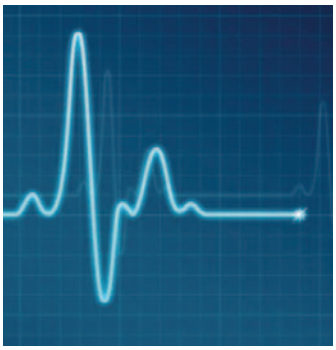


Long-Term Cocaine Abuse Linked With Impaired Heart Function

Long-term regular cocaine abuse impairs cardiac left ventricular function in African-Americans, say NIDA-funded researchers Dr. Shenghan Lai and colleagues at The Johns Hopkins Medical Institutions. Magnetic resonance imaging of heart muscle contractions disclosed lower pumping efficiency in areas of the left ventricular wall among 32 African-Americans who abused cocaine compared with 14 nonabusers. The study participants, men and women aged 25 to 54, were all in good health with no signs of heart disease; the findings suggest that prolonged exposure to the drug may cause subclinical impairment that increases risk for cardiac events. Acute cocaine abuse has previously been associated with several cardiac complications, including arrhythmia, ruptured aorta, heart attack, and sudden death.

> American Journal of Cardiology 97(7):1085-1088, 2006.

Bupropion Reduces Meth's Subjective Effects and Cue-Induced Craving

A small placebo-controlled trial produced evidence that the antidepressant bupropion may be useful for treating methamphetamine addiction. Drs. Thomas Newton and Richard De La Garza at the University of California, Los Angeles, and Dr. John Roach and colleagues, at the University of Texas, San Antonio, divided 20 methamphetamine-addicted individuals into two groups for 6 days of treatment: one group received bupropion (150 mg/d) throughout the trial and the other, placebo. At baseline and the end of the trial each participant received three infusions; one of an inert vehicle and two of methamphetamine (15mg and 30 mg), spaced over 2 hours. Before and at frequent intervals after each infusion, participants reported on their subjective reactions. Compared to baseline, those who received bupropion experienced reduced highs and slightly decreased cravings at the end of the trial, while those who received placebo experienced significantly more craving.

> Neuropsychopharmacology 31(7):1537-1544, 2006.

Cocaine Can Mobilize Stored Dopamine

Cocaine increases dopamine levels primarily by preventing the neurochemical from being transported back into its releasing cell, leaving more outside the neuron, where it contributes to the drug's euphoric effects. Dr. R. Mark Wightman and colleagues of the University of North Carolina at Chapel Hill and Dr. George Augustine of Duke University have recently shown that cocaine also can tap into an intracellular dopamine reserve pool. As far back as the 1970s, some researchers suspected this could occur, but they could not confirm it. Now, thanks to advances in molecular genetics and techniques to study neurotransmission, scientists have learned in studies with mice that proteins called synapsins, under the control of three genes, lock up the reserve pool by tethering its vesicles to the neuron's internal structural framework. When the cell is called upon to release extraordinary amounts of the neurotransmitter, a chemical reaction relaxes the synapsin's grasp on reserve pool vesicles, allowing them to join the releasable pool . "Although this extra mechanism is definitely not the most important action of cocaine, it points to a way that the drug can switch dopamine cells into a sustained-release mode, promoting the activation that dopamine exerts on its target neurons," says Dr. Wightman.

> The Journal of Neuroscience 26(12):3206-3209, 2006.

Researchers Develop a New Tracer for Cannabinoid Receptor

Cannabinoid receptors appear to play a role in several conditions—including schizophrenia, depression, obesity, and drug abuse—but a radiolabel has not been available for imaging them in the brain. Drs. Andrew G. Horti and Dean F. Wong and colleagues at the Johns Hopkins Medical Institutions synthesized a new chemical (^{11}C-JHU75528) for this purpose. The tracer readily entered the brains of mice and baboons and bound specifically to cannabinoid receptors (CB1), unlike candidates tested in prior research. The chemical also did not induce any noticeable side effects in the animals. The researchers have also successfully tested ^{11}C-JHU75528 in preliminary human imaging studies and are hopeful that they will someday be able to use it to clarify the relationship between CB1 and specific aspects of drug abuse and other neurological conditions.

> Journal of Nuclear Medicine 47(10):1689-1696, 2006.

Sertraline Does Not Help Methamphetamine Abusers Quit

Selective serotonin reuptake inhibitors do not relieve the depressive symptoms of methamphetamine withdrawal and may produce unpleasant side effects.

BY ELIZABETH ASHTON,
NIDA Notes Staff Writer

In a recent NIDA-funded study, the antidepressant sertraline (Zoloft) made quitting methamphetamine harder. Prescribed to relieve depression during the methamphetamine withdrawal process, sertraline produced a number of unpleasant side effects and may have interfered with behavioral interventions as well.

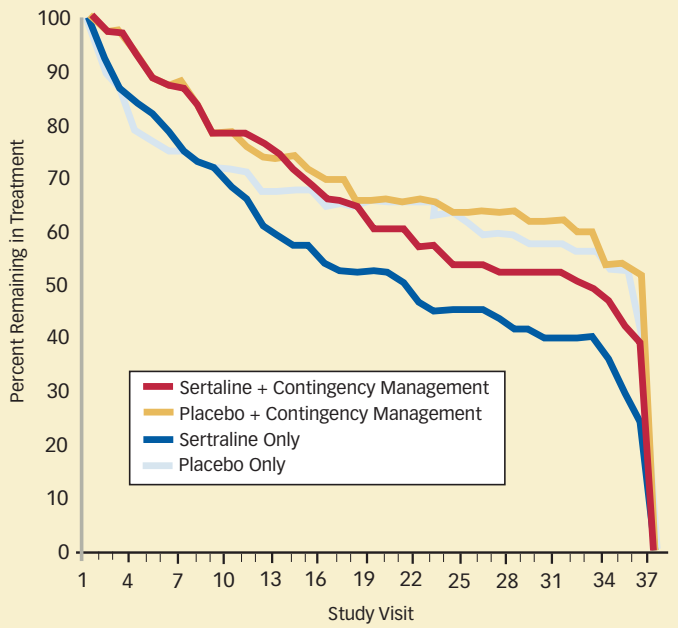
Dr. Steven Shoptaw, Alice Huber, Dr. Walter Ling, and their colleagues at the University of California, Los Angeles (UCLA) noted that methamphetamine abusers in withdrawal frequently complained of fatigue, lack of pleasure, sad mood, and persistent daytime sleepiness. The researchers hypothesized that the sertraline might alleviate these symptoms and promote abstinence because:

- methamphetamine is toxic to several pathways that produce the neurotransmitter serotonin
- sertraline belongs to a class of antidepressant medications, the selective serotonin reuptake inhibitors (SSRI), that treat major depression by raising serotonin levels in the brain

HYPOTHESIS DISPROVED

The team recruited 229 men and women who were addicted to methamphetamine. All were between the ages of 18 and 65, and all were seeking treatment. The trial began with a 2-week preparation process. The researchers performed baseline testing and encouraged the participants to stop taking methamphetamine with the help of twice-weekly recovery skills groups. At the end of 2 weeks, they randomly assigned the participants to one of four groups: sertraline with contingency management (CM), sertraline alone, placebo with CM, and placebo alone. All participants provided urine samples on Mondays, Wednesdays, and Fridays and attended a 90-minute psychological support group three times a week based on the Matrix Model relapse prevention program. This standardized, manual-driven model is evidence-based and incorporates social learning, behavioral and cognitive therapies, and psychological and HIV-risk education.

A TREATMENT FAILS THE TEST Participants receiving sertraline alone stayed in treatment for significantly less time than participants in all other treatment conditions.



The researchers evaluated methamphetamine use, time spent in the program, methamphetamine craving, and depressive symptoms. They found that:

- more participants in the CM program achieved 3 consecutive weeks of abstinence than participants who were not in the CM program (47 vs. 33 percent); all participants who received CM benefitted from this therapy, but its positive effects were blunted in the sertraline-with-CM group.
- fewer participants on sertraline alone, as compared with those on placebo alone (34 percent vs. 47 percent) achieved the goal of at least 3 consecutive drug-free urine samples during the study's 12-week treatment phase; participants on sertraline alone also attended fewer relapse prevention sessions and were more likely to drop out.
- craving and depressive symptoms were affected only by time since the last

methamphetamine dose, and neither sertraline nor CM changed either of these two measures.

In addition, the sertraline group reported significantly more sexual, gastrointestinal (including nausea), and anticholingeric side effects.

RETHINKING WITHDRAWAL SUPPORT

The researchers concluded that treatment with sertraline did not relieve the depression associated with methamphetamine withdrawal or decrease methamphetamine use, and its side effects reduced the amount of time participants spent in treatment. Those who took sertraline also seemed to benefit less from behavioral interventions, and the researchers speculated that this might be due to the dampening effect of the medication since they had excluded all other possible factors in the statistical analysis.

The team recommends that clinicians not give SSRIs to people withdrawing from methamphetamine unless an underlying primary depressive disorder is definitively diagnosed. The recommendation reflects their own results and those of previous smaller studies with fluoxetine (Prozac) and paroxetine (Paxil), both of which were also found to have no effect on depressive symptoms during methamphetamine withdrawal. Together, these findings suggest that the etiology of mood disorder during methamphetamine withdrawal differs from that of primary depression.

The UCLA researchers suggest that clinicians offer people addicted to methamphetamine an effective behavioral intervention for depressive symptoms during the withdrawal process before prescribing any of the currently available pharmacotherapies for depression. If medication is needed, only non-SSRI antidepressants, such as bupropion, should be used.

"The SSRI sertraline is not only inefficacious for the treatment of methamphetamine dependence, but also produces a number of unprecedented side effects and has no effect on the secondary depression experienced during methamphetamine withdrawal," says Dr. Ivan Montoya, Clinical Director of NIDA's Pharmacotherapies and Medical Consequences of Drug Abuse Branch. "In addition, the negative effects of this SSRI in methamphetamine users are so powerful that they can dampen the strong therapeutic effects of contingency management. If these reactions can be traced to their source, they may help us understand the extent and duration of the effects of methamphetamine on the brain."

"We are trying to determine what people withdrawing from methamphetamine need to make withdrawal easier," Dr. Shoptaw says. "We've figured this out for other drugs, such as cocaine and heroin, but finding medications that counter the withdrawal symptoms of methamphetamine addiction is still a work in progress. We need this information so we can design treatment programs that help people get off and stay off this damaging drug." ■

SOURCE

Shoptaw, S., et al. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence* 85(1):12-18, 2006.

COMBINATION TREATMENT

[*Continued from page 1*]

bonus voucher worth $10. A full 14-week run of weekly drug-free samples would net vouchers worth $570, which were redeemable for retail goods or services.

The CBT included 50-minute weekly sessions involving motivational counseling, drug refusal, and coping skills. To encourage cooperation with the urine screens and help equalize retention and treatment contact across the groups, researchers paid the CBT-only participants $5 in vouchers each time they showed up for a screen, regardless of their test results. Complete adherence to the sessions and screens would earn $140 over the 14-week period.

During treatment, vouchers-only patients produced the most marijuana-negative urine specimens (55 percent versus 43 percent for combined treatment and 32 percent for CBT only), weeks of continuous abstinence (mean 6.9 versus 5.3 for combined treatment and 3.5 for CBT only), and continuous abstinences lasting 6 or more weeks (50 percent versus 40 percent for combined treatment and 17 percent for CBT only). In addition to duration of abstinence, researchers measured days of self-reported marijuana abuse, changes in marijuana-related problems, and psychosocial outcomes. Participants in all three groups showed similar improvements in these areas at the end of treatment (see chart).

COMBINED TREATMENT BENEFITS

At the end of treatment and at each of four quarterly followups, patients who received the combined treatment had the highest abstinence prevalence, averaging 38 percent over the 12 months, compared with 23 percent for vouchers only and 20 percent for CBT only. The combined treatment group also had the highest rate of continuous abstinence throughout treatment and followup, 37 percent, compared with 30 percent for CBT and 27 percent for vouchers. On average, patients who received the combination treatment used marijuana 13 days out of 30 during followup, compared with 18 days among patients who received the single treatments.

"The findings of this study show that vouchers are effective in producing initial abstinence during treatment," says Ms. Debra Grossman of NIDA's Division of Clinical Neuroscience and Behavioral Research. "The addition of cognitive-behavioral therapy did not enhance initial abstinence, but helped maintain abstinence and produced better long-term outcomes. These findings are consistent with other studies." In two previous studies with cocaine abusers, vouchers alone performed as well as vouchers plus CBT during treatment. One of the studies indicated that CBT augmented the effects of the vouchers during the posttreatment period.

Dr. Budney says his team set the value of the vouchers arbitrarily, with the aim of keeping costs down; he believes bigger payoffs would produce better outcomes. The escalating values for consecutive negative urine samples progressively strengthened the incentive for participants to avoid lapses; each time a participant submitted a positive sample or missed a screening, the reward for the next negative sample reverted to the original $1.50 voucher. Dr. Budney suggests that future studies might cut costs by incorporating behavioral therapy only at key points in the treatment, rather than weekly throughout. In the researchers' experience, such a point often comes in the fourth to sixth week of abstinence, when patients may start to lose motivation and become vulnerable to relapse.

Fewer than half of the participants in Dr. Budney's study had positive outcomes, indicating that more effective treatments are needed for marijuana dependence. "Despite the promising findings, the majority of patients are not being sufficiently helped, and thus we need continued research focused on maximizing the outcome," Ms. Grossman notes. "Marijuana is the most commonly used illegal drug in the United States, yet among the least studied, and treatment based on abstinence-based vouchers has been found to be effective for other drugs of abuse." ■

VOUCHERS BOOST ABSTINENCE RATES DURING TREATMENT Participants in the vouchers-only group had better abstinence outcomes than those in the combination or CBT-only groups during treatment. All three groups reported substantial improvements over the 14-week period, but no significant intergroup differences, on measures such as the number of days participants used marijuana and how often they experienced marijuana-related problems.

	CBT	CBT+V	V
Primary abstinence outcomes			
Mean weeks of continuous abstinence [a]	3.5	5.3	6.9
% of participants who achieved 6 or more weeks of continuous abstinence [a,b]	17.0	40.0	50.0
% marijuana-negative urine specimens	32.0	43.0	55.0
Secondary self-report measures			
Number of days marijuana used during prior month [c]			
Intake	26.1	24.8	25.8
End of treatment	8.6	9.7	11.3
Number of times marijuana used per day [c]			
Intake	3.7	4.2	3.8
End of treatment [a]	1.6	2.7	2.6
Marijuana Problem Scale [c]			
Intake	7.9	7.8	7.8
End of treatment	5.1	3.6	4.1

Data for all analyses were based on all participants (n = 30 per treatment condition). Mean data reflect means adjusted for abstinence prior to treatment.
[a]CBT vs. V, comparison $p < .05$
[b]CBT+V vs. CBT, comparison $p < .05$
[c]Significant main effect for time, $p < .01$

SOURCE

Budney, A.J., et al. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *Journal of Consulting and Clinical Psychology* 74(2):307-316, 2006.

Not All Mesolimbic Dopamine Neurons Are Alike

Understanding the receptor composition of circuits governing pleasure and motivation could help fine-tune drug treatment.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

NIDA-supported neuroanatomists have shown that the neurons that deliver dopamine to two regions of the brain's mesolimbic reward system respond differently to opioids. The finding adds to scientists' evolving picture of a key system in the brain's response to drugs, reveals opportunities for more detailed investigations, and may eventually enable pharmacologists to develop medications to specifically target each of the regions.

Dr. John T. Williams and colleagues at Oregon Health Sciences University (OHSU) studied neurons that originate in the brain's ventral tegmental area (VTA) and release dopamine in the nucleus accumbens (NAc) and the basolateral amygdala (BLA). Dopamine release in the NAc is the biochemical source of our feelings of pleasure and reward when we achieve a goal, as well as the highs produced by opioids and other drugs of abuse. However, less is known about the role of the BLA or the regional dynamics of the system as a whole.

The OHSU team showed that the VTA neurons that serve the NAc were inhibited more when an opioid compound was used to stimulate kappa receptors; VTA neurons that serve the BLA responded more to mu opioid activation. Opioid compounds, including medications and illicit drugs, stimulate both kappa and mu receptors, but they vary in the intensity with which they stimulate each. The magnitudes of each compound's intensities of kappa and mu activation contribute to its distinct properties in comparison with other opioids—for example, variations in pain control and addictivity.

"The main import of our work is that it should be possible to selectively regulate dopamine-releasing neurons in the nucleus accumbens and amygdala," Dr. Williams says. If researchers can raise dopamine levels in the NAc while holding them steady in the BLA, or vice versa, they will be able to elucidate each region's separate role in the response to opioids and—more generally—in promoting a wide variety of experiences and behaviors.

FILLING IN THE MESOLIMBIC MAP

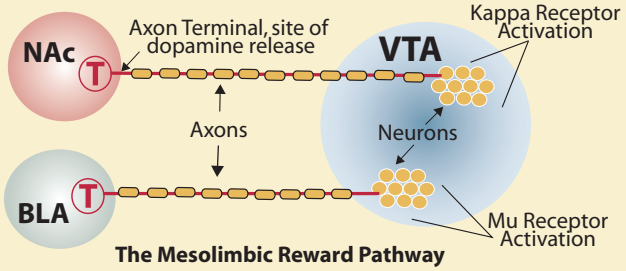
The researchers first mapped the sets of neurons serving the NAc and BLA of laboratory mice using fluorescent microspheres. Injected into either the NAc or BLA of each animal, the microspheres entered neurons at the axon terminals—where neurons release neurochemicals like dopamine—and migrated along the axons to the neuronal cell bodies in the VTA. When the researchers examined brain slices from the animals, the pattern of fluorescence revealed that the neurons serving the NAc had their cell bodies in one part of the VTA—the posterior/medial portion—while those that went to the BLA originated in the anterior/lateral region.

To confirm that the fluorescent neurons really were the type that produces dopamine, the researchers tested for the presence of an enzyme that is a marker for such cells. They found sufficient quantities of tyrosine hydrolase, which aids dopamine synthesis, to conclude the affirmative.

Next, the investigators examined the neurons' functional characteristics. "We hypothesized that because these target areas serve different functions, the neurons projecting to them would exhibit different properties," Dr. Williams says. In particular, they looked at the kappa and mu opioid receptors on the neurons' cell bodies. When the VTA was exposed to a chemical—U695930—that stimulates only kappa receptors, the neurons projecting to the NAc conveyed a stronger inhibitory current, as measured in picoamperes (10^{-9} ampere), than did those that projected to the BLA. The application of [Met] enkephalin (ME), which activates mu receptors, had the opposite effect: it generated a stronger current in the neurons going to the BLA than those going to the NAc.

"Studying the brain disease of addiction involves looking for chronic dysfunction in the brain's reward and motivational pathways," comments Dr. Woody Lin of NIDA's Division of Basic Neuroscience and Behavioral Research. "To understand how drugs modify this circuitry, we need to know how it functions normally. This research gives us a better understanding of how specific brain regions function, and provides insights into potentially important sites for intervention." In terms of developing medications to treat substance abuse, the OHSU team's work suggests that it may be possible to alter specific aspects of the response to drugs by regulating release in one or the other part of the mesolimbic reward system. ■

MAPPING NEURONAL CIRCUITRY Researchers injected fluorescent microspheres into the nucleus accumbens (NAc) and the basolateral amygdala (BLA) of mouse brains in order to track dopamine pathways back to two separate points of origin within the ventral tegmental area (VTA).



The Mesolimbic Reward Pathway

SOURCE

Ford, C.P.; Mark, G.P.; and Williams, J.T. Properties and opioid inhibition of mesolimbic dopamine neurons vary according to target location. *Journal of Neuroscience* 26(10):2788-2797, 2006.

Alcohol Abuse Makes Prescription Drug Abuse More Likely

Those under age 25 are particularly vulnerable to dual abuse.

BY ELIZABETH ASHTON,
NIDA Notes Staff Writer

Men and women with alcohol use disorders (AUDs) are 18 times more likely to report nonmedical use of prescription drugs than people who don't drink at all, according to researchers at the University of Michigan. Dr. Sean Esteban McCabe and colleagues documented this link in two NIDA-funded studies; they also discovered that young adults were most at risk for concurrent or simultaneous abuse of both alcohol and prescription drugs.

"The message of these studies is that clinicians should conduct thorough drug use histories, particularly when working with young adults," says Dr. McCabe. "Clinicians should ask patients with alcohol use disorders about nonmedical use of prescription drugs [NMUPD] and in turn ask nonmedical users of prescription medications about their drinking behaviors." The authors also recommend that college staff educate students about the adverse health outcomes associated with using alcohol and prescription medications at the same time.

TWO STUDIES

The authors' first study looked at the prevalence of AUDs and NMUPD in 43,093 individuals 18 and older who participated in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) between 2001 and 2005. Participants lived across the United States in a broad spectrum of household arrangements and represented White, African-American, Asian, Hispanic, and Native American populations. Although people with AUDs constituted only 9 percent of NESARC's total sample, they accounted for more than a third of those who reported NMUPD.

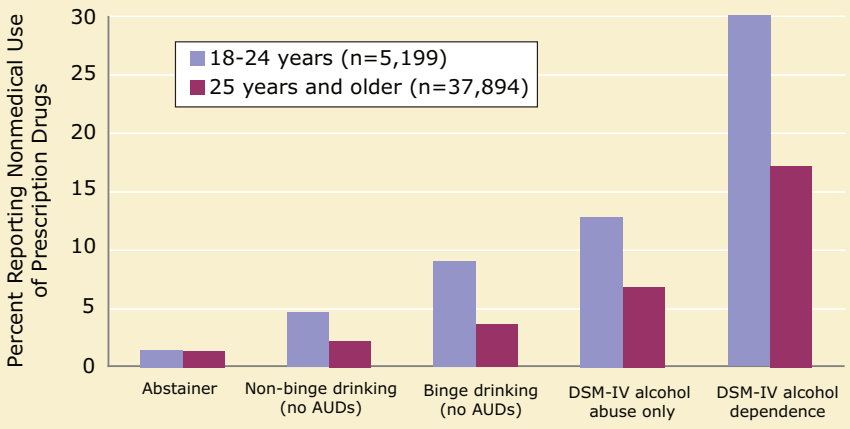
Since the largest group of alcohol/prescription drug abusers were between the ages of 18 and 24, the team's second study focused entirely on this population and involved 4,580 young adults at a large, public, Midwestern university. The participants completed a self-administered Web survey, which revealed that 12 percent of them had used both alcohol and prescription drugs nonmedically within the last year but at different times (concurrent use), and 7 percent had taken them at the same time (simultaneous use).

When alcohol and prescription drugs are used simultaneously, severe medical problems can result, including alcohol poisoning, unconsciousness, respiratory depression, and sometimes death. In addition, college students who drank and took prescription drugs simultaneously were more likely than those who did not to blackout, vomit, and engage in other risky behaviors such as drunk driving and unplanned sex.

WHO, WHAT, AND WHEN

The prescription drugs that were combined with alcohol in order of prevalence included prescription opiates (e.g., Vicodin, OxyContin, Tylenol 3 with codeine, Percocet), stimulant medication (e.g., Ritalin, Adderall, Concerta), sedative/anxiety med-

PAST-YEAR NONMEDICAL USE OF PRESCRIPTION DRUGS BY PAST-YEAR DRINKING STATUS Prescription drug misuse rises with drinking severity. Increases are most pronounced in adults aged 18-24.



ication (e.g., Ativan, Xanax, Valium), and sleeping medication (e.g., Ambien, Halcion, Restoril). The college study asked about the respondent's use of medications prescribed for other people while the NESARC explored both use of someone else's prescription medications as well as the use of one's own prescription medications in a manner not intended by the prescribing clinician (e.g., to get high).

The researchers found that the more alcohol a person drank and the younger he or she started drinking, the more likely he or she was to report NMUPD. Compared with people who did not drink at all, drinkers who did not binge were almost twice as likely to engage in NMUPD; binge drinkers with no AUDs were three times as likely; people who abused alcohol but were not dependent on alcohol were nearly seven times as likely; and people who were dependent on alcohol were 18 times as likely to report NMUPD (see figure, page 8).

While the majority of the respondents in both studies were White (71 percent in NESARC and 65 percent in the college group), an even higher percentage of the simultaneous polydrug users in the college study were White males who had started drinking in their early teens. The NESARC study also found that Whites in general were two to five times more likely than African-Americans to report NMUPD during the past year. Native Americans were at increased risk for NMUPD, and the authors indicated that this subpopulation should receive greater research attention in the future.

Dr. McCabe emphasizes that many people who simultaneously drink alcohol and use prescription medications have no idea how dangerous the interactions between these substances can be. "Passing out is a protective mechanism that stops people from drinking when they are approaching potentially dangerous blood alcohol concentrations," he explains. "But if you take stimulants when you drink, you can potentially override this mechanism and this could lead to life-threatening consequences."

Dr. James Colliver, formerly of NIDA's Division of Epidemiology, Services and Prevention Research, offers perspective on these studies. "Prescription sedatives, tranquilizers, painkillers, and stimulants are generally safe and effective medications for patients who take them as prescribed by a clinician," Dr. Colliver states. "They are used to treat acute and chronic pain, attention deficit hyperactivity disorder, anxiety disorders, and sleep disorders.

"The problem is that many people think that, because prescription drugs have been tested and approved by the Food and Drug Administration, they are always safe to use; but they are safe only when used under the direction of a physician for the purpose for which they are prescribed." ■

Nonmedical Use of Prescription Drugs

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), sponsored by the National Institutes of Health, defines nonmedical use as follows:

Using drugs that were not prescribed to you by a doctor, or using drugs in a manner not intended by the prescribing clinician (e.g., to get high). Nonmedical use does not include taking prescription medications as directed by a health practitioner or the use of over-the-counter medications.

SOURCES

McCabe, S.E., et al. The relationship between past-year drinking behaviors and nonmedical use of prescription drugs: Prevalence of co-occurrence in a national sample. *Drug and Alcohol Dependence* 84(3):281-288, 2006.

McCabe, S.E., et al. Simultaneous and concurrent polydrug use of alcohol and prescription drugs: Prevalence, correlates, and consequences. *Journal of Studies on Alcohol* 67(4):529-537, 2006.

Chromosome 17 Harbors Opioid Dependence Genes

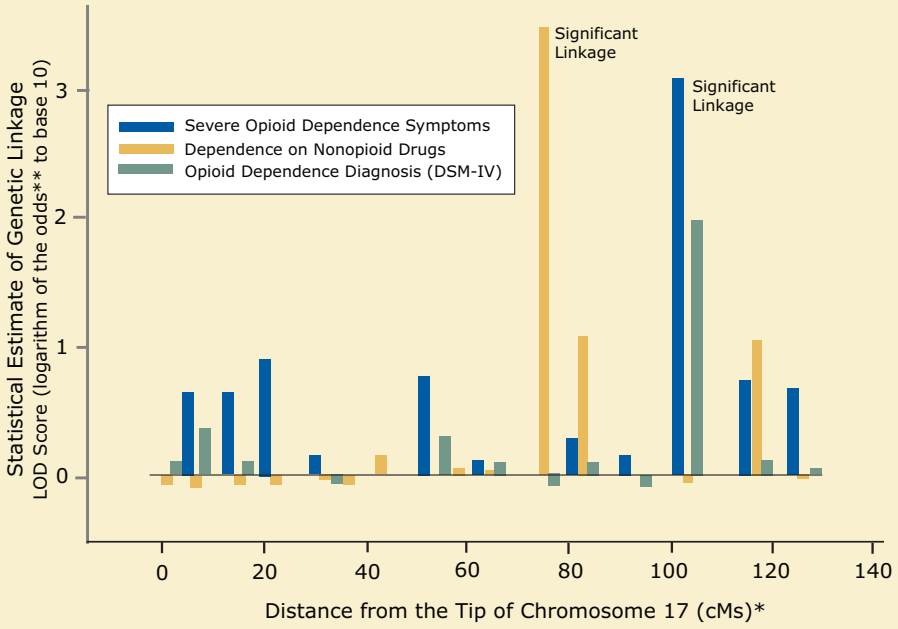
A comparison of genetic markers of opioid abusers and their relatives brings scientists closer to identifying those that contribute to abuse and dependence.

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA-funded investigators are homing in on the location of genes that may influence the risk of opioid dependence. Dr. Joel Gelernter, at Yale University School of Medicine, Henry Kranzler, at the University of Connecticut, and colleagues led a study that has shown a statistical link between one region on chromosome 17 and an increased risk of opioid dependence.

"Opioid addiction results from the activities of multiple genes, many environmental factors—obviously including drug exposure—and interactions among them. Our findings point to specific chromosomal areas as the sites of some of the contributing genes," says Dr. Gelernter. Prior studies that estimated the relative contributions of genes and environmental factors by comparing rates of addiction in twins indicated that genes alone account for an estimated 45 percent to 50 percent of opioid addiction. Twin studies also suggest that certain genes may increase the risk of opioid addiction without affecting the likelihood of addiction to other drugs.

RESEARCHERS LINK TWO SITES ON CHROMOSOME 17 WITH DRUG ABUSE RISK Bars on the graph indicate regions on chromosome 17 associated with increased risk of drug abuse. Genes linked with opioid dependence and abuse of other drugs are most likely to be found near these locations.



*One cM equals roughly 1 million base pairs.

**The likelihood that a specific region or marker on the chromosome is linked with an increased risk of drug abuse.

SCANNING FOR GENETIC MARKERS

At four sites in the eastern United States, Dr. Gelernter and colleagues recruited 393 families with at least one member who abused opioids; in 235 of the families (60 percent), two or more members abused the drugs. The investigators assessed every study participant and categorized those who reported abusing drugs as exhibiting either "low opioid abuse," "moderate opioid abuse," "severe opioid abuse," "abuse of nonopioid drugs," or "severe opioid abuse mixed with dependence on other substances." Participants in the "severe opioid abuse" cluster reported the highest rates of long-term heavy abuse, injection of opioids, and attempts to quit.

The researchers scanned each participant's DNA for genetic markers—segments of DNA that occur at known locations on a particular chromosome. These scans revealed that certain markers were shared with increased frequency among family members with drug abuse diagnoses or phenotypes; the specific genes that influence risk for opioid dependence are likely to be found near these markers.

Among the markers with the strongest statistical links Dr. Gelernter's team identified were two on the long arm of chromosome 17 (see chart). One of these was connected with severe symptoms of dependence on opioids, but not other drugs, among both African-American and

European-American participants. Among European-American participants only, a second site was linked with dependence on other drugs, including cocaine, nicotine, alcohol, and marijuana.

Although the sites on chromosome 17 were the only ones to show statistically significant linkages, the analyses suggested that the short arm of chromosome 11 and the long arm of chromosome 3 may also feature genes that influence dependence on nonopioid drugs. Among African-American participants only, analyses suggested a link between opioid dependence and a site on chromosome 2. The genetic sites linked with risk of many health problems differ between European- and African-Americans. Known racial differences in the patterns of drug abuse and risk factors for addiction also support somewhat separate etiologies, although there is likely much overlap.

The findings generally accord with those of prior studies. For example, other researchers have linked sites on chromosome 17 with the risk of smoking and conduct disorder. Further, chromosome 17 has a site, albeit in a different location than the ones found by Dr. Gelernter's team, with a suggestive linkage to heroin abuse among almost 200 families from Yunnan Province in China, according to preliminary findings from NIDA-funded investigators Drs. Ming T. Tsuang and Stephen J. Glatt and colleagues. Similarly, prior studies have linked sites close to the ones observed by Dr. Gelernter's team on chromosome 11 with risk of nicotine and alcohol addiction and areas of chromosome 3 with risk of cocaine abuse and conduct disorder.

IDENTIFYING SPECIFIC GENES

Studies such as Dr. Gelernter's suggest that certain areas of the genome are statistically most likely to harbor genes that play a role in drug abuse. Researchers will next turn their attention to the question: Which of the genes that reside in these areas might explain that increased likelihood? Prime candidates will be any genes whose activities affect physiological responses to drugs or behavioral characteristics associated with vulnerability to drug abuse. "Each chromosome site where we observed a link could have perhaps 30 to 100 genes, maybe more, and my team is currently assigning each region a priority for further study," says Dr. Gelernter. Scientists may investigate candidate genes' impacts in a variety of ways, including statistical studies to determine the effects of eliminating, activating, or inactivating the genes on animals' responses to drugs.

"The findings of both genomewide and candidate-gene studies represent a good return on NIDA's investment in genetics research and contribute useful and complementary information," says Dr. Harold Gordon of the Division of Clinical Neuroscience and Behavioral Research. "Besides identifying genes that put people at risk for the disorder, they help us understand how these genes affect neural function and behavior, and facilitate the development of medications tailored to the individual."

By scanning for genetic markers common among a subgroup of individuals with the most severe opioid abuse symptoms, Dr. Gelernter's team was able to home in on sites that may harbor genes linked with the unique risk for opioid dependence, as well as those linked to substance abuse in general, Dr. Gordon notes. In future studies, the team hopes to use a newer genomewide scanning technique that can dramatically speed the identification of specific genes. ■

SOURCE

Gelernter, J., et al. Genomewide linkage scan for opioid dependence and related traits. *American Journal of Human Genetics* 78(5):759-769, 2006.

Chronic Cocaine Abusers Have Occult Insomnia in Early Abstinence

Patients in early treatment may not recognize their own sleep impairment or its impact on their performance.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Chronic cocaine abusers may feel they are sleeping better and better during early abstinence, but objective measures show the opposite happens. A team of NIDA-funded addiction and sleep researchers at the Yale and Harvard Schools of Medicine found evidence of insomnia, with learning and attentional deficits, on days of taking the drug and after 2.5 weeks of abstinence. The researchers believe cocaine may impair the brain's ability to gauge its own need for sleep, and patients' ability to benefit from early treatment may suffer as a result.

"Problems in memory and attention are linked with increased treatment dropout and likely affect patients' ability to 'take in' lessons from drug abuse counseling," says Dr. Robert Malison of Yale, a co-investigator on the study. If the results are confirmed, clinicians and patients may want to consider addressing sleep disorders in early therapy, perhaps with the use of medications or behavioral treatments.

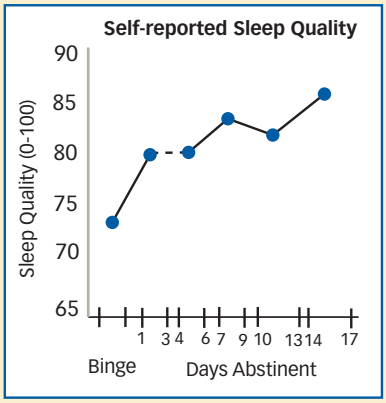
The researchers recruited 10 men and two women aged 24 to 49 who, on average, had abused cocaine for 17 years and had used $500 worth of the drug per week. All the participants declined an offer of drug abuse treatment. Urine tests indicated that cocaine was the only drug any of them had abused during the week before the study.

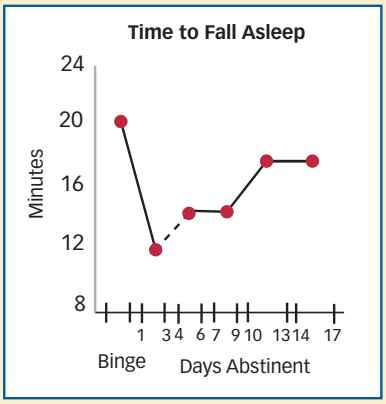
At the outset of the study, participants self-administered cocaine from a pump under physician oversight, building up to a dose of 32 mg/kg of body weight over 1.5 hours, then repeating this dose essentially at will, but no less than 5 minutes apart, for another 1.5 hours. Subsequently, they self-administered the higher dose with the same minimal restriction for 2 hours on each of three consecutive days, either on days 4-6 or 18-20. This schedule simulated chronic cocaine abusers' typical bingeing pattern of drug abuse and allowed researchers to monitor each participant's sleep and cognitive performance for 17 days after a binge.

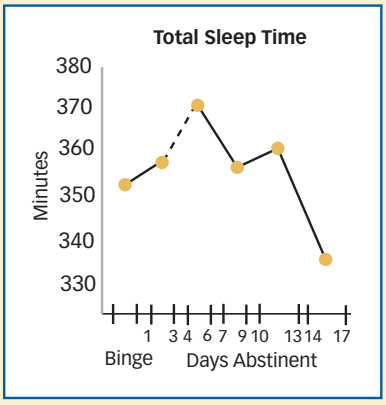
Research staff made sure the participants stayed awake from 7:45 AM to 9:30 PM, and let them sleep through the night. At night, the participants wore Nightcap sleep monitors, a bandana-like device that records eye and body movements that indicate whether someone is awake, asleep and dreaming, or sleeping dreamlessly. On most nights participants also wore

OBJECTIVE MEASURES BELIE PATIENTS' IMPRESSIONS OF SLEEP IMPROVEMENT

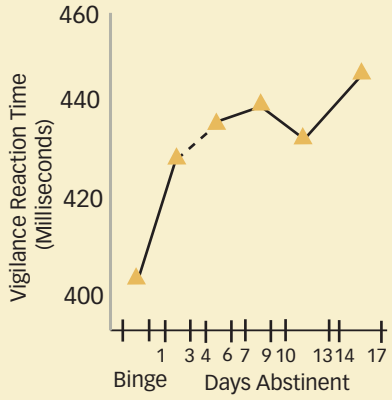
Patients thought their sleep was better (left), but objective measures (right) showed that after an initial improvement they started to need longer to fall asleep and their total sleep time went down.



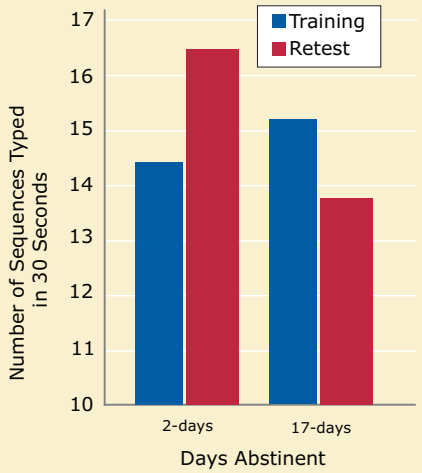




ALERTNESS IMPAIRMENTS PARALLEL SLEEP DEFICITS In the Digital Vigilance Test, participants were required to press a button when they saw a target number on the right side of the screen while viewing a rapidly changing number sequence in the middle of the screen. Poor performance on the task corresponded with sleep deficits at 14-17 days of abstinence.



PERFORMANCE DECLINES WITH SLEEP QUALITY In the Motor-Sequence Task, participants typed a five-digit sequence of four keys with their non-dominant hand, a skill that improves after a night's sleep. Cocaine abusers showed improvement after two but not 17 days of abstinence.



polysomnographic (PSG) devices that continuously assessed brain activity with electroencephalography (EEG) and measured eye and muscle movements associated with different sleep stages. Combining the information gathered by these measures with participants' responses to daily questionnaires on their sleep experience and with cognitive testing, the researchers demonstrated that the participants had:

- *Sleep deficits*—After 14 to 17 days of abstinence, the study group exhibited sleep deficits on several measures, relative to healthy, age-matched peers who participated in prior studies. For example, they had less total sleep time (336 versus 421–464 minutes) and took longer to fall asleep (19 versus 6–16 minutes).
- *Declines in sleep quantity and quality*—The time participants took to fall asleep and their total time asleep transiently improved during the first week of abstinence, but then reverted to the patterns recorded on days of cocaine taking. On abstinence days 14-17, participants took an average of 20 minutes to fall asleep (from a low of 11) and slept for 40 minutes less than their minimum. Slow-wave sleep—a deep sleep that often increases following sleep deprivation—rose during the binge and on abstinence days 10-17.
- *Lack of awareness of their sleep problems*—In contrast to the evidence of objective measures, the study participants reported steadily improving sleep from the beginning to the end of their days of abstinence.
- *Impairments in learning and attention*—As with sleep quality, participants' performance on tests of alertness and motor-skills learning initially improved and then deteriorated. On abstinence day 17, they registered their lowest scores on alertness and ability to learn a new motor skill.

INCREASED RISK OF RELAPSE

"Unlike most people with chronic insomnia, including alcoholics, cocaine abusers do not perceive sleep problems and may not ask clinicians for treatment to improve sleep," says Dr. Malison. The problem often goes unaddressed and persists as a result, and the accompanying impairments in attention and learning may affect how well they respond to drug abuse treatment (see "Cocaine Abusers' Cognitive Deficits Compromise Treatment Outcomes," *NIDA Notes*, Vol., 19, No. 1). Clinical studies have shown that poor objective sleep during the first 2 weeks of abstinence predicts relapse to alcohol 5 months after treatment.

In fact, the insidious nature of cocaine-related insomnia may directly trigger relapse, suggests Dr. Peter Morgan, lead investigator of the study. "Addicted people may take cocaine to improve sleep-related cognitive functioning deficits—unaware that they are abusing, in part, to 'solve' these problems."

Dr. Morgan adds, "Cocaine abusers who recognize their cognitive problems often report that it takes them 6 months to a year to turn the corner—a clinical observation that points to the need for longer term studies of sleep and treatment outcomes among this population." In addition to studies with larger numbers of participants, the investigators say there is a need to investigate possible gender differences in cocaine-related sleep problems. Dr. Morgan and his team are currently testing two medications, tiagabine and modafinil, to see if they can improve cocaine abusers' sleep and restore cognitive performance.

"Experts believe that not getting enough sleep is an unmet public health problem in the general population. These findings highlight this important problem in cocaine abusers," says Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience and Behavioral Research. ■

SOURCE

Morgan, P.T., et al. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: Evidence for occult insomnia. *Drug and Alcohol Dependence* 82(3):238-249, 2006.

Researchers Report on Progress of NIDA's Southern Africa Initiative

Research projects conducted under NIDA's Southern Africa Initiative help universities and other organizations in southern Africa build research capacity and infrastructure in the area of addiction, particularly drug-related HIV transmission. The Initiative, administered by NIDA's Special Populations Office (SPO) with assistance from the International Program, comprises 12 research projects. NIDA-funded investigators based in the United States and African collaborators recently reported on the progress of their projects, most of which have taken place or are ongoing in the Republic of South Africa.

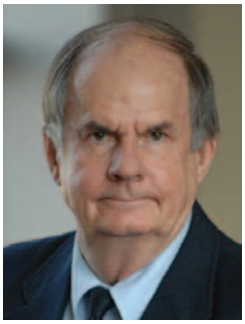
Dr. Torrance Stephens of Morehouse School of Medicine and Dr. Sibusiso Sifunda of the South African Medical Research Council described the development and testing of a peer-led intervention to prevent about-to-be-released prison inmates from spreading sexually transmitted diseases, including HIV, to community residents. The intervention—which included cultural perspectives on manhood and responsibility, videotaped stories from role models, and group discussions—improved participants' attitudes regarding safe sex and their motivation to reduce risky behaviors. The research team worked closely with the South African minister of corrections and the Department of Correctional Services (DCS) in nine provinces and four prisons to provide training for DCS staff and peer education for ex-inmates.

Dr. Murelle Harrison of Southern University in Baton Rouge, Louisiana and Dr. Dorothy Malaka of the University of Limpopo, South Africa, reported on a comparison of African-American and South African families living in rural areas. They observed similar sociodemographic and family characteristics and youth behaviors in both populations. For example, children who spent more time interacting with their mothers also showed better self-control and cognitive development. The team hopes the baseline data will serve as a foundation for a subsequent family intervention. In other project results, 22 South African students were trained in epidemiological data collection methods, two South African researchers observed rural data collection in the United States and sharpened skills with computer software for data analysis, and 18 primary school teachers and nine principals received assistance with educational computer technology.

Dr. Donnie Watson of the Friends Research Institute in Torrance, California and Dr. Solomon Rataemane of the University of Limpopo reviewed preliminary findings from a comparison of three different approaches to teaching experienced drug abuse counselors cognitive-behavioral therapy: (1) in-person training with subsequent supervision, (2) distance learning of the same training with subsequent telephone-based supervision, and (3) self-study with a therapy manual after an initial orientation. The in-person and distance-learning approaches were well-received, and the team continues to recruit licensed clinicians who work in 30 South African National Council on Alcoholism and Drug Dependence treatment centers.

"The Southern Africa Initiative represents a relatively small investment, $2 to $2.5 million, with a tremendous payoff for all participants," says SPO Chief Dr. Lula Beatty. "After hearing reports on the research projects, my colleagues and I were struck by the immediate impact that some of the collaborations had on communities." NIDA hopes that information obtained from the projects will facilitate the use of evidence-based interventions that are culturally appropriate for southern Africa and that the training activities will strengthen addiction research in the region.

Scientific Society Honors Dr. Kenner Rice's Research



Dr. Kenner Rice, Chief of NIDA's Chemical Biology Research Branch, has received the 2007 Smissman Award from the American Chemical Society (ACS). The award recognizes significant contributions to fundamental knowledge in medicinal chemistry, and the ACS presented the honor to Dr. Rice in August at its National Meeting and Exposition in Boston. Dr. Rice's basic research on neurochemicals led to the development of compounds with the potential to prevent and treat drug addiction (for example, a medication that prevents cocaine self-administration in monkeys).

Dr. Rice joined the National Institutes of Health (NIH) in 1972 and NIDA in 2006. During his 35-year career at NIH, Dr. Rice mapped the location of cannabinoid receptors, demonstrated biochemical differences in the receptors of opioid-exposed animals, and determined how abused drugs affect brain cells. His research led to the discovery of a radiotracer that neuroscientists can use in imaging studies of opioid addiction. Dr. Rice designed and developed the NIH Opiate Total Synthesis, a practical method for the large-scale production of medicinal opioids and opioid blockers.

Teen Substance Abuse Continues to Decline

Use of illicit drugs by students in the 8th, 10th, and 12th grades declined 24 percent over the past 6 years, according to the 2007 Monitoring the Future (MTF) survey. The rate of past-month illicit drug use dropped from 19.4 percent in 2001 to 14.8 percent in 2007, which indicates that an estimated 860,000 fewer teenagers are current users.

Declines among 8th graders were particularly noteworthy. Illicit drug use and cigarette smoking declined significantly not only in the past 6 years, but also since 2006. Typically, year-to-year changes are within a margin of error and therefore not large enough to be considered significant.

NIDA Director Dr. Nora Volkow said the smoking rate for all three grades combined (13.6 percent) was the lowest in the MTF's 33-year history. "We are especially heartened to see the decrease in smoking among 8th graders and will be watching the next 2 years closely to see if this decline will stick as these kids get older," Dr. Volkow said. "If this change in attitude is carried with them throughout the rest of their teen years, we could see a dramatic drop in smoking-related deaths in their generation."

Marijuana, methamphetamine, and amphetamines are among the drugs most responsible for the overall decline in abuse of illicit drugs over the past 6 years. Although marijuana continued to be the most widely abused illicit drug, past-month abuse rates fell 25 percent, from 16.6 percent to 14.8 percent, since 2001. Past-month meth abuse dropped 64 percent (from 1.4 percent to 0.5 percent) and abuse of amphetamines fell 32 percent (from 4.7 percent to 3.2 percent).

PRESCRIPTION MEDS: AN ONGOING CONCERN

Contrary to the general trend, nonmedical use of prescription medications "is holding at near record levels," said Dr. Lloyd Johnston of the University of Michigan, the study's principal investigator. Abuse of prescription painkillers such as OxyContin and Vicodin by teenagers is a new phenomenon that has emerged in the past 5 years; these medications are being prescribed in record numbers and kept in households where kids have access to them, observed Dr. Volkow. In 2007, 15.4 percent of 12th graders reported abuse of prescription drugs in the past year; Vicodin had the highest rate of abuse—9.6 percent.

Another concern is an apparent softening of attitudes toward MDMA (ecstasy) and LSD among 8th and 10th graders, fewer of whom said they perceived these drugs as harmful. Ecstasy abuse by teenagers in all three grades has decreased over the past 6 years, but 10th and 12th graders reported an increase in past-year abuse in 2007. Dr. Johnston noted that these results are worrisome because perceived risk is an important predictor of abuse.

For the second year, the survey included questions about the abuse of over-the-counter cough medicines. In both 2006 and 2007, rates of abuse were 4 percent for 8th graders and 5 percent for 10th graders; for 12th graders, the rate dropped from 7 percent to 6 percent, a change that was not statistically significant. Taking large quantities of cough medicines with the active ingredient dextromethorphan in order to get high, a practice referred to as "robotripping," can cause brain damage and even death. Robitussin, Coricidin HBP, Vicks NyQuil, and Vicks Formula 44 are among the most commonly abused brands.

The 2007 survey covered 48,025 students in 403 public and private schools across the United States. Participants reported on their use of an extensive list of illicit drugs and other substances in the past month, past year, and in their lifetime. Further information and the full text of the survey are available at *www.drugabuse.gov/drugpages/MTF.html* and at *www.monitoringthefuture.org*.

Change in Illicit Drug Use by 8th, 10th, and 12th Graders Since 2001

Percent Reporting Past Month Use

	2001	2007	Change as a % of 2001
Any Illicit Drug	**19.4%**	**14.8%**	**-24***
Marijuana	16.6%	12.4%	-25*
MDMA (Ecstasy)	2.4%	1.1%	-54*
LSD	1.5%	0.6%	-60*
Amphetamines	4.7%	3.2%	-32*
Inhalants	2.8%	2.6%	-7
Methamphetamine	1.4%	0.5%	-64*
Steroids	0.9%	0.6%	-33*
Cocaine	1.5%	1.4%	-7
Heroin	0.4%	0.4%	0
Alcohol	35.5%	30.1%	-15*
Cigarettes	20.2%	13.6%	-33*

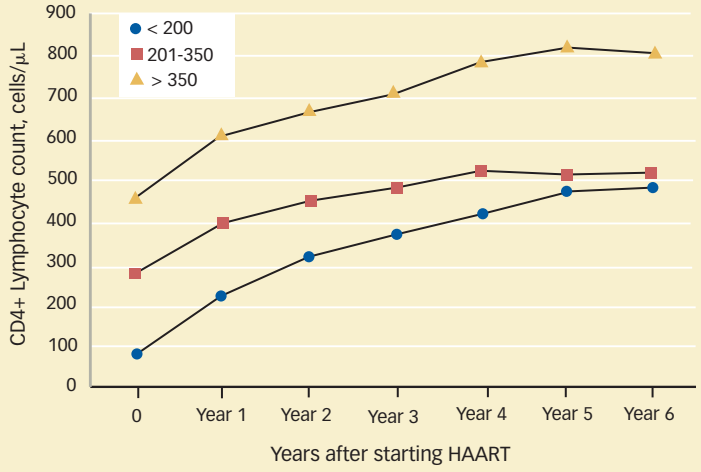
*Denotes statistically significant change from 2001.

Note: Past month use, 8th, 10th, and 12th grades combined; percent chance calculated from figures having more precision than shown.

Source: University of Michigan, 2007 Monitoring the Future survey.

WHAT THE NUMBERS SAY

HIV Patients Show Better Immune Recovery With Early Initiation of HAART



Among 655 men and women with HIV, CD4+ count at HAART initiation predicted subsequent recovery of this important immune system cell. Patients receiving HAART showed an improvement after 4 years of treatment and maintained these levels for the next two. The researchers note, however, that those who began treatment after their CD4+ levels fell below 350 cells/µL failed to recover to normal levels. To achieve better recovery, the authors suggest that HAART therapy be initiated when the CD4+ cell count is greater than 350 cells/µL.

SOURCE: Moore, R.D. and Keruly, J.C. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clinical Infectious Diseases* 44(3):441-446, 2007.

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