NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Volume 18, Number 5

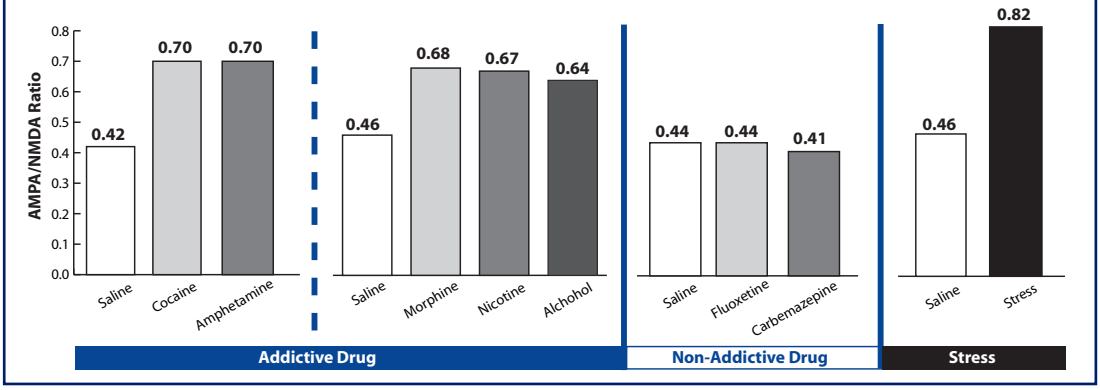
Addictive Drugs and Stress Trigger Similar Change in Brain Cells, Animal Study Finds

By Patrick Zickler, NIDA NOTES Staff Writer

Preventing relapse is the most formidable challenge to successful treatment of drug addiction. After months or even years of abstinence, former users may experience powerful cravings that lead to resumption of drug abuse. A single exposure to drugs, an environmental cue associated with past drug taking, or a stressful event can precipitate renewed, uncontrollable drug seeking and abuse.

Susceptibility to relapse, like the onset of addiction, is in part a consequence of changes to nerve cells in the brain.

Addictive Drugs and Stress Increase Sensitivity of Dopamine Cells in Mice



Researchers injected mice with either saline, an addictive drug (cocaine, amphetamine, morphine, nicotine, or alcohol), or a nonaddictive drug that is active in the brain (carbemazepine or fluoxetine). Twenty-four hours later, the scientists measured the electrical properties of dopamine cells from the animals' ventral tegmental area (VTA). Cells from mice exposed to addictive drugs exhibited a higher ratio of AMPA to NMDA currents than did those of mice exposed to nonaddictive drugs or saline, indicating establishment of long-term potentiation (LTP), a condition that causes the cells to release dopamine more abundantly than they previously would have. The researchers also exposed mice to stress, but not to any drugs, and found the same LTP "fingerprint" when they examined VTA cells 24 hours later.

What's Inside

In recent experiments aimed at increasing understanding of the nature of these changes, NIDA researchers have established that most major drugs of abuse can induce long-term potentiation (LTP) in dopamine-releasing cells in an area of the brain called the VTA (ventral tegmental area). LTP primes these cells to react more strongly—and release dopamine more abundantly—in response to future exposures to the drug. Because dopamine's roles include alerting the mind that something important is happening or about to happen and triggering feelings of pleasure, this finding could help explain addiction's extraordinary and long-lasting hold over people. The researchers showed that

continued on page 6

Marijuana's Persistent Impact on Cognition, p. 8

Electronic Delivery of NIDA NOTES, p. 14

Research Findings

Research News

Director's Column

Bulletin Board

Tearoff

NIDA News and Information at Your Fingertips

Information about NIDA research, programs, and events is quickly and easily accessible through **NIDA's home page** on the World Wide Web.

NIDA's home page: www.drugabuse.gov

NIDA's home page includes:

- Information on Drugs of Abuse
- Publications (including *NIDA NOTES*)
- Calendar of Events
- Links to NIDA Organizational Units
- Funding Information
- International Activities
- Links to Related Web Sites

The Dual Challenge of Substance Abuse and Mental Disorders

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

Multidisciplinary research studies can give us a better understanding of the origins and progression of comorbid substance abuse and mental disorders that will enable us to respond effectively to the problem.

As many as 6 in 10 people who abuse drugs and alcohol also suffer from mental illnesses, according to epidemiological studies. Conversely, some 25 to 60 percent of individuals with mental illnesses also have substance abuse disorders. The overwhelming reality of these concurrent disorders presents huge challenges for drug abuse research, prevention, and treatment.

Our attempts to understand substance abuse and mental illness comorbidity are complicated by the many ways these complex conditions can develop. Research suggests that some people's genetic makeup may put them at higher risk for psychiatric and substance use disorders. In some instances, individuals with mental illness may begin to abuse drugs in attempts to alleviate distressing symptoms of the disease, putting themselves at risk for addiction. In other cases, substance abuse and its associated neurobiological changes appear to increase vulnerability to and possibly trigger mental disorders. Research funded by the National Institute of Mental Health (NIMH) and NIDA that followed more than 700 individuals from early childhood into their late twenties recently concluded that early substance abuse is associated with and significantly predicts later occurrence of psychiatric disorders, including major depressive disorder (MDD). The study's findings suggest that there are common risk factors for both substance abuse and MDD and that once abuse begins, it becomes an additional risk factor for MDD (see, "Early Use of Drugs May Lead to Later Psychiatric Disorders," p. 5).

Multidisciplinary research studies can give us a better understanding of the origins and progression of comorbid mental and substance abuse disorders that will enable us to respond effectively to the problem. Thus, NIDA and NIMH are increasing research to identify genetic variations that increase vulnerability to mental and substance abuse disorders and clarify how individual, social, and environmental factors influence the development and course of comorbidity. This research has the potential to bolster our ongoing efforts to develop effective approaches to preventing comorbidity and treating the vast majority of substance abuse patients who suffer from this devastating condition.

MDD, other mood disorders, conduct and personality disorders, posttraumatic stress disorder (PTSD), and schizophrenia are mental disorders that often accompany substance abuse. However, mood disorders are among the most commonly diagnosed mental illnesses in people who abuse substances. Basic research has found that drug-dependent individuals and people with depression exhibit similar alterations in brain activity. For example, drug withdrawal symptoms such as irritability, dysphoric mood, and an inability to experience pleasure are associated with changes in neurotransmission regulated by the chemical messengers dopamine and serotonin and the stress-related peptide corticotropin-releasing factor.

continued on page 4

The Dual Challenge of Substance Abuse and Mental Disorders

continued from page 3

Research has documented similar changes in the activity of these neurotransmitters in depression. To clarify the role such changes play in drug abuse and mood disorders, NIDA and NIMH recently awarded more than a dozen research grants to spur the development of new imaging compounds that will enable further exploration of the neurochemical receptors and brain regions associated with substance abuse and mental disorders. This important research could pave the way for the development of new medication strategies to treat both conditions.

Increased understanding of how biological and environmental factors affect mentally ill individuals' susceptibility to substance abuse is central to developing new programs to prevent comorbidity. We know from decades of drug abuse research that modifying factors known to foster initial drug use can prevent it from occurring and reduce the risk of progression to more severe drug abuse. We also know from NIDA's extensive program of drug abuse vulnerability research that childhood conduct disorders, anxiety disorders, and other psychiatric disorders may increase the risk of later substance abuse. While we don't know if early intervention with children with such disorders can prevent substance abuse from occurring during adolescence, several studies have found that treating children with attention-deficit/hyperactivity disorder (ADHD) with stimulant medications reduces their likelihood of developing substance abuse disorders later in life (see "Studies Link Stimulant Treatment of ADHD in Childhood to Lower Risk of Later Substance Abuse." *NIDA NOTES*, Vol. 18, No.1).

For the last 5 years, an ongoing NIDA program that has been exploring the links between childhood psychopathology and subsequent substance abuse has established the scientific basis for tackling this question. Last year, the program culminated in a joint NIDA/NIMH request for research aimed at identifying risk factors, causal mechanisms, and childhood mental health interventions that may prevent or inhibit later substance use. This year, the Institutes will jointly fund roughly 10 new studies under this initiative. These studies should enhance our understanding of how biological vulnerability and environmental challenges in these children's lives contribute to the chain of events that results in coexisting mental health and substance abuse disorders. In turn, this information will provide the basis for new and more effective prevention strategies.

To help patients whose problems fall within our health missions, NIDA and NIMH have joined hands to support research that will increase fundamental knowledge about drug abuse and mental health comorbidity, advance efforts to prevent this destructive combination, and treat those already afflicted.

While striving to find ways to prevent comorbidity, NIDA continues to support research to meet the treatment needs of substance-dependent patients with concurrent mental illness. Overlapping symptoms of the coexisting disorders greatly increase the difficulty of diagnosing and treating either separately. However, NIDA-funded research suggests that integrating pharmacological or behavioral therapies for mental disorders with drug abuse treatment may improve outcomes for both illnesses. Researchers have found, for instance, that giving antidepressant medications to adult patients in methadone treatment reduced their craving for drugs and their drug use as well as their comorbid mood disorder (see "Treating Mood Disorders in Drug Abuse Patients Yields Improvement in Both Conditions," *NIDA NOTES*, Vol. 13, No. 6). Combining an effective behavioral therapy for PTSD with cognitive behavioral therapy for cocaine abuse also has been found to produce substantial improvement in both disorders (see "Joint Treatment of PTSD and Cocaine Abuse May Reduce Severity of Both Disorders," *NIDA NOTES*, Vol. 18, No. 1).

That most individuals with substance abuse disorders also struggle with mental illnesses is today's reality. It does not have to be tomorrow's. To help these patients whose problems fall within our health missions, NIDA and NIMH have joined hands to support research that will increase fundamental knowledge about drug abuse and mental health comorbidity, advance efforts to prevent this destructive combination, and treat those already afflicted. NIDA's broad program of scientific investigation into the origins and pathways of comorbidity promises new prevention and treatment vehicles that can reduce the incidence of both diseases among vulnerable individuals and put those who already suffer from dual disorders on the road to recovery. NN

Early Use of Drugs May Lead to Later Psychiatric Disorders

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

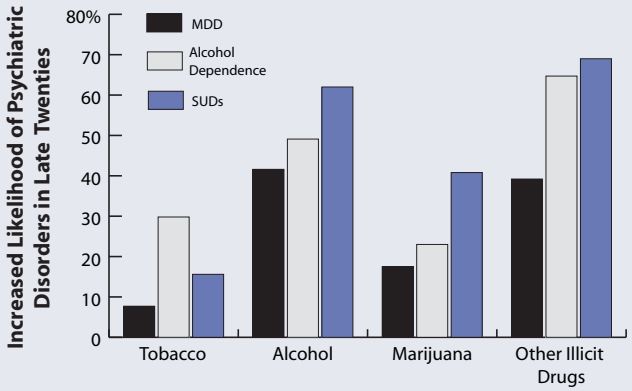
One of the challenges of research into comorbidity—the co-occurrence of substance abuse and mental disorders—is determining the order in which these disorders occur and the factors that they share. Recent findings from a longitudinal study that followed more than 700 individuals from early childhood into their late twenties now confirms one sequence of events in the comorbidity conundrum.

Dr. Judith S. Brook and Dr. David W. Brook of New York's Mount Sinai School of Medicine and Dr. Patricia Cohen of Columbia University, also in New York, provide evidence that substance abuse significantly predicts the later occurrence of psychiatric disorders, including major depressive disorder (MDD), alcohol dependence, and substance use disorders (SUDs). Moreover, their findings suggest that there are common risk factors for both substance abuse and MDD and that once abuse begins, it becomes an additional risk factor for MDD.

"Most studies obtain data on psychiatric disorders and drug abuse simultaneously, so it's almost impossible to determine which came first," says Dr. Judith Brook. "This longitudinal data set is unique because it follows one group of people through their lives, collecting data roughly every 5 years on drug abuse patterns, psychiatric disorders, and other factors. This approach allows us to study the progression of drug abuse, how it affects a person's functioning, and how it relates to subsequent psychiatric disorders."

Researchers from the City University of New York randomly selected 736 survey participants in 1975 as part of an effort to identify the health needs of children in Albany and Saratoga, New York. The ratio of boys to girls in the study reflected that of the population of children in both cities, as did the level of family intactness, family income, and parents' education level. The children were, on average, 6 years old when the study began.

Early Substance Abuse Increases Likelihood of Developing Psychiatric Disorders in Late Twenties



Longitudinal study participants who abused tobacco, alcohol, marijuana, and other illicit substances in earlier years were more likely to have diagnoses of major depressive disorder (MDD), alcohol dependence, or substance use disorders (SUDs) in their late twenties.

Eight years later, Dr. Judith S. Brook and Dr. Cohen acquired the original data set and study population with support from NIDA and the National Institute of Mental Health (NIMH). Subsequent interviews were completed at approximately 5-year intervals. Participants were asked about tobacco, alcohol, marijuana, and other illicit drug abuse during each set of interviews, and psychiatric disorders were measured.

"Overall, alcohol and substance abuse during the early years was significantly related to later psychiatric disorders, even after we statistically controlled for age, sex, parents' education level, family income, and episodes of prior psychiatric symptoms," says Dr. Brook. "The cumulative frequency of substance abuse from childhood through early adulthood is strongly associated with episodes of MDD, alcohol dependence, and SUDs in the late twenties."

Earlier marijuana and tobacco use were each more strongly related to participants' development of MDD in their late twenties than more recent use of these substances. However, the opposite was true for alcohol use and other illicit drug use—recent use was more strongly related to development of MDD in the late twenties. The relationship between earlier use of all four substances—tobacco, alcohol,

continued on page 13

Addictive Drugs and Stress Trigger Similar Change in Brain Cells, Animal Study Finds

continued from page 1

stress also induces LTP in VTA cells, a possible clue to the long-observed connection between stress and relapse.

Addictive Drugs and LTP

Dr. Robert Malenka at Stanford University in Palo Alto, California, and colleagues at Stanford and the University of California, San Francisco, first demonstrated that a single exposure to cocaine can establish LTP in the brain cells of mice (see "Altered Cellular Activity May Be First Step in Progression to Cocaine Addiction," *NIDA NOTES* Vol. 16, No. 5). Subsequently, the researchers set out to determine whether other addictive drugs have a similar effect on dopamine cells in the VTA. Dr. Malenka explains, "We found that amphetamine, morphine, nicotine, and alcohol, each of which is addictive but has its own molecular mechanisms of action, all trigger the same change that we saw with cocaine. We also found that medications that are active in the brain but not addictive do not have this effect."

In their studies, the investigators demonstrated LTP by documenting an increase in the electrical activity in a VTA cell component called the AMPA receptor. When stimulated, AMPA receptors generate an electrical current that prompts the cell to release dopamine, with the strength of the current determining how much dopamine is released. In general, a repeated application of the same stimulus will result in the same amount of AMPA current and dopamine release. When a drug or other stimulus establishes LTP, however, subsequent exposures to it generate higher AMPA currents and more copious dopamine release.

The increase in AMPA activity that signifies LTP is confirmed experimentally by showing an increased ratio of AMPA current to the current generated by another cell component, called the NMDA receptor. Dr. Malenka and his colleagues measured AMPA:NMDA ratios in mouse VTA cells before and after a single exposure to an addictive drug or a psychoactive medication. The ratios increased, indicating LTP had been established after exposure to amphetamine, morphine, nicotine, or alcohol. There was no increase, however, after exposure to the nonaddictive medications fluoxetine (an antidepressant) or carbemazepine (an antiseizure medication).

> ***The finding that stress alone can induce changes similar to those caused by drugs in VTA cells indicates the possibility of a priming mechanism that could make someone who has experienced stress much more vulnerable to addiction.***

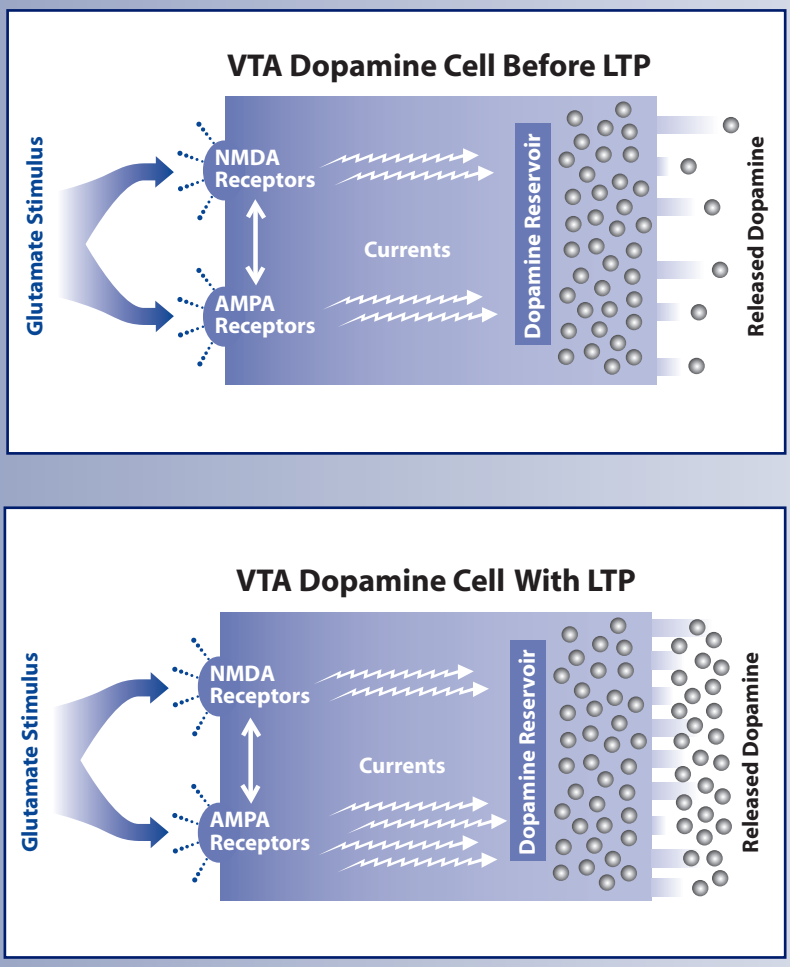
"These observations are an intriguing followup to the results the research group found when they looked at the impact of cocaine alone," says Dr. Susan Volman of NIDA's Division of Neuroscience and Behavioral Research. "The study's finding that dissimilar addictive drugs act in a similar way to usurp an important neurobiological process supports the hypothesis that LTP plays a role in the transition from drug abuse to addiction and might contribute to relapse."

Stress and LTP

Laboratory studies have shown that stress can cause reinstatement of drug taking in animals, and researchers believe that for some people, stress may play a role in the initiation of drug use or relapse to use after a period of abstinence. To examine this relationship, Dr. Malenka and his colleagues investigated whether stress in the absence of drug taking can induce LTP. Mice that had not been exposed to drugs were forced to swim for several minutes in a water tank with no escape. When investigators examined the animals' VTA cells 24 hours later, they found the same increased AMPA:NMDA ratios they had observed in mice exposed to addictive drugs.

The association of stress with LTP helps explains what seems at first to be a puzzling relationship between stress and the development of addiction, Dr. Volman observes. "Stress is unpleasant, a negative stimulus. Addictive drugs, on the other hand, have a pleasurable effect, at least initially. The finding that stress alone

Long-Term Potentiation in Dopamine Cells



Long-term potentiation (LTP) is one of the brain's key mechanisms for registering experience and using it to shape future responses, as in learning and remembering. When an experience or other stimulus induces LTP in a cell, the cell responds more strongly to future exposures to the same stimulus. For example, if you hit a fast ball for a home run, LTP is part of the reason you might get excited the next time you are at the plate and see a fast ball coming.

The images at left illustrate how LTP occurs, using the example of dopamine cells in the brain's ventral tegmental area (VTA). **Top image**: The process begins when a drug or other stimulus raises the level of the brain chemical glutamate. The glutamate in turn stimulates specific sites, called AMPA receptors and NMDA receptors, on the dopamine cells. The two receptors then interact to produce an electrical current that causes dopamine to flow from the cell's reservoir through the cell's membrane into the space outside the cell. **Bottom image**: Once LTP has been established, subsequent exposure to the same stimulus results in a higher AMPA current than occurred in response to the initial exposure, resulting in greater dopamine release.

can induce changes similar to those caused by drugs in VTA cells indicates the possibility of a priming mechanism that could make someone who has experienced stress much more vulnerable to addiction," says Dr. Volman.

LTP could also be part of a neurobiological mechanism that explains the observed association between stress and drug reinstatement in animals or relapse by humans.

"Reinstatement and relapse are like reawakening a learned behavior. It is possible that the effect of stress, like that of drugs, plays a role in this reawakening," Dr. Volman says.

"The changes we see in dopamine cells in the VTA may be a key neural adaptation that contributes not only to addiction, but also to the interaction of stress with drug abuse and addiction," concludes Dr. Malenka. "This adaptation may also represent a potentially important target for therapeutic intervention in the treatment of addictive disorders."

Source

• Saal, D.; Dong, Y.; Bonci, A.; Malenka, R. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 37(4):577-582, 2003. NN

Cognitive Deficits in Marijuana Smokers Persist After Use Stops

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

NIDA-funded scientists have found that cognitive impairments resulting from smoking marijuana can last up to at least 28 days after an individual last smoked the drug. The more a person had smoked prior to abstinence, the more profound this impairment, with marijuana smokers with lower IQs faring worse than their higher IQ peers, even if the latter had routinely smoked more of the drug.

NIDA-funded researchers Dr. Karen Bolla from the Johns Hopkins University School of Medicine in Baltimore and Dr. Jean Lud Cadet from NIDA's Intramural Research Program (IRP) admitted marijuana smokers to IRP's Clinical Inpatient Research Unit on Hopkins' Bayview campus, tested them to ensure they abstained from marijuana use throughout their 4-week stay, and gave them a battery of neurocognitive tests at the end of the study.

Twenty-two individuals participated. Their average age was 22, 86 percent were male, and all reported consuming fewer than 14 alcoholic drinks a week. The researchers estimated that the group had been smoking marijuana for an average of 4.8 years. Based on participants' reports of their current levels of marijuana use, the researchers grouped them as light, medium, or heavy smokers. "Determining an exposure index—how many joints participants smoked per week—and looking at the range of use in the study population strengthened our ability to make causal inferences," says Dr. Bolla.

Very heavy abusers smoked an average of 94 joints a week and scored worse than light abusers (average 11 joints per week) on 24 of the 35 neurocognitive tests, even after 28 days of abstinence. The measures on which the heavy abusers had comparative deficits included verbal and visual memory, executive functioning, visual perception, psychomotor speed, and manual dexterity. On some tests, quantity of marijuana use accounted for more than half the variance in test scores. "We found a dose-response relationship," says Dr. Bolla. "The more marijuana people used, the worse they performed on the tests, especially those for memory."

"We know a lot about the acute effects of marijuana use, but researchers are just now beginning to look at the long-term effects," says Dr. Jag Khalsa of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "This study demonstrates that marijuana smoking has chronic, dose-related effects on cognitive impairments up to 28 days after last use. But how long do these effects persist beyond that point? That's something we have to examine."

"We have shown that marijuana use is associated with persistent detrimental cognitive effects," explains Dr. Bolla. "These results are not attributable to use of other drugs, because participants were excluded for current or past history of significant use of other substances, including alcohol. Marijuana appears to be harmful when smoked in very large quantities."

The study results also suggested that some people are at higher cognitive risk from smoking marijuana than others. Cognitive performance in individuals with lower IQ scores decreased as the number of joints smoked per week increased, while those with higher IQ scores had fewer decrements even as marijuana use increased. "This finding demonstrates the concept of cognitive reserve," says Dr. Bolla. "People with higher IQs do better than those with lower IQs; the fewer cognitive reserves you have, the more impact you will see from a slight change in brain function."

The results of this study are consistent with study findings obtained by Dr. Harrison Pope, Jr., at Harvard University McLean Hospital in Belmont, Massachusetts (see *NIDA NOTES*, Vol. 11, No. 3). Dr. Pope and his colleagues found that memory and learning problems caused by heavy marijuana smoking lasted for at least a week after use stopped, although the problems disappeared within a month. "Since marijuana has a half-life of 4 days, the neurocognitive effects seen in Dr. Pope's study after 7 days indicate that marijuana does have residual effects," says Dr. Khalsa. "Study differences in longer term effects could be explained by differences in the study population."

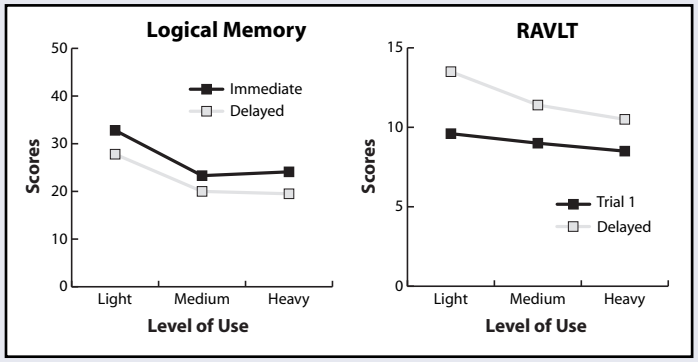
"In the Harvard study," Dr. Bolla notes, "participants were older, ranging from age 30 to 55; had higher IQs; were more affluent; and were more likely to be employed. Our inpatient study was conducted in the inner city with a younger, poorer population that used marijuana more heavily. Plus, Dr. Pope measured lifetime episodes of smoking marijuana, not the current number of joints smoked per week." In Dr. Bolla's study, duration of use was associated with a decrease in performance on just one neurocognitive test, which measured participants' ability to copy a complex figure.

Source

• Bolla, K.I., et al. Dose-related neurocognitive effects of marijuana use. *Neurology* 59(9):1337-1343, 2002. NN

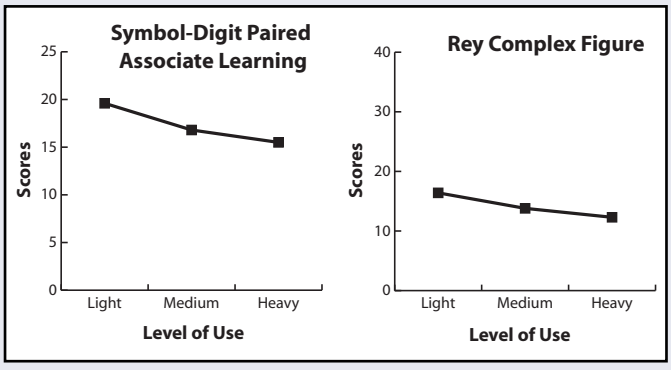
Severity of Cognitive Deficits Varies by Level of Marijuana Use

Verbal Memory. In tests of logical memory, participants were read a paragraph and then asked questions about it immediately and again after 30 minutes. The Rey Auditory Verbal Learning Test (RAVLT) involved listening to 15 words and then repeating them either immediately (Trial 1) or after 30 minutes. The response patterns suggest difficulty with information recall, not with the acquisition or retention of information, according to the researchers.



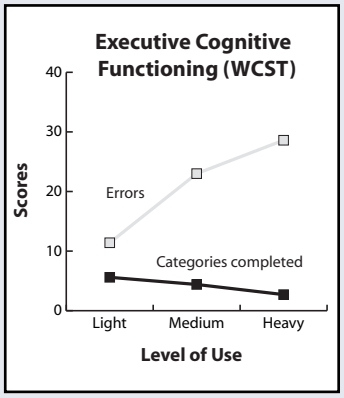
Heavy marijuana users scored below light users on all measures of verbal memory, although they had no problems recognizing previously learned material.

Visual Memory. In the Symbol-Digit Paired Associate Learning test, seven flash cards featuring a symbol and a number were displayed; test subjects were then shown only the symbol and asked to supply the number that originally accompanied that symbol. In the Rey Complex Figure tests, participants were shown a complex figure and asked to draw it from memory.



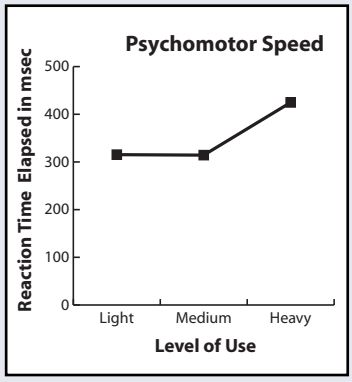
Heavy marijuana use affected visual learning and memory.

Executive Cognitive Functioning. In the Wisconsin Card Sorting Test (WCST), participants are asked to sort cards by three different concepts that the tester changes. This exercise tests the subject's ability to switch cognitive sets based on feedback. Poor performance indicates difficulty incorporating feedback to guide and change incorrect response selection.



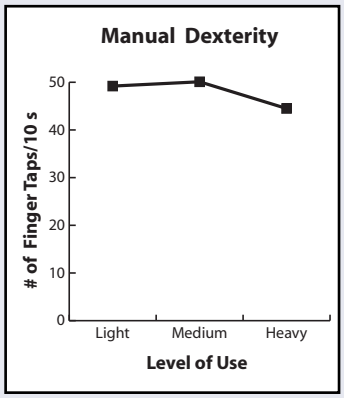
Greater marijuana use was associated with lesser executive cognitive functioning.

Psychomotor Speed. Participants were given the California Computerized Assessment Package (CALCAP) to measure their psychomotor speed. In this test, they were asked to hit a button when they saw a light flash. Reaction time measured the milliseconds that elapsed between the light flashing and the participant hitting the button.



Heavy marijuana users showed slower reaction times on a test of simple reaction time.

Manual Dexterity. For this test, participants were asked to tap a finger on their left hand. Manual dexterity was determined by the number of taps made in 10 seconds.



Heavy marijuana use was associated with lower performance on manual dexterity measures.

Researchers, Practitioners "Blend" Knowledge to Enhance Drug Abuse Treatment

By Mary Beth Hatem, NIDA NOTES Contributing Writer

NIDA Director Nora D. Volkow, M.D., presented the keynote address to nearly 700 participants at the 2003 Blending Conference.

September's 2-day NIDA conference, "Blending Clinical Practice and Research: Forging Partnerships in the Rocky Mountain States to Enhance Drug Abuse Treatment," drew an overflow crowd of 680 drug abuse researchers, administrators, and treatment providers to Westminster, Colorado. This was the third in the conference series established by NIDA to help narrow the gap between clinical practice and clinical research.

"Blending is NIDA's short name for some of its most important work," explained NIDA Director Nora D. Volkow, M.D. "By blending, we mean the integrated research-practice partnership so necessary to achieve our full potential and relieve the suffering and waste of human life caused by drug abuse and addiction."

Conference co-sponsors included NIDA and the Rocky Mountain Clinical Trials Network (CTN) Node, one of 17 regional research and training centers within NIDA's nationwide CTN system. CTN, now in its fifth year, was developed to test the effectiveness of new and improved interventions in community-based treatment settings with diverse populations. The CTN has completed five clinical studies, and 21 other studies are underway or in development. Other key conference partners were the University of Colorado Health Sciences Center, home of the Rocky Mountain CTN node; the Colorado State Office of Alcoholism and Substance Abuse Services; the Alcoholism and Substance Abuse Providers of Colorado; the Mountain West Addiction Technology Transfer Center; and Signal Behavioral Health, Inc., the largest managed services organization for publicly funded treatment in Colorado.

Twelve topical workshops facilitated research-practice partnerships by highlighting research findings and implications, as well as considerations for putting research into practice and for future research. Each workshop presented critical issues and opportunities facing the drug abuse treatment and research communities, including assessment and treatment of psychiatric comorbidity, new brain research on craving and decision making, and treatment of opioid dependence with buprenorphine/Nalaxone combination tablets. Issues specific to Colorado were also on the agenda, including blending research and practice in Native American populations and ruralizing urban treatment. At the conclusion of the conference, clinical skills training workshops were held on evidence-based treatment approaches.

In her keynote address, Dr. Volkow drew on her dual clinical and research backgrounds in discussing progress in integrating drug abuse research into clinical practice. The gap between research and practice exists in every medical field, she noted, but closing that gap is imperative. "Knowledge is not a luxury," she commented. "Science that is not used is useless." Dr. Volkow reviewed recent scientific investigations that are enhancing our understanding of drug abuse and addiction and providing new treatment options through painstaking study of the workings of genes, protein expression, neurological circuitry, human behavior, and social networks. "Understanding drug abuse and addiction requires a systems approach . . . and treatment requires a multipronged approach," she said.

Although advances in science are leading to improved treatment options, Dr. Volkow observed, much more work is needed to ensure that they are used in community treatment settings. Toward that end, she said, NIDA will be increasing funding for research on translating research findings into clinical practice and

continued on page 14

Hard-to-Treat Smokers May Benefit From Medication That Acts on Dopamine

By Patrick Zickler, NIDA NOTES Staff Writer

Nearly 23 percent of Americans 18 and older smoke cigarettes. Although this figure represents a substantial decrease since smoking rates were at their highest in 1965, most current smokers say they would like to quit. According to the Centers for Disease Control and Prevention, 71 percent of smokers interviewed in 2000 said they wanted to quit smoking, with 41 percent having tried to quit in the preceding year.

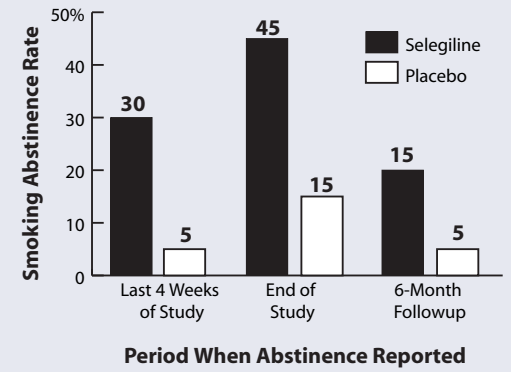
Many of those who still smoke are the hardest to treat, having failed to stop despite numerous attempts. Their efforts to quit are frustrated by nicotine's addictive effects, which result in large part from the drug's ability to trigger and sustain release of the pleasure-producing neurotransmitter dopamine in the brain. At Yale University in New Haven, Connecticut, NIDA-supported researchers have found that selegiline, a medication currently used by physicians primarily to delay the progression of symptoms in Parkinson's disease, can help smokers who want to quit but have been unsuccessful with other treatments.

"Our research group focused on difficult-to-treat smokers, who aren't responsive to nicotine replacement therapy or to bupropion," says Dr. Tony George of Yale University School of Medicine. "Many smokers who attempt to quit fail because of the powerful withdrawal symptoms smokers experience when they stop smoking. There is strong evidence that the symptoms of nicotine withdrawal are associated with sharp declines in dopamine levels, so we thought a medication that acts to boost dopamine levels might be of benefit." In Parkinson's disease, which involves massive loss of dopamine-producing cells, treatment with selegiline helps the brain retain its stores of dopamine longer by inhibiting the activity of monoamine oxidase-B, an enzyme that breaks down dopamine.

To evaluate the effect of selegiline in smoking cessation treatment, the researchers recruited 40 smokers (75 percent Caucasian, 15 men, 25 women, average age 49) who had unsuccessfully tried (at least 3 times and some as many as 20) to stop smoking and described themselves as highly motivated to quit. Over 8 weeks, all participants received weekly smoking cessation counseling that included motivational enhancement for the first 3 weeks of the study and work on relapse prevention strategies for the last 5 weeks. They took pills containing either placebo or 5 mg selegiline once a day for the first week and twice a day for the remaining 7 weeks. Twenty participants (8 men, 12 women) received selegiline and 20 (7 men, 13 women) received placebo. All participants were allowed to smoke during the first 2 weeks of the study, and a "quit date" was set for the first day of the third week.

At the end of the eighth week, 45 percent of the participants who received selegiline reported they had not smoked during the preceding week, compared with 15 percent of those receiving placebo. Measurement of carbon monoxide levels in the participants' exhaled breath verified their self-reports. The difference between the two treatment groups was even more pronounced when reports of 4-week abstinence were considered: Compared with 5 percent of the placebo group, 30 percent of those who received selegiline reported they had not smoked in the last 4 weeks of the study. Six weeks after the study ended, 20 percent of the selegiline group were still not smoking, compared with 5 percent of those who received placebo.

Selegiline Helps Smokers Quit, Remain Abstinent Longer



Smokers who received selegiline plus counseling were more likely to stop smoking and remain abstinent than smokers who received placebo and counseling.

"In this study, selegiline appeared to substantially improve outcomes for smokers who have had a difficult time stopping," says Dr. Ivan Montoya of NIDA's Division of Treatment Research and Development. "The results, which are better than those typically achieved by smokers using nicotine replacement therapy to help them quit, offer strong confirmation that controlling the dopamine system could be an important approach to successful treatment of nicotine addiction, particularly for smokers with a history of unsuccessful quit attempts. Our next step is to confirm this in a much larger trial with several hundred smokers."

Source

George, T.P., et al. A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biological Psychiatry* 53(2):136-143, 2003. NN

School Prevention Program Effective With Youths at High Risk for Substance Use

By Robert Mathias, NIDA NOTES Staff Writer

Science-based drug abuse prevention programs designed for all students in the same middle school grade have significantly reduced early use of alcohol, tobacco, and other substances. The benefits of these programs persist through later grades, resulting in reductions in substance use through high school. Originally developed and tested among white students in suburban schools, such universal prevention programs subsequently have been shown to deter racially diverse, multiethnic students in urban schools from initiating substance abuse. Now, a NIDA-supported study has shown that the prevention effects of one such program extend not only to students who are initially at low or moderate risk of early drug abuse, but also to those at higher-than-average risk of initiating substance abuse.

The study found that Life Skills Training (LST), a thoroughly tested, school-based, universal prevention program, significantly reduced initiation of drug use among urban, minority middle school students who were doing poorly academically and had substance-abusing friends. Previous research has linked these academic and social factors to increased risk of subsequent substance abuse. Yet 1 year after the LST program, these high-risk youths reported lower rates of cigarette, alcohol, and inhalant use than a comparable group of nonparticipating students. Moreover, LST participants who reported using these substances used them in lower amounts than nonparticipants.

"This study shows that a school-based universal prevention program, like LST, can have substantial prevention effects for diverse youths, regardless of their level of risk for substance abuse," says Dr. Gilbert J. Botvin, who developed the LST program and directs the Institute of Prevention Research at Weill Medical College of Cornell University in New York City. This finding counters the prevailing notion that while universal programs are effective with broad groups of youths, more targeted and tailored interventions are needed for high-risk youths, Dr. Botvin says.

In the study, Drs. Botvin and Kenneth W. Griffin, also of Cornell, tested the LST program's effectiveness in a controlled trial with minority, mostly African-American and Hispanic, inner-city students in 29 New York City schools. Schools were randomly assigned to receive either the LST program or the standard New York City substance abuse education curriculum. Regular classroom teachers delivered LST to participating 7th-graders in 15 sessions, each approximately 45 minutes long, that inculcated anti-drug norms and taught drug refusal, personal management, and general social skills.

After determining that the LST program substantially reduced early drug use among participants in the broad student population, the researchers focused on a subgroup of 426 students identified as being at higher-than-average risk of initiating substance abuse. These students had Cs or lower grades and friends who used both alcohol and tobacco. The study also identified and tracked a control group of 331 students with a similar high-risk profile.

Baseline assessments found no significant differences in substance abuse rates between the two groups prior to the intervention. Assessments conducted 1 year later found lower rates of smoking, drinking, and inhalant and polydrug (multiple substance) abuse among participants than were seen in students in the control group. For example, 22.1 percent of control students reported smoking in the past month, compared with 15 percent of students who participated in the LST program—almost a one-third reduction in the rate of smoking. Similarly, compared with controls, program participants had a 20.8 percent lower rate of drinking, a 21.1 percent lower rate of marijuana abuse, a 90.5 percent lower rate of inhalant use, and a 30.5 percent lower rate of polydrug abuse.

Just in from the 2003 Monitoring the Future study:

- Use of any illicit drug declined significantly for 8th- and 10th-graders, for the second year in a row.
- MDMA (ecstasy) use is down significantly among 8th-, 10th-, and 12th-graders.
- Marijuana use declined significantly among 8th-graders.
- Amphetamine and tranquilizer use are down among 10th- and 12th-graders
- Steroid use declined among 10th-graders.
- Heroin and crack use remained mostly stable, with some decline among 10th- graders.
- Lifetime cigarette use dropped in all three grades, and past-month use was down among 12th-graders.
- Alcohol use was unchanged in 2003, after declining in 2002.
- Increases in past-year inhalant use by 8th-graders signal a potential problem.
- Use of Vicodin, the illicit drug most used after marijuana, and Oxycontin are high enough to raise concern.

MTF is an annual survey conducted by the University of Michigan under a NIDA grant. Since its launch in 1975, the study has surveyed high school seniors; 8th- and 10th-graders were added in 1991. The 2003 sample includes 48,467 public and private school students from 392 schools.

Students who participated in the LST program also had lower scores than did control students in composite measures of the frequency and quantity of smoking, drinking, and inhalant and polydrug abuse in the past month. Significant program impact on marijuana abuse was not found in composite measures or in rate of use 1 year after the program ended.

Additional research is needed to determine whether the initial prevention effects LST achieved in this study will lead to later reductions in more severe levels of drug abuse among high-risk youths, Dr. Botvin says. However, his past research has shown that LST's initial reductions in experimental substance abuse in general populations of students resulted in later reductions in pack-a-day cigarette smoking and polydrug use. A more recent study by Dr. Botvin extended this finding of LST's long-lasting prevention effects to the incidence of binge drinking (three or more drinks per episode) in later years among inner-city minority youths. "The proportion of binge drinkers was more than 50 percent lower in the intervention group than in the control group at both the 1-year (8th grade) and 2-year followup assessments," he notes.

"We are not saying that a universal prevention program eliminates the need for more targeted prevention and treatment programs down the line that meet the specific needs of high-risk kids who already have more severe drug and alcohol abuse problems," Dr. Botvin cautions. "Rather, we are saying that this body of research culminating in our study of high-risk students shows the utility of a universal prevention approach for reducing initial substance use across the board from lower to higher risk white and minority youths in suburban and inner-city schools. By doing that, you'll likely also reduce more severe levels of later drug involvement."

Prevention Program Reduces Substance Abuse Rates Among High-Risk Students

Substance	LST Participants	Control Group
Cigarettes	15%	22.1%
Alcohol	16.4	20.7
Marijuana	11.2	14.2
Inhalants	0.2	2.1
Polydrug*	12.6	19.7

* Past-month use of multiple substances.

One year after participating in the Life Skills Training program, urban minority students at high risk for substance use reported lower rates of past-month substance use than peers who did not participate in the program.

Sources

• Botvin, G.J., et al. Preventing binge drinking during early adolescence: One- and two-year follow-up of a school-based preventive intervention. *Psychology of Addictive Behaviors* 15(4):360-365, 2001.

• Griffin, K.W.; Botvin, G.J.; et al. Effectiveness of a universal drug abuse prevention approach for youth at high risk for substance use initiation. *Preventive Medicine* 36(1):1-7, 2003.

NN

Early Use of Drugs May Lead to Later Psychiatric Disorders

continued from page 5

marijuana, and other illicit drug use—was more strongly related in every case to later alcohol dependence or SUDs than to later episodes of MDD.

Dr. Brook cites results related to marijuana use as a particularly key finding. Earlier marijuana use showed substantial effects on later incidence of MDD, alcohol dependence, and SUDs—17, 23, and 40 percent more likely, respectively. "Use of marijuana during childhood and adolescence should not be treated as benign, but rather may signal the later development of MDD, alcohol dependence, and SUDs," she says.

Treatment providers may benefit by considering the relationship between early substance abuse and later psychiatric disorders. "Well-coordinated interventions against the earliest use of drugs may alleviate the physiological and psychosocial problems that are related to adult psychiatric disorders," says Dr. David W. Brook.

Dr. Leslie Cooper of NIDA's Division of Epidemiology, Services and Prevention Research agrees that the findings in this study are significant. She cautions, however, that results must be interpreted carefully because the study sample is 92 percent white, with 93 percent of the participants having received at least a 12th-grade education. Although the sample is not representative of the general population, it was representative of the Northeast's population when the data were originally collected, she notes. "This longitudinal data set is extremely valuable because it allows us to track the relationship between early drug abuse and later psychiatric disorders," Dr. Cooper says. "But we can't generalize these results to other populations. We need to build on this study and gather information on other populations."

Dr. Brook will continue collecting data on this cohort every 5 years. "We will be able to watch these individuals as they move into their thirties and forties and see how earlier substance use affects their functioning at that age. We can also look at transmission across generations: How will the children of participants fare?"

Source

• Brook, D.W.; Brook, J.S.; et al. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Archives of General Psychiatry* 59(11):1039-1044, 2002.

NN

You've Got Mail: *NIDA NOTES* Online Delivery Coming Soon

NIDA NOTES subscribers can soon opt to receive our newsletter by e-mail, which links to the online version on NIDA's Web site. You are welcome, of course, to receive both the traditional print version and e-mail notification or choose the one delivery option that works best for you.

Why choose e-mail delivery? *NIDA NOTES* will be available electronically roughly 2 weeks before our print version hits the streets—giving you a jump on the latest news in drug abuse and addiction research. And with a couple of mouseclicks, you can send others an article or an entire issue, including full-color graphics and links to abstracts or the full text of articles cited in references. However you receive *NIDA NOTES*, our newsletter will continue to provide you with coverage of critical drug abuse and addition topics, including:

- costs to society
- health consequences, including HIV/AIDS
- origins and causes
- pharmacology
- prevention
- short- and long-term effects
- treatment
- trends and patterns
- and more.

NIDA supports over 85 percent of the world's research on drug abuse and addiction. Soon, you can know even faster the results and promise of that research. For an e-mail subscription, please visit www.drugabuse.gov or e-mail your request for electronic delivery to nidanotes@masimax.com. NN

Researchers, Practitioners "Blend" Knowledge to Enhance Drug Abuse Treatment

continued from page 10

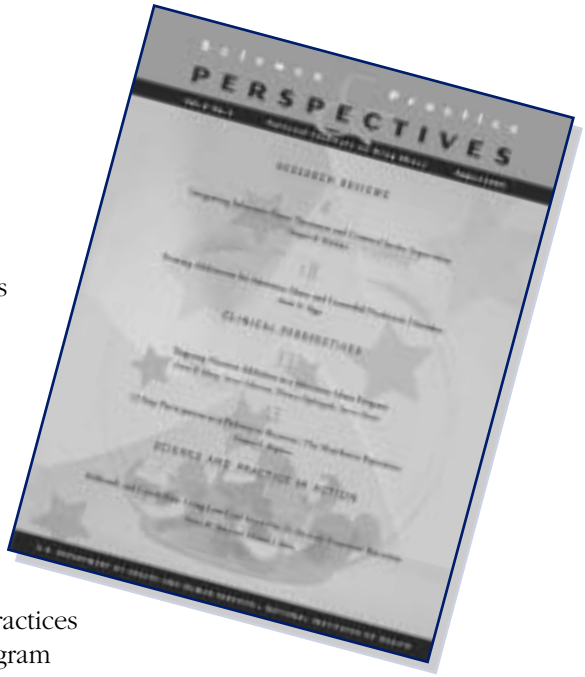
considering how the CTN might be helpful in this respect without detracting from its primary mission.

In his plenary address, Thomas J. Crowley, M.D., University of Colorado School of Medicine, reviewed the relationship between research and practice based on his 40-year career. Through the years, science and practice have partnered in "an intimate relationship" that requires both following and leading, he noted. As a medical student, Dr. Crowley was taught that alcohol and drug use was evidence of moral deterioration. He urged participants not to forget that this position changed because of laboratory results—evidence that drugs of abuse produced drug-seeking in animals. Science and practice have each advanced the other, Dr. Crowley observed, and will continue to do so. Likewise, advances in the lab and the clinic continue to impact the social context of funding and treatment. "As scientists, clinicians, and administrators—we all walk the same journey and we are each part of a social movement."

T. Ron Jackson, M.S.W., executive director of Evergeen Treatment Services in Seattle, Washington, delivered the inaugural Eileen Pencer Lecture in honor of the dedicated and talented CTN leader and administration of New York's Lower Eastside Service Center who died this year. "Eileen wanted us to keep the research real, never letting us forget than the patient is CTN's target," Mr. Jackson recalled. He urged treatment providers to incorporate research results into their own practices, while cultivating a research mindset as part of their professional development. "We need to think of research as a systematic, disciplined way of listening to our patients."

Closing remarks by clinician and researcher Paula Riggs, M.D., Principal Investigator of the Rocky Mountain CTN addressed the future of research-practice integration. She observed that the CTN's hard work and concrete accomplishments are reasons for optimism, as are the week's events. "The hope of all of us who worked on this year's program," said Dr. Riggs, "is that this conference will create a legacy of initiatives for blending research and practice for years to come." NN

Researcher-Practitioner Dialogue Continues in NIDA Journal



The second issue of *Science & Practice Perspectives*, published in August, exemplifies how the vital dialogue between scientific investigators and clinical practitioners is improving drug abuse treatment and research. NIDA Director Dr. Nora D. Volkow says, "The blending of drug abuse research and clinical practice can spur progress, so this journal represents some of our most important work."

In the new issue of *Perspectives*, a biannual publication, authoritative researchers and clinicians address topics from criminal justice supervision of drug abuse treatment to the melding of 12-step treatment with other addiction therapies. Research Reviews include:

- "Integrating Substance Abuse Treatment and Criminal Justice Supervision," by Dr. Douglas B. Marlowe. The author describes a research-based strategy for coordinating substance abuse treatment and criminal justice supervision to achieve more economical use of resources as well as levels of monitoring appropriate to individual clients' drug use and criminal justice history.
- "Treating Adolescents for Substance Abuse and Comorbid Psychiatric Disorders," by Dr. Paula D. Riggs. The author presents up-to-date research-based guidelines for treating adolescents with both substance abuse and psychiatric problems and identifies key issues for further investigation.

Clinical Perspectives authors and articles are as follows:

- "Targeting Nicotine Addiction in a Substance Abuse Program," by Dr. James R. Sharp, Steven Schwartz, Thomas Nightingale, and Dr. Steven Novak. The authors describe the rationale, history, policies, and practices of a smoking cessation program that is obligatory for all clients of an inpatient substance abuse program.
- "12-Step Participation as a Pathway to Recovery: The Maryhaven Experience and Implications for Treatment Research," by Dr. Gregory S. Brigham, of Maryhaven, Inc., analyzes how 12-step treatment works as part of a total addiction recovery, focusing on the example of one longstanding, community-based treatment facility.

Both Clinical Perspectives articles recommend how other programs can adapt these approaches to their own treatment program and how additional research could lead to understanding and better treatment outcomes.

In the article "Fishbowls and Candy Bars: Using Low-Cost Incentives To Increase Treatment Retention," Drs. Nancy M. Petry and Michael J. Bohn discuss their experience with low-cost contingency management approaches to drug abuse treatment. Along with the research background, they offer experience-based advice on successful implementation and mistakes to avoid, tips on overcoming common problems, and illustrative accounts of patient responses.

Also in this issue:

- Panel discussions examine and expand the implications of issues raised in each Research Review and Clinical Perspectives article;
- "Graphic Evidence" presents a striking visual representation of brain activity during cue-induced craving; and
- A continuing education (CE) quiz for counselors provides an opportunity for readers to earn two NAADAC-certified CE hours.

Perspectives is mailed to more than 25,000 drug abuse researchers and prevention/treatment providers nationwide and is available at NIDA's Web site (www.drugabuse.gov). Individuals and organizations can subscribe to the journal at no cost online or by e-mailing nidaperspectives @masimax.com. NN

NIDA NOTES

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

Managing Editor (Acting): Martha Pien, *MasiMax Resources, Inc.*

Editorial Board: David Anderson, *Cochair; Public Health Advisor, Public Information and Liaison Branch, Office of Science Policy and Communications*

Beverly Wyckoff Jackson, *Cochair; Chief, Public Information and Liaison Branch, Office of Science Policy and Communications*

Thomas G. Aigner, Ph.D., *Division of Neuroscience and Behavioral Research*

Khursheed Asghar, Ph.D., *Chief, Basic Sciences Review Branch, Office of Extramural Affairs*

Jessica J. Campbell, Ph.D., *Health Science Administrator, Division of Epidemiology, Services and Prevention Research*

J.C. Comolli, *Public Health Advisor, Center on AIDS and Other Medical Consequences of Drug Abuse*

Lee Cummings, *Special Assistant to the Director, Division of Treatment Research and Development*

Bennett Fletcher, Ph.D., *Research Psychologist, Division of Epidemiology, Services and Prevention Research*

Robin Mackar, *Office of Science Policy and Communications*

Wallace Pickworth, Ph.D., *Pharmacologist, Intramural Research Program*

Vincent Smeriglio, Ph.D., *Research Psychologist, Center on AIDS and Other Medical Consequences of Drug Abuse*

Jack Stein, Ph.D., *Chief, Services Research Branch, Division of Epidemiology, Services and Prevention Research*

Frank Vocci, Ph.D., *Director, Division of Treatment Research and Development*

Cora Lee Wetherington, Ph.D., *Psychologist, Behavioral Sciences Research Branch, Division of Neuroscience and Behavioral Research*

Staff Writers: Robert Mathias and Patrick Zickler, *MasiMax Resources, Inc.*

Contributing Writers: Contributing Writers: Martha Pien, *MasiMax Resources, Inc.*, Mary Beth Hatem, and Jill Schlabig Williams

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

This publication was produced and printed by MasiMax Resources, Inc., under Contract No. N01DA-1-1107 from the National Institute on Drug Abuse.

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

NIDA NOTES covers drug abuse research in the areas of treatment and prevention, epidemiology, neuroscience, behavioral science, health services, and AIDS. The publication reports on research; identifies resources; and promotes communication among clinicians, researchers, administrators, policymakers, and the public. Readers are encouraged to identify subject areas they would like to see highlighted.

NIDA NOTES is a publication of the U.S. Government produced by the National Institute on Drug Abuse. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget. Except for material specifically identified as copyrighted, all materials appearing in **NIDA NOTES** are in the public domain and may be reproduced without permission. Citation of the source is appreciated.

Subscriptions and Changes of Address

To subscribe free to **NIDA NOTES**, or to change the address for your current subscription, contact the **NIDA NOTES** Subscriptions Department at:

MasiMax Resources, Inc.
1375 Piccard Dr., Suite 175
Rockville, MD 20850
Fax: 240-632-0519 **E-mail:** nidanotes@masimax.com
Phone: 240-632-5614

Additional Copies

To order additional copies of **NIDA NOTES**, contact:

National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, MD 20847-2345
Phone: 800-729-6686 or 301-468-2600
TDD number: 800-487-4889
Fax: 301-468-6433 **E-mail:** info@health.org

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Institute on Drug Abuse
6001 Executive Boulevard
Room 5213
Bethesda, MD 20892-9561

ADDRESS SERVICE REQUESTED

Official Business
Penalty for Private Use $300

PRSRT STD
POSTAGE AND FEES
PAID
DHHS/NIH
PERMIT NO. G-827

NIH Publication No. 04-3478
Printed December 2003