NIDA NOTES

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Cocaine-Related Environmental Cues Elicit Physiological Stress Responses

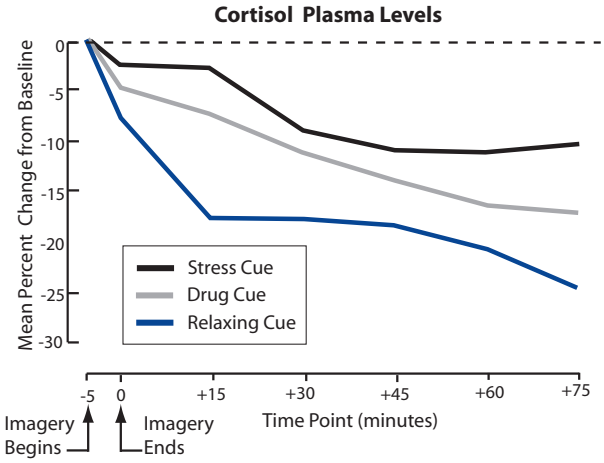
By Lori Whitten, *NIDA NOTES* Staff Writer

Overcoming addiction is in part a learning process, and people in recovery work to make and maintain healthy changes. In behavioral therapy, clinicians help patients learn techniques to avoid or navigate safely through experiences that evoke powerful urges to consume drugs: stressful situations and the people, places, and things the patient associates with past drug-taking experiences. Recent NIDA-funded research has demonstrated that cocaine-addicted patients respond to these drug-associated features in the environment as if they were stressful situations, with the release of adrenaline and other hormones that increase pulse rate and blood pressure, among other effects. The investigators also found that these responses of cocaine abusers take a long time to normalize, perhaps indicating that the drug heightens sensitivity to stress.

Dr. Rajita Sinha and colleagues at the Yale University School of Medicine in New Haven, Connecticut, conducted their study with 54 cocaine-addicted men and women, aged 21 to 50, at an inpatient research facility. Before entering treatment, the patients had abused cocaine for an average of 9 years; immediately prior to treatment, they had, on average, consumed the drug 3 or more times per week and spent $224 weekly to buy the drug. Almost all (94 percent) consumed cocaine in its smoked form (crack).

What's Inside

Drug Cues Induce Physiological Stress Responses in Cocaine-Addicted Patients



Cortisol levels, which normally decline in the morning, remain relatively high in cocaine-addicted patients after they listen to a five-minute tape of a stressful or drug-related experience, but not after they listen to a relaxing tape. Cue-induced elevations in cortisol and other stress hormones persisted for up to 30 minutes.

Each patient had been abstinent for 2 weeks prior to the laboratory sessions.

To study physiological and emotional responses to stress and cocaine-related cues in the laboratory, the investigators drew on the patients' individual experiences. They elicited from each patient detailed accounts of three past personal experiences: one very stressful, one relaxing, and one specifically related to taking cocaine. From each patient's stories, the researchers created three tape recordings that would, when played back, rekindle his or her feelings of stress, relaxation, and cue-induced craving (see "Reliving A Stressful Situation: Excerpt From a Guided Imagery Tape"). To enhance the strength of the responses,

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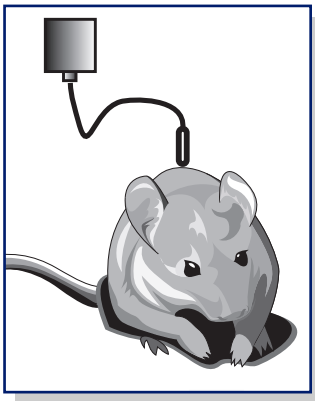

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NIDA News and Information at Your Fingertips

Information about NIDA research, programs, and events is quickly and easily accessible through **NIDA's home page** at ***www.drugabuse.gov***.

NIDA's home page includes:

- Information on Drugs of Abuse
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- Calendar of Events
- Links to NIDA Organizational Units
- Funding Information
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NIDA Intensifies Focus on Marijuana Abuse

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

More than 96 million Americans have smoked marijuana at least once. Marijuana abuse is particularly prevalent among adolescents: Of the more than 2 million people who abuse the drug for the first time every year, two-thirds are between 12 and 17 years of age.

The damaging effects of marijuana fall heavily on adolescents and young adults. Half of all patients admitted to treatment for marijuana abuse are younger than 21. Cognitive impairments caused by marijuana linger a month or more after an individual's last exposure, and the damage is dose dependent—the more a person smoked prior to abstinence, the more marked are the deleterious effects on visual perception, verbal and visual memory, executive function, and manual dexterity, among other mental capabilities (see "Cognitive Deficits in Marijuana Smokers Persist After Use Stops," *NIDA NOTES*, Vol. 18, No. 5, p. 8). Loss of social and intellectual growth because of these impairments may have a lifelong impact on a person's experience and achievement. As well, compared with teens who never smoke marijuana, a boy or girl who smokes marijuana before age 17 is more than twice as likely to abuse opioids, three times as likely to abuse cocaine or other stimulants, and nearly four times as likely to abuse hallucinogens later in life (see "Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence," *NIDA NOTES*, Vol. 18, No. 4, p. 11).

NIDA is intensifying efforts to fully understand the effects of marijuana exposure from the earliest ages through adolescence and young adulthood. This research (see RFA DA-04-016, "Consequences of Marijuana Use on the Developing Brain," at *http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-04-016.html*) will provide new insight into the mechanisms by which marijuana affects brain development, a continuum that begins before birth and lasts into early adulthood. We are encouraging research projects that focus on the effect of marijuana during all phases of neurological development, from the neurogenesis and cell differentiation that takes place in the womb to the refinement of connections among cells that continues past adolescence. Our research initiative will produce a fuller understanding of normative brain development. It also will illuminate the importance of family and social contexts in adolescence as well as the differing biological and environmental factors that precede marijuana use or nonuse.

NIDA also is expanding support of research to develop treatments for marijuana abuse (see RFA DA-04-014, "Medications Development for Cannabis-Related Disorder," at *http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-04-014.html*). There is a clear public health need for interventions to alleviate withdrawal symptoms and to help chronic abusers deal with social and other factors that make stopping marijuana abuse difficult. NIDA's expanded research agenda will encourage development of medications to counter marijuana dependence through animal studies as well as Phase I and Phase II clinical trials with humans. Some medications will be aimed at marijuana-associated disorders such as intoxication, delirium, psychosis, and anxiety. Other medications may address specific aspects of addiction recovery, such as withdrawal, craving, relapse, and complications such as cognitive impairment, sleep disorders, and depression and other mood disorders that often accompany marijuana abuse.

Successful comprehensive treatment of marijuana-related disorders will require a multidisciplinary approach. Therefore, NIDA's marijuana medications development initiative will encourage investigation of treatments that include behavioral intervention. This broad focus, building on the insights to be gained through increased understanding of marijuana's developmental impact, will help reduce the health costs and alleviate the damage inflicted by widespread abuse of this dangerous drug. NN

ATHENA Program Reduces Substance Abuse By Girls on High School Sports Teams

By Patrick Zickler, *NIDA NOTES* Staff Writer

High school girl athletes who participated in a recently evaluated NIDA-supported nutritional and behavioral guidance program were less likely than non-participating peers to engage in substance abuse and other high-risk behaviors. Girls on teams that used ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives) were less likely than girls on teams that received only printed information to use diet pills or so-called performance-enhancing substances such as steroids, amphetamines, and muscle-building supplements. The ATHENA team members also were less likely to be sexually active and more likely to wear seat belts, and they experienced fewer injuries during the sports season.

In the ATHENA program, developed at the Oregon Health & Science University in Portland by Drs. Diane Elliot and Linn Goldberg, selected team leaders receive a 90-minute orientation and then conduct discussion and activity sessions during scheduled team practices. Each team leader works with a squad of approximately six teammates, following a manual that is much like a playbook, with scripts for eight 45-minute sessions dealing with the harmful consequences of substance abuse and other unhealthy behaviors and the beneficial effects of good diet and exercise. Along with providing information, the workbook engages the girls in activities such as critiquing magazine advertising and other media influences on self-image; classifying various foods according to carbohydrate, fat, and protein content; and determining the best balance of dietary fuels for athletic training and competition. Each ATHENA athlete uses a pocket-sized nutrition and training guide to monitor diet and exercise. Coaches and other staff members receive an orientation to assist the team leaders as timekeepers and facilitators for the sessions.

To evaluate ATHENA, the researchers recruited 40

ATHENA's Impact on Behavior and Nutrition

	Control Group		Experimental Group	
	Before Intervention	After Intervention	Before Intervention	After Intervention
Nutrition, Exercise Abilities, and Beliefs*				
Tracking protein intake	2.11	2.03	2.16	2.54
Eating more protein in the last 2 months	3.95	3.92	4.19	5.10
Knowing how to lift weights to improve strength	5.48	5.61	5.15	5.92
Self-rating of skill in strength training	5.48	5.61	5.15	5.92
Believing that nutrition affects sport performance	5.75	5.64	6.06	6.01
Additional Health-Influencing Behaviors				
Rode in a car with an alcohol-consuming driver**	0.44	0.42	0.41	0.26
Knowing how to turn down unhealthy weight-loss behaviors*	5.80	5.77	5.91	6.14
No. of sport injuries so could not train in the last 3 months	0.32	0.36	0.32	0.26
Intentions Toward Future Disordered Eating Behaviors and Drug Use*				
Diet pill use	1.74	1.79	1.87	1.62
Vomiting to lose weight	1.66	1.76	1.62	1.57
Tobacco use	1.56	1.79	1.55	1.58
Creatine (muscle-building supplement) use	1.87	1.77	1.72	1.51

Data are significant differences expressed as the mean.
**Scored using a seven-item agreement scale ranging from 1 (strongly disagree) to 7 (strongly agree).*
***Scored 0 to 4 for times occurred with 0 indicating none; 1, once; 2, two or three times; 3, four or five times; or 4, six or more times.*

High-school girls who participated in the ATHENA curriculum were less likely to engage in drug abuse or other unhealthy behaviors than were girls given printed information about drugs and nutrition.

girls' sports teams in 18 public high schools in northwest Oregon and southwest Washington. Teams from half the schools followed the ATHENA program. The other teams received printed information about eating disorders, substance abuse, and sports nutrition, but did not take part in discussion or group activities. Before the first practice of their sports season and again within 2 weeks after the season ended, each girl filled out a questionnaire about her eating patterns; nutritional awareness; use of diet pills, amphetamines, anabolic steroids, and muscle-building supplements; and other health-related behaviors.

Preseason survey results were essentially the same for girls on ATHENA teams and those in the control group, but in postseason surveys the ATHENA participants reported significant decreases in risky behaviors. According to Dr. Elliot, the control athletes were three times more likely to begin using diet pills and almost twice as likely to begin using other body-shaping substances, including amphetamines, anabolic steroids, and muscle-building supplements, during the season. The use of diet pills went up among control girls, while it fell to approximately half its preseason level among ATHENA girls. ATHENA athletes also were more likely to use seatbelts and less likely to ride in a car with a driver who had been drinking, to believe claims in advertising, or to agree with the statement that men find thin women most attractive.

Adolescent girls experience social and cultural pressure about body image, and they look to each other for role models more than they follow the guidance offered in classrooms, research has shown. The competitive environment of athletic programs may compound the pressure, leading to disordered eating and the use of body-shaping substances such as steroids, diuretics, laxatives, and even tobacco, Dr. Elliot says. However, the athletic environment can exert positive peer pressure also. The researchers modeled ATHENA's use of sports teams as a forum to promote healthy lifestyles on a similar program they developed for male high school athletes (see "Like ATHENA, ATLAS Targets High School Athletes"). "We found that the team-based approach used in ATLAS [Athletes Training and Learning to Avoid Steroids] produced greater positive change than did a more conventional classroom-style approach," Dr. Elliot says.

"Two features of the ATHENA program are striking," says Dr. Larry Seitz of NIDA's Division of Epidemiology, Services and Prevention Research. "One is the peer-based rather than classroom-based approach, and the other is the effect on a wide spectrum of linked behaviors, from vomiting to induce weight loss to believing nutritional claims in advertising. Improvements like these can help young female athletes make healthier choices throughout life, not just during the sport season."

The Oregon Health & Science University Sports Medicine Web site, *www.ohsu.edu/hpsm/index.html*, provides more information about ATHENA and ATLAS.

Like ATHENA, ATLAS Targets High School Athletes

ATLAS (Athletes Training and Learning To Avoid Steroids), the result of 5 years of NIDA-supported development, is a program for male high school athletes to help reduce use of anabolic steroids and other sport supplements, alcohol, and other drugs. ATLAS emphasizes the immediate impact of alcohol and other drugs on athletic performance and conditioning rather than potential and abstract long-term effects. An evaluation of the program in 15 high schools showed that, compared with a control group, 1 year after completion of the program, ATLAS-trained students had:

- Half the incidence of new use of anabolic steroids and less intention to use the drugs in the future;
- Less use of alcohol, marijuana, amphetamines, and narcotics;
- Less use of "athletic enhancing" supplements;
- Less likelihood of engaging in hazardous substance abuse behaviors such as drinking and driving;
- Reduced substance abuse risk factors; and
- Improved substance abuse protective factors.

Source

• Elliot, D.L., et al. Preventing substance use and disordered eating: Initial outcomes of the ATHENA program. *Archives of Pediatric and Adolescent Medicine* 158(11):1043-1049, 2004.

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Cocaine-Related Environmental Cues Elicit Physiological Stress Responses

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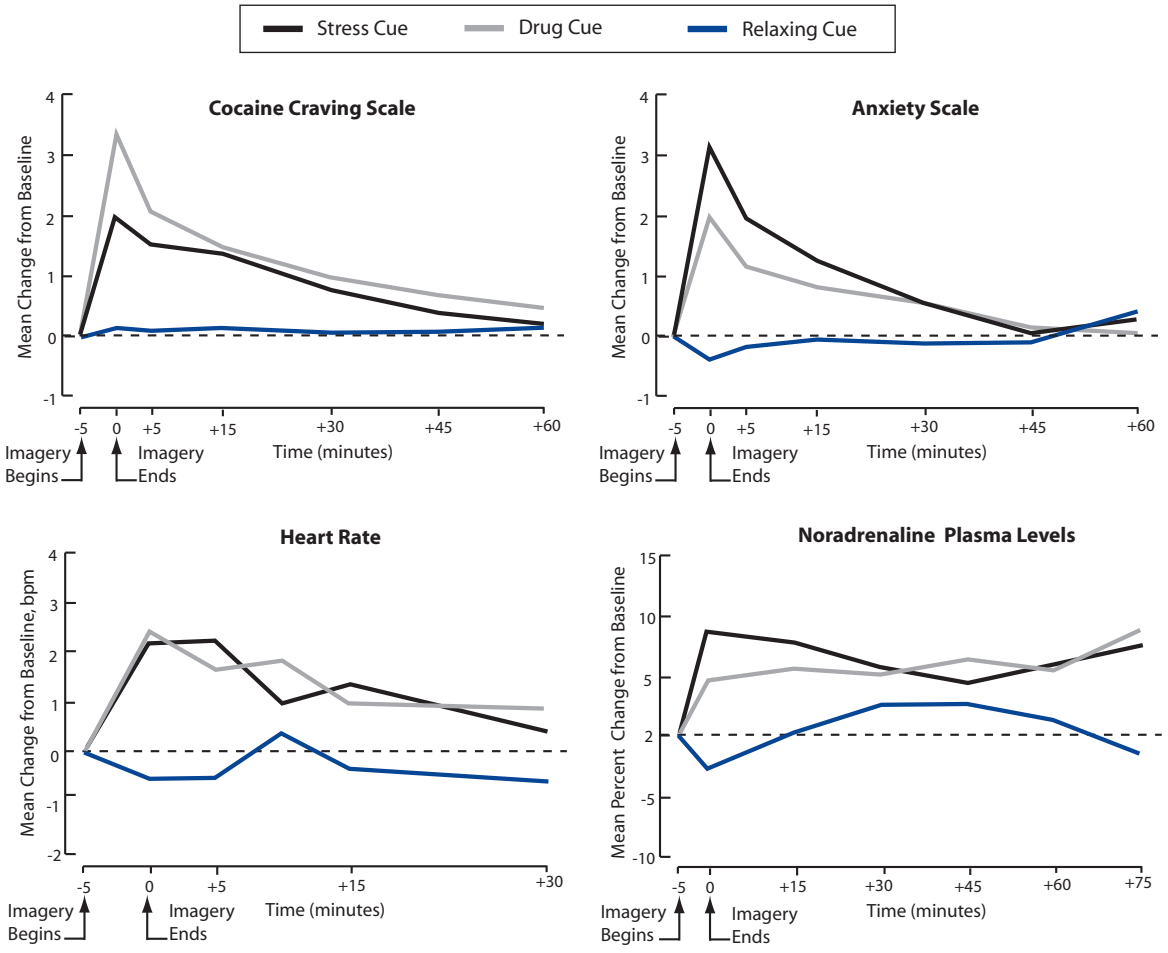
the researchers trained the patients in guided imagery—how to relive a scene mentally while listening to a tape, as if it were happening at that moment.

Each patient participated in three 3-hour testing sessions. Throughout each session, the patient sat on a hospital bed wearing headphones, an intravenous catheter in one arm for drawing blood, a blood pressure monitor on the other arm, and a pulse sensor on one finger. For the first hour, an adaptation period, the patient practiced tape-guided progressive relaxation while periodically reporting anxiety and craving levels. Next, the patient heard one of the 5-minute tapes based on his or her own experiences, introduced with a message to "Close your eyes and imagine yourself in the following situation." Over the three testing sessions, conducted on different days, the patient relived all three of his or her stressful, drug-related, and relaxing experiences. When the tape finished, the patient rated the vividness of the scenes and his or her cocaine craving and anxiety. A nurse monitored the patient's pulse and blood pressure and drew blood samples periodically during the testing and for 75 minutes after the tape ended.

The researchers found similar responses to the stressful and drug-related tapes. Patients' pulses increased and their blood pressure rose while they listened to both. Blood levels of biochemicals involved in the stress response—including noradrenaline, cortisol, prolactin, adrenocorticotropic hormone, and adrenaline—were elevated when participants listened to stressful and drug-related tapes compared with when they listened to the relaxing tapes. Stressful and drug-related tapes also increased participants' subjective responses—craving and anxiety—compared with the relaxing tapes.

The stress responses generated in the study were in keeping with previous laboratory studies with cocaine abusers, says Dr. Sinha. "Stress reactions after both the stressful and drug-related tapes in this study were similar to or higher than those observed when researchers have used other techniques to induce stress—for example, requiring participants to prepare and give a speech in 5 minutes."

Drug and Stress Cues Induce Arousal, Craving, and Anxiety in Cocaine-Addicted Patients



Cocaine-addicted patients showed greater arousal and increased pulse and biochemical stress response, as well as increased craving and anxiety, when they mentally relived a 5-minute stressful or drug-related personal experience than when they listened to relaxation tapes. Arousal persisted for up to 30 minutes after the imagery stopped.

Stress Response Persists

Normally the stress response, including the adrenaline rush and increased heart rate, breathing, and blood pressure, returns quickly to normal once a threat has passed. "What was different and striking in our patients was that they continued to show stress after the tape was over—up to 30 minutes longer than would be expected," says Dr. Sinha. The results suggest that cocaine abusers' stress responses may take longer to normalize, perhaps indicating a heightened reactivity to stress.

Dr. Sinha and her colleagues are following up with patients in this study to determine whether those with more intense biological reactions and craving in response to the tapes are more likely to relapse. Similarly, they are using brain-imaging technology to determine whether neural activation after patients listen to stressful and cocaine-related tapes predicts relapse. In addition, to determine whether drug abuse is related to a heightened stress response, Dr. Sinha is planning studies that compare the stress reactivity of addicted and non-addicted people.

"Understanding the effects of chronic drug use on how people handle stress—particularly the craving and biological responses that occur after stressful situations—will allow us to develop medications that are effective against craving induced by drug and stressful environmental cues," says Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment.

Source

• Sinha, R., et al. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology* 170(1):62-72, 2003. NN

Reliving a Stressful Situation: Excerpt From a Guided Imagery Tape

There is a knock on the door. You feel tense all over your arms, legs, back, and forehead. "You are going to get evicted," he says. Your heart beats faster. You had been paying rent to your boyfriend, but he never gave it to them. You feel the butterflies in your stomach. You have no place to go. "The second notice will be here in a couple of days," he is saying, but your mind is racing. You feel shaky all over. "What am I going to do? Where will I go?" you say. You have cramps in your stomach. You grit your teeth and call your mother. She has no money to help you. You've run out of options. There is a deep intense pain inside you and tears come to your eyes. NN

Brain Awareness Week Teaches Kids How Their Brain Works

The fifth annual Brain Awareness Week took place March 14-18 at the National Museum of Health at the Walter Reed Medical Center in Washington, D.C., as part of a worldwide series of coordinated events designed to teach young people about the brain. NIDA, along with other participating NIH Institutes, presented short lessons on brain health and neuroscience to area students.

Brain Awareness Week mobilizes an international partnership of government agencies, scientific organizations, universities, and volunteer groups organized by the Dana Alliance for Brain Initiatives, a nonprofit organization of more than 200 pre-eminent neuroscientists dedicated to advancing education about the brain. The Week is designed to communicate the progress and promise of neuroscience research to an ever-larger worldwide audience.

NIDA's portion of the Washington-area event was "Who Wants To Be a NIDA Neuroscientist?" Patterned after the popular TV program "Who Wants To Be a Millionaire," the game encouraged students to test what they know about how illicit drugs and nicotine act in the brain. If they were unsure of an answer, a NIDA neuroscientist was on hand to serve as their "lifeline." Winners received a certificate, and everyone received NIDA publications designed for students and parents.

NIDA Science Education Coordinator Dr. Cathrine Sasek asks students a question as part of the "Who Wants To Be a NIDA Neuroscientist?" game at the Brain Awareness Week program in Washington, D.C.

NIDA Science Education Coordinator Dr. Cathrine Sasek said, "As in the past, this year's Brain Awareness Week activities were wonderfully successful. The students had a great time playing the game, and those who won received a certificate signed by [NIDA Director] Dr. Nora D. Volkow declaring them a 'Neuroscientist for the Day.' In addition, NIDA gave out bags of our many publications for kids to each student."

The Dana Alliance hosts a Brain Awareness Week Web site for the public at *http://www.dana.org/brainweek*, which includes an international calendar, education resources, downloadable graphics, puzzles, publications, and general information about the Week. NN

Researchers Investigate Cocaine "Abstinence Syndrome"

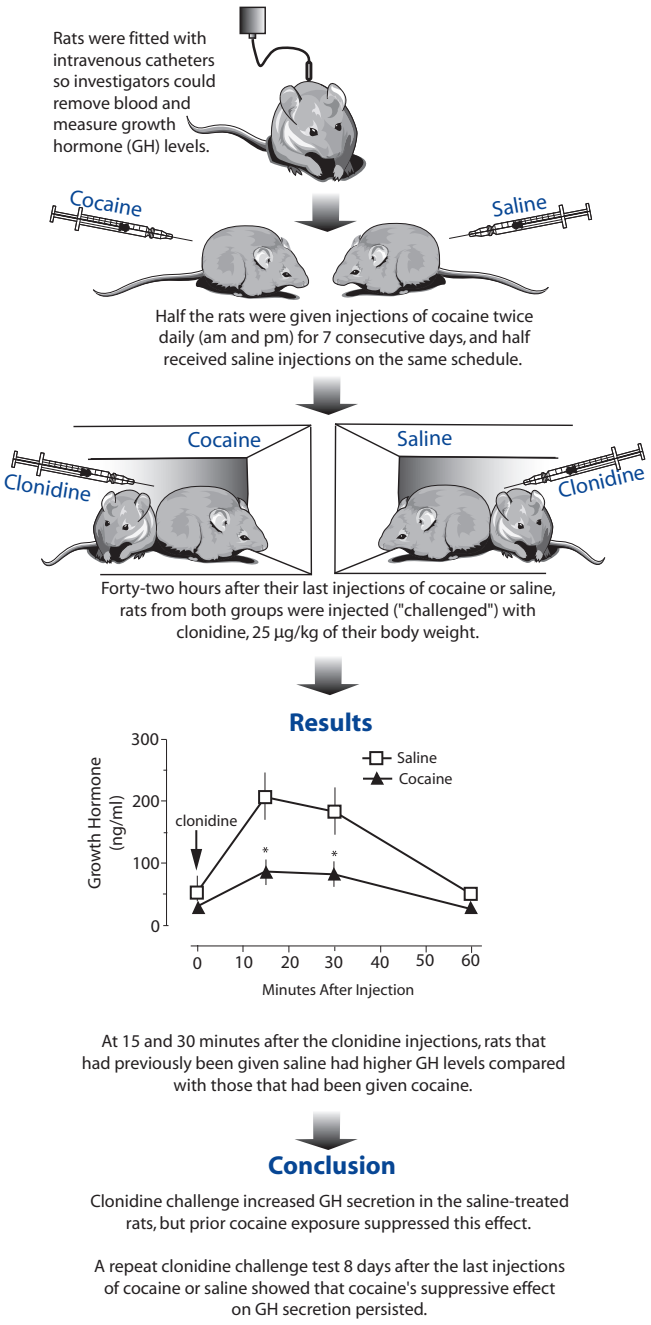
By Lori Whitten, *NIDA NOTES* Staff Writer

Researchers have long focused on motivation as the centerpiece of the addiction puzzle, based on the observation that in many addicted individuals, compulsive drug-seeking behavior overtakes the most fundamental motivators, including food and sex. Now, however, researchers are beginning to examine another aspect of addictive drugs—their powerful and long-lasting effects on mood. People who have recently stopped abusing stimulant drugs commonly experience "abstinence syndrome": low energy, irritability, restlessness, an inability to feel pleasure, and problems with concentration. Anxiety and panic attacks also are sometimes associated with cocaine abstinence. Addiction researchers are examining the neurobiology underlying abstinence syndrome with an eye toward improving current therapies' ability to alleviate these symptoms and prevent relapse.

NIDA investigators concentrated recently on the impact of cocaine on the neurotransmitter norepinephrine (NE), one of the two neurochemicals most responsible for mood. Stimulation of brain cells by serotonin and NE is central to positive mood, feeling energetic, and maintaining focus as well as sleep, appetite, and coping with stress. Two recent animal studies, one conducted by investigators at NIDA's Intramural Research Program (IRP) in Baltimore and another by NIDA-funded researchers at Harvard Medical School's New England Primate Research Center in Southborough, Massachusetts, suggest that cocaine may compromise NE's ability to stimulate brain cells by altering a communication protein, called the α2-adrenergic receptor, on the surfaces of the cells.

In the Baltimore study, Dr. Michael Baumann and colleagues hypothesized that by giving rats cocaine regularly—twice-daily injections at 15 mg/kg of the animals' body weight for 7 days—and then abruptly stopping it, they would reduce the α2-adrenergic receptors' responsiveness. To assess the adrenergic system in the cocaine-exposed, now "abstinent" rats, the researchers used the clonidine challenge procedure, which indirectly indicates α2-adrenergic receptor activity by measuring how much plasma levels of growth hormone (GH) increase following exposure to the drug clonidine (see "Clonidine Challenge Test Results Suggests That Cocaine Abuse Desensitizes Adrenergic System"). Confirming the researchers' hypothesis, the cocaine-exposed animals showed a blunted GH response—less than half that of saline-exposed animals—15 and 30

Clonidine Challenge Suggests That Cocaine Abuse Desensitizes Adrenergic System



Clonidine elevates growth hormone (GH) secretion in rats, a response mediated through the α2-adrenoreceptors in the brain. When rats are exposed to repeated cocaine injections, GH secretion in response to clonidine is lowered. The clonidine challenge test is used to measure α2-adrenoreceptor sensitivity in humans as well as animals.

minutes after the clonidine challenge. The rats' response was still low, but returning toward normal, when the researchers repeated the challenge procedure 8 days after daily injections stopped.

The findings suggest that cocaine consumption and cessation may lower recovering individuals' moods by desensitizating the α2-adrenoreceptors, but the results are preliminary. "The adrenergic system is complex, with multiple pathways in the brain and body," says Dr. Baumann. "We still have much to learn about how drug exposure affects all these pathways, how it affects serotonin, and how they both influence growth hormone."

People with depression secrete less GH in response to the clonidine challenge than do those without the condition, a clinical finding that suggests possible links between NE receptor function, mood disorders, and cocaine withdrawal. "Although investigators are only beginning to characterize norepinephrine's role in addiction, a growing body of animal and clinical research suggests important connections between the adrenergic system, mood and anxiety disorders, and the depression-like symptoms experienced by people trying to overcome cocaine addiction," Dr. Baumann says.

A Role in Relapse?

In a study that explored the chemical basis of mood and cocaine relapse, Dr. Roger Spealman and colleagues hypothesized that blocking α2-adrenergic receptors in monkeys would generate anxiety and induce a resumption of previously extinguished cocaine-seeking behavior.

The researchers trained monkeys to seek cocaine by pressing a lever. When the monkeys reached a high rate of lever pressing, the researchers disconnected it from the injection device. The monkeys kept trying the lever for a while, but with no more cocaine forthcoming, gradually left off. The investigators hypothesized that giving monkeys a drug to reduce NE activity would make the animals anxious, and the anxiety would intensify their urge for cocaine to the point where they would resume pressing the lever despite recent experience of its futility.

Dr. Spealman and colleagues gave the now "abstinent" animals various doses of two α2-adrenergic blocking agents, yohimbine and RS-79948, in separate test sessions. Both α2-adrenergic receptor blockers set the animals to pressing the lever again. The increase ranged from 1.5 to 4 times the response to injections of sterile water, depending on the dose and drug. The yohimbine injections also increased physiological and behavioral signs of anxiety: salivary cortisol levels and self-grooming and scratching.

> ***"It makes sense physiologically that the adrenergic system might play a role in addiction; cocaine activates norepinephrine as much as it stimulates dopamine."***

To confirm that yohimbine's behavioral effects were due to its inhibition of the α2-adrenergic system, rather than any of the other neurotransmitter systems this agent affects, the researchers conducted further experiments. First, they gave the monkeys yohimbine plus clonidine, a drug that selectively blocks yohimbine's effects on the α2-adrenergic receptors. With this regimen, the animals resumed lever pressing hardly or not at all. Next, the researchers gave the monkeys yohimbine plus flupenthixol, a drug that reduces dopamine activity and has no effect on yohimbine's inhibition of α2-adrenergic activity. Under this regimen, the animals did resume lever pressing. Both of these findings pointed to α2-adrenergic suppression as the key to yohimbine's effects in the first experiment. Yohimbine did not stimulate movement or make the animals restless, which indicates that it worked by blocking receptors, not simply by mimicking the stimulant effects of cocaine.

"It makes sense physiologically that the adrenergic system might play a role in addiction; cocaine activates norepinephrine as much as it stimulates dopamine," says Dr. Spealman. Work by others suggests that cocaine abuse leads to long-term desensitization of the NE system in areas of the brain involved in reward and stress-induced reinstatement of drug-seeking. "This has led some researchers to speculate that the desensitized adrenergic system increases vulnerability to further norepinephrine disturbances—for example, those caused by stress or drug re-exposure—which may increase relapse risk," explains Dr. Spealman.

Researchers continue to seek to unravel the complexities underlying withdrawal and relapse to drug-taking. If, as scientists now think, these phenomena arise from sequential alterations in both the reward and mood pathways, "addiction medications may have to target different neurotransmitters at various stages of abstinence," says Dr. Minda Lynch of NIDA's Division of Basic Neurosciences and Behavior Research.

Sources

- Baumann, M.H.; Milchanowski, A.B.; and Rothman, R.B. Evidence for alterations in α2-adrenergic receptor sensitivity in rats exposed to repeated cocaine administration. *Neuroscience* 125(3):683-690, 2004.
- Lee, B.; Tiefenbacher, S.; Platt, D.M.; and Spealman, R.D. Pharmacological blockade of α2-adrenoreceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology* 29(4):686-693, 2004.

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First-Grade Intervention Reduces Smoking Initiation in Middle School

By Lori Whitten, *NIDA NOTES* Staff Writer

First graders who receive systematic help in learning to concentrate and control their behavior are less likely to begin smoking in the middle-school years than children who receive no special intervention, a NIDA-funded study has found. Investigators at the Center for Prevention and Early Intervention at The Johns Hopkins Bloomberg School of Public Health in Baltimore developed two interventions that are broad-based rather than specific to substance abuse, and have been testing them in schools since the early 1990s.

In 1993, Drs. Sheppard Kellam, Nicholas Ialongo, and colleagues randomly assigned first-grade teachers and 678 of their students in Baltimore public schools to either a classroom-centered or a family-school partnership (FSP) intervention, or to the standard curriculum. During the summer, the investigators gave the teachers who would participate in the classroom-centered intervention 60 hours of training in strategies for managing behavior and helping children overcome academic problems. This training used detailed manuals, checklists, and other standardized materials. Meanwhile, the teachers, school social workers, and psychologists who would participate in the FSP intervention learned how to conduct workshops designed to help parents improve their behavior management and homework-assistance skills and partner with school professionals.

School staff delivered both interventions throughout the students' year in first grade. During this time, the investigators visited the classrooms and conducted regular assessments of the interventions, and met monthly or as often as needed with the participating school staff.

At the end of seventh or eighth grade, when the children were 13 years old on average, the researchers followed up to see whether those who received the interventions had fared any differently from the control group. Overall, 39 percent of the 566 young people they were able to assess at this time had initiated smoking. Of those who participated in the classroom-centered or FSP interventions, however, a significantly lower percentage had begun smoking—34 and 36 percent, respectively—compared with 47 percent of the control group. The classroom-centered intervention was associated with a smaller prevalence of reported cocaine and heroin use in middle school—3 percent compared with 7 percent in the standard curriculum; however, the researchers note that only 29 of 566 participants had tried these drugs, a number of subjects too small to draw definitive conclusions. Although many youths in both the intervention and control groups had tried alcohol, marijuana, or inhalants, the percentage was marginally smaller among those who experienced the interventions.

Dr. Ialongo cites the long-term significance of the findings and advocates extending such efforts throughout children's school careers. "Fewer kids smoking in middle school eventually should produce a measurable clinical and public health impact in the form of reduced smoking-related disease in these children's later lives. These gains probably will be more sizable if teachers present these interventions throughout elementary school and add standard approaches to drug abuse prevention in the middle-school years," he says.

Building the Interventions

The classroom-centered and FSP programs represent the culmination of more than three decades of research on human development and problem behaviors. Evidence from studies in the 1970s and 1980s suggested that certain characteristics evident as early as first grade—poor academic achievement, difficulty with concentration, and aggressive and shy behaviors—are associated with later substance abuse, depression, and antisocial behavior. However, the field lacked randomized, controlled intervention trials showing that a reduction of these characteristics can reduce later problem behaviors in the general population of children. Dr. Kellam, then at the Prevention Intervention Research Center at The Johns Hopkins

University, and his colleagues Lisa Ulmer and Hendricks Brown, began in the mid-1980s to develop, refine, and assess interventions that address antecedents of problem behaviors—efforts that eventually produced the classroom-centered and FSP programs.

"Effective prevention programs encompass key elements of raising healthy children—positive child-rearing practices at home, good behavior management at school, and a strong school-family connection. Youths need consistent messages and support at home and school for healthy development. Forging a strong link between the activities, values, and practices across the family, school, and community throughout childhood and adolescence has enduring effects," says Dr. Shakeh Kaftarian of NIDA's Division of Epidemiology, Services and Prevention Research.

Dr. Ialongo and his colleagues have shown other lasting effects of the interventions in previous studies. For example, boys who showed aggressive behavior at the beginning of first grade and received the intervention improved by sixth grade.

"It's common sense that improvements in first-graders' concentration and readiness to learn produce better students and citizens and may delay or prevent tobacco and illegal drug use. But it's not enough to intervene once in first grade to improve academic achievement and classroom behavior—prevention is a long-term commitment," says Dr. Ialongo.

Source

• Furr-Holden, C.D.M., et al. Developmentally inspired drug prevention: Middle school outcomes in a school-based randomized prevention trial. *Drug and Alcohol Dependence* 73(2):149-158, 2004. NN

How Much Will it Cost? Is it Feasible?

Researchers at the Center for Prevention and Early Intervention are conducting an economic evaluation of the classroom-centered and family-school partnership (FSP) interventions. To date, investigators have identified the cost of particular program elements, but do not yet have a cost-benefit analysis of the program as a whole. For example, the mathematics and reading enhancements offered in the classroom-centered intervention cost about $1,200 per classroom or $9.60 per student, given that the materials could be used for about 5 years. Adding one senior teacher to help with implementation and tutoring students who have difficulties would cost about $65,000 per year for salary and benefits.

To maximize economies, the investigators worked within the school system's established planning structure and training programs to implement the interventions. In the classroom-centered intervention, for example, the school system incorporated the mathematics and reading enhancements into its scheduled curriculum revision and long-term investment plan. This approach avoided duplication of materials and training effort.

Teachers learned how to implement the interventions during regularly scheduled training sessions. Ongoing supervision of the program, which requires about 10 hours a week per classroom, usually is assumed by a seasoned teacher on staff who is already accustomed to mentoring. This teacher is formally designated to assist other teachers in implementing the classroom-centered intervention and to work with children who need additional help with school assignments or behavior. Even using these cost-saving strategies, a typical elementary school with an 18-teacher staff would need to add at least one senior teacher.

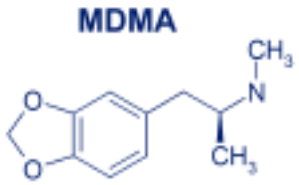
Elements of the FSP intervention—including parent workshops, childcare, and incentives for participation—present costs beyond what is typically allotted in most elementary school budgets. But educators and researchers can mitigate these costs by marshalling resources already in place. Offering parent workshops during scheduled parent-teacher conferences, for example, does not add costs and makes these activities possible for busy parents. Parent-teacher organizations can enhance parental involvement and provide childcare. Schools serving socioeconomically disadvantaged communities are eligible for Federal funds, which they may use to hire a parent liaison who can help mobilize parents' participation.

It is easier to calculate the costs involved in the program than it is to determine the benefit, or the money saved, for example, in reduced special education assessment and services. As the students in the Baltimore study progress through life—they are now in 12th grade—the investigators will follow up and measure how the experience benefited them. Next year the researchers will determine if more children in the intervention groups completed high school, a long-term economic benefit.

Even in a large economically challenged school system such as Baltimore's, Dr. Ialongo believes that "programs such as ours are not outside the realm of possibility. The key point is that prevention requires a sustained and highly organized effort that identifies the necessary resources and uses them in a cost-effective way." NN

Plant Derivative Blocks MDMA's Hyperthermic Effects

By Patrick Zickler, *NIDA NOTES* Staff Writer



The club drug MDMA ("Ecstasy") suppresses the body's temperature-regulating system, occasionally with fatal consequences. Abusers have developed temperatures as high as 109°F, suffered multiple organ failure, and died. Treatment in these emergencies has been limited mainly to cooling the victim with ice or refrigerating blankets. Now, NIDA-supported research suggests that nantenine, a compound derived from the berries of a plant used in Asian traditional medicine (*Nandina domestica*, or heavenly bamboo), may be able to block and reverse hyperthermia and other effects of MDMA.

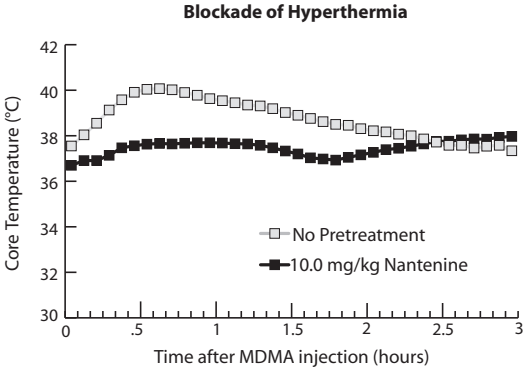
Dr. William Fantegrossi began investigating nantenine's properties after seeing a diagram of its chemical structure presented by Dr. Yasushi Ohizumi of Tohoku University in Sendai, Japan. "The compound's chemical structure suggested that it might have neurobiological activity," Dr. Fantegrossi says. "It looks like two MDMA molecules joined at the hip." Dr. Fantegrossi speculated that nantenine, like MDMA, might bind in the brain to serotonin and α1-adrenergic receptors. If so, nantenine could block MDMA from occupying those sites and causing destructive changes.

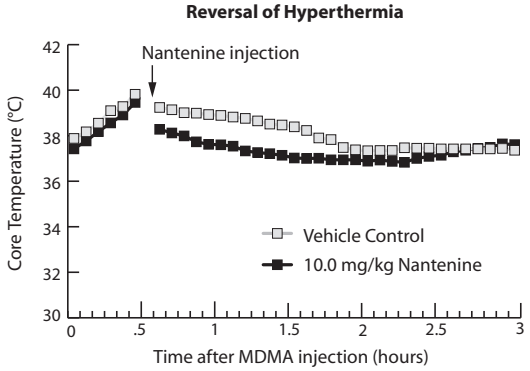
To test this possibility, Dr. Fantegrossi and colleagues at the University of Michigan in Ann Arbor injected mice with nantenine and MDMA. In a first study, nantenine pretreatment protected mice from developing a hyperthermic response when they were subsequently injected with MDMA. "The complete attenuation of hyperthermia following pretreatment with nantenine was interesting," Dr. Fantegrossi observes, "but a far more useful clinical effect would be reversal of hyperthermia previously induced by MDMA." To test for this effect, the scientists injected mice with MDMA, and 30 minutes later, when the mice were hyperthermic, injected half of them with nantenine. Body temperatures of the mice receiving nantenine rapidly returned to baseline, while the other mice remained hyperthermic for close to 3 hours.

Further tests confirmed nantenine's ability to block some of MDMA's other effects. In one group of mice, pretreatment with nantenine reduced MDMA-induced motor activity: One hour after injection with MDMA, untreated mice were three times as active as mice pretreated with nantenine. In another part of the study, researchers injected mice pretreated with nantenine with a lethal dose of MDMA; the nantenine reduced mortality by 50 percent. Research now under way, says Dr. Fantegrossi, suggests nantenine has similar anti-MDMA effects in monkeys.

"If nantenine has effects in humans similar to those we've seen in mice, it will be an enormous benefit," Dr. Fantegrossi says. "In emergency rooms today, doctors have no medication much more sophisticated than ice to treat patients for the hyperthermia sometimes triggered by MDMA." The compound also has important potential as a tool for use in other research projects, observes Dr. Jerry Frankenheim of NIDA's Division of Basic Neurosciences and Behavior Research. "There are few MDMA-specific research tools that we can use to investigate the mechanisms of MDMA action in the body," he says. "At least in animals, this molecule looks very promising."

Nantenine Blocks and Reverses MDMA's Hyperthermic Effect





Source

• Fantegrossi, W.E., et al. Nantenine: An antagonist of the behavioral and physiological effects of MDMA in mice. *Psychopharmacology* 173(3-4):270-277, 2004.

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CTN UPDATE: Blending Initiative Introduces Two New Training Programs

By Lori Whitten, *NIDA NOTES* Staff Writer

Addiction treatment providers will soon have access to two training programs designed to help them integrate buprenorphine treatment protocols and the Addiction Severity Index (ASI) into clinical practice. The training programs address the needs of counselors, nurses, and other providers besides physicians. The training on ASI, a widely used substance abuse assessment instrument, will help counselors use ASI to develop individualized treatment plans and to monitor patient progress.

The Blending Initiative—NIDA's landmark collaboration with the Substance Abuse and Mental Health Services Administration's Addiction Technology Transfer Center (ATTC) Network—developed both training programs.

Buprenorphine Training

The Blending Initiative training product is the first to focus on the needs of drug abuse counselors, psychologists, and nurses. "There was a definite training void," says Dr. Gregory Brigham, a member of the Buprenorphine Blending Team and the Ohio Valley node of the Clinical Trials Network (CTN). "The physicians in our treatment center had no trouble finding buprenorphine training, but there were no courses for nurses who assess opioid withdrawal, administer medication, and monitor patients' progress or for clinicians providing concurrent psychosocial therapies."

Treatment programs send providers for training at one of 14 regional ATTC sites. In a 1-day session, providers learn about buprenorphine treatment, the neurobiology of opioid addiction, and the differences among currently available pharmacotherapies.

"Doctors don't prescribe addiction medications in a vacuum. Drug abuse counselors, psychologists, and nurses who provide and support treatment need knowledge of how the medication works and awareness of the basic issues—for example, medically assisted withdrawal—so they can better contribute to the therapeutic process," says Dr. Thomas Freese, Director of the Pacific Southwest ATTC, Director of Training for the CTN Pacific Region node, and leader of the Buprenorphine Blending Team.

S.M.A.R.T. Treatment Planning

The Blending Initiative developed a program on treatment planning in response to a shift in the addiction treatment field toward tailored treatments based on individual patient assessments. During the 1-day in-person training session at an ATTC center or the online course, clinicians obtain hands-on experience with the Specific Measurable Attainable Realistic and Time-limited (S.M.A.R.T.) treatment planning, which focuses on developing therapeutic priorities and using ASI results to write a treatment plan and progress notes. The integration of assessment and treatment planning helps clinicians remove barriers to treatment for patients. "If the assessment highlights that someone needs English-language or GED classes, then counselors can help find the appropriate wraparound services—which helps the patient's overall functioning and ability to focus in treatment," says Dr. Deni Carise, a senior scientist at the Treatment Research Institute of Philadelphia and a member of the ASI Blending Team.

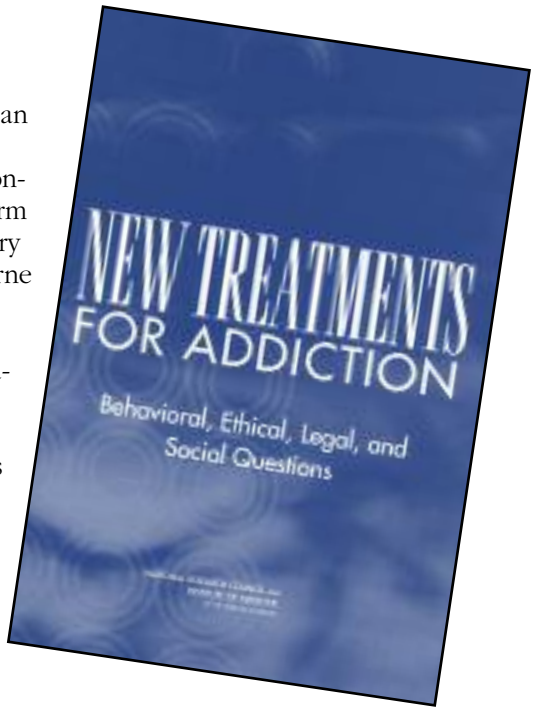
Participants receive materials that allow them to share their learning. Educators can obtain a CD-ROM version for incorporation within college courses. The online version is currently available for use by ATTCs or other public institutions. The Mid-America ATTC makes PDF versions of the materials available free of charge at *www.mattc.org*. NN

NIDA Deputy Director Honored With Presidential Award

Dr. Timothy P. Condon, Deputy Director of NIDA, was awarded the 2004 Presidential Rank Award for Meritorious Senior Professionals. This honor is awarded each year to a small number of career Senior Executives in recognition of exceptional long-term accomplishments. There were only 24 Meritorious Senior Professional Rank Awards conferred in 2004, honoring executives, professionals, and scientists who achieve results and consistently demonstrate strength, integrity, industry, and a relentless commitment to excellence in public service. Dr. Condon, who earned a Ph.D. in neuroscience from the College of Medicine, Ohio State University, joined NIDA in 1992. In 1996, he became NIDA's first Associate Director for Science Policy. In January 2004, NIDA Director Dr. Nora D. Volkow named Dr. Condon Deputy Director of NIDA. NN

Institute of Medicine Report Recommends NIDA Research Agenda for New Addiction Therapies

By Patrick Zickler, *NIDA NOTES* Staff Writer



A mother asks a pediatrician to vaccinate her child against nicotine's pleasurable effects, practically eliminating the possibility that the child will become a smoker. A patient in treatment for heroin addiction receives an injection of sustained-release medication that will prevent her from feeling the drug's euphoric effects for a year. As current drug abuse research brings such scenarios closer to realization, NIDA has begun to study the broad implications of these and other new types of preventive treatment. These therapies underscore the need to balance therapeutic benefits and ethical considerations, particularly if the person receiving treatment—a minor child or a person involved in the criminal justice system, for example—is not the person who chooses it.

At NIDA's request, the National Research Council's Institute of Medicine (IOM) identified ethical, legal, and behavioral issues that must be considered in the development and application of active and passive immunotherapies and sustained-release medication. The Institute's 306-page report recommends a set of guiding principles as NIDA-supported research pursues the development of these potentially powerful new preventive interventions.

Immunotherapies destroy drug molecules before they reach the brain. Active immunotherapy involves a vaccine that stimulates the body's immune system to create antibodies against drugs in the same way that an inoculation creates antibodies against polio or measles virus. Passive immunotherapy involves periodic injections of antibodies rather than stimulation of the immune system; an example of this type of therapy is tetanus immune globulin, which contains antibodies to provide short-term protection for someone whose injury may have exposed them to soil-borne tetanus bacteria. Sustained-release therapies involve injection or implantation of long-acting formulations of medications that are released over a period of weeks or months to block the effect of drugs in the brain.

The IOM report identifies ways to meet the challenges these interventions are likely to pose for researchers, treatment providers, policymakers, parents, and the public. Because the treatments may have lifelong effects, IOM recommends long-term studies involving animals of different ages, as well as their offspring, before human studies are undertaken.

IOM also recommends studies that can be used to establish clear guidelines for use of the new therapies in circumstances that are inherently coercive or nonconsensual, such as in the criminal justice system, child welfare cases, or the protective immunization of minor children. What, for example, are the possible legal consequences of administering immunotherapy medications to children or adolescents? Competent adults have the right to decline medical treatment, but the legal situation is more complicated when the patient is a minor and decisions made by others on his or her behalf may have a lifelong effect. Immunotherapies will leave long-lasting biological traces that can be detected in routine blood or urine tests. Such markers could label patients as drug abusers long after they have entered sustained recovery, which could discourage some from utilizing these treatments. In its report, IOM says the development of immunotherapy and sustained-release medications highlights the need to understand addiction as a chronic medical condition that requires long-term management, a partnership between primary medical care and addiction treatment, and integration of psychosocial services into the treatment environment. The IOM report recommends that NIDA support models that integrate the new pharmacotherapies with psychosocial services in addiction treatment and primary care settings that reduce the stigma of substance abuse treatment.

The full report, *New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions*, is available online at *www.nap.edu/catalog/10876.html.* NN

Brain Power! Aims To Instill Lifetime Interest in Science

Brain Power! The NIDA Junior Scientist Program takes students through a step-by-step exploration of science. The Web-based program describes what scientists do, the various functions of the brain and nervous system, and the effects of drugs on the nervous system and other parts of the body. In-class science investigations, videotapes, and supplementary activities linked to other areas of the curriculum enable students with different learning styles and strengths to engage in the material. *Brain Power!* makes learning fun and sets young students on the road to a lifelong interest in science.

There are two Junior Scientist programs, one geared toward kindergarten and first-grade students, the other for second- and third-graders. The programs begin with the premise that a group of children has formed a *Brain Power!* Club that receives missions from NIDA to solve problems or scientific questions. To maneuver through these challenges, students turn to Corty, an animated brain that helps them ask appropriate questions and ultimately solve the problems. The programs are structured so that each of the five or six (depending on the program) modules builds on the knowledge gained in previous ones. Students first learn about scientists who study the brain. Subsequent topics follow logically and progress from meeting these scientists to learning about the brain and how to keep it healthy.

Brain Power! materials consist of a video, written materials for students, a parent newsletter, and a teacher's guide for each module. The program conforms to the National Science Education Standards, which encourage scientific exploration, development of hypotheses, and interactive group work and presentation. NIDA is developing materials for children in the fourth and fifth grades.

The Brain Power! curriculum is available through the National Clearinghouse for Alcohol and Drug Information at *www.health.org*, and at *www.backtoschool.drugabuse.gov*. NN

NIDA Junior Scientist Curricula Lay The Foundation for Substance Abuse Prevention

The modules in the Brain Power! curricula build on each other to instill essential knowledge and critical thinking skills. The second- and third-grade curriculum provides the following lesson plan:

- **Module 1**: *Ooey Gooey! Making Sense of Scientific Inquiry*, an introduction to the steps of scientific inquiry: to observe, hypothesize, experiment, and conclude.
- **Module 2:** *Brains in a Box: What Your Brain Can Do*, describes the functions of the four major parts of the brain—cerebral cortex, cerebellum, brain stem, and limbic system.
- Module 3: *Sending and Receiving Messages*, presents the basics of neurotransmission—the process of nerve cells communicating with each other.
- **Module 4:** *Medicines and Drugs: What's Helpful, What's Harmful*, teaches the differences between medicines and drugs.
- **Module 5:** *The Science Behind Smoking*, discusses nicotine, how it changes the brain, and how those changes may result in addiction to tobacco products.
- **Module 6:** *What Drugs Really Do*, tops off the curriculum with an embedded assessment for the entire program.

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