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New Avenues of Research Explore Addiction's Disrupted and Destructive Decision Making

By Arnold Mann, NIDA NOTES Contributing Writer, and Patrick Zickler, NIDA NOTES Staff Writer

One of the hallmarks of addiction is the compulsive seeking and use of drugs, even in the face of mounting harmful consequences. Addicted individuals repeatedly make self-destructive decisions—for example, choosing immediate gratification, such as relief from craving, despite that choice's long-term negative consequences, which include loss of health, employment, and quality of life. These decisions are made in the brain's frontal region, where benefits and risks are weighed and choices are made. NIDA-supported research has begun to shed light on the underlying neurobiological mechanisms by which drugs disrupt the "thinking" regions of the frontal brain and lead to the destructive decisions that characterize addiction.

At the University of Iowa, Dr. Antoine Bechara and colleagues evaluated decision making through use of a computerized card game that involved a conflict between short- and long-term gain or loss. In an initial study, they found that a majority of substance-dependent individuals made poor decisions, choosing high immediate gratification without regard

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Substance Abusers Choose Short-Term Rewards Despite Mounting Losses

Researchers used a computerized card game to study substance abusers' decision making. The player above has clicked on Deck A, turning up both a $100 win and a linked $300 loss (screen captures). Besides analyzing how players changed their game strategies in response to such results, the researchers measured their level of excitement with skin sensors.

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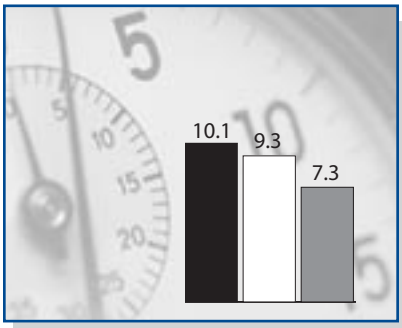

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Correction

In our story "Relationships Matter: Impact of Parental, Peer Factors on Teen, Young Adult Substance Abuse" in Volume 18, Number 2, the percentages given for substance abuse initiation in the entire study group include only illicit drug use, not tobacco use.

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The Addicted Brain: Why Such Poor Decisions?

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

The exploration of drugs' effects on decision making is a logical extension of NIDA's decades-long scientific inquiry into the neurobiology of drug abuse and addiction.

One central puzzle haunts any consideration of drug addiction, for research scientists as well as for the rest of the population: Why do men and women who have developed addiction obsessively seek and use drugs, even after the drugs no longer produce pleasure? Why do individuals who are addicted to drugs persist in behavior that damages their health and corrodes the quality of their lives? How can they make such poor decisions?

We are far from having complete answers to these questions, but NIDA-sponsored research has begun to provide clues that might lead to answers. We are beginning to understand that drugs exert persistent neurobiological effects that extend beyond the midbrain centers of pleasure and reward to disrupt the function of the brain's frontal cortex—the thinking region of the brain, where risks and benefits are weighed and decisions made.

The exploration of drugs' effects on decision making is a logical extension of NIDA's decades-long scientific inquiry into the neurobiology of drug abuse and addiction, which was the focus of a 2-day symposium held in May to honor the accomplishments of the late Dr. Roger Brown, associate director for neuroscience in NIDA's Division of Neuroscience and Behavioral Research (see "Dr. Roger M. Brown: Drug Abuse Neuroscience Pioneer," *NIDA NOTES* Vol. 17, No. 3). Many of the presentations given at that meeting summarized research that has led to our detailed understanding of crucial midbrain dopamine pathways in the ventral tegmental area and nucleus accumbens, where drugs trigger pleasure and establish reinforcement—the desire to repeat the behavior that produces the pleasure.

Other presentations described changes in distribution and density of dopamine receptors in the frontal cortex in animals and humans after drug use. Still other presentations depicted the network of neural circuits that use dopamine and other neurotransmitters to maintain finely tuned two-way communication among brain regions. These networks allow the midbrain regions, where drugs act as reinforcers, to influence and be influenced by the frontal cortical regions, the site of control over motivation, behavior, and inhibition. Taken together, these presentations sketch a rough outline of addiction as an integrated process that may explain how exposure to a drug triggers changes throughout the brain, leading from initial intoxication and reinforcement through craving to compulsive, continued drug use despite destructive consequences.

NIDA-supported research has established that the brain's frontal regions, in particular the orbitofrontal cortex, play a role in all stages of the development of addiction. For example, imaging studies conducted within NIDA's Intramural Research Program (IRP) and at Harvard Medical School show changes in cortical blood flow during initial drug exposure (see "Cocaine's Effects on Cerebral Blood Flow Differ Between Men and Women," *NIDA NOTES* Vol. 17, No. 2).

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The Addicted Brain: Why Such Poor Decisions?

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Research described in this issue (see "New Avenues of Research Explore Addiction's Disrupted and Destructive Decision Making" on page 1) shows that drug addiction is associated with altered cortical activity and decision making that appears to overvalue reward, undervalue risk, and fail to learn from repeated errors.

These recent studies illustrate the similarity of addiction to some disorders that are not associated with drugs. For example, compulsive behavior and poor choices are hallmarks of obsessive-compulsive disorder and pathological gambling. These disorders, too, are characterized by disruption of the frontal brain's capacity for reason and control. NIDA and the National Institute of Mental Health are collaborating to investigate such commonalities by developing new chemical "labels" that will allow us to use brain imaging techniques to study in more detail the structure and activity of frontal brain regions in patients suffering addiction or other decision-making disorders.

The emerging picture of addiction as a disease of compulsion and disrupted control and not merely pursuit of pleasure suggests new possibilities for treatment.

The emerging picture of addiction as a disease of compulsion and disrupted control (the frontal brain) and not merely pursuit of pleasure (the midbrain) suggests new possibilities for treatment. The neural networks that link brain regions—particularly the interwoven connections between the ventral tegmental area, nucleus accumbens, and prefrontal cortex—may offer targets for pharmacological therapies to modulate signaling that results in compulsive behavior or destructive choice.

Studying the role of frontal brain function also will contribute to development of new behavioral therapies, which help patients recognize conditions that trigger drug craving and alter their behavior to resist the compulsion. Investigators can test these cognitive-behavioral therapies in the same way, and with the same patients, that they have employed to study craving and decision making—through imaging that provides real-time images of the functioning brain.

How do drugs lead to such destructive decisions? Answering this question will not answer all questions about drug abuse and addiction. It will not tell us what role genetics or environment plays in the progression from initial pleasure to crippling compulsion. It will not explain whether a dysfunction in decision making predisposes one person to drug use, while in another person drug use triggers such a dysfunction. But looking for the answer will bring us closer to developing a comprehensive understanding of addiction and, more important, closer to more effective treatment for men and women whose lives are diminished by decisions that bring only harm. NN

Dr. Volkow Receives Aebersold Award

In addition to serving as Director of NIDA, Dr. Volkow is a leader in drug addiction research. To honor her achievement in the field, the Society of Nuclear Medicine (SNM) awarded her the 2003 Paul C. Aebersold Award for outstanding achievement in basic science applied to nuclear medicine. Dr. Volkow received the award at the Society's 50th Annual Meeting in New Orleans in June.

The first woman to serve as NIDA's director, Dr. Volkow has a long history of accomplishment in drug addiction research. Her work has focused on dopamine systems in the brains of addicted, obese, and aging individuals. She was the first to use imaging to investigate the neurochemical changes associated with addiction. Dr. Volkow has produced more than 290 peer-reviewed publications and 50 book chapters, edited 3 books, and received numerous awards, including selection in 2000 as "Innovator of the Year" by U.S. News and World Report.

The Aebersold Award is named for Dr. Paul C. Aebersold, a pioneer in the biological and medical application of radioactive materials and the first director of the Atomic Energy Commission's Division of Isotope Development at Oak Ridge, Tennessee. The Society made its first Aebersold Award in 1973. NN

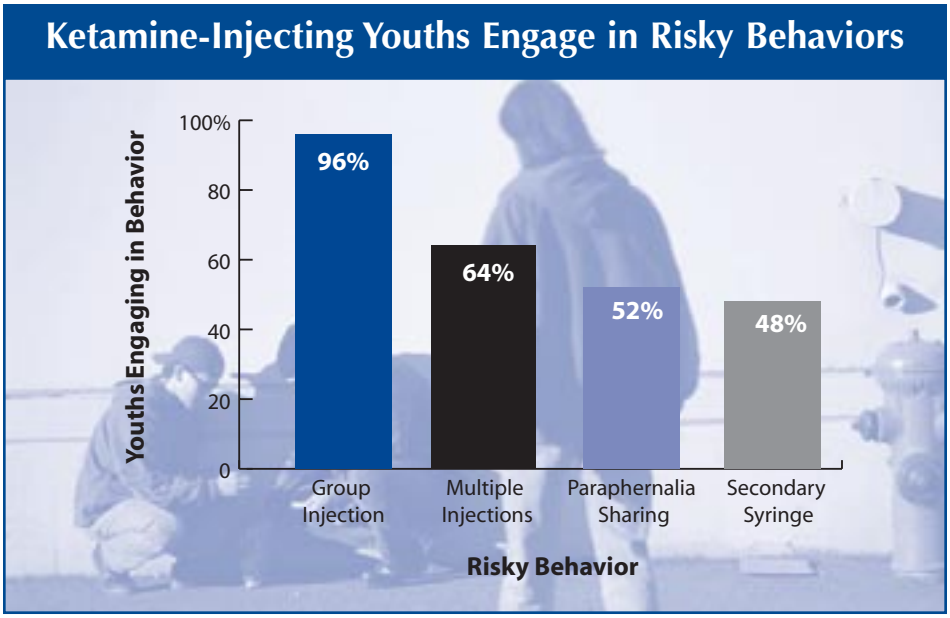
Study Suggests Ketamine Injection Poses New Disease Risk for Street Youths

By Robert Mathias
NIDA NOTES Staff Writer

Ketamine, a fast-acting, potentially lethal, general anesthetic, is abused for its dreamlike or hallucinatory effects. In recent years, drug abuse surveys have indicated that abuse of ketamine, typically by teens and young adults who snort the drug at raves and clubs, has been at low levels in the United States. Initial data from a NIDA-funded ethnographic study, however, suggest ketamine injection may be an emerging problem among young people who generally do not appear on the radar screens of formal drug abuse surveys—homeless and other street-involved youths.

A group of these high-risk youths in New York City reported they had injected ketamine many times during the past year. Moreover, they said they had participated in injection sessions in cities across America, where they often shared both the drug and injection equipment with large numbers of other youths.

"We found that ketamine injection practices among street-involved youths differ from those of other commonly injected drugs," says Dr. Stephen Lankenau of Columbia University, who led the study. Typically, drugs such as heroin, methamphetamine, or cocaine are injected intravenously (IV), once or twice in a session, and by users alone or in small groups. Injectors of these other drugs also frequently draw the drug from shared "cookers," the containers in which it is prepared for injection. By comparison, the study found that while some ketamine abusers also inject IV, more commonly abusers inject the drug into a muscle (IM), and do so many times in a single session in large groups. Instead of cookers, ketamine injectors said they generally drew the drug into their syringes from shared bottles of liquid ketamine. Though wary of the dangers of IV injection, ketamine injectors seem less aware that they also are at risk of infectious diseases, such as hepatitis C and HIV, from their IM ketamine injection practices, Dr. Lankenau says.



Youths in a New York City study reported participating in ketamine injection sessions in many cities involving multiple injections, shared bottles of ketamine, and use of syringes obtained from secondary sources—practices that increase risk for hepatitis C, HIV, and other infectious diseases.

While doing ethnographic research among young men who have sex with men, Dr. Lankenau and co-investigator Dr. Michael Clatts, of National Development and Research Institutes, Inc., in New York City, became aware that street-involved youths in the City were injecting ketamine. To examine ketamine injection practices and risks, they recruited 25 youths, most of them white males in their early twenties, from streets and parks in lower Manhattan. All the participants had injected ketamine at least once and were homeless at the time of the study and/or actively involved in "hustling" money on the street via such activities as dealing drugs, selling sex, or panhandling. In exploratory interviews, the youths detailed their most recent ketamine injection, the effects of injection, and their history of injecting ketamine and other drugs.

Although most youths in the study said their most recent ketamine injection had occurred in the New York metropolitan area, others said they last injected the drug in other cities, such as Portland, Oregon, and San Francisco, or during outdoor raves in rural areas of West Virginia and Montana. These youths also said they had previously injected ketamine in more than 30 other cities, ranging

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New Avenues of Research Explore Addiction's Disrupted and Destructive Decision Making

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for higher future costs. A subsequent study revealed that a large subgroup of these individuals are so hypersensitive to reward—either immediate or delayed—that they make choices without regard for punishment or harm. At the University of California, San Diego, Dr. Martin Paulus and other researchers combined decision-making tasks with brain imaging and found that methamphetamine-addicted individuals displayed distinctive patterns of frontal brain activity that resulted in decision making in which habit and compulsion overrode recognition of harm associated with repeated errors.

Choosing High Reward Despite High Costs

Dr. Bechara's research grew out of the observation that many substance-dependent individuals appear to exhibit a decision-making impairment similar to that of patients who have suffered injury or disease of the brain's ventromedial (VM) prefrontal cortex. Both groups appear to make choices based on the prospects for immediate benefit rather than on future consequences—either positive or negative.

In an initial study designed to confirm the hypothesis that the VM cortex plays a role in decisions made by substance abusers, the researchers evaluated decision making in three groups of participants using a computerized version of a gambling task developed by Dr. Bechara for patients with VM cortex dysfunction. The task simulated real-life decisions involving reward, punishment, and uncertain outcomes. One group included 46 individuals (21 men, 25 women, average age 33) receiving treatment for dependence on alcohol, cocaine, or methamphetamine; the second group consisted of 10 VM patients (5 men, 5 women, average age 45); and the third group had 49 people (21 men, 28 women, average age 38) with no history of either substance abuse or VM damage.

Researchers assessed participants' decisions as they made selections from four sets of cards offering different monetary rewards or punishments. Two of the sets offered high immediate gains but were poor choices over the long run; continued selection from those sets of cards eventually resulted in net monetary losses. The two other sets represented good choices, offering smaller immediate reward but yielding modest winnings over the long term. The researchers also used perspiration sensors to assess participants' physiological responses during the test as they pondered their choices and were rewarded or penalized for their decisions.

Two-thirds of the substance-dependent individuals showed impaired performance and anticipatory responses similar to those of ventromedial patients.

Substance-dependent individuals in this study fell into two categories. One group, roughly a third, was indistinguishable from the healthy controls in their decision-making performance and their anticipatory/emotional responses to reward and punishment, or loss. Two-thirds of the substance-dependent individuals, however, showed impaired performance and anticipatory excitement similar to those of the VM patients, with continued preference for immediate high gains despite mounting long-term losses. "This supports the hypothesis that poor decision making by some substance-dependent individuals is associated with a dysfunctional VM cortex," explains Dr. Bechara.

The researchers then used a variation of the gambling task to further analyze the decision-making patterns displayed by substance abusers in the first task. This time, the researchers arranged cards into two sets. One set included some high immediate losses but long-term rewards; the other set yielded small immediate losses, even smaller immediate rewards, and long-term losses. This test was designed to determine whether hypersensitivity to reward or an inability to observe and act on patterns of results drove substance abusers' choices.

Showing High Sensitivity to Reward

Taken together, two variations of the gambling task identified three distinct subgroups among substance-dependent individuals—a subgroup with apparently normal decision-making patterns and two subgroups with impaired decision making.

- For one group (36 percent), performance was indistinguishable from that of normal controls.
- A second group (23 percent) made decisions that matched the pattern of patients with VM lesions to the prefrontal cortex: They made choices that favored short-term rewards, even though

this strategy resulted in long-term loss.

- The largest group (41 percent) appeared to make decisions that were driven primarily by a hypersensitivity to reward. They chose from decks that offered either immediate or delayed reward, irrespective of short- or long-term loss. "Their impaired behavior and choices did not seem to be tied to dysfunction in the thinking prefrontal region but to the presence or prospect of pleasure," Dr. Bechara says. This group had abnormally high physiological responses when they uncovered a high-payoff card, greater excitement when choosing from decks with larger rewards, a willingness to accept greater punishment to obtain a larger reward, and high pleasurable expectations for reward. "For them, drugs are overwhelmingly attractive; their foot is really on the accelerator," says Dr. Bechara.

"This research reveals important variations in performance among individuals with addiction and that a chronic pattern of substance abuse may be attributable to different dysfunctions in the decision-making processes," according to Dr. Steven Grant of NIDA's Division of Treatment Research and Development. "It also suggests the possibility of developing assessment tools to identify different types and degrees of drug-induced impairment or vulnerability and tailoring treatments to address specific behavioral manifestations of addiction."

Linking Disrupted Brain Activity to Impaired Decision Making

In a study that combined brain imaging and analysis of decision making, Dr. Paulus and his colleagues directly examined brain regions and functions that may underlie skewed decision making among methamphetamine-dependent individuals. The researchers found that methamphetamine dependence is associated with decisions based more on habit than on evaluation of possible success or failure. Moreover, functional magnetic resonance imaging (fMRI) showed that methamphetamine-dependent participants had different patterns of brain activity when making decisions than did those who were not dependent on the drug.

By revealing different degrees of impairment, this research may hold clues to treatment success and aid the selection of appropriate therapeutic approaches.

"The decisions they make and the brain regions involved in making decisions suggest that the responses of methamphetamine-dependent individuals are not controlled by consideration of what works over what does not," Dr. Paulus says.

Dr. Paulus's study included 14 methamphetamine-dependent men (average age 41) enrolled in an inpatient treatment program. On average, they had used the stimulant for 17 years and at the time of the study had been abstinent for 25 days. The study also included 10 men and 4 women (average age 39) with no history of substance abuse or dependence.

The researchers used fMRI to monitor brain activity while participants tried to predict whether an image of a car would appear on the left or right side of a computer screen. As in Dr. Bechara's gambling task, the game was rigged: The researchers manipulated the computer so that each participant's predictions were correct exactly half the time during one round of the game, 80 percent of the time during another round, and only 20 percent during a third round. The researchers then observed the participants to see how they adjusted their prediction-making strategies when their error rates changed.

The researchers focused on a particular strategy, "win-stay/lose-shift"—that is, choosing the left or right screen again if it was correct on the last response, and choosing the other side if it was incorrect. Both groups of participants used this simple and natural strategy some of the time. However, participants with no history of methamphetamine abuse moved away from it as their error rates rose, apparently seeking an alternative approach that would yield better results. Methamphetamine abusers, in contrast, tended to stick with the win-stay/lose-shift strategy no matter how often their predictions were wrong. When analyzed statistically, their responses were related only to their most recent result, rather than their overall degree of success or failure.

"Our findings suggest that stimulant dependence is a state dominated by habit-based learning, in which a response is made irrespective of associated outcomes. Studies that investigate these patterns of response can begin to explain the mechanisms that underlie either the susceptibility to drug taking in some individuals or the consequences of repeated drug taking. Understanding these mechanisms may ultimately lead to identifying people at risk for addiction or susceptible to relapse," Dr. Paulus says.

"In this study, the decisions made by methamphetamine abusers look to some extent like those exhibited by

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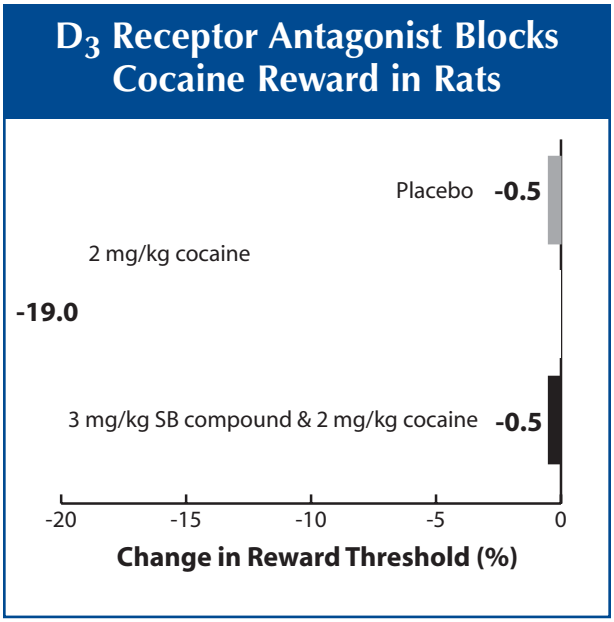
Animal Studies Suggest D_3 Receptors Offer New Target for Treatment Medications

By Jill Schlabig Williams
NIDA NOTES Contributing Writer



Cocaine exposure lowered by 19 percent rats' reward threshold, the amount of current needed to motivate an animal to push a lever to activate electrical stimulation of its brain reward system. When rats were given the D_3 antagonist before being given cocaine, however, their reward threshold remained the same as when they were given placebo.

Collaboration between a NIDA scientist and a researcher from St. John's University in Jamaica, New York, has identified a chemical compound that prevents animal responses to cocaine that correspond to human drug liking, seeking, and relapse. While the compound is not suitable as a medication, the researchers believe its mechanism of action—restricting neurotransmitter access to the dopamine D_3 receptor—may provide a basis for pharmacological treatments for addiction to cocaine and other drugs.

The chemical messenger dopamine plays a critical role in networks of brain cells that trigger the rewarding feelings that result when we engage in pleasurable activities, such as eating. Drugs of abuse activate hot buttons, called receptors, on these brain cells, flooding the brain's reward pathways with dopamine and producing intense pleasure. With continued drug abuse, overstimulation of these pathways changes the brain, leading to the intense craving and uncontrollable pursuit of drugs that mark addiction.

To derail this process, research has focused on the use of agonists, compounds structurally similar to dopamine that bind to and stimulate dopamine receptors and seem to inhibit drug-seeking behavior, and antagonists, which bind to and block these receptors. Until now, researchers have tried developing a treatment medication that can counter the addictive effects of abused drugs at two different dopamine receptors, called D_1 and D_2, with little success. Potential treatment agonists that activated these receptors produced such strong stimulation that it seemed likely they themselves would be abused. And the antagonists used to block the pleasurable effects of abused drugs at these receptors produced aversive, unpleasant effects. However, recent NIDA-funded research on use of an antagonist designed to target a less-studied dopamine receptor called D_3 offers new promise. Researchers Dr. Charles Ashby, Jr., of St. John's University, and Dr. Eliot Gardner, of NIDA's Intramural Research Program, note that D_3 appears to play a major role in addiction and may be the elusive target for medications that could help control addictive behavior.

Scientists have identified five subtypes of dopamine receptors, each with distinct properties and each found in varying densities in different areas of the brain. To date, most research has focused on the roles of the D_1 and D_2 receptors, which occur in higher densities and more places in the brain than do D_3 receptors. Nevertheless, several characteristics of the D_3 receptor suggested that medications that interact with it may have promise as treatments for cocaine addiction. D_3 receptors are mainly concentrated in the brain's reward pathway. In addition, dopamine is attracted more strongly to the D_3 receptors than to other receptors. Yet researchers found that D_3 agonists caused rats to resume drug-seeking behavior more quickly after a period of abstinence. This reaction suggested that a compound capable of selectively blocking this receptor—an antagonist—could be important in developing a medication to reduce or block craving.

The D_3 antagonist compound used in the Ashby-Gardner studies, called SB-277011-A, is highly selective, with an 80- to 100-fold preference for D_3 over D_2 receptors and 66 other receptors, enzymes, and ion channels. When the compound was first developed in 1997, Drs. Ashby and Gardner saw its potential. "Until then, study of the D_3 receptor was hampered because the available compounds antagonized D_2 as well as D_3 receptors to some extent, making it difficult to sort out which was responsible for the observed effects. As a result, research on the D_3 receptor and compounds that affect it had yielded inconsistent and contradictory results," explains

Dr. Ashby. "We knew this compound and its unambiguous selectivity for D_3 receptors would allow us to test the role of these receptors, while offering promise as a treatment for addiction."

Drs. Ashby and Gardner performed three types of animal experiments. "Each experiment used the D_3 antagonist to focus on a unique aspect of addiction, and all three yielded promising results," says Dr. Ashby. "Antagonizing the D_3 receptor appears to weaken cocaine's rewarding effects, reduce cocaine-induced conditioned place preference, and block reinstatement of drug-seeking behavior. And the compound we were testing was not found to be rewarding or aversive."

Cocaine's Rewarding Effects

In the first set of studies, researchers used brain stimulation reward experiments to measure the direct rewarding properties of cocaine. This type of experiment is thought to produce the closest equivalent in animals to the cocaine-induced subjective high experienced by humans. The researchers implanted brain stimulation electrodes in rats and trained the animals to press a lever to self-administer electrical stimulation that produced feelings of pleasure or euphoria. Baseline reward thresholds, the amount of current below which the animal no longer finds the stimulation rewarding enough to press the lever, were determined for each animal. Drugs of abuse, which activate the same neurons in the brain's reward system as the electrical current, increase the amount of pleasure obtained from a given amount of current and therefore decrease the reward threshold. The difference between baseline reward threshold and the reward threshold after administration of a drug gives a measure of the rewarding potency of the drug being tested.

After establishing the rats' baseline reward thresholds, researchers injected the animals with placebo, 2 mg/kg cocaine, or 3 mg/kg SB compound followed by 2 mg/kg cocaine; researchers then retested the rats. As expected, the reward threshold of animals injected with placebo remained unchanged; those injected with cocaine had an average 19-percent decrease in their reward thresholds. Rats pretreated with the D_3 antagonist and then given cocaine had no change in their reward thresholds, indicating that the antagonist completely abolished the enhancing effect of cocaine on brain reward.

varying doses of the SB compound—and then confining them to one chamber of a two-room cage. The rats were subsequently given cocaine and confined to the other chamber. Each chamber had distinct visual and tactile furnishings. Rats were then allowed to freely explore the entire cage for 15 minutes, while researchers measured their time in each chamber.

Rats given placebo and then cocaine spent roughly two thirds of their time in the chamber they associated with cocaine. However, rats pretreated with the D_3 antagonist (SB compound) spent, on average, less time in the cocaine-associated chamber, with the minutes spent in that chamber decreasing as the D_3 antagonist dose increased from 0.3 mg/kg to 1 mg/kg, 3 mg/kg, and up to 10 mg/kg. Rats pretreated with the highest dose of the D_3 antagonist spent about 40 percent fewer minutes in the cocaine-associated chamber than did rats in the placebo-cocaine group. The results indicate that the D_3 antagonist blocked the rats' motivation to seek out cocaine, eliminating their acquisition and expression of cocaine-induced conditioned preference.

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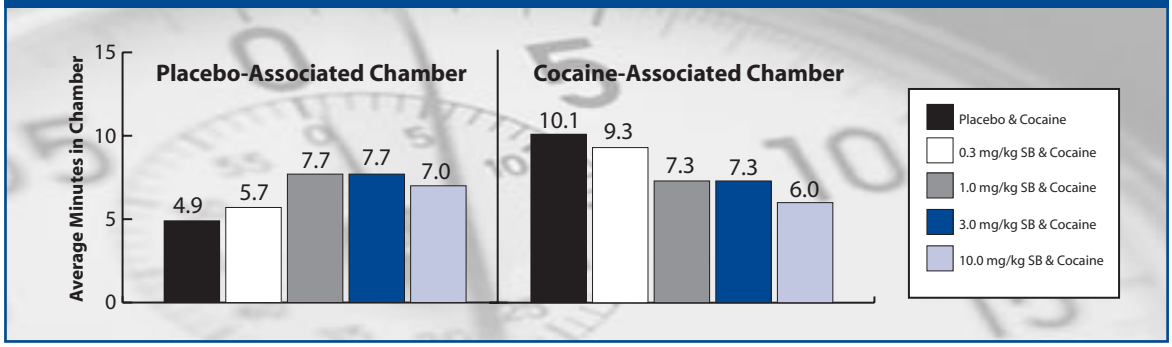
D_3 Receptor Antagonist Blocks Rats' Incentive to Seek Cocaine



Rats were given placebo and confined to one chamber of a two-chamber cage, then given cocaine and confined to the other chamber. They were then allowed to roam throughout the cage for 15 minutes, with researchers measuring the time spent in each chamber . This exercise was repeated with four other groups of rats, which were given either 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg D_3 antagonist (SB compound) and then cocaine. Rats treated with the SB compound before receiving cocaine spent significantly less time in the cocaine-associated chamber than rats pretreated with placebo.

Cocaine-Seeking Behavior

The second set of experiments used conditioned place preference, aiming to measure cocaine-seeking behavior evoked by environmental cues associated with cocaine. The experiments involved providing rats one of five pretreatments—placebo or

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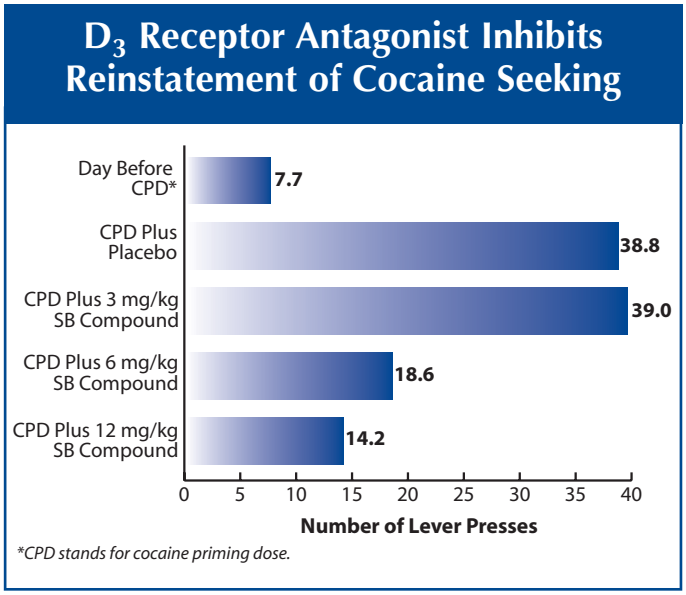
Reinstatement of Drug Seeking

The final set of experiments focused on cocaine self-administration and reinstatement. The researchers implanted an intravenous catheter in the rat's external jugular vein and trained the animal to self-administer cocaine by pressing a lever. The daily 3-hour sessions continued until the rat was self-administering consistent amounts of the drug every day. The researchers then phased out the lever-pressing behavior by substituting saline for the cocaine; since pressing the lever no longer resulted in cocaine, the rats lost interest and pushed the lever much less often. At this point, the researchers gave rats that had been pretreated with placebo or the SB compound a priming dose of cocaine (1 mg/kg) normally sufficient to trigger reinstatement of the drug-seeking, lever-pressing behavior. The rats returned to the lever, and the researchers counted how many times they pressed it.

On the day before they were given the priming dose of cocaine, rats pressed the active lever an average of 7.7 times. After receiving the priming dose, the rats pretreated with placebo pressed the lever an average of 38.8 times, while rats pretreated with 3, 6, or 12 mg/kg of the D_3 antagonist pressed the lever an average of 39.0, 18.6, and 14.2 times, respectively. Pretreatment with the D_3 antagonist thus produced a dose-related weakening of cocaine-triggered resumption of the drug-seeking behavior.



After receiving a priming dose of cocaine, rats pretreated with placebo resumed cocaine-seeking behavior, pressing a lever to self-administer cocaine. However, rats pretreated with the D_3 antagonist (SB compound) pressed the lever fewer times as the SB compound dose increased.

Future of D_3 Antagonist Research

The researchers are optimistic about the future of this line of research. "The SB compound has jumped through many hoops already," says Dr. Ashby. "It's been shown in our studies and other studies to block cue-induced, drug-induced, and stress-induced relapse to cocaine-seeking behavior, and acquisition and expression of heroin-induced conditioned place preference. It is neither rewarding nor aversive and has been found to work on cocaine, heroin, and nicotine. We've seen no significant adverse effects of the compound in animals. We think antagonizing the D_3 receptor represents a breakthrough for addiction treatment."

"In more than 35 years in the field, this D_3 antagonist research is the most promising thing I have ever seen," Dr. Gardner says. "No one else has assembled such a variety of animal evidence showing that acute administration of a compound so profoundly modifies the addictive properties of cocaine as this selective D_3 antagonist."

Both Drs. Ashby and Gardner are quick to note, however, that much work lies ahead. "We don't know if these results will hold up in long-term studies," says Dr. Gardner. "We think the reason this compound is successful in animal studies is because of its D_3 antagonist action. To verify this, we still need to develop other, chemically different D_3 antagonists and redo all the tests. If we obtain the same results with these other D_3 antagonists, then we'll be more comfortable that we are on the right track and that D_3 receptor antagonism is truly responsible for our findings."

More animal experiments are planned to focus on other drugs of abuse and other animal paradigms, such as progressive ratio studies that measure a drug's motivational potency. Studies with chronic administration and with other mammalian species also will be needed, as will toxicology studies. The human pharmacokinetics of the compounds also will have to be improved; for instance, the current compound has a very short half-life, lasting only about 30 minutes in primates.

"Almost without fail, people I've spoken with who are addicted to drugs express a strong desire for clinically effective anticraving, antirelapse medication," says Dr. Gardner. "We hope this research takes us in that direction."

Source

• Vorel, S.R.; Ashby, C.R., Jr.; Paul, M.; Liu, X.; Hayes, R.; Hagan, J.J.; Middlemiss, D.N.; Stemp, G.; Gardner, E.L. Dopamine D_3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *Journal of Neuroscience* 22(21):9595-9603, 2002. NN

Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence

By Patrick Zickler
NIDA NOTES Staff Writer

Many genetic, biological, and environmental factors can influence whether and when an individual initiates drug abuse or develops drug dependence or addiction. One tool that helps scientists isolate and evaluate the effect of different factors is research on twins, who share many inherited biological traits and environmental influences. In a study of more than 300 pairs of same-sex twins, NIDA-supported investigators found that smoking marijuana before age 17 is linked to a greater likelihood of proceeding to serious problems with marijuana or other drugs.

"This finding underlines the significance of early drug initiation," says Dr. Wilson Compton, director of NIDA's Division of Epidemiology, Services and Prevention Research. "Identical twins had the same inherited biological characteristics, and fraternal twins shared half their genes. All the twins had common family influences and social environments. Even though they had so much in common, something influenced one twin to take drugs earlier than the other, and that difference had a profound impact on later experience with drugs."

The same-sex twin pairs grew up in the same households and attended the same schools. In each pair, one twin smoked marijuana before his or her 17th birthday and the other did not. "When we interviewed the twins as adults, the early users were more than twice as likely to have taken other illicit drugs. They also were from two to five times more likely to move on to abuse or dependence on alcohol, marijuana, stimulants, opioids, or sedatives," says Dr. Michael Lynskey, who conducted the study with colleagues at the Washington University School of Medicine in St. Louis, Missouri; the Queensland Institute of Medical Research in Brisbane, Australia; and the University of Missouri in Columbia.

The researchers asked both members of 2,765 twin pairs included in the Australian Twin Register if they had ever smoked marijuana and, if so, how old they were when they smoked it for the first time. The researchers identified 311 pairs of same-sex twins (average age 30) in which one twin first smoked marijuana before age 17 and the other twin had either never smoked the drug (77 pairs) or did so for the first time at age 17 or older (234 pairs). Of the 311 twin pairs, 136 (74 female, 62 male) were identical and 175 (84 female, 91 male) were fraternal. The interviews were conducted by phone in Australia and the data analyzed by scientists at Washington University and the University of Missouri.

The investigators defined "use" as drug taking on one or more occasions for a nonmedical reason. The

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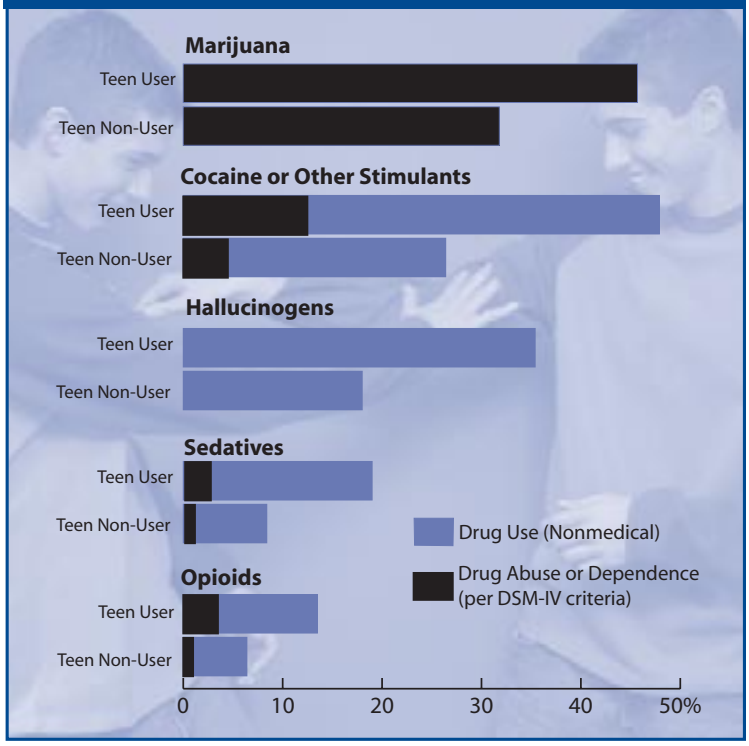
Marijuana-Using Twin Teens More Likely To Use Drugs, Become Dependent



Researchers investigated the drug use patterns of same sex twin pairs in which one twin first smoked marijuana before age 17 and the other either never smoked marijuana or first smoked the drug at age 17 or older. As adults (average age 30), those who had smoked before age 17 were more likely than their siblings to have used other illicit drugs and to develop symptoms of abuse or dependence on marijuana, cocaine or other stimulants, opioids, or sedatives.

New Avenues of Research Explore Addiction's Disrupted and Destructive Decision Making

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psychiatric patients with disorders associated with the brain's frontal regions," Dr. Grant observes. "The methamphetamine abusers don't shift strategies even when things are going wrong. It's not clear why this occurs. They appear to be unable to effectively recognize a pattern of persistent error and adjust appropriately."

Because fMRI produces real-time images of activity throughout the brain, the researchers were able to see that methamphetamine-dependent participants used different brain regions during the task; in some regions, this difference—like the differences in decisions themselves—was related to error rates. "In individuals who were not addicted to methamphetamine, frontal brain areas that are critical for decision making were more active at lower error rates, when they were successfully predicting the outcome," Dr. Paulus says. "These areas were most active in methamphetamine abusers when error rates were highest and the outcome was most unpredictable. In short, the fMRI findings and the behavioral results support a hypothesis that the subjects do not rely on the likelihood of success or failure."

"Neurochemical changes in the midbrain occur in the earliest stages of drug abuse and addiction," says Dr. Grant. "But the frontal regions, which are connected to the midbrain with intricate feedback circuits, are the site of compulsion and cognition. Disrupted function of these sites is crucial to the impaired decision making by which addiction is maintained.

"These decision-making studies don't yet tell us whether drugs act directly in the frontal region to disrupt function or whether the damage done in the midbrain reward system is transferred to the frontal cortex through altered neurochemical pathways. But at the very least, they demonstrate a widespread impact of drugs on the brain and the crucial role of the frontal cortex in maintaining addiction," Dr. Grant explains.

By revealing different degrees of impairment, this research may hold clues to treatment success and aid the selection of appropriate therapeutic approaches to help patients overcome addiction's destructive pattern of decision making.

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Study Suggests Ketamine Injection Poses New Disease Risk for Street Youths

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in size from Los Angeles and Seattle to Asheville, North Carolina, and Grand Rapids, Michigan.

The diverse geographic areas where this small but highly mobile sample of high-risk youths say they have injected ketamine raises the possibility that the practice may be more common and widespread than indicated by recent epidemiological data, the study's researchers say. Additional field data gathered to support a large, recently launched NIDA-funded study of ketamine injection indicate it is definitely occurring among street youths in Los Angeles, New Orleans, and New York City, Dr. Lankenau says.

More than half of the youths in the New York City study said they had previously injected other drugs, such as heroin or cocaine. However, almost half (44 percent) said that ketamine was the first drug they had ever injected. The same percentage also indicated that ketamine was the only drug they abused during their last injection session. More than half the youths said they had injected ketamine 10 or more times during the last year.

Injecting ketamine produced an intense psychological and physical state, called the "k-hole," and did so more reliably and strongly than sniffing the drug, the youths reported. In the k-hole, perceptions of time and space are distorted and hallucinations occur. The k-hole lasts from 10 to 60 minutes and closes rapidly once the body processes the drug, but it can be reentered quickly with another injection. This effect may account for the 8 to 10 times some youths said they typically injected ketamine in a single session, concomitantly raising the risks of disease transmission.

More than two-thirds of the youths said they injected the drug IM rather than IV during their most recent injection. "Blood typically is not pulled into the needle or syringe barrel with IM

All About Ketamine

Ketamine is a fast-acting anesthetic. Approved more than 30 years ago for both human and animal medical use in the United States, ketamine now is used mainly as an animal sedative in veterinary settings.

Ketamine is available on the street in liquid, powder, or pill form. Though it can be swallowed, smoked, drunk, snorted, or injected, it is most commonly snorted by teens and young adults in club settings. Depending on the dosage, ketamine's effects can range from those of stimulants to the dreamlike or psychedelic experiences of hallucinogens. At high doses, ketamine can cause delirium, amnesia, impaired motor function, high blood pressure, and potentially fatal respiratory problems. These effects are intensified when ketamine is taken with sedatives or depressants, such as alcohol, as may occur at clubs and raves. Nearly three out of four ketamine-related emergency department visits reported in 2001 involved more than one drug—most typically, MDMA (34 percent) or alcohol (33 percent).

injection, diminishing HIV transmission risk," notes Dr. Lankenau. "However, the risk of transmitting bloodborne diseases, particularly hepatitis C, still exists," he stresses. "While youths may be clear-headed and cautious at the start of an injection session, as they continue to inject the drug repeatedly in a typical session, they may lose track of the syringe they are using or how many times it has been inserted into a shared vial of liquid ketamine."

"Ketamine injectors are aware that sharing syringes is risky, and few participants in our study shared them," Dr. Lankenau says. "However, a majority of youths in our study did share vials of liquid ketamine or cookers in which powdered ketamine was prepared for injection. While it is difficult to develop a broad-based prevention strategy for this hard-to-reach population, distributing educational information about disease risks associated with specific ketamine injection practices at health services programs and youth drop-in centers may enable street-involved kids to reduce these risks," he explains.

"Ethnographic studies such as this one are crucial to understanding and responding effectively to possible emerging drug use trends among hidden populations," says Dr. Jessica Campbell of NIDA's Division of Epidemiology, Services and Prevention Research. "This study identifies key cultural and behavioral characteristics of street-involved youths who are injecting ketamine," she says. Further delineation of these characteristics by Dr. Lankenau's current tri-city study should provide additional information about ketamine injection practices that can be applied to the development and implementation of targeted HIV and drug-abuse prevention programs for street-involved youths."

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Buprenorphine Work Group Receives HHS Award for Distinguished Service

The Buprenorphine Work Group, comprising representatives from NIDA, the Food and Drug Administration (FDA), and the Substance Abuse and Mental Health Services Administration (SAMHSA), was honored at the 2003 Department of Health and Human Services (HHS) Honor Awards ceremony on June 11 in Washington, D.C. The Work Group received the Secretary's Distinguished Service Award for its diligence and dedication and the impact of its contribution on the citizenry of our Nation.

October 2002 was a crowning moment in the Work Group's efforts, marking FDA approval of buprenorphine for treatment of opiate dependence, nearly a decade after the last breakthrough medication for opiate addiction. FDA approval allows physicians to dispense buprenorphine in their offices to patients addicted to heroin and prescription pain relievers, enhancing convenience and privacy.

This achievement was truly a joint effort. NIDA members worked with the pharmaceutical company Reckitt Benckiser to perform the studies necessary to establish safety and efficacy. NIDA also teamed with SAMHSA on implementation issues, such as physician training and waiver certification to allow physicians to prescribe buprenorphine.

HHS Deputy Secretary Claude Allen presented the award to the group. Current and former NIDA employees honored include Peter Bridge, M.D.; Lee Cummings, J.D.; Timothy Condon, Ph.D.; Dorynne Czechowicz, M.D.; Nora Chiang, Ph.D.; Joel Egertson; Ahmed Elkashef, M.D.; Liza Gorgon; Charles Grudzinskas, Ph.D.; Richard Hawks, Ph.D.; Mary Mayhew; Susan Herbert (posthumously); James Hill, Ph.D. (posthumously); Moo Park, Ph.D.; James Terrill, Ph.D.; Frank Vocci, Ph.D.; and Robert Walsh.

Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development, noted the individual strengths of team members in this joint effort and highlighted one member's work. "Of all the individuals honored, I'd like to single out Sue Herbert. During the last 2 years of her life, Sue underwent treatment for the cancer to which she ultimately succumbed. She missed very little work and made it clear to me that the buprenorphine project was very important to her. Sue's dedication was inspirational; the work and the award are now part of her personal legacy." NN

Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence

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researchers defined "abuse" and "dependence" according to criteria adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). Abuse was understood to involve taking the drug in physically hazardous situations or circumstances that interfered with major obligations. According to the DSM-IV criteria, twins described as drug- or alcohol-dependent had two or more of the following symptoms: needing increasingly larger amounts to achieve drug effect, using for longer periods or more frequently than intended, and continuing to use despite associated emotional problems or recurrent desire to cut down use.

Overall, the researchers found, twins who smoked marijuana before age 17 were more than twice as likely as their sibling to use opioids, three times as likely to use sedatives, three times as likely to use cocaine or other stimulants, and nearly four times as likely to use hallucinogens. Those who smoked marijuana before age 17 also were from 1.6 to 6 times as likely to have reported abuse or dependence on alcohol or an illicit drug. Nonetheless, Dr. Lynskey points out, the majority (52 percent) of twins who smoked marijuana before age 17 did not go on to develop abuse or dependence. The increased odds of using other drugs or for developing abuse or dependence were not greater for identical than for fraternal twins, nor for males or females.

"While these study findings indicate that early marijuana use is associated with increased risk of progression to other illicit drug use and possibly to drug abuse or dependence, it is not possible to draw strong causal conclusions solely on the basis of these associations," Dr. Lynskey cautions. Additional research in other cultures, using a range of research designs, will be needed to determine the causes of the association, he says.

"Given that early initiation of marijuana smoking appears to be associated with increased risks," says Dr. Lynskey, "there is a need for greater physician awareness of those risks. Focused interventions also are needed to prevent escalation to use of other drugs among young people identified as being at risk."

Source

• Lynskey, M.T., et al. Escalation of drug use in early-onset cannabis users vs. co-twin controls. *Journal of the American Medical Association* 289(4):427-433, 2003. NN

NIDA-Funded Research Drives Revision of Guide to Prevention Programming

NIDA has released the second edition of its highly regarded *Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders* in the fall of 2003. Like the first edition, published in 1997, this booklet offers parents, educators, and community leaders, as well as prevention practitioners, the latest findings from NIDA-funded prevention research. Accompanying this edition is an *In Brief* companion piece for quick reference. The goal of both publications is clearly defined: to help communities apply the findings from research-based prevention studies in addressing drug use among children and adolescents.

In the last 5 years, NIDA's prevention research program has more than doubled in size and scope to address all stages of youth development, a mix of audiences and settings, and the delivery of effective services at the community level. Research funded by NIDA and other Federal research organizations—such as the National Institute of Mental Health and the Centers for Disease Control and Prevention—shows that early intervention can prevent many adolescent risk behaviors.

NIDA-funded research has identified interventions that can minimize or prevent risks for drug abuse and other problem behaviors that can occur at every step along a child's development path. Working with families, schools, and communities, scientists have found effective ways to help people gain skills and learn strategies that can stop problem behaviors before they occur and strengthen factors that protect youths from vulnerability to drug use.

Sixteen fundamental prevention principles, derived from research on effective prevention programs, frame the guide's discussion. Using a question-and-answer format, the booklet addresses

- key factors that place youths at risk for drug use, as well as those that confer protection;
- how to plan prevention programs tailored to community needs; and
- core elements of effective programs, which should be retained when adapting programs to match a community's characteristics.

Each chapter ends with a "Community Action Box" that provides clear advice to parents, educators, and community leaders on how to apply that chapter's information.

The revision also describes more than 20 prevention programs, tested and proven in controlled trials by researchers throughout the Nation. Programs are described by the setting where they are implemented—*the family, school, or community*—and by the audience they target—all youths (*universal programs*), those at greater risk (*selective programs*), and those already involved with drugs or other problem behaviors (*indicated programs*). Some of the programs described are *tiered*, targeting more than one audience. Selected resources and references point to additional information to guide program planning and implementation.

To view additional NIDA publications and videos on drug abuse prevention, visit www.drugabuse.gov/PubCat/PubsIndex.html and select "Preventing Drug Abuse." NN

Community Action Box

PARENTS can use information on risk and protection to help them develop positive preventive actions (e.g., talking about family rules) before problems occur.

EDUCATORS can strengthen learning and bonding to school by intervening early to address aggressive behaviors and poor concentration—risks associated with later onset of drug use and related problems.

COMMUNITY LEADERS can assess community risk and protective factors associated with drug problems to appropriately target prevention services.

Example of a Community Action Box, offering straightforward tips on how parents, educators, and community leaders—the guide's primary readers—can apply the information found in each chapter.

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