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School-Based Program Promotes Positive Behavior, Reduces Risk Factors for Drug Use, Other Problems

By Susan Farrer, NIDA NOTES Contributing Writer

Addressing a young student's classroom antics may do more than allow his teacher to get through a lesson. Comprehensive, school-based programs can reduce young children's antisocial behavior while boosting their social competency, academic performance, and commitment to school, recent NIDA-funded research suggests. Such programs hold promise for reducing risk factors for drug use, violence, school dropout, and other problem behaviors during adolescence, the researchers say.

Dr. Richard Catalano and colleagues at the University of Washington in Seattle evaluated initial 18-month results of the Raising Healthy Children (RHC) program, designed to reduce antisocial behaviors and academic failure while promoting prosocial behaviors by working closely with students and their teachers and parents. First implemented with NIDA funding in 1994, RHC offers children in grades 1 through 12 age-appropriate services at school and at home. This unique long-term intervention addresses key factors that affect a child's social development at each age and either protect against or increase the risk of drug use and other problems. The original RHC program participants, who were 1st- and 2nd-graders in 1994, are now in 11th and 12th grades and still participating in the program.

"Elementary school interventions are relatively rare but are potentially very powerful if we can determine exactly what the target risk and protective factors are and how to get to them early," notes Dr. Aria Crump of NIDA's Prevention Research Branch. "If we can intervene early—by addressing precursors to antisocial behaviors—then we're getting a head start on preventing problems."

RHC is founded on the social development model, which hypothesizes that elementary school children learn behavior patterns from teachers and peers at school as well as their families, with peer influence increasing as children age. The model also suggests that consistent patterns of socialization with prosocial individuals create social bonds that positively influence behavior. RHC strategies seek to engender consistent, positive socialization and prosocial development within children's classrooms, peer groups, and families.

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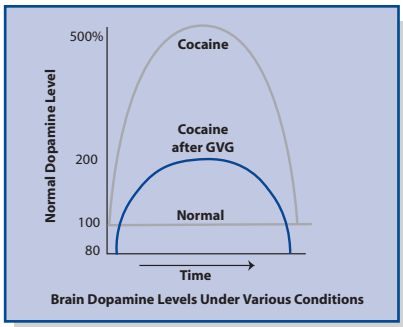

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NIDA News and Information at Your Fingertips

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- International Activities
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Beyond the Brain: The Medical Consequences of Abuse and Addiction

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

Drug addiction is essentially a brain disease, but of course drugs' destructive health effects extend beyond the intricate chemical pathways of the brain.

Through 30 years of scientific inquiry, NIDA research has demonstrated that drug addiction is essentially a brain disease, but of course drugs' destructive health effects extend beyond the intricate chemical pathways of the brain. Drug abuse and addiction have consequences that can be seen throughout the body—not just in brain scans, but in chest x-rays and blood tests.

For some drugs, these consequences are already well documented, yet the list of health warnings continues to grow. We know that nicotine addiction increases risks of heart and lung disease, cancers, and strokes. As dire as that list already is, NIDA-supported scientists are uncovering evidence of still more medical problems linked to smoking. For example, NIDA-supported researchers at Brookhaven National Laboratory in Upton, New York, recently demonstrated that smoking decreases levels of an important enzyme in the brain, heart, lungs, kidneys, and spleen. This enzyme, monoamine oxidase B (MAO-B), helps break down compounds that elevate blood pressure and plays a role in regulating dopamine levels in the brain. In smokers, MAO-B activity is reduced by one-third to one-half that seen in nonsmokers. This finding, which will be discussed in an upcoming issue of *NIDA NOTES*, may help clinicians identify—and treat—previously hidden health consequences of smoking.

Our picture of the medical consequences of other drugs is less comprehensive, but still grim. Abuse of heroin and other opiates is associated with consequences ranging from nausea and constipation to glomerulosclerosis, a life-threatening kidney disorder, and destruction of dental and orofacial structures. PCP (phencyclidine, or "angel dust") decreases heart rate and blood pressure, triggers violent aggression, and may trigger muscle contractions strong enough to break a bone. Methamphetamine ("meth," "speed," or "ice") causes cardiac damage, elevates heart rate and blood pressure, and can cause convulsions. Methamphetamine can also cause hyperthermia—elevated body temperature that results from disruption of the body's temperature-regulating mechanism. Methamphetamine increases wakefulness and physical activity, creating the potential for a combination of activity and overheating that leads to convulsions and dangerous, sometimes lethal elevation of body temperature.

NIDA-supported research has shown that cocaine restricts blood flow to the brain, increases heart rate, and elevates levels of blood components that promote clotting—effects that can lead to stroke or heart attack even in those not otherwise at risk for these dangerous cardiovascular events. Now, NIDA research suggests that cocaine also limits the body's ability to fight infection, putting cocaine abusers at greater risk for illnesses ranging from the common cold to hepatitis, sexually transmitted diseases, and HIV/AIDS (see "Cocaine

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May Compromise Immune System, Increase Risk of Infection," on page 5).

The club drug ecstasy (methylenedioxymethamphetamine, or MDMA) can cause hyperthermia and is associated with kidney and liver damage. New NIDA-supported research suggests that MDMA also acts on serotonin receptor sites on heart valve cells, stimulating excessive cell growth. This overgrowth of heart valve cells in humans can lead to valvulopathy—a condition in which the valve becomes inefficient and blood leaks back into the heart (see "MDMA Use May Increase Risk for Cardiac Valve Disease" on page 12). NIDA-supported studies have shown that marijuana is associated with increased prevalence of respiratory problems, such as bronchitis, and possibly increased risk of cancers of the lung, head, and neck. We also are beginning to understand the scope of harm done by inhalants. Volatile solvents such as toluene damage the protective sheath around nerve fibers throughout the body. Chronic exposure to inhalants can produce significant damage to the heart, lungs, liver, and kidneys.

Some of the destructive medical consequences of drug abuse and addiction are temporary—the conditions improve after patients receive treatment and are able to stop their drug use. Other consequences may be more persistent, diminishing the quality of patients' health long after drug use has stopped.

The extent of drugs' impact on general health was recently highlighted in a study by NIDA-supported investigators at the University of California, San Francisco, and the Kaiser Permanente health maintenance organization (HMO). The researchers compared the general health of 747 patients enrolled in the HMO's drug dependence treatment programs with that of more than 3,600 health plan members without any history of substance abuse. They found that substance-abusing patients also suffer from a wide variety of other health problems, including injuries associated with overdose; pain-related conditions such as headache, lower back pain, and arthritis; hypertension; pneumonia; heart disease resulting from decreased blood supply to cardiac muscle; pulmonary disorders; and asthma.

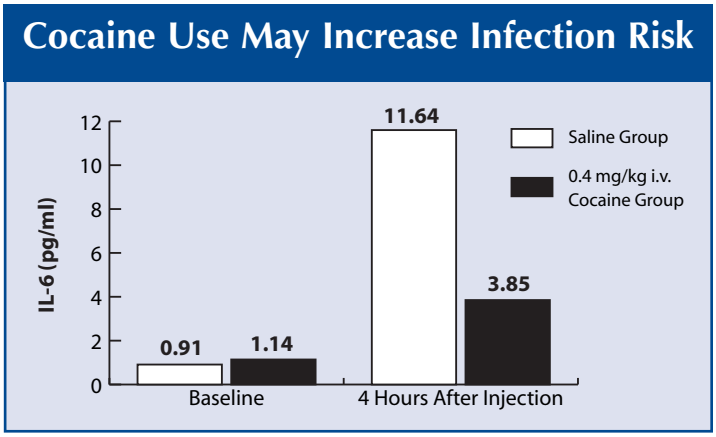
Some of the destructive medical consequences of drug abuse and addiction are temporary—the conditions improve after patients receive treatment and are able to stop their drug use. Other consequences may be more persistent, diminishing the quality of patients' health long after drug use has stopped. Whether short-lived or chronic, the growing list of recognized health consequences of abuse and addiction underscores the fact that drug abuse is not just a brain disease that exists in medical isolation—it manifests itself throughout the body with a broad array of medical consequences. Thus, it is important for the entire medical community—general practitioners, pediatricians, and dentists as well as addiction specialists—to recognize a full range of diagnostic signs of abuse and addiction. Drug abuse treatment can be integrated into the spectrum of care provided by the general medical community. For example, buprenorphine and naloxone now can be used to treat opiate addiction in a physician's office rather than in a specialized clinic setting.

Our research adds important detail to the terrible picture of addiction's pervasive harm—which cannot and should not be considered in isolation from general health issues—and it may also reveal new possibilities for treatments that heal not just the brain, but the whole body.

NIDA's interest in the medical consequences of addiction extends beyond the brain and includes all age groups and every abused drug. Our research adds important detail to the terrible picture of addiction's pervasive harm—which cannot and should not be considered in isolation from general health issues—and it may also reveal new possibilities for treatments that heal not just the brain, but the whole body. NN

Cocaine May Compromise Immune System, Increase Risk of Infection

By Patrick Zickler, NIDA NOTES Staff Writer



Elevations in the protein interleukin-6 (IL-6) play a key role in resisting infections when viruses, bacteria, or foreign objects, such as a catheter, enter the body. IL-6 elevations following insertion of a catheter were smaller in volunteers given cocaine than in volunteers given saline, suggesting that the drug may impair cocaine users' ability to fight off infectious diseases.

Cocaine abusers are more likely than nonusers to suffer from HIV, hepatitis, sexually transmitted diseases, and other infections. Most of this increased incidence is the result of conditions and behaviors—for example, injecting drugs, poor nutrition, and unsafe sex—that often are associated with drug abuse. Now, NIDA-supported investigators at the McLean Hospital Alcohol and Drug Abuse Research Center in Belmont, Massachusetts, have found that cocaine itself has a direct biological effect that may decrease an abuser's ability to fight off infections.

Dr. John H. Halpern, along with colleagues at McLean Hospital and Harvard Medical School, found that a key immune system component, a protein called interleukin-6 (IL-6), responded less robustly to an immunological challenge in male and female abusers injected with cocaine than in those who received placebo. "When your body detects a foreign object, IL-6 helps trigger the release of a cascade of other immune system components that isolate and neutralize the threat," explains Dr. Halpern. "If the balance of this response is disrupted, your body cannot fight infection as effectively as it should."

The study involved 30 participants (16 women, 14 men, ages 21-35) with a history of cocaine abuse, including at least one drug administration within the past month. The investigators placed an intravenous catheter in one arm of each participant and measured IL-6 levels. The catheter is detected as foreign by the body's immune system and triggers an immune response. After 30 minutes, the researchers injected cocaine or saline solution (0.4 mg/kg) into each participant's other arm; 4 hours later, they measured IL-6 levels again. In participants given saline, IL-6 levels had more than quintupled in response to the presence of the catheter, increasing from an average of less than 2 trillionths of a gram (picograms, or pg) per milliliter of blood to an average of more than 11 pg/ml. In men and women who received cocaine, however, IL-6 levels barely doubled—from less than 2 pg/ml to an average of 3.8 pg/ml.

"The findings in this study show that in people with a history of cocaine abuse, exposure to the drug establishes conditions that can lead to immediate harm," Dr. Halpern says. "In such subjects, we found that cocaine impairs the body's defense system for at least 4 hours. We can't rule out the possibility that IL-6 response returns to normal shortly after that time. But even if the blunted immune response lasts only a few hours, it makes it more likely that an infection like HIV or just a common cold can take hold," Dr. Halpern says.

"This research suggests a link between cocaine use and compromised immune response and could help explain the high incidence of infectious disease among drug abusers," observes Dr. Steven Grant of NIDA's Division of Treatment Research and Development. "It reminds us that the health consequences of drug abuse reach far beyond disruption of the brain systems involved in abuse and addiction."

The findings also have significance in another context, Dr. Grant adds. "The IL-6 findings are a small but possibly significant part of a much larger study designed to gather a wide range of information on the acute and chronic effects of abused drugs on the brain, endocrine system, and immune function. This kind of discovery-based research can yield unexpected, sometimes important, insights."

Source

Halpern, J.H., et al. Diminished interleukin-6 response to proinflammatory challenge in men and women after intravenous cocaine administration. *Journal of Clinical Endocrinology and Metabolism* 88(3):1188-1193, 2003. NN

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Dr. Catalano, who with Dr. David Hawkins helped craft the social development model, notes that it emerged from a growing understanding of the developmental etiology of substance use and other problem behaviors. The model suggested that prevention interventions delivered to preadolescents might be effective.

"Longitudinal research has shown that risk and protective factors are present before adolescence and that we might set kids on a different developmental path if we can change these factors early in life," Dr. Catalano explains. "Building on this knowledge, our research focuses on incorporating a developmental approach into intervention efforts and addressing risk factors as they become salient."

The RHC program includes:

- Teacher workshops and booster sessions that support classroom instruction—proactive classroom management, cooperative learning methods, and techniques to improve children's interpersonal and problem-solving skills, for example—to reduce academic failure and early aggressive behaviors and enhance the protective factor of commitment to school.
- Parent training and involvement strategies implemented by school-home coordinators through parenting workshops and in-home family services to reduce family management problems, family conflict, and academic failure and enhance family bonding and clear standards for behavior.
- Summer camps and in-home services for students identified by teachers or parents as being at risk for academic failure or in need of enhanced social competence.

The RHC study included 938 1st- and 2nd-graders enrolled in 10 suburban public schools in the Seattle area in 1994. After the schools were paired by socioeconomic status and attendance patterns, one school in each pair was randomly assigned to the RHC group and the other to a control group.

Data were collected from classroom teachers and parents just before the study was launched and at the 6-month, 1-year, and 18-month marks. Additional data were gathered from students through simple surveys they completed 6 and 18 months after the study began. Teachers and parents rated children's antisocial behavior, social competency, academic performance, and commitment to school. Students rated their own antisocial behavior and social competency.

The Raising Healthy Children (RHC) program incorporates strategies for teachers, parents, and students in grades 1–12. RHC seeks to develop students' prosocial behaviors, lessen antisocial behaviors, reduce academic failure, and prevent adolescent problem behaviors, such as drug use and violence.

For purposes of this study, examples of antisocial behavior include intentionally breaking things, taking others' things, lying extensively, and initiating fights. Social competency includes, among other behaviors, understanding others' feelings, cooperating with peers, sharing things, and accepting responsibility for one's actions.

Students appear to have benefited from the RHC program after only 18 months of participation. The teachers' reports revealed that the intervention students were significantly more committed to school and had higher academic performance than students in the control group. According to the teachers, RHC students also displayed significantly more social competency than did control students, with social competency levels increasing for participants as they decreased for those in the control group. The teachers' reports also indicated that program students exhibited less antisocial behavior than their control group peers. Further, the rate of new displays of antisocial behavior declined in RHC students, whereas the rate in control students increased.

Parent-reported data confirmed that program students had significantly higher levels of academic performance and commitment to school than did the control group. However, neither the parent-reported nor student-reported data showed significant differences between the two groups in social competency and antisocial behavior after researchers controlled for gender, low income, and baseline conditions.

The investigators say the lack of parent-teacher agreement on items assessing children's behavioral outcomes is not surprising because this result is consistent with previous research. "Generally, if you look at studies involving teacher and parent reports, parents are less able to

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MDMA Use May Increase Risk for Cardiac Valve Disease

By Arnold Mann, NIDA NOTES Contributing Writer

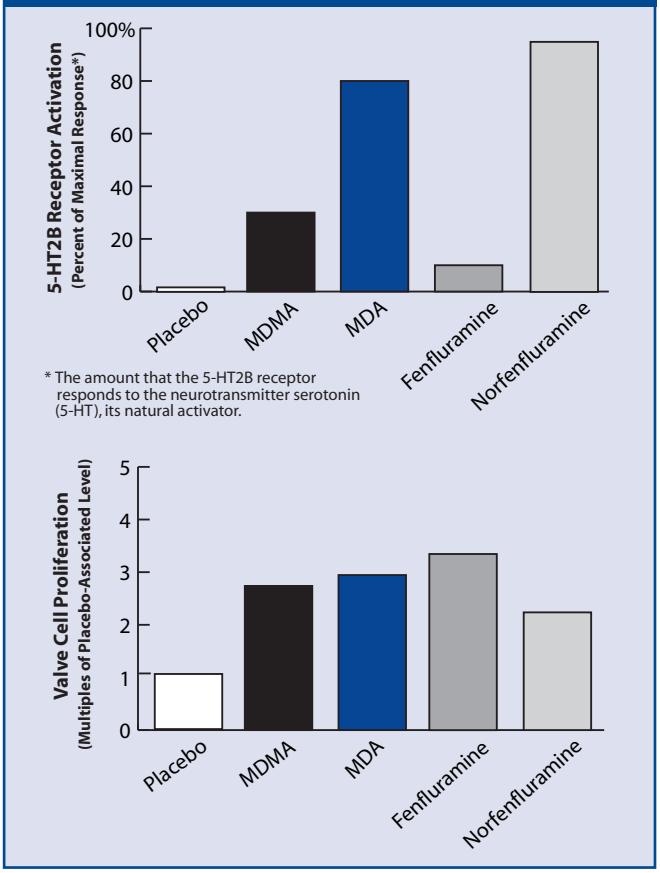
Users of the club drug ecstasy (or MDMA) may be putting themselves at risk for the same type of valvular heart disease (VHD) that developed in some users of the banned diet drug fenfluramine. In a recent NIDA-funded study, researchers demonstrated in cultured heart valve cells in the laboratory that MDMA and its metabolite MDA both provoke the same abnormal activity that underlies fenfluramine-associated VHD. Although the clinical significance of the new finding is still uncertain, the intensity of the activity was similar to that associated with fenfluramine.

The study, led by Dr. Bryan Roth, director of the National Institute of Mental Health's Psychoactive Drug Screening Program at Case Western Reserve University, showed in test tubes that MDMA and MDA activate the same 5-hydroxytryptamine 2B (5-HT2B) receptor site on heart valve cells as fenfluramine, stimulating overgrowth of heart valve cells similar to that induced by fenfluramine and its major metabolite, norfenfluramine. This overgrowth of heart valve cells in humans can lead to valvulopathy, whereby the valve becomes inefficient and blood leaks back into the heart. The chambers of the heart become overloaded with blood, enlarging the heart and impairing its ability to send blood throughout the body. If detected in time, valvulopathy can be treated with valve replacement surgery. Often, however, people with valvulopathy do not experience symptoms and some go undiagnosed for years, until they progress to heart failure.

Studies estimate that 10 to 15 percent of individuals who took the weight loss drug fenfluramine for extended periods developed VHD to some extent. In the current study, MDMA and MDA caused levels of 5-HT2B receptor site stimulation and valve cell overgrowth comparable to those produced by fenfluramine. So while it may take years for epidemiologists doing echocardiograms to confirm these test tube findings, there is evidence enough in the minds of the researchers that ecstasy users should be warned.

"As far as we're concerned, the association between 5-HT2B receptor activation and VHD is nailed down," says Dr. Roth, "and both MDMA and MDA activate this receptor site." Adds Dr. Richard Rothman, of NIDA's Intramural Research Program and one of the study's authors, "This study demonstrates that MDMA and MDA are both 5-HT2B agonists, stimulating cardiac valve cells in the laboratory to overproliferate." If this is happening in people, as Dr. Rothman suspects it may be, "these individuals would be at risk for developing VHD."

MDMA Use Activates Heart Valve Receptors, Triggering Valve Cell Overgrowth



MDMA—a recipe for valvular heart disease? The top graph compares the impacts of placebo, MDMA and its metabolite MDA, and the banned diet drug fenfluramine and its metabolite norfenfluramine in activating 5-HT2B receptor sites on heart valve cells. The bottom graph shows the relative levels of valve cell proliferation in response to each.

Drs. Roth and Rothman did not set out to look for an MDMA-VHD or MDA-VHD connection, but were screening both drugs to see which receptors they target. Valve cells were obtained from donor human hearts, and specimens were processed, incubated, filtered, and grown in test culture dishes. Several laboratory tests—including those for dopamine, norepinephrine, and serotonin release—were used on the cultured

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The Neurobehavioral Legacy of Prenatal Tobacco Exposure

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

More than 17 percent of pregnant women between the ages of 15 and 44 smoke, according to the 2002 National Survey on Drug Use and Health. Much is known about the adverse effects of smoking during pregnancy: Cigarette smoke reduces blood flow through the placenta by as much as 38 percent, and pregnant smokers are more than twice as likely as nonsmokers to have an infant with low birthweight. New research by NIDA-funded investigators now provides the first evidence of toxic effects of prenatal exposure to tobacco smoke on newborn neurobehavior. This finding begins to fill in our picture of how the adverse neurological effects of prenatal exposure manifest from the earliest days of life to later observed effects, including lower IQ and increased risk of developing attention-deficit/hyperactivity disorder.

Drs. Barry M. Lester and Karen L. Law and their colleagues at Brown Medical School in Providence, Rhode Island, used the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) to document the effects of maternal smoking on 1- to 2-day-old infants. The researchers found significant differences in short-term neurobehavioral status in tobacco-exposed newborns compared with unexposed newborns and noted that neurobehavioral impact worsened as the mothers' smoking levels rose.

"This study offers the first solid evidence of a dose-response relationship between maternal smoking during pregnancy and newborn neurobehavior," says Dr. Lester. "Babies born to mothers who smoked while pregnant are stressed, which could affect their development."

"Focusing on newborn neurobehavioral outcomes is important," comments Dr. Vincent Smeriglio, Chair of NIDA's Child and Adolescent Work Group. "It invites us to think about the continuity of consequences, as we see these very early behavioral

Tobacco-Exposed Infants Exhibit Significant Neurobehavioral Effects

NNNS Category	Tobacco-Exposed Infants (N=27)	Non-Exposed Infants (N=29)	Measure Description, Number of Items, and Range
Handling	0.57	0.44	Mean number of strategies used to maintain infant's alert state (8 items, 0-1)
Excitability	3.08	1.91	Sum of items measuring excitable behavior (15 items, 0-15)
Hypertonicity	0.37	0.00	Sum of items measuring excess muscle rigidity response (10 items, 0-10)
Total Stress/Abstinence (Withdrawal)	0.12	0.05	Mean number of observed stress/abstinence signs (50 items, 0-1)
Central Nervous System Stress	0.16	0.09	Subscale of total stress/abstinence score (range 0-1)
Gastrointestinal Stress	0.16	0.02	Subscale of total stress/abstinence score (range 0-1)
Visual Stress	0.11	0.01	Subscale of total stress/abstinence score (range 0-1)

The NICU Network Neurobehavioral Scale (NNNS), developed with NIDA funding to study prenatal drug exposure, was used to assess the effects of prenatal nicotine exposure on 56 newborns within 48 hours of birth. Infants prenatally exposed to tobacco were highly aroused and reactive, with more rigid muscles than non-exposed infants. Tobacco-exposed infants also scored higher on a checklist of 50 items that serve as markers of stress or drug withdrawal in high-risk babies, with significant results evident for central nervous system, gastrointestinal, and visual stress. Data shown are adjusted scores; statistical analyses controlled for parity, 5-minute Apgar score, and birthweight.

differences in prenatally exposed children and consider them in light of effects in older children" (see sidebar, "Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers"). "This research is providing an important piece of the puzzle linking prenatal exposure to cigarette smoke and long-term behavioral outcomes," Dr. Smeriglio says.

The researchers conducted their study with 56 new mothers, ages 18 to 35, and their newborns at a Providence hospital. Recruited shortly after they had given birth, the mothers—27 smokers and 29 nonsmokers—had not used any illegal drugs during their pregnancy and consumed fewer than four alcoholic drinks per month. Mothers who smoked reported smoking fewer than seven cigarettes per day, with tobacco use confirmed by measuring saliva levels of cotinine, the primary metabolite of nicotine. Only healthy newborns whose weights were appropriate to their gestational ages were included in the study; the researchers controlled for birthweight so the effects they found on neurobehavior could not be attributed to the effects of maternal smoking on birthweight.

A certified examiner who was unaware of the mother's smoking status administered the NNNS to each newborn within 48 hours of birth. The test examines an infant's neurological state, considering muscle tone, reflexes, and integrity of the central nervous system (CNS); behavior, including attention, arousal, and excitability; and a checklist of 50 items shown by previous research to be markers of stress or—in high-risk babies—of drug withdrawal. Dose-response effects were determined by evaluating the relationship between measures of maternal smoking (cotinine and self-report) and NNNS scores.

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Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers

Teenage children of mothers who smoked during pregnancy perform more poorly on tests of general intelligence and on tasks requiring auditory memory than do children who were not exposed to cigarette smoke before birth, according to NIDA-supported researchers at Carleton University in Ottawa, Canada. Dr. Peter Fried and his colleagues, who have followed the development of children born to smoking mothers as part of the Ottawa Prenatal Prospective Study, previously reported poorer cognitive abilities in children of smokers when the children were ages 5 to 6 and 9 to 12. "The results we see now that the children are 13- to 16-year-olds continue to suggest that exposure to cigarettes before birth has negative impact on general IQ and on auditory memory. And the effects are dose-related: The deficits are more severe in children of heavy smokers," Dr. Fried says.

The scientists administered a battery of tests to 145 13- to 16-year-olds (78 boys, 67 girls) whose mothers smoked heavily (more than a pack per day), lightly (less than a pack per day), or not at all during their pregnancies. The tests included measures of general achievement (reading and language skills), visual memory (identifying a missing number from a random sequence of numbers from 1 to 10), auditory memory (repeating tape-recorded sentences of increasing length and complexity), and general intelligence (IQ scores). In some tests there were no significant differences among the children. In tests of general intelligence and auditory memory, however, children born to smokers had lower scores than did children of nonsmokers, and children born to heavy smokers had poorer scores than children of light smokers. For example, in the general intelligence test, for which scores from 99 to 109 are considered "normal," children of nonsmokers had an average score of 113.4; of light smokers, 109.8; and of heavy smokers, 105.2.

In some areas of cognitive function, the gap in test results between exposed and unexposed children has narrowed as the children have grown, observes Dr. Fried. This improvement is most notable in tests that measure achievement rather than innate ability. For instance, although measured IQ remains lower for exposed children, their scores on reading and language skills are equivalent to those of unexposed children. "This comparative improvement in achievement is associated most strongly with the educational level of the parents. Achievement tests are in many ways a measure of formal learning acquired at home and in school. It appears that family and environmental factors that support learning can help moderate the negative effects seen in measures of ability," Dr. Fried explains.

"The improvements found in this most recent evaluation of these children are encouraging," says Dr. Vincent Smeriglio, chair of NIDA's Child and Adolescent Work Group. "Nonetheless, the continued finding of poorer performance as the exposed children enter adolescence underscores the damage that appears to be done by smoking during pregnancy. These kids may be catching up in some ways, but they started out with a serious disadvantage."

Source

• Fried, P.A.; Watkinson, B.; Gray, R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratolgy* 25(4):427-436, 2003. NN

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discriminate differences in behavior," Dr. Catalano says.

The differences in teachers' and parents' reports on prosocial behavior may relate to several factors. First, parents may not have as many opportunities as teachers do to see their children interact in structured environments. Second, parents may have less exposure to children's social behaviors, and their comparisons may be limited to a small group of their children's friends.

The researchers suggest that data collection issues may account for child-reported data not showing significant differences between program participants and nonparticipants in social competency and antisocial behavior. For example, the children's young age precluded asking them a sufficient number of questions to measure all of the relevant dimensions. In addition, data were not collected from the children before the intervention began, so data provided by parents were used as baseline measures.

"The significant findings are that the intended targets for intervention have been changed," Dr. Catalano observes. "On the risk side, it appears that we've reduced antisocial behavior and academic failure. On the protective side, we appear to have increased kids' social competency and commitment to school."

The researchers observe that the study provides only preliminary results of the longitudinal RHC intervention, and a NIDA-funded study of long-term RHC outcomes in middle school and high school students is now underway. With its encouraging initial findings, this research appears to support other evidence of the effectiveness of social development interventions in young children. Dr. Catalano notes that the RHC program replicates and extends the Seattle Social Development Research Project (SSDP), but focuses on institutionalizing intervention practices school-wide. Evaluation of the SSDP showed short-term success in increasing academic performance and reducing violent behavior. It also showed long-term success in increasing academic performance and decreasing substance use, drug-selling, and other problem behaviors.

"Because we've tried to find ways to enhance implementation of the practices and update the practices, we really have a second generation of these studies," Dr. Catalano explains. "That makes it a stronger contribution than a single study. The message is that developmental prevention can work and can be replicated."

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MDMA Use May Increase Risk for Cardiac Valve Disease

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cells to determine MDMA's affinity for specific receptor sites and the resulting extent of valve cell proliferation. Their findings build on NIDA-funded research published in 2000 that identified how fenfluramine causes VHD. Particularly alarming, notes Dr. Rothman, is the present study's observation that MDMA and MDA stimulated 5-HT2B overgrowth at typical street doses.

In addition to testing MDMA and MDA, the researchers also screened medications known to induce VHD—pergolide, used to treat Parkinson's disease, and the migraine medication dihydroergotamine. These medications also targeted the 5-HT2B receptor site, confirming the association between this receptor site, VHD, and the ability of the laboratory tests used to identify medications that might produce VHD.

MDA, Dr. Roth observes, was more potent than MDMA in activating the VHD receptor site. "MDA is not as available to drug abusers as MDMA," he says, "probably because it's more difficult to produce. However, the individuals I've talked with who have taken both drugs seem to prefer MDA when they can get it. Whether it's MDA or MDMA, the potential for cardiac damage is real."

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The Long Road to Medication Development: Cocaine Treatment Moves to Clinical Trials

By Neil Swan, NIDA NOTES Contributing Writer

At the culmination of a research journey that began more than 20 years ago, GVG (vigabatrin)—a medication widely used to treat epilepsy outside the United States—is about to be tested in large-scale clinical trials that will determine whether its promising pharmacological properties can translate into effective treatment medication for cocaine abuse. Winning FDA approval of any pharmaceutical therapy for use in the United States is an exacting, costly, time-consuming process. It involves lengthy research, testing in animals and, finally, testing in increasingly larger groups of selected, medically suitable humans to show that the drug is not only therapeutically effective, but safe to use. Testing medications to treat drug addiction is especially challenging, as it involves recruiting—and gaining the support and cooperation of—drug-addicted people.

After more than 20 years, it appears that GVG is nearing the final hurdles to winning FDA approval for use in treating cocaine addiction. Detailed below is this long journey, not untypical of the process many medications go through before providing relief to their intended recipients.

Identifying GVG's Promise

In the 1980s, Dr. Stephen L. Dewey of Brookhaven National Laboratory in Upton, New York, and a colleague, Dr. Jonathan D. Brodie of the New York University School of Medicine in New York City, were seeking new treatments for schizophrenia. "Very few people in the mid-1980s looked at interactions between neurotransmitter systems, but rather examined transmitter systems independently," explains Dr. Dewey. As studies continued over years and preliminary research showed that GVG modulates GABA, which in turn reduces dopamine levels, the scientists launched a long series of preclinical experiments testing GVG's potential as a treatment medication for addiction.

"Two decades and 15 publications later, we knew that GVG can safely block the biochemical effects of addictive drugs—nicotine, morphine, methamphetamine, amphetamine, ecstasy, and alcohol—including the increased brain dopamine levels they trigger," Dr. Dewey says. "This medication can also block the behavioral fallout from dopamine surges: drug

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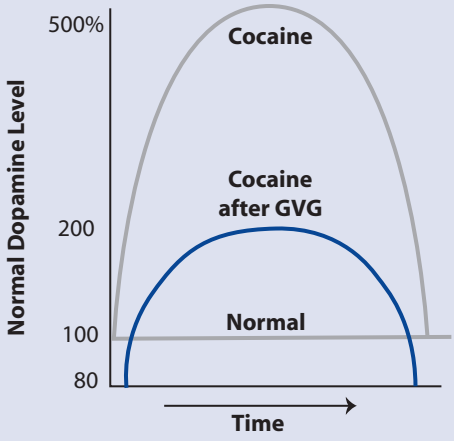
GVG Blocks Cocaine-Triggered Dopamine Increases in Animals



Brain Dopamine Levels Under Various Conditions

Cocaine increases dopamine levels in animals to as much as 500 percent of normal levels in critical brain areas. However, when animals are given GVG before being given cocaine, their dopamine levels increase to no more than twice normal levels, indicating the reward-reinforcement response has been blocked or greatly reduced.

Developing a medication to treat cocaine addiction has long been a research priority of NIDA's Medications Development Program. According to the National Survey on Drug Use and Health, an estimated 2 million people were current cocaine users in 2002. The available treatment offerings for these individuals as well as people addicted to methamphetamine and other stimulant drugs are exclusively behavioral, as no treatment medications have yet proven effective.

Dr. Frank Vocci, Director
Division of Treatment Research and Development

The Long Road to Medication Development: Cocaine Treatment Moves to Clinical Trials

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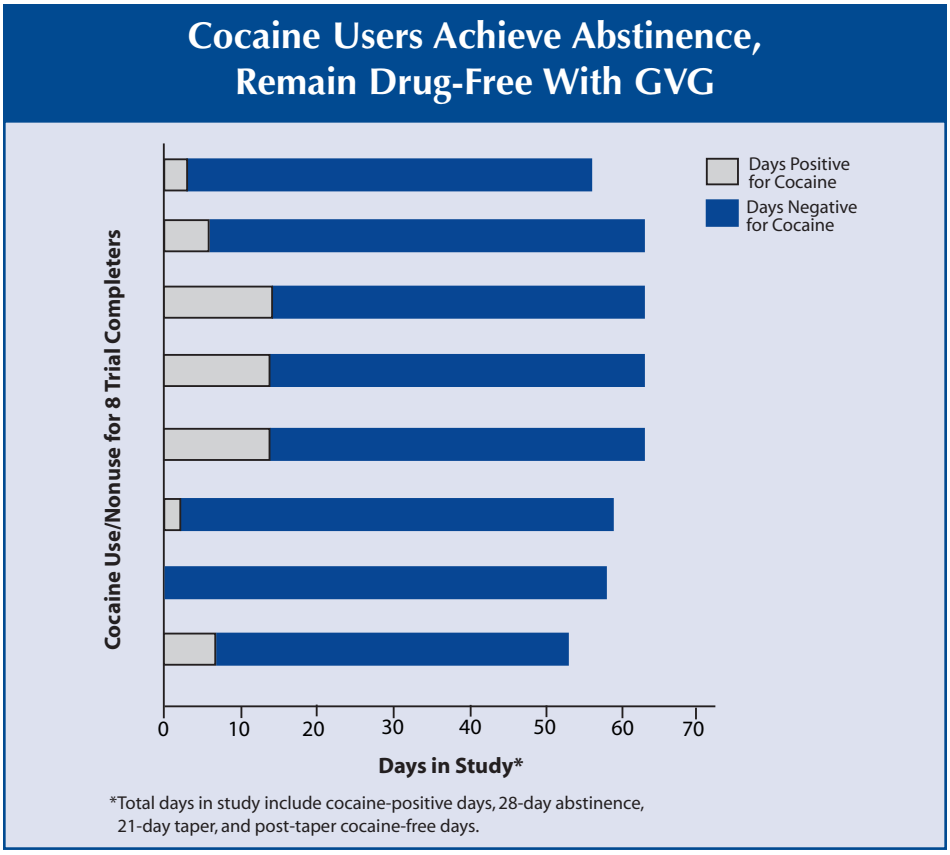
self-administration, changes in brain-stimulation reward threshold, relapse resulting from addiction-induced cues, and drug sensitization—the need to consume more and more of a drug to achieve dopamine-based feelings of pleasure."

With evidence of GVG's ability to block the addictive effects of all psychostimulants, the researchers focused their research on its potential as a pharmaceutical therapy for cocaine addiction. Throughout this research, Dr. Dewey charted how dramatically GVG therapy inhibits cocaine-induced increases in brain dopamine levels in animals. However, plans to test GVG as a treatment for cocaine abuse in humans were sidetracked in 1998, when research showed that 10 to 30 percent of epilepsy patients taking the drug lost some portion of their normal field of vision.



Of 20 cocaine abusers enrolled in a GVG clinical trial, 8 completed the trial (28-day abstinence plus 21-day taper) and were drug-free for 46 to 58 days total. Once cocaine use ceased, 6 of the 8 completers were entirely drug-free for the duration of the study. Most patients who completed the trial reported that their craving for cocaine stopped 2 to 3 weeks after receiving GVG.

Meeting a Safety Challenge

Not willing to give up on GVG's potential, Dr. Dewey and his Brookhaven colleagues set out to find a low-dosage course of GVG that could effectively block the addictive responses of cocaine in rats without impairing their vision. The researchers' strategy: compare the effects of a single large dose of 150-450 mg/kg GVG with those of the same total dose administered over 3 days, at 50-150 mg/kg per day. The scientists found that the anti-addictive effect of GVG persists when it is administered gradually. The drug inhibited the effect of cocaine after a 3-day "washout" period when GVG administration stopped. Further, the inhibitory effect of gradual administration actually exceeded in magnitude and duration the effect of the identical total one-shot dose, the researchers found.

The researchers concluded that people can probably sustain GVG maintenance therapy, possibly for years, with little or no increased risk of developing medication-induced vision defects.

Launching Clinical Trials

Using human dosages based on the GVG dosages that safely countered cocaine's effect in rats and primates, Drs. Dewey and Brodie launched a clinical trial with 20 cocaine abusers in a drug treatment center directed by Dr. Emilia Figueroa in Mexicali, Mexico. Following the dosing strategy devised for animals, the researchers introduced GVG therapy with a strategy of "ramping the patients' doses up, and then tapering them off," explains Dr. Dewey.

Of the 20 patients enrolled in the study, 8 remained in the program and were drug-free for periods of 46 to 58 days. Twelve enrollees failed to complete the clinical trial; of these, 8 dropped out within the first 10 days, having decided they were not ready to stop abusing cocaine. Four enrollees participated in the study for 25 to 43 days while continuing to abuse cocaine, albeit in greatly reduced amounts. Most patients who completed the trial reported losing their craving for cocaine after 2 to 3 weeks of GVG. Once they stopped cocaine abuse, 6 of the 8 completers

were drug-free for the duration of the study. No vision problems were reported.

Encouraged by the Mexico results, the researchers look forward to the next step—a larger, double-blind, placebo-controlled trial that they hope to initiate soon in Toronto, Canada. Catalyst Pharmaceutical Partners, which holds the license from Brookhaven to develop GVG as a treatment for drug addiction, has helped move this trial forward. Another smaller trial is also being projected for the United States. Dr. Frank Vocci, Director of NIDA's Division of Treatment Research and Development, says that NIDA is ready to cooperate once FDA gives its approval to go ahead.

"We are still early in the clinical trial process," notes Dr. Vocci. "However, if additional trials safely and successfully replicate early treatment results, GVG has the potential to provide us with an effective medication for preventing relapse in cocaine-dependent patients."

If additional trials safely and successfully replicate early treatment results, GVG has the potential to provide us with an effective medication for preventing relapse in cocaine-dependent patients.

Commenting on the impressive GVG research record, Dr. Vocci concludes, "The data these researchers have compiled is the most comprehensive on a potential medication for addiction therapy that we've seen," he says. "It's a very interesting medication that involves a very interesting mechanism."

Sources

- Brodie, J.D.; Figueroa, E.; and Dewey, S.L. Treating cocaine addiction: From pre-clinical to clinical trial experience with γ-vinyl GABA. *Synapse* 50(3):261-265, 2003.
- Schiffer, W.K.; Marsteller, D.; and Dewey, S.L.. Sub-chronic low dose γ-vinyl GABA (vigabatrin) inhibits cocaine-induced increase in nucleus accumbens dopamine. *Psychopharmacology* 168(3):339-343, 2003. NN

The Neurobehavioral Legacy of Prenatal Tobacco Exposure

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"Infants exposed to tobacco in the womb showed statistically significant differences that suggest toxic effects of prenatal tobacco exposure on the newborn neurological system," says Dr. Lester. The tobacco-exposed infants were highly aroused and reactive as indicated by the higher excitability and handling scores, and their muscles were more rigid. They also showed signs of stress and drug withdrawal consistent with what has been reported in infants exposed to other drugs. When the total stress/abstinence scores were broken down into subscales, exposed infants showed significant CNS, gastrointestinal, and visual effects. Further, infants prenatally exposed to tobacco required more handling to keep them in a quiet and alert state.

"These infants' higher scores in such areas as excitability and arousal reflect that nicotine is a stimulant," says Dr. Lester. The researchers also found consistent dose-response relationships for both the cotinine bioassay results and the self-reports of number of cigarettes smoked per day. "These results indicate that greater exposure to tobacco smoke is related to increasingly negative neurobehavioral effects," he adds, "and that these children may be at increased risk for future neurobehavioral problems."

Dr. Lester is currently designing a larger, multisite study focusing on the neurobehavioral effects of prenatal exposure to cigarette smoke. Future research will attempt to pinpoint which components of tobacco are responsible for the known neurobehavioral effects; determine whether those effects are long-term; clarify whether newborns experience nicotine withdrawal; and separate the effects of prenatal exposure from those of postnatal exposure through second-hand smoke or breastfeeding.

With valid information on the potential neurobehavioral effects of prenatal tobacco exposure, more pregnant women may be swayed to quit smoking, notes Dr. Lester. "The smoking effects observed in our study underscore the importance of smoking cessation programs, particularly for women of childbearing age," he says.

Source

- Law, K.L.; Stroud, L.R.; LaGasse, L.L.; Niaura, R.; Liu, J.; Lester, B. Smoking during pregnancy and newborn neurobehavior. *Pediatrics* 111(6):1318-1323, 2003. NN

NIH Roadmap to Medical Research Funding

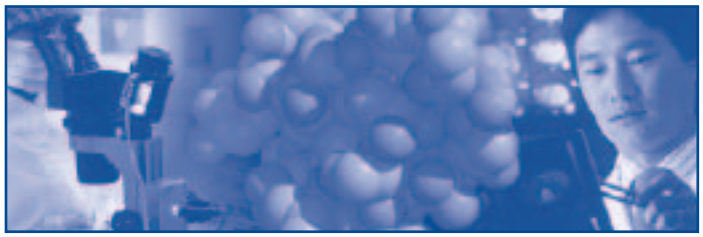
NIDA wants drug abuse researchers to help lead a journey of scientific inquiry that promises to transform biomedical research in the United States. The Institute is encouraging grantees to apply for funds through Requests for Applications (RFAs) under NIH Director Elias Zerhouni's "Roadmap for Medical Research." The Roadmap charts a course to optimize the Nation's medical research resources and bring all 21st-century scientific tools and knowledge to bear on conquering disease.

"NIDA researchers, who are already involved in many of these areas, can significantly contribute to advancing the goals of this initiative," says NIDA Director Dr. Nora D. Volkow. However, timing is critical in pursuing funding opportunities under the Roadmap's initial round of initiatives; most applications are due in February and March. If the letter of intent date has passed, please call NIDA program staff to discuss submitting an application. For more information on the following RFAs, visit http://nihroadmap.nih.gov.

New Pathways to Discovery

This research area focuses on the building blocks of the body's cells and tissues and how complex biological systems operate; structural biology; molecular libraries; imaging technologies; bioinformatics and computational biology; and nanotechnology.

- Metabolomics Technology Development (RFA-RM-04-002). *Letter of intent*: February 24, 2004; *application*: March 24, 2004. *Contacts*: Dr. Rao Rapaka (301-435-1304) or Dr. Christine Colvis (301-435-1323).
- National Technology Centers for Networks and Pathways (RFA-RM-04-005). *Letter of intent*: February 15, 2004; *application*: March 16, 2004. *Contacts*: Dr. Jonathan Pollock (301-435-1309) or Dr. Christine Colvis (301-435-1323).



- Centers for Innovation in Membrane Protein Production (RFA-RM-04-009). *Letter of intent*: February 5, 2004; *application*: March 11, 2004. *Contact*: NIDA Program Officer.
- National Centers for Biomedical Computing (RFA-RM-04-003). *Letter of intent*: December 29, 2003; *application*: January 23, 2004. *Contact*: NIDA Program Officer.

Research Teams of the Future

Interdisciplinary research, high-risk research, and public-private partnerships are the focus of initiatives in this area.

- Supplements for Methodological Innovations in the Behavioral and Social Sciences (RFA-RM-04-013). *Letter of intent*: January 13, 2004; *application*: February 13, 2004. *Contact*: NIDA Program Officer.
- Interdisciplinary Health Research Training: Behavior, Environment, and Biology (RFA-RM-04-010). *Letter of intent*: February 11, 2004; *application*: March 11, 2004. *Contact*: NIDA Program Officer.
- Short Programs for Interdisciplinary Research Training (RFA-RM-04-008). *Letter of intent*: January 14, 2004; *application*: February 11, 2004. *Contact*: NIDA Program Officer.
- Curriculum Development Award in Interdisciplinary Research (RFA-RM-04-007). *Letter of intent*: January 27, 2004; *application*: February 24, 2004. *Contact*: NIDA Program Officer.
- Exploratory Centers (P20) for Interdisciplinary Research (RFA-RM-04-004). *Letter of intent*: January 30, 2004; *application*: February 24, 2004. *Contact*: NIDA Program Officer.

Re-engineering the Clinical Research Enterprise

RFAs that fall under this research area target clinical research workforce training, interdisciplinary integration of clinical research networks, and translational research centers and services.

- Re-engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks (BAA-RM-04-23). *Letter of intent*: January 30, 2004; *application*: March 5, 2004. *Contact*: NIDA Program Officer.
- Dynamic Assessment of Patient-Reported Chronic Disease Outcomes (RFA-RM-04-011). *Letter of intent*: February 22, 2004; *application*: March 22, 2004. *Contact*: NIDA Program Officer.
- Multidisciplinary Clinical Research Career Development Programs (RFA-RM-04-006). *Letter of intent*: February 23, 2004; *application*: March 23, 2004. *Contact*: NIDA Program Officer. NN

Window on America: Drug Use Among Racial/Ethnic Minorities

This fall, NIDA released a revised edition of *Drug Use Among Racial/Ethnic Minorities*, a resource for policymakers, program leaders, health administrators, researchers, and others seeking information on illegal drug use, alcohol and tobacco use, and associated attitudes, behaviors, and consequences among racial/ethnic minority populations nationwide.

Major demographic changes affecting the United States provide the context for this report. For example, by 2030, racial/ethnic minorities are expected to constitute one-half of the Nation's K-12 student population. Non-Hispanic whites are expected to comprise 60 percent of the total population by that year, a decline from 75 percent in the early 1990s. The report notes, however, that a serious analysis of illegal drug use and racial/ethnic minorities must address current definitions of race and ethnicity, with controversy surrounding how best to sort individuals into racial/ethnic minority groups. Employing the 2000 U.S. Census race/ethnicity categories, the report cites the variation that exists within minority populations—a reality that means statements that might be true for a given population may be untrue for subgroups within it. With that caveat in mind, key points made in the report's discussion of drug use among each race/ethnicity follow.

American Indian/Alaska Natives. From NIDA-sponsored research at the Tri-Ethnic Center for Prevention Research in Fort Collins, Colorado, and other studies designed to cover American Indians/Alaska Natives, data suggest heavy use of alcohol, tobacco, and other drugs as serious public health problems among this population. Research indicates more excessive drinking and illegal drug use among some groups of American Indians/Alaska Natives than among most, if not all, other racial/ethnic minority groups. Prevalence studies show that American Indian/Alaska Native youth age 12 and older use marijuana, cocaine, cigarettes, and alcohol at more than twice the rate of Hispanic and non-Hispanic whites and blacks.

African Americans. Non-Hispanic African Americans comprise about 12 percent of the total U.S. population and have roughly equivalent prevalence estimates, 6 percent, for illegal drug use as whites. However, while illegal drug use and trafficking continue to be major problems within African-American communities, social factors, such as racial profiling, lead to overrepresentation of African Americans in criminal justice statistics and public drug treatment programs, making precise estimates difficult.

Asian/Pacific Islanders. During the 1990s, Asian/Pacific Islanders experienced one of the fastest growth rates among the Nation's racial/ethnic groups, as identified by the Census Bureau. The heterogeneity within this population category is reflected in dramatic subgroup variations in drug involvement within this population. Although there is a widely held belief that illegal drug use is less frequent among Asian/Pacific Islanders than other segments of the U.S. population, estimates for Korean Americans and Japanese Americans are not too dissimilar from general population estimates.

Hispanics. Heterogeneity also characterizes the Hispanic-American population. One of the youngest and fastest growing segments of the U.S. population, the Hispanic population is projected to double to 24 percent of the population by 2050. Recent data on active and current drug use among 12th-graders indicate Hispanic high school seniors have the highest prevalence of cocaine, crack, and heroin abuse.

The report's final chapter notes that current estimates of illegal drug use in minority populations may underrepresent the extent of the problem, as some national statistics and surveillance systems collected data before the latest recommended classifications for racial and ethnic groups were in place. Other sources of underrepresentation may result from reluctance to report illegal drug use because of English language difficulties or concern about reprisal. The report calls for an improved conceptual framework and better theoretical models for conditions and processes that affect risk for and protection from illegal drug use and cites the need to identify the best intervention choices from among those available.

Among progress and successes cited are the increasing number of completed studies of illegal drug use among minorities in the past two decades. Some studies have targeted groups considered at high risk for substance abuse—school dropouts, runaways, and arrestees. Including more minority researchers in leadership roles within the scientific community and increasing collaboration with people of color in research planning are among the suggestions for enhancing data collection on drug use among racial/ethnic minorities.

For electronic access to the revised edition of this report, visit NIDA's Web site at www.drugabuse.gov; print copies can be ordered at 1-800-729-6686. NN

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