NIDA NOTES

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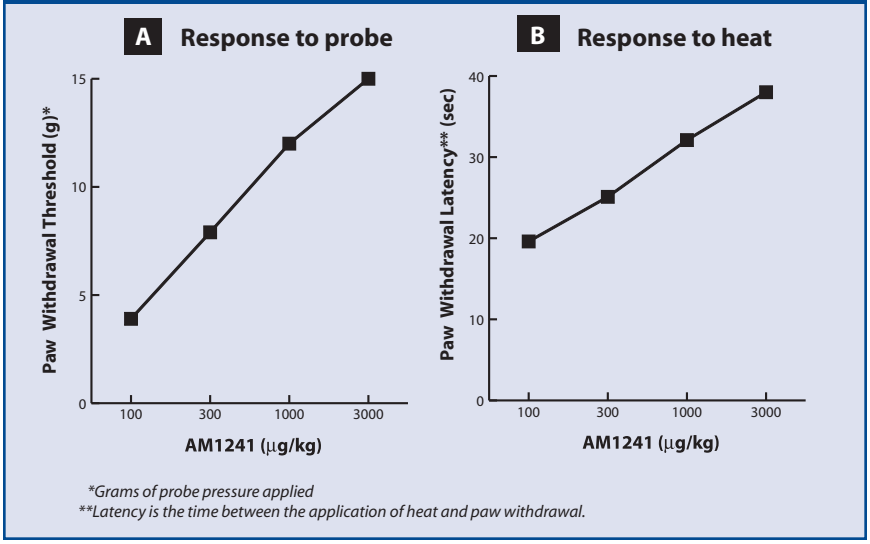
# Novel Cannabinoid Appears Promising For Treatment of Chronic Pain

By Robert Mathias, *NIDA NOTES* Staff Writer

Trauma, infection, and diseases such as diabetes can damage nerves, causing pain that persists long after the acute condition has been resolved. Such chronic pain, called neuropathic to signify that it is caused by injuries to nerves themselves rather than to surrounding tissues, is difficult to treat. The strongest analgesics, the opioids, such as morphine and fentanyl, often only partially control it. Moreover, the opioids' side effects, which include constipation, nausea, anxiety, sedation, and respiratory depression, make long-term dosing to control persistent, intractable pain problematic. The opioids' potential for physical dependence and addiction places additional constraints on long-term use.

Better relief may be on the way, however, for patients with chronic neuropathic pain as well as others. NIDA-funded researchers recently created and tested a new experimental analgesic compound that reduced pain caused by nerve damage in mice and rats without apparent undesirable side effects. Further, the compound also showed efficacy in inflammatory pain. If these preliminary findings hold up, the compound could fulfill a longstanding need for controlling pain due to neuropathy and also to conditions, such as cancer, that can cause pain through multiple mechanisms.

## AM1241 Reverses Pain Responses in Sensitized Rats




*Grams of probe pressure applied
**Latency is the time between the application of heat and paw withdrawal.

*Following surgery that increased rats' sensitivity to painful stimuli, the animals' ability to tolerate pressure from a probe (A) or heat from a lamp (B) increased proportionally with increases in AM1241, a cannabinoid agonist. Higher doses increased their ability to tolerate heat well beyond levels established before the surgery.*

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## Minimizing Side Effects

Dr. Alexandros Makriyannis, of the University of Connecticut in Storrs, developed the compound, a new synthetic molecule belonging to the class of chemicals called cannabinoids. The cannabinoids, which are similar to THC, the active ingredient in marijuana, have analgesic effects; however, like opioids, most also produce sedation, anxiety, and other side effects that preclude their administration in doses high enough to manage severe pain.

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## Correction

Our story "Smoking Decreases Key Enzyme Throughout Body," in Volume 19, Number 1, incorrectly stated the number of deaths resulting from tobacco-related diseases in the United States each year. The correct estimate is more than 400,000 deaths.

## NIDA News and Information at Your Fingertips

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- Links to Related Web Sites

# NIDA's Brain, Behavior, Health Initiative: Multidisciplinary Exploration of the Brain

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

NIDA's mandate in drug abuse science is guided by a fundamental principle: our recognition that addiction is a brain disease. We know that to develop more effective prevention and treatment strategies we must deepen our understanding of how drugs affect the complex inner workings of the brain. Thanks to remarkable advances in bioscience, and particularly in the neurosciences over the past decade, this is a realistic goal. The challenge is to create from the avalanche of new data a coherent picture of biological events interacting with environmental factors and eventuating in the dysfunction we call addiction. Our Brain, Behavior, and Health Initiative, begun this past year, is a comprehensive strategy for realizing this vision.

The way the brain works can be analyzed from a number of perspectives. At the foundation are genes, where enormous progress has been made with the mapping of both mouse and human genomes and the sequencing of functional units within them. Genes build proteins, whose structure and function are elucidated by another burgeoning scientific discipline, proteomics. Proteins and the reactions between them operate within cells, a separate field of study. The cells that make up the organ of the brain form circuits and pathways—the province of neurobiology. And the consequence of activity along these brain pathways is the full range of thought and action we call human behavior.

The reality is far more complex than even this analysis suggests. Not only do genes affect proteins and cells, brain circuits and behavior, but events on the level of behavior (such as drug taking) influence brain circuits, proteins, and genes. We cannot understand the brain fully by looking only at its parts, and the ultimate aim is a unified vision of the brain.

The more we know about the brain at each level, the greater the depth and detail in which we can study addiction. For example, specifying which genes are switched on when an individual becomes addicted to cocaine, how these genes interact and affect the development of new proteins, and how these proteins alter cellular function might guide research toward novel kinds of pharmacotherapy. We know that signaling between the ventral tegmental area and the nucleus accumbens constitutes a major brain pathway stimulated in addiction to cocaine and other drugs of abuse. A deeper understanding of this system could pave the way to a different set of intervention strategies.

Clearly, what is needed is a radical departure from the traditional scientific landscape of researchers working within the isolation of separate disciplines: geneticists identifying genes in a small area of tissue, proteomics researchers focused on single protein complexes, neurobiologists probing brain circuits—each group speaking its own language within its own closed circle.

To navigate this vast and varied territory, we need a map, and the first big step of the NIDA Brain, Behavior, and Health Initiative has been to create one: the brain project matrix. Developed by NIDA health scientist administrators, the matrix brings together an immense amount of information in a computer-interactive chart, divided into sections that correspond to the five areas that represent the entire field of neuroscience research: genes, proteins, cells, brain circuits and pathways, and behavior.

For each area, key questions are set forth. For genes, for example, what is the genetic basis of brain function and behavior? How and under what conditions do genes function differently in different parts of the brain? How do gene variants, subtly different versions of the same gene, impact brain function and disease?

The matrix then captures the scientific approaches used to address each question and lists the major research centers, consortia, Government agencies, university programs, and private companies that are engaged in this work (including some, like the Department of Energy, whose research is not explicitly biological in nature). Many of these listings are hyperlinked to Web sites where the details about the program, and in some cases many of its data, can be accessed. The next column of the matrix lists the current technology applied to exploring the question, and the last indicates the technology and other resources needed to pursue answers more fully.

Simply moving among sections of the matrix conveys the multidimensional depth and breadth of neuroscience. Researchers can survey ongoing projects relevant to their work, in their own and other disciplines. Policymakers and others charged with planning and developing the research enterprise can assess more deftly the needs of the future.

The matrix is a work in progress. To bring the full light of neuroscience to bear on research into addiction and other brain diseases, a future map will have to make data from diverse disciplines broadly accessible and comprehensible—a neuroinformatics effort that will bring computer scientists and mathematicians into the mix. The task is just beginning, and NIDA is proud to be at its cutting edge. NN

# Learning the Science of Drugs Helps Teens Master Biology, Chemistry

By Susan R. Farrer, *NIDA NOTES* Contributing Writer

Learning the science behind cocaine, drug testing, and nerve gas can help high school students understand basic biology and chemistry concepts, a NIDA-funded study has found. Test scores of students who were exposed to drug-related modules in science classrooms were higher than scores of students whose science classes did not include the modules.

In an unusual research alliance, Dr. Rochelle Schwartz-Bloom, a pharmacology professor at Duke University Medical Center in Durham, North Carolina, and Dr. Myra Halpin, a high school chemistry teacher at the North Carolina School of Science and Mathematics, also in Durham, developed and tested a novel science curriculum founded on the idea that teenagers will learn more if they perceive the course content as relevant to their lives. The project, called the Pharmacology Education Partnership (PEP), is supported by a NIDA Science Education Drug Abuse Partnership Award (SEDAPA). The SEDAPA grant program funds the development and evaluation of innovative model programs and materials to enhance knowledge of neuroscience and the biology of drug abuse and addiction among K-12 students, their parents, and other groups.

The PEP curriculum used in the study included four modules that biology and chemistry teachers integrated into their normal curricula. Three of the modules covered the biological and chemical aspects of abused drugs and drug testing, and the fourth module discussed the science of nerve gas. The modules were built around drug topics, but each module was designed to teach standard high school science content, such as molecular structure, cellular structure, anatomy, physiology, oxidation and reduction, and enzyme action.

"Getting kids interested and holding their attention is the most important thing in teaching," explains Dr. Schwartz-Bloom, the study's principal investigator. "If you can't do that, then students will learn very little. Whether you are teaching about drug abuse or something else, using topics that fascinate this population gets their attention so they want to learn."

Dr. Cathrine Sasek, NIDA's science education coordinator, observes that the PEP curriculum takes an innovative teaching approach. "It doesn't bring the kids in and say, 'Okay, today we're talking about drug abuse.' Instead, it teaches biology, chemistry, and biochemistry concepts kids need to learn, using drugs as examples," she says. "In addition, it allows teachers to tailor the curriculum, which immediately has appeal for them."

Dr. Schwartz-Bloom and Dr. Halpin designed the PEP curriculum and then measured how well teaching with the modules stacked up against teaching with schools' usual biology and chemistry curricula. Pairs of experienced biology and chemistry teachers from 25 high schools nationwide were recruited to learn how to use the PEP modules and to field-test the modules in their classrooms. The teachers were randomly assigned to either an experimental group or a control group.

In the first year, teachers for the experimental groups attended a 1-week summer workshop at Duke University to learn basic pharmacology and to design classroom activities that would reinforce the PEP module content. They incorporated the modules and activities into their teaching during the following school year. Each teacher was encouraged to use as many of the four modules as possible, but the investigators did not prescribe methods for using the modules or the number of modules to use.

The control group attended the same workshop the next summer and then integrated the PEP modules into their teaching during the following school year. This wait-listed strategy

allowed the researchers to rule out the possibility that the experimental group included better teachers, despite random assignment.

At the end of year one, both the experimental and control group teachers gave their students a brief, unannounced, multiple-choice test to assess their knowledge of biology and chemistry facts and concepts as well as their science reasoning skills. "Basic knowledge" questions addressed knowledge and skills contained in the National Science Education Standards, and "advanced knowledge" questions targeted new drug knowledge obtained from the teaching modules. At the end of year two, the same test was given to students in the current experimental groups after the teachers had used the modules in their classrooms. Nationwide, more than 4,000 students in grades 9 through 12 took the end-of-course tests over the 2 years.

Use of the PEP modules was significantly associated with students' end-of-course test scores for both the basic and advanced knowledge questions. As the number of PEP modules used in the classroom increased, so too did the students' test scores. On average, students scored 6, 12, and 20 percentage points higher on the basic knowledge questions when two, three, and four modules were used, respectively, than when no modules were used. Similarly, for the advanced knowledge questions, students scored 6, 11, and 28 percentage points higher when two, three, and four modules were used, respectively, compared with no use of modules.

Dr. Schwartz-Bloom likens these findings to a dose-response relationship seen in pharmacology. "The bigger the dose, the bigger the effect," she says, adding that the increment in test scores as more modules were used may have resulted from the repetition built into the modules "to keep driving home basic biology and chemistry concepts."

The researchers further note that in classes where two or more modules were used, students were able to answer both biology and chemistry questions correctly, regardless of whether they were enrolled in biology or chemistry classes. Dr. Schwartz-Bloom asserts that this finding is interesting, particularly because interdisciplinary teaching is now of great interest in science education. "The interdisciplinary nature of the design really worked," she says. "We got the biology kids to learn chemistry and we got the chemistry kids to really beef up on biology. That was icing on the cake."

Additionally, the investigators found that the PEP project benefited the teachers, who received training and professional development during the summer workshops at Duke University. Tests given to the teachers before and after the workshops showed significant gains in their knowledge of biology, chemistry, and pharmacology—and that many of them had retained the knowledge when tested a year later.

"The amount of information the teachers retained was very impressive," Dr. Sasek notes. "The teachers are using what they learned and are retaining it, which is really important."

Since completing the initial 4-year PEP study, Drs. Schwartz-Bloom and

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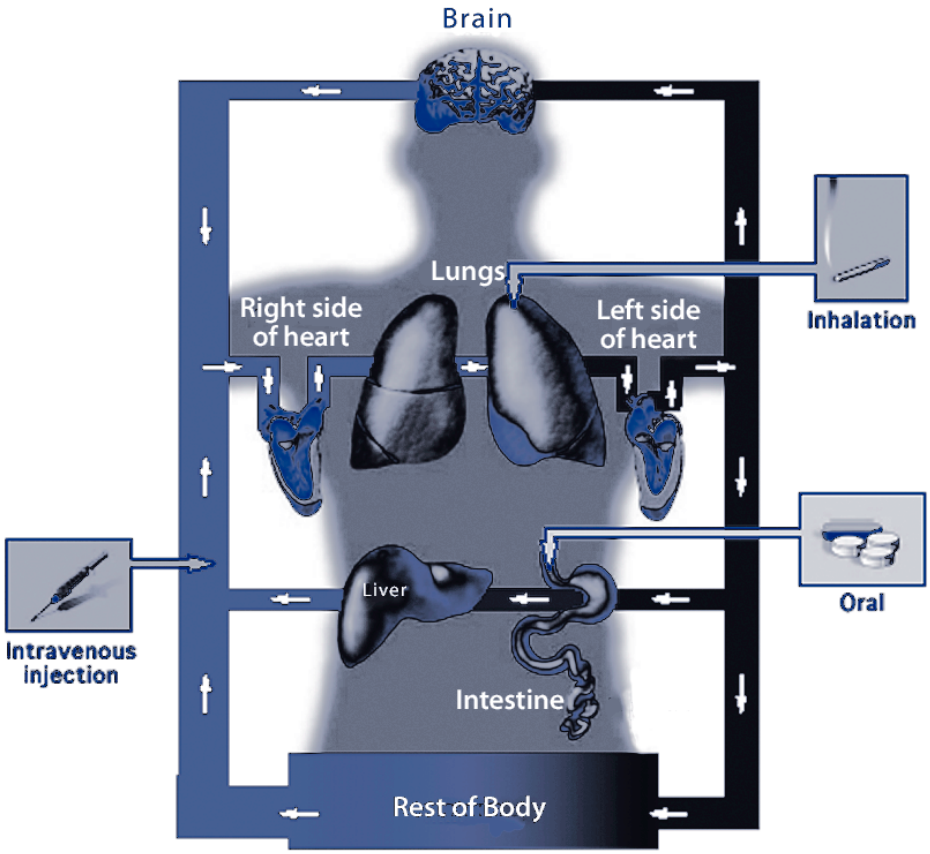



*This image, developed for a PEP module entitled "Acids, Bases and Cocaine Addicts," depicts the three most common modes of drug administration and how the drug then moves through the body. The black outline is the arterial side of the heart; blue is the venous side.*

## Learning the Science of Drugs

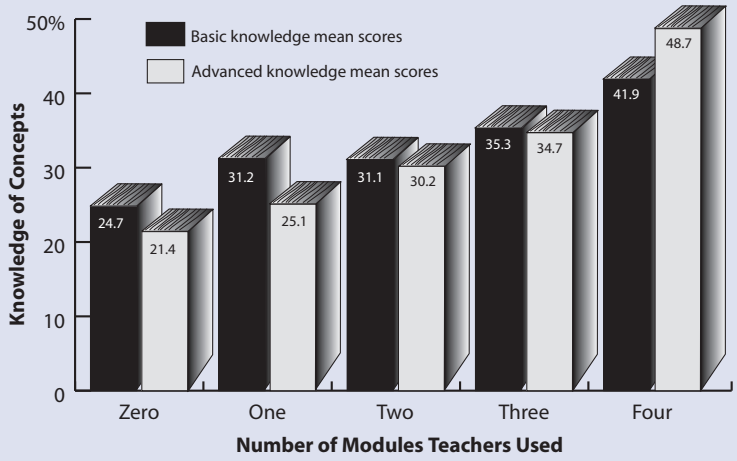
*continued from page 5*

Halpin have been awarded a second SEDAPA grant to continue their work. The new funding has allowed them to create two new PEP modules and to develop an interactive Web site that provides access to the teaching modules and lets teachers and students input data. The site, www.thepepproject.net, will be available in June 2004. The new grant also will enable the researchers to expand the number of students tested to 16,000—a sample size large enough to permit reliable analysis of the data by race and gender.

### Source

• Schwartz-Bloom, R.D., and Halpin, M.J. Integrating pharmacology topics in high school biology and chemistry classes improves performance. *Journal of Research in Science Teaching* 40(9):922-938, 2003. NN

## Students' Biology and Chemistry Knowledge Increases With Number of PEP Modules Teachers Use




*Note: Numbers in bars are scores out of a possible 100 percent.*

*The PEP modules incorporated drug abuse and addiction topics into high school biology and chemistry curricula. Using topics of interest to students helped increase their mastery of basic and advanced biology and chemistry concepts. The surprise test included biology and chemistry questions, but many of the students had taken biology only.*

RESEARCH NEWS

## *NIDA NOTES*: Just a Mouseclick Away

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## Novel Cannabinoid Promising

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Dr. Makriyannis's molecule, however, called AM1241, possesses an unusual feature that distinguishes it from most other cannabinoids. While the others activate two types of cellular receptors, called $CB_1$ and $CB_2$, AM1241 activates only the latter. While $CB_1$ receptors are concentrated on nerve cells in the brain and spinal cord (central nervous system, CNS), $CB_2$ receptors primarily occupy various types of cells in the rest of the body.

Dr. Makriyannis's rationale in creating AM1241 was that the cannabinoids' side effects appeared to reflect their activity in the CNS, while at least some of their pain relief might derive from their stimulation of the $CB_2$ receptors. If so, AM1241 might relieve pain without the usual cannabinoid side effects. To test whether it would, Dr. Makriyannis teamed with Dr. T. Philip Malan, Jr., of the University of Arizona in Tucson.

The researchers first demonstrated that AM1241 reduced rats' sensitivity to acute pain induced by heat. In a subsequent study, they surgically increased pain sensitivity in nerves adjacent to the spinal cord, a procedure that mirrors human chronic neuropathic pain conditions. They then established baseline tactile and heat pain thresholds in the sensitized rats by timing how long it took for the animals to withdraw a paw when the researchers applied a probe or focused a lamp on it.

"Using the animals' pain thresholds to measure their responses to painful stimuli means they can free themselves from whatever we are doing to them as soon they are uncomfortable enough to want to move," Dr. Malan explains. "They simply lift their paw and the stimulus is withdrawn."

When the hypersensitized rats were given AM1421, they withstood more pressure from the probe or heat from the lamp before withdrawing their paws than they had before being given the compound. Furthermore, the animals' tolerance for pressure or heat increased proportionally with larger doses of AM1241. "We were even able to increase the rats' pain sensitivity thresholds beyond levels established before the chronic pain condition was induced," Dr. Malan says.

"AM1241 provides pain relief equal to that seen with opioids, which is the fullest we're capable of producing in animal models," says Dr. Malan. In addition, the compound did not produce any of the sedative effects seen with broader cannabinoid agonists. "We looked at the dose that produced maximum pain relief, then we went as high as 10 times that dose and still did not see any CNS effects," he says. "While we haven't done real toxicology studies pushing doses super high, we have used doses in other tests that are as much as a hundredfold the doses required to relieve pain and we haven't seen any untoward effects from that."

### Goals of Further Research

"While AM1241 is looking very good in terms of being effective, it is a big step to go from a successful animal model to treating humans in pain," Dr. Malan cautions. Before that can occur, the researchers need to answer many questions about the compound, such as how it works to relieve pain. "We know that $CB_2$ receptors, where AM1241 works, are at their highest concentration in the immune cells," he says. "And the fact that AM1241 can block acute pain caused by a brief application of heat that doesn't damage tissue makes us think whatever we are blocking or stimulating is coming from cells that are there all the time," as opposed to cells that migrate to sites of tissue inflammation or nerve injury.

Mast cells, one class of immune cells distributed throughout the body, are particularly intriguing candidates. They are always present and tend to sit next to nerve endings, suggesting that AM1241 might affect mast cells in ways that indirectly alter the pain sensitivity of nearby nerve cells. "However, we have evidence for a number of possibilities and are not ready to say what the mechanism is," says Dr. Malan.

In addition to trying to nail down AM1241's mechanism of action, the researchers are continuing to study its ability to reduce various types of pain. In a just-completed study, Dr. Malan and his team showed that AM1241 can reduce inflammatory pain in rats. In humans, inflammatory pain can be acute when it results from injury or surgery, or chronic when it stems from diseases such as arthritis. "It is difficult to put some pains into one classification or another," Dr. Malan says, adding, "one source, such as cancer, can cause pain by a variety of mechanisms." Currently, no single medication can relieve acute pain caused by stimulation of localized receptors, chronic neuropathic pain, and inflammatory pain. "Thus far, AM1241 looks promising for doing that," he says. Noting again that it is difficult to predict how well the findings will hold up in pilot studies with human subjects, Dr. Malan adds, "I think this compound has as much potential to treat chronic and acute pain, based on what we see in animals, as anything that's come along at this stage of development."

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# Early Nicotine Initiation Increases Severity Of Addiction, Vulnerability to Some Effects Of Cocaine

By Patrick Zickler, *NIDA NOTES* Staff Writer

Most tobacco use begins during adolescence, and people who start in their teens are more likely to become life-long smokers than are those who first light up as adults. Adolescent smokers are more likely than adult smokers to become dependent on nicotine. And when compared with nonsmoking peers, young smokers are more likely to be abusers of other drugs: In 2002, the National Survey on Drug Use and Health reported that roughly half (48.1 percent) of youths aged 12 to 17 who smoked cigarettes in the past month also used an illicit drug, whereas only 6.2 percent of nonsmoking youths reported using an illicit drug in the past month.

These observations suggest that teen smokers are especially vulnerable to the physiological effects of nicotine. Two recent NIDA-supported animal studies lend support to this interpretation of the epidemiological data. The results indicate that smoking may be more addictive if it is initiated during adolescence and that early exposure to nicotine may heighten response to other addictive drugs. An additional finding was that males and females may differ in their susceptibility to these effects.

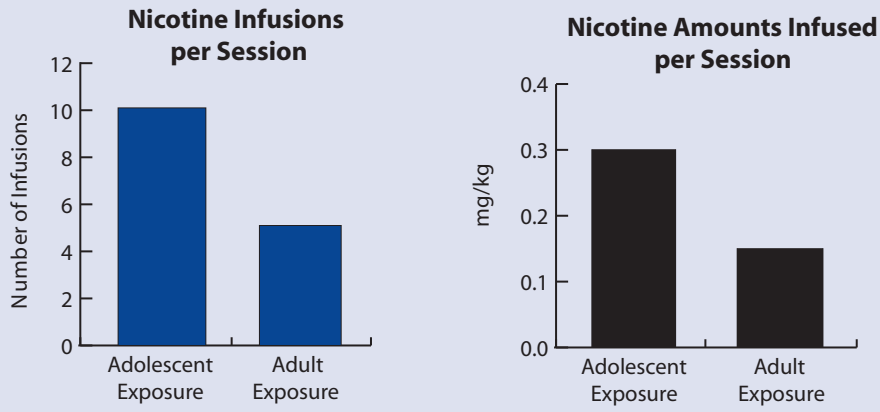
## Early Initiation to Nicotine

Dr. Edward Levin and colleagues at Duke University in Durham, North Carolina, investigated whether the developmental period during which rats are first exposed to nicotine makes a difference in their subsequent drive to obtain the drug. One experiment looked at short-term effects, the other at long-term effects.

In the first experiment, the researchers showed that adolescent initiation to nicotine produced a greater intensity of nicotine taking in the days immediately following exposure than was seen in rats initiated to nicotine in adulthood. The researchers trained eight female adolescent rats and seven female adult rats to press a lever to obtain an intravenous injection of nicotine. Following this 2-week training, the researchers gave the rats, now 54 to 62 days old (adolescents) and 84 to 90 days old (adults), free access to the lever daily for 1 hour. The nicotine dosage delivered with each lever push changed each day, in different order for each rat, but over the 8 days of the study every animal had one day each with dosages of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, or 0.08 mg/kg of its body weight. Regardless of dose, the adolescent animals administered more injections each day (average 10.4) than the adults (average 7.5).

Dr. Levin and colleagues next demonstrated that this greater propensity of adolescent-initiated female rats to self-administer nicotine persists into their adulthood. The researchers trained 13 adolescent and 7 adult rats to self-administer nicotine, then tracked their nicotine self-administration for 4 weeks, during which time the adolescents matured into adulthood. Throughout this period, the rats exposed as adolescents pressed the lever for nicotine (at a dose of

**Rats Exposed to Nicotine in Adolescence Self-Administer More Nicotine Than Rats First Exposed as Adults**




*Female rats first exposed to nicotine as adolescents self-administered nicotine more often and in higher total doses per session than rats first exposed as adults.*

0.03 mg/kg) more often than the rats initially exposed as adults (10.1 times per session versus 5.1 times per session).

"At the end of this 4-week period, the adolescent-onset rats were at least 82 days old and were themselves adult," says Dr. Levin. "This finding suggests that those who begin smoking during adolescence are at greater risk for increased smoking over the long term."

These findings are likely to be meaningful for humans as well as lab animals, Dr. Levin observes, since human brains as well as rat brains continue to develop during adolescence. "Self-administration of nicotine during teenage years, when the brain is still developing, may cause some of the developmental processes to proceed inappropriately, in effect sculpting the brains of these adolescents in ways that facilitate the addiction process."

Animal self-administration studies have become a standard tool in nicotine research, but investigation into a possible link between adolescent exposure and severity of addiction has been limited and most work has involved male animals, Dr. Levin points out. In humans, there are notable differences between adult men and women smokers. Men tend to be heavier smokers than women, for example, and women report more severe withdrawal symptoms than men. It is possible that sex differences also occur in adolescent smoking, Dr. Levin observes. "An animal study that uses female rats will more closely model adolescent-onset smoking in teenage girls, a group that is showing a rise in smoking rates," he says.

"Epidemiological data show that adolescent girls exhibit signs of nicotine dependence sooner than adolescent boys. Animal studies show that adult females exhibit greater motivation to self-administer nicotine than do males," points out Dr. Cora Lee Wetherington, NIDA's women and gender research coordinator. "The growing body of evidence on sex differences in response to nicotine emphasizes the importance of including females in animal models of adolescent nicotine use. Dr. Levin's plan to follow up these intriguing findings with a parallel study with males is particularly important," she adds.

***Smoking may be more addictive if it is initiated during adolescence and early exposure to nicotine may heighten response to other addictive drugs. Males and females may differ in their susceptibility to these effects.***

## Sensitization Differs in Males, Females

Repeated exposure to the same dose of an addictive drug may result in increasingly more intense behavioral response. A dose of cocaine, for example, may elicit more activity on the second day of exposure than did the same dose a day before. This phenomenon, called sensitization, involves drug-induced brain changes that may underlie addiction and can be used to identify differences in susceptibility to the effects of drugs.

Dr. Sari Izenwasser and Dr. Stephanie Collins at the University of Miami found that female adolescent rats show more rapid and pronounced sensitization to behavioral effects of nicotine than adolescent males or adult rats of either sex. In addition, when the researchers administered cocaine to adolescent and adult rats previously exposed to nicotine, adolescent males, but not adolescent females or adults of either sex, exhibited sensitization to some effects of cocaine.

The researchers administered nicotine (0.4 mg/kg of body weight) daily for 7 days to 20 rats, 5 adolescents and 5 adults of each sex. After each injection, the animals were placed in activity monitors—chambers equipped with infrared light beams aimed at detectors on the opposite wall—for 60 minutes while the researchers monitored two aspects of their behavior. Horizontal locomotion was measured by counting the number of times an animal broke light beams. Stereotypy, which involves repetitive actions such as head bobbing, was measured by counting repeated breaks of the same beam. Adolescent females showed increased stereotypy and locomotion in response to nicotine on their second exposure, signifying sensitization, which persisted over the 7 days of repeated administration. Adolescent males, in contrast, showed no locomotor sensitization to nicotine and no stereotypy sensitization until the fourth day of repeated exposures. Adult male and female rats showed sensitization (stereotypy and locomotion) after the fifth day of repeated exposures.

On the eighth day of the study, the researchers investigated the extent to which nicotine exposure affected

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## Early Initiation to Nicotine

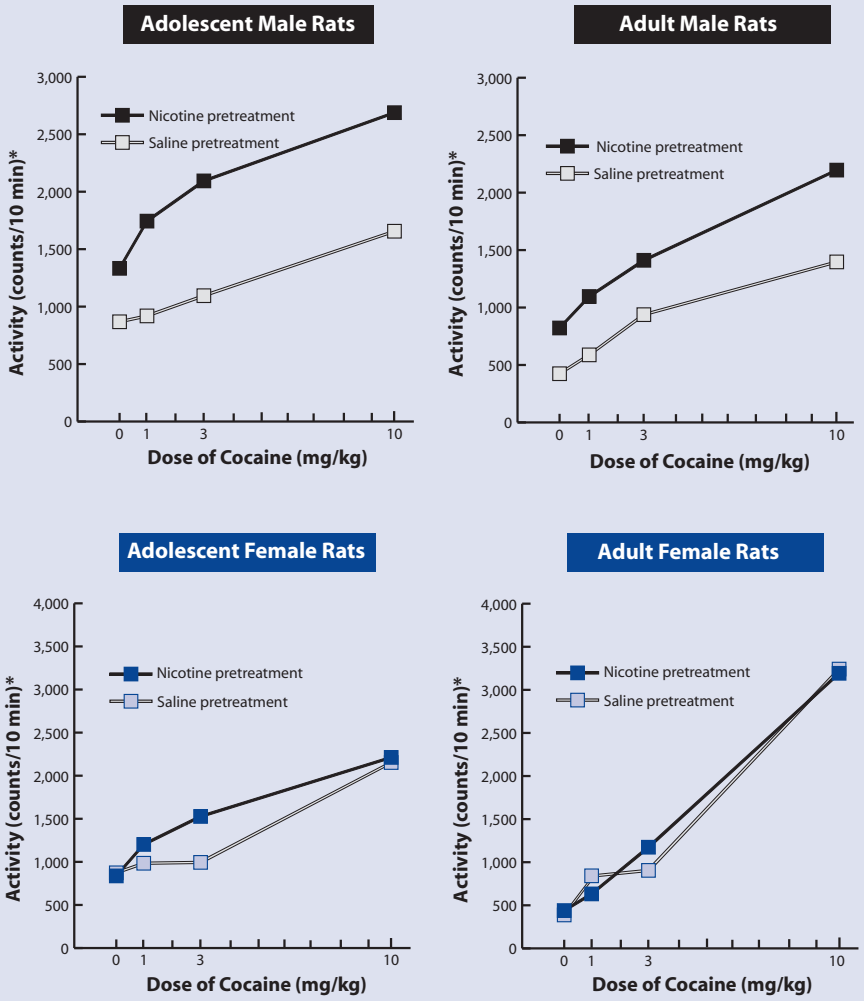
*continued from page 9*

sensitization to cocaine. They administered cocaine to all the rats in three sequential injections (1, 2, and 7 mg/kg) and monitored the animals' activities for 10 minutes after each injection. For females, previous exposure to nicotine was associated with cocaine sensitization as evidenced by cocaine-induced stereotypy—but not by horizontal movement. Adult males that received nicotine exhibited sensitization to cocaine's effect on horizontal movement but not stereotypy. Adolescent males exposed to nicotine also exhibited greater sensitization than did adult males to cocaine's effect on horizontal movement and were the only group to exhibit sensitization in both stereotypy and horizontal movement.

"Overall, it appears that sensitization to cocaine is more pronounced in adolescent than in adult rats after treatment with nicotine. This suggests that early nicotine use may create an increased risk for young people who subsequently use cocaine, and that adolescent males who smoke may be particularly vulnerable to the risk of cocaine abuse," Dr. Izenwasser says.

"Animal studies such as these are an important addition to a research base that suggests that adolescents show a very different responsiveness to nicotine—upon both acute and chronic or repeated administration—than do adults. The rapid sensitization of adolescent females to nicotine's behavioral effects highlights the need to be aware of gender differences in addictive processes during adolescence," observes Dr. Minda Lynch of NIDA's Division of Neuroscience and Behavioral Research. "Studies such as these also raise important questions about vulnerability to nicotine addiction and on nicotine's potential for cross-sensitization to other drugs of abuse in adulthood or adolescence.

**Rats First Exposed to Nicotine in Adolescence Show Greater Sensitization to Cocaine Than Rats First Exposed as Adults**




**Activity level after cocaine administration was measured by counting the number of times in 10 minutes each rat crossed light beams projected in a grid across its cage.*

*Rats exposed to nicotine in adolescence and then exposed to cocaine were more sensitive to cocaine's locomotor stimulating effects that rats first exposed to nicotine as adults. Nicotine-induced presensisitization to cocaine was greatest in young male rats.*

And they illustrate the importance of studying drug effects, and the neurological changes they trigger, in the context of the dynamic processes that characterize adolescent brain development."

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# New Index Measures Self-Control, Predicts Drug Abuse Vulnerability in Adolescent Boys

By Marion Torchia, *NIDA NOTES* Contributing Writer

Researchers at the University of Pittsburgh's Center for Education and Drug Abuse Research have identified a set of characteristics that appears to predict a boy's vulnerability to substance use disorder (SUD) in young adulthood. Once validated for use with the general population, this new construct, "neurobehavioral disinhibition," may help clinicians tailor drug abuse prevention programs for children most in need of support.

Under the direction of Dr. Ralph E. Tarter, the researchers have conducted comprehensive longitudinal studies to understand how neurobehavioral disinhibition may relate to the genetic, biological, psychological, and environmental factors that are thought to predispose individual boys to SUD. They have developed an index that links the set of personality characteristics to a quantitative scoring system. The index appears to identify as early as age 10 children who are especially vulnerable to drug problems in adolescence.

Neurobehavioral disinhibition comprises a cluster of emotional tendencies, behavioral symptoms, and problems in cognitive function that indicate that a child has not adequately developed psychological self-regulation, a capacity that depends on normal neurological development (see "Neurobehavioral Disinhibition: A Closer Look").

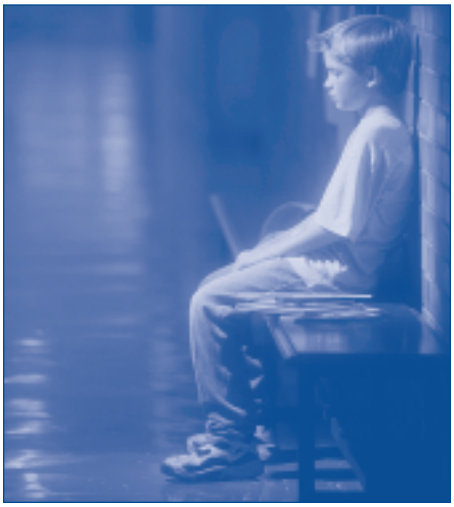
According to Dr. Tarter, the construct's key strength is its biological basis: Its elements closely relate to what is known about the brain's development. "Neurobehavioral disinhibition points to deficiencies in those higher level brain functions—self-control and deliberate, goal-directed action—that we know are managed in the prefrontal cortex."

According to Dr. Kevin Conway, director of the Program on Antisocial Behaviors and Related Vulnerability in NIDA's Epidemiology Research Branch, Dr. Tarter's research shows that the construct actually works. He notes that Dr. Tarter and his colleagues followed the same group of children for more than a decade and that "the children's early scores for neurobehavioral disinhibition predicted with amazing accuracy whether or not they would develop SUD and how severe their problems would be." He adds that "Dr. Tarter's study takes earlier research on vulnerability to drug abuse a step forward and points to particular components of a person's biological makeup that may be at the root of the problem."

## Construct Developed, Tested

To develop their construct and its numerical scoring system, Dr. Tarter's group tracked from childhood to young adulthood 47 boys at high average risk and 65 boys at low average risk of SUD based on their status as biological offspring of fathers with or without SUD as defined by the American Psychiatric Association's diagnostic criteria (DSM-III-R). The investigators limited this particular study to boys because the girls in their longitudinal research program were enrolled later and had not been followed long enough to make valid predictions and match the outcomes to them.

The neurobehavioral disinhibition construct was developed by assessing the children in the study using a series of existing tools that measure dysregulated emotions, behavioral undercontrol, and executive (higher order) cognitive capacity. To measure emotion, for example, the researchers used the "difficult" temperament index from the Revised Dimensions of Temperament Survey. They measured behavior "undercontrol" using two diagnostic tools, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, as rated by the children's mothers, and the Disruptive Behavior Disorders Rating Scale, as measured by their teachers. A battery of neurological tests measured cognitive processes that depend on the prefrontal cortex.



*Researchers hope that early identification and treatment of neurobehavioral disinhibition can help at-risk children develop self-control and avoid drug initiation and abuse.*

The next step, verifying the construct by a statistical technique called factor analysis, confirmed that the separate components of neurobehavioral disinhibition—personality style, behavior, and brain function—tend to occur together. This suggests that neurobehavioral disinhibition is driven by a single process involving prefrontal cortex functioning. Says Dr. Tarter, "We are looking at the integrity of the brain by measuring its activities."

## Index Predicts SUD Vulnerability

To test the hypothesis that the neurobehavioral disinhibition score is correlated with expected risk of future SUD, Dr. Tarter's team compared the scores of the high-risk boys in the study with those of the low-risk boys. The boys at higher risk had significantly higher scores at ages 10 to 12 on several,

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though not all, of the component indicators of neurobehavioral disinhibition. When the boys were tested again at age 16, the higher risk boys had scores consistent with neurobehavioral disinhibition on every component indicator of the trait.

Moreover, the boys' disinhibition scores at ages 10 to 12 predicted with nearly 70-percent accuracy whether they would actually develop SUD by age 19. Even more strikingly, their disinhibition scores at age 16, combined with their frequency of drug use in the previous 30 days, predicted with 85-percent accuracy their likelihood of developing SUD by age 19. In fact, the boys' disinhibition scores at age 16 were better predictors of SUD at 19 than the frequency of their drug use at age 16. In addition, their disinhibition scores were strongly predictive of the general severity of their problems as measured by the "overall problem density score" on the revised Drug Use Screening Inventory. This score includes health, behavior, school, family, and social adjustment problems.

The scores have both positive and negative predictive value, according to Dr. Tarter's research report. However, some of the data indicate that a high disinhibition score predicts that a boy will have SUD with a greater degree of probability than a low score predicts that he will avoid the disorder. The boys' high scores at age 16 predicted future SUD with 97-percent accuracy; on the other hand, low scores at this age predicted with only 61-percent accuracy that SUD would not develop.

## Value of Findings Cited

"From NIDA's perspective, this research is a long-term investment," notes Dr. Conway. "Because it is a longitudinal study, Dr. Tarter and his colleagues have been able to gather a broad range of information about the boys, so that the effect of the multiple factors known to be related to SUD can be traced over time."

The next phase of the study will be especially interesting, because the first group of boys will have entered young adulthood, when SUD most often emerges. The researchers will continue to track the young men even as new participants join the study.

The findings should not be assumed to apply to all children, Dr. Tarter cautions. Before the trait can be considered universally valid and ready for use in working with children, much larger studies will be needed involving the general population, including both genders and diverse ethnic and socioeconomic groups.

"It is important that our new knowledge be used to bring about constructive change," Dr. Tarter adds. "An index of neurobehavioral disinhibition has potential value because it offers an opportunity to monitor children's development and detect those children with significant deviations, who may be at heightened risk of SUD. If teachers, counselors, and parents can identify a child's problems early, they can structure environmental conditions to promote a healthy outcome and avoid the path to SUD."

## Source

• Tarter, R.E., et al. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry* 160(6):1078-1085, 2003. NN

## Neurobehavioral Disinhibition: A Closer Look

The construct developed by Dr. Tarter and his colleagues includes many symptoms that characterize attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder. But it reaches beyond those diagnostic categories to describe emotional states and neurological capacities as well as their behavioral manifestations.

Compared to his peers, a "disinhibited" child can be described as "difficult." His (or her) moods are volatile, and he often exhibits restlessness and an inability to persevere in a task. Poor self-management often reveals itself in risky, even reckless behavior. Neurological tests reveal a lack of certain capacities that originate in the part of the brain that manages higher level thinking. Three dimensions of his problem are especially important:

- **"Difficult" temperament.** A disinhibited child is irritable and easily thrown off balance and has a harder time than other children returning to a comfortable emotional state after a stressful or arousing experience. His emotions seem to be more intense than those of his peers. These characteristics commonly provoke negative responses from adults and other children. If so, a vicious cycle can develop, and the child's reactions can become more extreme as time goes on.
- **Undercontrolled behavior.** The disinhibited child's behavior is chronically out of touch with the demands of the situation. He or she has a hard time meeting a school's learning requirements and does not relate easily to either adults or peers. He may engage in "externalizing behavior" or "acting out," typically through disruptiveness, unprovoked aggression, defiance of authority, or delinquency. His behavior is also marked by impulsivity and an inability to persist in pursuing his goals.
- **Deficiencies in complex brain functions.** The prefrontal cortex in the human brain manages an individual's purposeful activities. It is possible to measure a child's ability to pay attention, to remain aware of what is going on in the environment, and to complete a task or a coordinated sequence of actions. For example, researchers can see whether a child can turn away from a signal and deliberately look in the opposite direction when asked to do so. A disinhibited child will have trouble with this simple task, which requires deliberate control over eye movement, a capacity that resides in the prefrontal cortex.

# Animal Study Finds Effects on Behavior, Brain Chemistry of Prenatal MDMA Exposure

By Betsy Earp, *NIDA NOTES* Contributing Writer

Because women of childbearing age are among the population most involved with MDMA (methylenedioxymethamphetamine, ecstasy), the consequences of prenatal exposure to the drug are an important concern. Studies have demonstrated subtle long-term behavioral abnormalities in animals exposed to MDMA during the mid- to late gestational period. Now, NIDA-funded researchers have documented marked behavioral abnormalities in rats exposed to MDMA during early *in utero* life. Moreover, the researchers correlated the exposed rats' abnormal behavior at 21 days of age with alterations in brain neurotransmitter systems that were passing through a critical early developmental stage at the time of their *in utero* exposure. These findings strengthen the evidence, which has been conflicting to date, that prenatal MDMA exposure has an impact on neurochemical development.

"This basic study is a significant step toward understanding the consequences for the offspring of MDMA exposure in early pregnancy," says Dr. Pushpa Thadani of NIDA's Division of Neuroscience and Behavioral Research. "More studies are needed, as well as monitoring of children prenatally exposed to MDMA."

Dr. Jack Lipton at Rush University Medical Center in Chicago injected pregnant albino rats with MDMA, 15 mg/kg of body weight, equivalent to a human recreational dose, twice daily when the animals were 14 to 20 days pregnant. A control group of pregnant albino rats received 1 mL/kg saline during the same pregnancy interval. During this time gestating rats pass through a critical brain developmental stage, corresponding to a stage that occurs during early pregnancy in humans, in which the dopamine and serotonin brain neurotransmitter systems first take shape. Dopamine is involved in motivated behaviors, including attention, sex, and drug taking, while serotonin helps regulate mood, sleep, and appetite.

After the rat pups were born, the researchers tested them at several ages for signs of structural changes in the dopamine and serotonin neurotransmitter systems and at postnatal day 21 for behavioral deficits. In the behavioral tests, they examined the rats' adaptation to a new environment by introducing the animals into an unfamiliar cage that was equipped to monitor the animals' ambulatory and fine motor movements. They found that at 21 days of age, the rats prenatally exposed to MDMA adapted more slowly to the novel environment and exhibited significantly more activity than the unexposed rats. The exposed rats maintained a 35-percent increase over their normal activity level throughout the 20-minute trial. In contrast, the activity level of rats in the control group fell off precipitously after the first 5 minutes of the trial as they adjusted to the new cage.

To investigate for possible MDMA-related abnormalities in brain chemistry and structure, the researchers measured the levels of dopamine and serotonin and their metabolites in selected brain regions in MDMA-exposed and unexposed male and female rat offspring at different postnatal ages. Although nothing was remarkable about these measurements at the 3-day mark, distinctions between the animals emerged at 21 days. At that age, rats that had been prenatally exposed to MDMA showed significant reductions in dopamine and serotonin metabolites and turnover in the nucleus accumbens and striatum. The researchers hypothesize that these changes reflect either a decrease in dopamine or serotonin release, a reduction in enzymatic activity, or an increase in dopamine neuron innervation.

The researchers also sought to determine whether prenatal exposure to MDMA had altered the dopamine nerve fiber density in several regions

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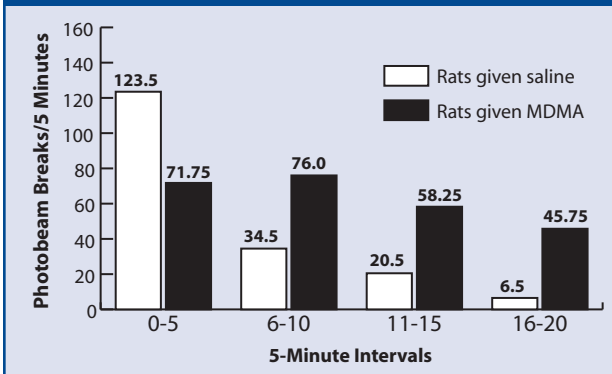
**Rats Prenatally Exposed to MDMA Are More Active Than Unexposed Rats**




*When 21 days old, rats prenatally exposed to MDMA and those from a control group were each placed in a new cage, equipped with photobeams to monitor their activity. MDMA-exposed rats were seven times as active as the control group rats by trial's end. Researchers do not know the reason for the difference.*

# Comorbidity Is Common Among Youths In Juvenile Detention

On a typical day in the United States, roughly 109,000 youths under age 18 are in jail. These teens have problems beyond their involvement with the law: Research suggests that, much more often than the general population, they are challenged by mental disorders and co-occurring abuse of alcohol and other substances. To better understand the extent of this problem, to explore treatment interventions for juvenile detainees, and to tailor prevention programs for high-risk youth, NIDA has focused on this special population.

A recent NIDA-funded study highlights data from the Northwestern Juvenile Project, a large-scale study of psychiatric disorders in detained adolescents. Dr. Karen Abram, Dr. Linda A. Teplin, and their colleagues at Northwestern University Feinberg School of Medicine and Children's Memorial Hospital in Chicago conducted diagnostic interviews of 1,829 youths ages 10 to 18 at the Cook County Juvenile Temporary Detention Center. More than 10 percent of male participants and almost 14 percent of female participants had a substance abuse disorder plus a major mental disorder, such as psychosis, manic episode, or major depressive episode. About 600 of these 1,829 adolescents had substance abuse disorders plus behavioral disorders.

In examining a subset of 305 youths with major mental disorders at the Center, the researchers found that more than half of the females and three-quarters of the males also reported a substance abuse disorder. When the scientists examined data from a different subset of 874 youths with substance abuse disorders, they found that 30 percent of the females and 21.4 percent of the males had a major mental disorder as well.

About 25 percent of these juvenile justice system detainees with major mental disorders reported that their psychiatric problem preceded their substance abuse disorder by more than 1 year. Almost 67 percent of females and more than 54 percent of males developed their mental and drug abuse disorders within the same year.

"As members of the medical community, we need to be aware of the high prevalence of comorbid disorders in this population and adjust our focus to include treating all of a person's health problems," says NIDA Director Dr. Nora Volkow. "We need

to recognize that these problems can be severe and can include physical injuries and serious mental disorders. Effectively addressing these concerns will be key to breaking the cycle of comorbid disorders.

"The findings indicate a need for additional research that delves further into comorbid substance abuse," concludes Dr. Volkow. "Improving our awareness of substance abuse as a condition that does not exist in isolation will contribute to more effective prevention and treatment interventions."

## Source

• Abram, K.M.; Teplin, L.A.; et al. Comobid psychiatric disorders in youth in juvenile detention. *Archives of General Psychiatry* 60(11):1097-1108, 2003. NN

## Prenatal MDMA Exposure

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of the brain. They found that fiber counts in the frontal cortex of the prenatally exposed 21-day-old rats had increased 502 percent more than counts seen in controls—of concern, as abnormal or excessive connections in the frontal cortex may result in aberrant signaling, possibly leading to abnormal behavior.

In summary, reductions in prenatally exposed rats' dopamine and serotonin metabolism, an inability to adjust to a new environment, and increases in dopamine fiber density demonstrate for the first time that prenatal MDMA exposure in rats may result in both behavioral and correlating neurochemical alterations. Dr. Lipton observes, "The health risks that MDMA exposure poses to fetuses are not fully known, and continued research into the consequences of exposure and monitoring of prenatally exposed children is certainly warranted."

## Source

• Koprich, J.B.; Chen, E.Y.; Kanaan, N.M.; Campbell, N.G.; Kordower, J.H.; and Lipton, J.W. Prenatal 3,4-methylenedioxymethamphetamine (ecstasy) alters exploratory behavior, reduces monoamine metabolism, and increases forebrain tyrosine hydroxylase fiber density of juvenile rats. *Neurotoxicology and Teratology* 25(5):509-517, 2003. NN

# NIDA's New Web Site for Teens Promotes Understanding of Drug Abuse

Knowledge is power, and a new NIDA educational product empowers teens to make healthful decisions about drugs. "NIDA for Teens: The Science Behind Drug Abuse" is an interactive Web site for adolescents ages 11 through 15, as well as their parents and teachers.

To ensure that the NIDA for Teens' content tackles issues of concern to kids, the Institute enlisted teenagers to help with its development. NIDA worked with a University of Baltimore design team that included youths and was funded through a National Science Foundation grant. The young group of content and usability "experts" critiqued and enhanced NIDA's concepts, many of which were based on the highly successful *Heads Up* campaign that partners NIDA and Scholastic Magazines, Inc., and reaches more than 8 million students a year. The young design team also helped NIDA sharpen the site's design, with an eye toward attracting and informing their media-savvy peers.

Because teens want information, not attitude, the site delivers science-based facts about how drugs affect the brain and body. Animated illustrations, quizzes, and games are used throughout the Web site to clarify concepts, test the visitor's knowledge, and make learning fun. Drugs currently featured on the site are marijuana, nicotine, ecstasy, and anabolic steroids, with sections on inhalants and stimulants coming soon. A primer on "The Brain and Addiction" explains why addiction is a brain disease, summarizing the key concepts of how drugs affect the brain.

"*Ask Dr. NIDA*," provides NIDA Director Dr. Nora D. Volkow's answers to the questions most frequently asked by teens, such as:

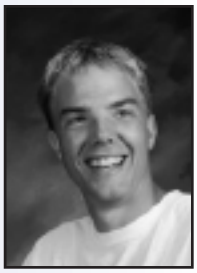
- Can one-time drug use lead to addiction?
- What drugs are commonly abused?
- What is withdrawal and how long does it last?
- What are the costs of drug abuse to society?
- If a pregnant woman abuses drugs, will it affect her baby?

In "NIDA for Teens: Real Stories," teens who have struggled with drug addiction share their personal experiences. For example, one teen discusses using and selling ecstasy to feel popular, but ending up completely alone. Another teen tells of smoking marijuana to escape his problems and fit in, but finds there's been a high price to pay for this choice. Still another teen recounts his experience as a top high school athlete who developed a two-pack-a-day habit and now can't run without wheezing (see "Meet Kevin").

On a lighter note, the site features "Have Fun & Learn," which invites teens to join "Sara Bellum" as she explores the brain's response to various drugs. In Dr. NIDA's challenge, teens explore the human body online to discover what happens when someone uses drugs. Visitors are invited to take the challenge to build a better body. NIDA Libs asks teens to fill in the blanks to create an article about marijuana.

The site also offers information for teachers, parents, and others involved in the lives of teenagers to help them better understand the science behind drug abuse by completing activities on the brain and addiction, various drugs, and the physical reality of drug use. Check back often at http://teens.drugabuse.gov, NIDA's site for teens and those who care about them. NN

## Meet Kevin



If you're looking for the Robinson Rams baseball team during fourth-period lunch, don't bother searching the cafeteria or the practice diamond. On most afternoons, you'll find a handful of the top players from Robinson Secondary School in Fairfax, Virginia, huddled in a friend's nearby basement. They eat pizza. They play Tony Hawk video games. And always—always—they smoke cigarettes.

"Kids hanging out. Whether it's a party or lunch, there are going to be smokes," says Kevin McNamara, an 18-year-old Robinson senior and a regular attendee at the basement brunch. Kevin is a star member of the school's golf team. He was also the Rams' ace pitcher until he tore a ligament in his knee. And, until recently, he smoked two packs a day. "Kevin's story is not unusual," says Dr. Bill Corrigall, director of NIDA's Nicotine and Tobacco Addiction Program. "Many teens and even pre-teens begin to experiment with smoking, but soon find they are smoking regularly—they're addicted."

## "I Want to Quit"

"I used to be able to run a mile under 6 minutes. Now I'm lucky to make it in 8. And I'm wheezing all the way," says Kevin, who's cut his daily use down to 10 cigarettes. "I want to quit. But it's not that easy."

More than ever, teens find that the best way to stop smoking is to never start at all. Teen smoking rates have steadily fallen since 1996, according to a NIDA-funded study. That's the good news. The bad news is that teen smoking numbers are still too high. Each day, more than 3,000 children and adolescents become cigarette smokers, notes the Centers for Disease Control and Prevention. That's more than 1 million teens a year. Roughly one-third of them will die from a smoking-related illness.

"There's hard evidence that smoking leads to addiction, health problems, and death," says Dr. Eric Moolchan, director of NIDA's Teen Tobacco Addiction Treatment Research Clinic. "Teens have a choice: They can become victims, or they can stop before they go too far. Better yet, they never have to start at all."

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