RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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New Therapy Reduces Drug Abuse Among Patients With Severe Mental Illness

A specially designed group intervention also improves patients' functioning in the community.

BY NIDA NOTES STAFF

A new intervention enhances prospects for substance abusers whose mental illness complicates the path to recovery. In a recent clinical trial, a 6-month course of Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness (BTSAS) reduced drug abuse, boosted treatment-session attendance, and improved the quality of life of outpatients with a wide spectrum of mental disorders.

A FOCUS ON EXTRA OBSTACLES

Dr. Alan S. Bellack and colleagues at the University of Maryland School of Medicine in Baltimore designed BTSAS to counter the factors that make recovery from addiction especially difficult for people who have co-occurring severe and persistent mental illness. These factors include frequent failure to meet their own and others' expectations, inconsistent motivation, and social and personal pressure to appear normal.

BTSAS therapy comprises six integrated components:

- motivational interviews (directive counseling that explores and resolves ambivalence) to increase the desire to stop using drugs;
- contingency contracts linking drug-free urine samples with small financial rewards;
- realistic, short-term, structured goal-setting sessions;
- training in social and drug-refusal skills;
- information on why and how people become addicted to drugs and the dangers of substance use for people with mental illness; and
- relapse-prevention training that inculcates behavioral strategies for coping with cravings, lapses, and high-risk situations.

Twice-weekly sessions begin with urine tests. Patients who have provided drug-free urine samples are praised by the therapists and group members. They also receive financial incentives that start at $1.50 for the first drug-free sample and increase in $0.50 increments for every consecutive one thereafter, up to $3.50. The amount is set back to $1.50 after a drug-positive sample or an absence.

When participants submit drug-positive samples, the group takes a nonaccusatory approach by focusing on problem solving to help them achieve

[*Continued on page 6*]

TREATMENT OUTCOMES

	BTSAS	STAR
Drug-free Urine Samples	59%	25%
Four Weeks of Abstinence	54%	16%
Multiple 4-Week Blocks	44%	10%
Eights Weeks of Abstinence	33%	8%

BTSAS: Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness; STAR: Supportive Treatment for Addiction Recovery.

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

Neuroscience Blueprint Promotes Efficiency, Synergy

In 2004, NIDA and 15 other NIH Institutes convened to address a challenge posed, in a sense, by an embarrassment of riches. In recent decades, neuroscientists had developed powerful new tools and techniques that yielded extraordinary insights into the working of the brain. The potential for future discoveries appeared limitless. However, without an overarching plan to assimilate, coordinate, and disseminate this burgeoning wealth of knowledge in an organized, coherent way, there was a risk that the resources could be wasted and progress slowed by inefficient or duplicative efforts.

The NIH Blueprint for Neuroscience Research is that plan. It provides a knowledge- and resource-sharing system for NIH-funded neuroscientists, allowing them access to an extraordinary array of data, advanced research tools, and technical assistance. More than 125 neuroscience program directors and staff contribute to the Blueprint's projects and initiatives.

The Blueprint consortium assesses the field's needs and sets annual goals. In 2005 and 2006, it concentrated on strengthening resources applicable across broad areas of neuroscience research, including animal models, informatics, gene and protein expression, neuroimaging, and behavioral assessments used in clinical research. From this focus emerged a variety of resources, all of which are available to all NIH researchers on the Blueprint Web site (*neuroscienceblueprint.nih.gov*). Among many other assets, researchers can find:

- A comprehensive menu of animal models for neurological research, with training in their use. Through this site, researchers can obtain and learn to use the appropriate models to study a particular neurological disease, for example, Alzheimer's or Parkinson's.
- The Neuroscience Information Framework (NIF), a Web site that organizes vast amounts of neuroscience research data from around the world. Here investigators can tap into, for example, databases of the nervous system as well as others involved with neurological diseases. In addition, scientists can access research tools, resources, and services for designing and interpreting gene expression studies.
- An NIH Toolbox for Assessment of Neurological and Behavioral Function, containing a set of standard assessment tests. Along with relieving researchers of the expenditures of time, effort, and funds needed to develop assessments on their own, this resource facilitates comparison and compilation of data across studies.

In 2007, the Blueprint consortium initiated a 3-year plan to develop and share research tools in neurodegeneration, neurodevelopment, and neuroplasticity. NIDA and the National Institute of Mental Health are leading the planning for the 2009 neuroplasticity initiative, which aims to accelerate advances in the understanding of how brain cells adapt to experience by forming new neural circuits. We anticipate that it will provide a wealth of insights into how the healthy brain grows and learns, as well as how it changes when affected by diseases such as drug addiction. ■

NIDA Notes

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Intervention Improves Employment Outlook For Methadone Patients

Assertive outreach and motivational techniques can enhance methadone patients' participation in vocational counseling and increase subsequent employment. In a study of 211 unemployed methadone patients at two facilities in New York City, Dr. Stephen Magura and colleagues at the National Development and Research Institutes found that 47 percent of participants assigned to the Customized Employment Supports (CES) intervention attended five or more vocational counseling sessions within 6 months of beginning the study. In contrast, only 12 percent of those in the clinic's standard vocational programs were as assiduous. CES counselors engaged patients in the program with tactics such as checking their clinic schedules and arranging impromptu visits; spent more time with patients in counseling sessions than counselors in the standard program; responded promptly to requests for help; accompanied patients in their job searches; and helped patients overcome barriers to employment. Among 168 participants interviewed 6 and 12 months after beginning the study, 41 percent in the CES group, compared with 26 percent of those who received standard counseling, reported paid employment at both followup assessments.

> Substance Use and Misuse 41(8):1125-1138, 2006; Substance Use and Misuse 42(5):811-828, 2007.

Morphine Speeds AIDS Onset in Monkeys

Dr. Anil Kumar and colleagues at the Ponce School of Medicine, Puerto Rico, have discovered key ways in which morphine may accelerate the progression of AIDS: The drug increases both viral replication and alterations in a particular part of the virus's coating. Monkeys exposed to long-term morphine administration—20 weeks prior to infection with simian/human immunodeficiency virus (SIV/SHIV) and throughout the 56-week study period—progressed to AIDS faster and showed more signs of compromised immune systems than comparison animals. Of the morphine-exposed animals that developed AIDS, three demonstrated higher viral replication in their blood and cerebrospinal fluid (CSF). When the researchers zeroed in on particular areas of the viral envelope—a lipid-protein covering that helps viruses penetrate cells—they found that morphine-exposed monkeys demonstrated a higher degree of change in the V4 region than control animals. This difference, which may expand the range of cells that HIV can infect, occurred in both CSF and blood. The extent of V4 evolution corresponded with rapid disease progression. Studies such as this aim to open new avenues for intervening against HIV.

> Virology 354(1):192-206, 2006; Virology 358(2):373-383, 2007.

Methamphetamine Restricts Fetal Growth, Increases Lethargy in Newborns

A NIDA-funded study found that newborns whose mothers abused methamphetamine during pregnancy showed higher rates of growth restriction compared with unexposed newborns. Dr. Barry M. Lester and colleagues at Brown Medical School and other institutions analyzed data from 1,618 mother-infant pairs, 84 of whom were meth-exposed. The meth-exposed newborns weighed 3,174 grams (7 pounds), on average, versus 3,381 grams (nearly 7.5 pounds) for unexposed newborns. The meth-exposed newborns also had a lower gestational age at birth (38.7 weeks versus 39.2 weeks). Although most infants were full term, methamphetamine infants were 3.5 times as likely to be small for gestational age—a finding that suggests fetal growth restriction.

In a followup with 166 infants from the study, the researchers assessed the newborns' behavioral capabilities within the first 5 days of life. The 74 meth-exposed newborns showed greater lethargy and were more difficult to awaken than the 92 unexposed newborns. Once aroused, however, meth-exposed newborns also showed a sign of physiological distress—difficulty maintaining normal, regular breathing. The differences held when the researchers took into account factors known to affect fetal growth, including maternal smoking and other drug abuse and socioeconomic status. In addition, higher concentrations of methamphetamine in samples of the babies' stool were related to increased central nervous system stress.

> Pediatrics 118(3):1149-1156, 2006; Neurotoxicology and Teratology 30(1):20-28, 2008.

NIDA's International Program

Linking NIDA to Researchers On a Global Scale

BY LORI WHITTEN,
NIDA Notes Staff Writer

Scientific opportunity and public health responsibility have no borders for NIDA, the world's largest supporter of research on drug abuse and its health and social consequences. Through its International Program (IP), NIDA strengthens research networks outside the United States—creating opportunities for global research collaboration, training, and scientific exchange.

International research and training have been a part of NIDA's mission since its inception in 1974. At that time, the IP primarily focused on information exchange. But its scope has grown over the decades; today the program has developed formal relationships with drug abuse research institutions in four countries and programs that reach scores of scientists and international organizations in Europe, Asia, and the Americas.

Dr. Steven Gust, a specialist in psychology and pharmacology, leads the program. He directs and coordinates NIDA's efforts to foster collaborative international research involving other U.S. Government agencies, foreign governments and institutions, and nongovernmental organizations. Working with Dr. Gust, Ms. Dale Weiss, a program analyst, manages the IP's Web-based training and scientific exchange initiatives, bringing low-cost training and science-based information to drug abuse researchers and public health workers worldwide. IP staff assist NIDA scientists with research-related international travel, identify regional experts in particular subjects, and determine how U.S. investigators might connect with international partners.

"Fostering addiction research networks in strategic regions is our primary approach."

"Fostering addiction research networks in strategic regions is our primary approach to tackling the international challenges of drug abuse and its related health consequences. Ultimately, helping regions build strong addiction research infrastructure leads to self-sustaining scientific networks that generate knowledge on the causes, prevention, and treatment of drug abuse—an investment that benefits the global community," says Dr. Gust.

For instance, when NIDA's Division of Basic Neuroscience and Behavioral Research identified a need to stimulate international collaborative research on inhalant abuse, the IP worked with the division to organize a scientific conference with interested Canadian and Mexican organizations. To perpetuate the relationships and extend the progress made there, the IP is building an online platform with virtual meeting capabilities, application sharing, and a discussion forum to help the participants advance inhalant abuse research. The IP also works with the Division of Epidemiology, Services and Prevention Research (DESPR) to help addiction researchers in other countries improve the quality of regional data on drug abuse. Using existing NIDA programs as models, DESPR and the IP have facilitated collaboration among epidemiologists, particularly in Southeast Asia and Latin America, through meetings and training activities.

The IP staff fulfill NIDA's international mission through activities that:

- **Strengthen Global Research Infrastructure**
  In March 2006, NIDA launched its Latin American Initiative. The IP partnered with the six member nations of the United Nations Office on Drugs and Crime's Regional Central American Substance Abuse Treatment Network—Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama—to establish a clinical research infrastructure and identify areas of focus for science and training. The IP also partnered with the Inter-American Drug Abuse Control Commission at the Organization of American States to plan a network to monitor regional drug abuse patterns at the community level and provide management training for the Latin American scientists who will lead the network. By working closely with international organizations already active in the region, NIDA ensures that its activities complement ongoing efforts.

- **Facilitate Professional Development**
  Since 1990, NIDA has supported 60 drug abuse professionals from 33 nations through Hubert H. Humphrey Fellowships. The fellowships bring mid-career professionals from other countries to U.S. universities for a year of academic coursework and participation in research with NIDA-funded investigators. NIDA's INVEST Drug Abuse Research

Fellowships, another program to build research capacity, has provided rigorous postdoctoral training for scientists from 26 nations since its inception in 1993. Traveling fellowship awards provide for brief research visits between international and U.S.-based NIDA grantees and enable international scientists to attend key meetings on drug abuse research.

NIDA-SUPPORTED INTERNATIONAL RESEARCHERS SHARE KNOWLEDGE
At the 2007 NIDA International Forum in Quebec City, Canada, Dr. Paulo Cunha of Hospital Israelite Albert Einstein in Brazil describes his research on the effects of neurocognitive deficits on treatment retention to Dr. Nancy Phaswana Mafuya of the South African Human Sciences Research Council.

■ **Support Research and Collaboration**

The Program supports international research on the causes, prevention, and treatment of drug abuse and addiction. Formal agreements with research institutes in Mexico, the Netherlands, Russia, and Spain ensure ongoing collaboration. For example, NIDA and the Dutch Addiction Program jointly fund several ongoing collaborations between researchers in the United States and the Netherlands. In one project, a U.S. team led by Dr. John Lochman of the University of Alabama developed and successfully tested an intervention to reduce the chances that children with disruptive behaviors will become substance abusers in adolescence. Working with partners in the Netherlands, the researchers subsequently demonstrated that the intervention could be successfully adapted to Dutch culture. Another U.S.—Dutch collaborative project used imaging techniques to examine the effects of adolescent marijuana abuse on brain development and decisionmaking.

International collaboration is vital to efforts to stem the global spread of drug-related HIV. NIDA relies on the scientific relationships fostered by the IP to facilitate collaborations with international partners in about 20 countries, develop research networks, and tailor the studies to local needs and conditions. Priority goes to projects in Russia, Eastern Europe, and Central and Southeast Asia, where a high percentage of HIV infections result from injection drug abuse or sexual liaisons with injection drug abusers.

■ **Share Knowledge**

The IP cosponsors scientific meetings with partner countries and international organizations, providing a forum in which drug abuse professionals can exchange information and initiate collaboration. Via its Web site, *international.drugabuse.gov*, the IP describes program initiatives and resources, findings, and funding opportunities.

Ms. Weiss oversees the initiatives that deliver relatively low-cost training and education programs to a diverse international audience—physicians and other medical professionals, scientists, community-based organizers, policymakers, and public health officials.

One such training tool, the Methadone Research Web Guide (*international.drugabuse.gov/methadone/methadone_web_guide/toc.html*), reviews research findings on the effectiveness of methadone maintenance to treat opiate addiction and provides science-based information about the public health benefits of the medication. Another online resource, created by the International Society of Addiction Journal Editors with support from the IP, provides addiction researchers with guidance on publishing research, including information on preparing manuscripts, identifying appropriate target journals, and the submission, acceptance, and revision processes (*www.parint.org*). The IP is now developing a Web space where international collaborators can work together in real time by using shared software and databases.

Looking to the future, Dr. Gust says IP priorities will include drug abuse treatment as a way to reduce HIV transmission; adolescent smoking and prenatal tobacco exposure; methamphetamine abuse; inhalant abuse; and driving under the influence of drugs. NIDA can best address these priorities and respond quickly to emerging problems, Dr. Gust says, through its development and support of networks that train international investigators and health professionals in the science of addiction and by facilitating their collaboration with U.S.-based researchers. ■

NEW THERAPY SUCCEEDS

[*Continued from page 1*]

future abstinence. Each participant agrees upon a personal goal for drug abuse reduction or abstinence that he or she believes is achievable during the coming week and signs a contract stating that he or she will strive for it. The rest of the session consists of drug abuse education plus training in social skills and relapse-prevention strategies.

SUPERIOR RESULTS

Substance abuse is common among the mentally ill. For example, surveys estimate that 48 percent of those with schizophrenia, 56 percent with bipolar disorder, and as many as 65 percent with severe and persistent mental illness have abused substances.

Dr. Bellack's research team recruited 175 patients from community clinics and a Veterans Affairs medical center in Baltimore. All had a dual diagnosis of severe and persistent mental illness and an addiction to cocaine, heroin, or marijuana. Among the participants, 38.3 percent met the diagnostic criteria for schizophrenia or schizoaffective disorders, 54.9 percent for major affective disorders, and the remainder for other mental disorders. Cocaine was the predominant drug abused by 68.6 percent of participants, opiates by 24.6 percent, and marijuana by 6.8 percent.

The researchers assigned half the trial participants to BTSAS group therapy and half to a program called Supportive Treatment for Addiction Recovery (STAR), which is the typical treatment at the University of Maryland clinics. Unlike participants in BTSAS, those in STAR do not follow a structured format but instead select their own topics and work at their own pace. Patient interaction with other patients is encouraged but not required as it is with BTSAS. Although urine samples are collected before each session, results are not discussed in the group, and no systematic feedback is provided to the patient.

Assignments to the BTSAS and STAR groups were balanced for gender, psychiatric diagnosis, type of drug dependency, and number of substance use disorders. Treatment groups of four to six participants met twice a week for 6 months. BTSAS and STAR group sessions were all led by trained therapists and lasted from 60 to 90 minutes. Group meetings were videotaped weekly and then reviewed and assessed by independent reviewers to verify that the therapists were following the programs' parameters correctly.

The BTSAS group fared better than the STAR group on a wide range of treatment-related criteria. For example, more people in the BTSAS group stayed in treatment throughout the 6-month trial period (57.4 percent versus 34.7 percent). The BTSAS group produced more drug-free urine samples and had longer periods of abstinence (see table, p. 1). They also had better clinical and general living outcomes than people in the STAR group (see table, below) and reported larger improvements in their ability to perform the activities of daily living.

"It was apparent from watching videotapes of treatment sessions that subjects in BTSAS valued the intervention and were learning important skills for reducing drug use," says Dr. Bellack. "We were very gratified that the data supported our clinical observations."

The researchers reported that the extra costs of running the BTSAS program were modest. For the 6-month trial, monetary rewards averaged roughly $60 per patient; total per-patient cost, including therapist time, was $372.

ONGOING REFINEMENTS

The trial data indicate that patients who remain in BTSAS for at least three sessions are much more likely to finish the 6-month program than patients who do not make it through the third session. Because a third of individuals initially recruited for the study left before the third treatment session, the researchers are currently developing new intervention strategies to keep people in the program until they have truly given it a chance. The innovation has two key components: a structured intervention to help patients overcome obstacles to treatment and an intervention to enlist family and friends as partners to connect patients with treatment.

"The BTSAS program will help clinicians make a difference in the lives of a very difficult-to-treat population," says Dr. Dorynne Czechowicz of NIDA's Division of Clinical Neuroscience and Behavioral Research. "One of its key strengths is that it positively affects many aspects of patients' lives. Moreover, as an outpatient treatment, it is well-suited to the situation. Most mentally ill people who abuse drugs live in the community, not in a sheltered facility, and this is where the majority of clinicians must treat them." ■

QUALITY-OF-LIFE OUTCOMES

	BTSAS		STAR	
	Pretreatment*	Posttreatment**	Pretreatment	Posttreatment
Frequency of Arrests	31.0%	12.8%	22.9%	27.3%
Inpatient Admissions***	29.5%	6.5%	20.4%	16.2%
Living Standards****	46.6%	69.2%	43.8%	51.5%

*Pretreatment: 90-day period before study
**Posttreatment: 90-day period following study
***Rates of inpatient admissions for either psychiatric problems or substance abuse
****Percentage of participants reporting having enough money for food, clothing, housing, and transportation

SOURCES

Bellack, A.S., et al. A randomized clinical trial of a new behavioral treatment for drug abuse in people with severe and persistent mental illness. *Archives of General Psychiatry* 63(4):426-432, 2006.

Kinnaman, J.E., et al. Assessment of motivation to change substance use in dually-diagnosed schizophrenia patients. *Addictive Behaviors* 32(9):1798-1813, 2007.

Behavioral Problems Related to Maternal Smoking During Pregnancy Manifest Early in Childhood

Researchers find probable precursors of adolescent conduct disorders in the behavior of toddlers and schoolchildren.

BY NIDA NOTES STAFF

Many studies have established that a pregnant woman's smoking raises her child's risk of disruptive behavior disorders and of delinquency in the teen and young adult years, but its behavioral effects in early life have been been difficult to trace. Now, however, NIDA-funded researchers have revealed associations between a child's *in utero* exposure to smoking and specific patterns of aberrant behavior as a toddler, at school age, and as a teen. The researchers propose that these patterns form a continuum, united by an underlying theme of disrupted social information processing.

AN EARLY START TO DISRUPTIVE BEHAVIOR

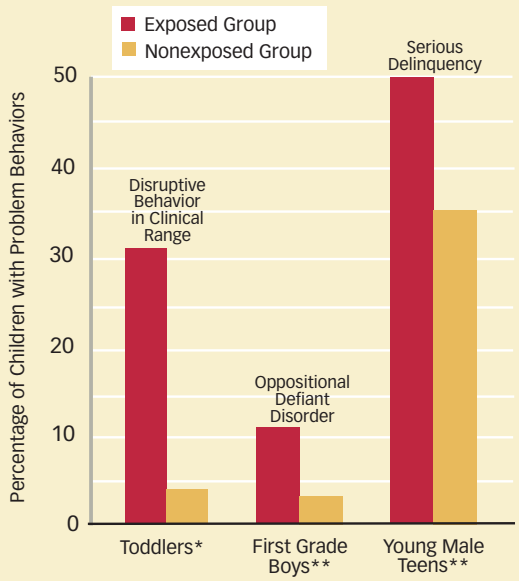
In an initial study, Dr. Lauren Wakschlag of the Institute for Juvenile Research at the University of Illinois at Chicago and her colleagues, Dr. Rolf Loeber of the University of Pittsburgh and Dr. Kate Pickett of The University of York in England, analyzed disruptive behavior patterns in first graders and subsequent problems that have been associated with later delinquency. Data were derived from the first-grade cohort of the Pittsburgh Youth Study (PYS), a community sample of boys at risk for delinquency who were followed over several decades under the direction of Dr. Loeber.

The researchers concentrated on 448 boys, who were roughly age 7 when the PYS study began. One hundred and sixty-six boys in this group had mothers who smoked during pregnancy. These boys developed the antisocial behavior pattern known as oppositional defiant disorder (ODD) at more than double the rate of the rest (see graph). Children with ODD demonstrate defiant, disobedient, and hostile behavior towards authority figures that persists for at least 6 months, and they are touchy, easily angered, and resentful. ODD is often considered a developmental precursor of conduct disorder (CD), a condition in older children and adolescents characterized by persistent antisocial behaviors such as lying, truancy, vandalism, and aggression.

Boys whose mothers smoked while pregnant did not have a higher incidence of attention deficit hyperactivity disorder (ADHD) without ODD than the nonexposed boys. However, the incidence of co-occurring ODD and ADHD—a combination that often results in chronic disruptive behavior problems—was nearly twice as high in the exposed group as in the nonexposed group. As the boys entered and traversed their teens, delinquent behavior began earlier and was more severe in the exposed group.

"All the children with ODD in the PYS study were diagnosed in first grade, meaning the disorder developed in the first 5 or 6 years of life. This provides evidence of a coherent developmental pathway from prenatal exposure to cigarettes to a subsequent sequence of conduct problems," Dr. Wakschlag says. "While previous research established a link between prenatal exposure to cigarettes and CD in older children, this study is the first to establish connections to ODD and to do so as early as first grade."

PATHWAY TO TROUBLE Children of mothers who smoked during pregnancy had higher rates of disruptive behavior throughout development. Toddlers were evaluated for disruptive behavior; first grade boys for oppositional defiant disorder; and young teenage boys for serious delinquency.



*Data from Family Health and Development Project
**Data from Pittsburg Youth Study

TODDLERS WITH TROUBLES

To look for exposure-related behavioral abnormalities at even younger ages, Dr. Wakschlag's team conducted the Family Health and Development Project (FHDP), in collaboration with colleagues from the University of Illinois, The University of York, the National Institute of Mental Health, and the University of Massachusetts-Boston. The researchers recruited 96 expectant mothers, age 18 and older, at several clinics. The women were predominantly white and working class. Along with the women's self-reports, the researchers collected biological data, such as measurements of the nicotine metabolite cotinine in urine samples, to assess fetal exposure to maternal smoking. These measurements, taken three times during pregnancy, indicated that 47 percent of the women smoked throughout their pregnancies. Ninety-three infants and their mothers completed the study's developmental phase, which lasted until the babies were 24 months old.

The babies were evaluated every 6 months. At the 12-, 18-, and 24-month evaluations, each mother filled out the Infant-Toddler Social Emotional Assessment (ITSEA). During 20-minute laboratory observations of the toddlers and their mothers interacting at 24 months, the researchers rated specific components of the toddlers' behavior using codes from the Disruptive Behavior Diagnostic Observation Schedule.

The results indicated that toddlers whose mothers had smoked during pregnancy demonstrated a high and escalating pattern of disruptive behavior from 12 to 24 months, whereas nonexposed toddlers exhibited a relatively stable pattern. A mother's smoking during pregnancy increased the likelihood of the observed atypical trajectory of behavior independent of several associated risk factors, including parental antisocial behavior, quality of parenting, and postnatal exposure to tobacco smoke. At 24 months, toddlers whose mothers had smoked while pregnant were more than 11 times as likely as nonexposed peers to exhibit clinically significant patterns of disruptive behavior, shown on the ITSEA.

To more precisely determine the nature of the boys' behavior problems, the researchers examined four components of disruptive behavior, each of which is considered a precursor to disruptive behavior patterns seen at later ages:

- Aggressive/destructive behavior, including threatening, hitting, and throwing or smashing toys;
- Dysregulated negative affect, characterized by persistent, uncontrolled outbursts of anger with loud yelling, intense crying, and temper tantrums;
- Stubborn defiance, marked by obstructive behavior that persists after the mother has increased expressions of support for her child and has tried several strategies to change her child's behavior; and
- Low social competence, where the child misses social cues and exhibits low social interest or concern.

These four behaviors, while viewed as normal in toddlers, are considered precursors to clinical problems if they are severe or pervasive.

The children whose mothers had smoked during pregnancy displayed lower social competence than other children and significantly higher levels of aggressive/destructive behavior and stubborn defiance. They were not more likely to exhibit dysregulated negative affect.

"Dr. Wakschlag has teased out some components of disruptive behavior problems when they first emerge between 18 and 24 months of age," says Dr. Nicolette Borek of NIDA's Division of Clinical Neuroscience and Behavioral Research. "This gives us a way to identify at-risk children early and raises interesting questions about the role of brain development in later-stage behavioral issues."

ON TO ADOLESCENCE

Dr. Wakschlag and colleagues have hypothesized that the resistant, hostile, and unresponsive patterns of behavior demonstrated in FHDP, PYS, and similar studies may reflect disruptions in social-information processing that resulted from prenatal exposure to cigarette smoke. To test this hypothesis, the team is conducting the NIDA-funded East Boston Family Study (EBFS), which includes 272 adolescents and is a followup to the Maternal-Infant Smoking Study of East Boston (MISSEB). Dr. Wakschlag and her colleagues are also examining the influence of genetic makeup on exposure-related disruptive behavior among these young people. The researchers are using maternal exposure data originally collected by MISSEB but applying more sophisticated methods to measure prenatal exposure to cigarette smoke. These new techniques, which combine maternal self-report and biological data, were developed from FHDP-derived data by Dr. Vanja Dukic at the University of Chicago in collaboration with Dr. Neal Benowitz of the University of California, San Francisco and Dr. Wakschlag.

"Maternal self-reports are affected by memory lapses and social pressure not to smoke, and biological methods can be inaccurate because the smoke-derived chemicals have a short half-life and rates of metabolism differ among individuals," says Dr. Wakschlag. "In addition, we know that smoking levels fluctuate throughout a pregnancy. The new technique incorporates the unique information from both of these methods to provide a more precise estimate of prenatal exposure to cigarettes." ■

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Morphine-Induced Immunosuppression, From Brain to Spleen

Morphine sets off a chain of biological events that stifles the immune response.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Morphine and other opioids suppress the immune system, the body's innate defense against infections. Because of this effect, doctors weigh the pain-relief benefits of opioids against the added risk of infection they pose to patients, particularly those being treated for severe burns or certain cancers. Opioid abusers, many of whom are already infection-prone due to unclean needles, repeated injections, and poor nutrition and living conditions, are rendered even more vulnerable by these drugs.

Morphine affects the body's immune cells in many ways, both direct and indirect. Recently, NIDA-funded scientists pinpointed the biochemical trigger that sets off a chain reaction that ultimately inhibits an immune cell that is key in fighting viruses and cancer. If validated in future studies, the work could lead to interventions to bolster the immunity of those who regularly take opioids.

MORPHINE, DOPAMINE, AND NATURAL KILLERS

Morphine suppresses the activity of three different types of white blood cells: T lymphocytes, B lymphocytes, and natural killer (NK) cells (see box). NIDA-funded investigators Dr. Donald Lysle, Dr. Timothy Saurer, and their colleagues at the University of North Carolina (UNC), Chapel Hill, concentrated on NK cells, and found that

- morphine-induced immunosuppression follows activation of dopamine-1 (D_1) receptors in the shell of the nucleus accumbens (NAc); and
- a train of biochemical events links stimulation of these D_1 receptors with reduced NK cell activity in the spleen.

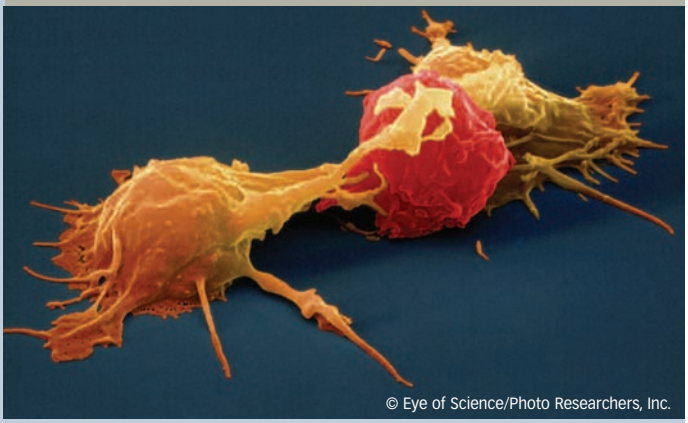
In previous studies, the UNC team had established that blocking one of morphine's pharmacological effects in the brain—a surge of dopamine into the NAc—averts suppression of NK cells in the spleen. This being the case, the researchers reasoned that morphine-induced NK suppression must start with something that dopamine does in the NAc.

Dopamine's main action in the NAc is to interact with proteins called dopamine receptors, which come in several subsets—D_1, D_2, for example. Accordingly, Dr. Lysle and colleagues conducted experiments to determine whether any of these receptors were involved in morphine inhibition of NK cells. They began by giving rats morphine (15 mg/kg) or saline. One hour later, they measured NK cell activity in the animals' spleens and found it to be lower by about 40 to 50 percent, on average, among

Natural Killer Cells Eliminate Compromised Cells

Natural killer (NK) cells constitute a rapid-response force against cancer and viral infections. These specialized white blood cells originate in the bone marrow, circulate in the blood, and concentrate in the spleen and other lymphoid tissues. NK cells key their activities on a subset of the histocompatibility proteins that occur on the surfaces of healthy cells but that virus- and cancer-weakened cells shed. When NK cells encounter cells that lack histocompatibility proteins, they attack and destroy them—thus preventing the cells from further spreading the virus or cancer. NK cells are distinguished from other immune system cells by the promptness and breadth of their protective response. Other white blood cells come into play more slowly and target specific pathogens—cancers, viruses, or bacteria—rather than damaged cells in general.

RAPID-RESPONSE FORCE Two natural killer cells attack a cancer cell.



the morphine-exposed animals, compared with those given saline. They then conducted a series of trials that showed:

- *Morphine-induced NK cell suppression depends on the activation of D_1 receptors.* Rats injected with a compound (SCH-23390) that prevents dopamine from accessing D_1 receptors did not develop immunosuppression when subsequently injected with morphine. In contrast, rats pretreated with a compound (raclopride) that blocks D_2 receptors did lose NK cell activity.
- *Specifically, D_1 receptors that reside in the part of the NAc called its shell must be activated for morphine NK cell suppression to occur.* Morphine inhibition of NK cell activity was abolished when researchers infused SCH-23390 into rats' NAc shell (see graph, left panel), but not the NAc core.
- *D_1 receptor activation in the shell of the NAc lowers NK cell activity even in the absence of morphine.* Rats given no morphine but a test compound (SKF 38393) that activates D_1 receptors demonstrated 35 to 39 percent less NK cell activity than a comparison group of rats injected with saline.

PATHWAY THROUGH THE BODY

Dr. Lysle and colleagues next turned their attention to the signaling chain that links D_1 activity in the NAc to NK cell inhibition in other organs. Prior studies had indicated that morphine activates the sympathetic nervous system, and sympathetic nerves communicate signals from the brain to NK and other white blood cells in the spleen. The specific chemical involved in conveying the message of NK inhibition from brain along the sympathetic system to the spleen, however, was unknown.

Dr. Lysle and colleagues focused on neuropeptide Y (NPY) as a likely candidate because it is released in the brain when sympathetic nerves are activated, is found at the nerves of the spleen, and interacts with receptors (Y_1) in the membranes of white blood cells. "Most important in elevating NPY as a candidate, however, was other researchers' finding that it suppressed the ability of natural killer cells to attack cultured tumor cells," says Dr. Saurer. "This suggested that it might modulate natural killer activity and perhaps the suppressive effects of morphine in rats."

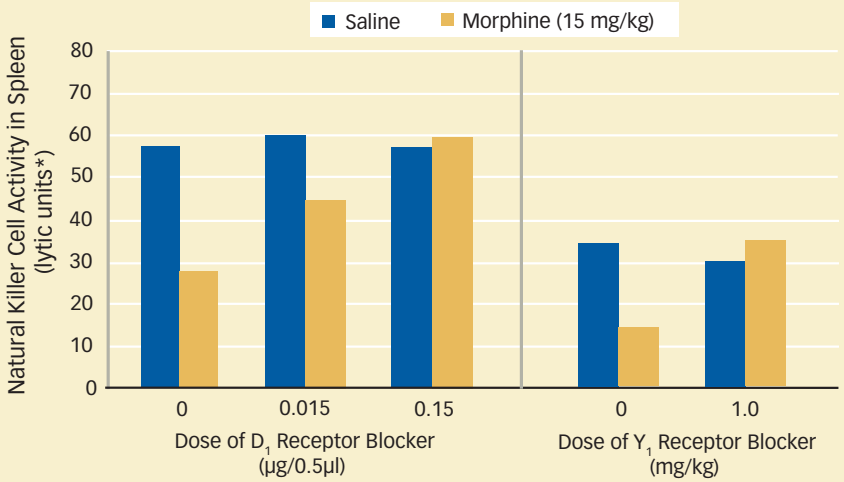
The investigators confirmed their hypothesis with an experimental strategy parallel to the one they had used to link the brain's D_1 receptors to morphine-induced NK cell immunosuppression: They showed that neither NK cell inhibition induced by morphine nor D_1-related NK inhibition occurs when NPY is prevented from interacting with its main receptor (Y_1) (see graph, right panel).

The researchers next wondered whether Y_1 receptor activation might underlie suppression of other white blood cells as well as suppression of NK cells. To find out, they stimulated rats' Y_1 receptors with injections of NPY (20 or 200 µg).

The infusion inhibited NK cell activity by 55 percent, on average, but had no effect on T and B white blood cells in the spleen. Similarly, rats infused with morphine while their Y_1 receptors were blocked did not develop NK cell inhibition, but their T and B white blood cells became inhibited.

The specificity of NPY's actions—affecting NK cells but not other white blood cells—is not surprising, says Dr. Lysle, because the brain generally seems to communicate with different immune system components in the body in very selective ways. "Our team has identified the language for the suppression of natural killer cells, but

HOW TO PREVENT MORPHINE-INDUCED SUPPRESSION OF NATURAL KILLER CELLS Blocking the D_1 receptor in a particular area of rats' brains (the nucleus accumbens shell) prevented morphine-induced inhibition of natural killer cells—key immune system cells that fight viral infections and cancers. Preventing neuropeptide Y from interacting with its Y_1 receptors in the body also counters morphine-induced inhibition of natural killer cells.



*One lytic unit is the number of natural killer cells required to destroy 20 percent of tumor cells. A higher number of lytic units indicates a more effective immune response.

Conditioned Responses Can Also Impair Natural Killer Cells

An environment linked with an immune system trigger such as an allergen will, after repeated pairings, incite an immune response in the absence of the trigger. Similarly, an environment associated with an immunosuppressant such as morphine weakens immune responses.

In these conditioned responses, the brain generates the initiating signal for immunosuppression. But where in the brain does the message start? And how does it travel to the distant organs where immune cells reside?

Dr. Donald Lysle, Dr. Timothy Saurer, and their colleagues at the University of North Carolina, Chapel Hill, proposed that the biochemical chain of events in conditioned immunosuppression recapitulates the one set off by the original immune-system-weakening stimulus. To put this idea to the test, they conducted experiments on rats that were similar to those they had performed to establish the mechanisms of morphine-induced natural killer (NK) cell suppression.

The researchers gave rats a dose of morphine (15 mg/kg) to suppress NK cell activity. They immediately placed the rats for 1 hour in special conditioning chambers that were distinct from the home cages—with different walls and floors and featuring a unique sound and smell. They returned the animals to the home cages and repeated the process 2 days later.

After two conditioning sessions and a 12-day break, the researchers left some rats in the home cages and returned others to the morphine-paired conditioning chambers. None of the rats was given morphine at this stage. After 1 hour, NK cell activity in the spleen was lower by about 50 percent, on average, among the animals in the morphine-linked chambers, compared with those in the home cages. The researchers then conducted a series of trials that showed:

- For conditioned NK cell suppression to occur, D_1 receptors must be activated.
- In conditioned NK cell suppression, D_1 receptors that reside in the part of the nucleus accumbens called its shell are critical.
- In conditioned NK cell suppression, Y_1 receptors in the spleen must be activated.

The findings confirm the researchers' hypothesis that the same biological train of events that underlies morphine immunosuppression also drives conditioned immunosuppression, which occurred, in this case, in response to an environment previously paired with morphine exposure. "The findings expand on the team's prior descriptions of the neurobiological mechanisms underlying the ability of opiates and environments associated with them to suppress various immune responses in animals," says Dr. Paul Schnur of NIDA's Division of Basic Neuroscience and Behavioral Research. "They suggest that opiate abusers are vulnerable to a weakened immune system in places previously associated with taking the drug."

Source: Saurer, T.B. et al. Neuroimmune mechanisms of opioid-mediated conditioned immunomodulation. *Brain, Behavior, and Immunity* 22(1):89-97, 2008.

other drugs of abuse and different immune system responses may speak distinct languages—ones that may be discovered in future research," he says.

"The team's findings suggest a brain-to-body pathway whereby morphine weakens the body's defenses," says Dr. Paul Schnur of NIDA's Division of Basic Neuroscience and Behavioral Research. "In future studies, researchers might examine immune responses after chronic self-administration of morphine to model more closely the possible immunosuppressant effects of drug abuse." ■

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Saurer, T.B.; Ijames, S.G.; and Lysle, D.T. Neuropeptide Y Y(1) receptors mediate morphine-induced reductions of natural killer cell activity. *Journal of Neuroimmunology* 177(1-2):18-26, 2006.

Mice With Genetic Alteration Eschew Cocaine

A South American caterpillar inspired a successful 10-year quest to desensitize the dopamine transporter to the drug.

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA researchers have desensitized mice to cocaine by genetically altering their dopamine transporters—proteins that are a key target of cocaine—to resemble ones found in the brains of some insects. If investigators can identify a compound that alters these transporters in the same manner, they might be one step closer to developing medications to treat cocaine addiction.

A South American caterpillar started the researchers on their path to the discovery. Larvae of the *Eloria noyesi* moth have a particular appetite for leaves of the coca plant. This preference has captured the interest of drug-control authorities, who view the caterpillar as a potential tool for eradication of coca crops. To Dr. Howard Gu at Ohio State University (OSU), however, the caterpillar's apparent immunity to the psychoactive properties of the coca leaf suggested something else: Perhaps cocaine's target protein in the caterpillar's brain—the dopamine transporter (DAT)—does not respond to the leaf. If so, he reasoned, an understanding of how the insect's DAT functions might provide a template for pharmacological agents to block the effects of the coca leaf's potent derivative, cocaine.

Scientists generally believe that cocaine produces its high by preventing DATs from regulating dopamine levels in the brain's reward system, resulting in a euphoria-producing buildup of the neurotransmitter in the nucleus accumbens (NAc). If an animal reliant on coca for nutrition were to be subject to this effect, however, surges of euphoria would occur whenever it ate and presumably be very disruptive of its functioning. "Because the caterpillar is interested in coca leaves as a food source, we hypothesized that its DATs might not interact with cocaine," Dr. Gu says.

FOOD NOT DRUG A coca leaf—the source of cocaine—is just food to the South American caterpillar *Eloria noyesi*. Like some other insects, its dopamine transporters are much less sensitive to cocaine than those of mice.

A SURPRISING TWIST

Dr. Gu undertook a 10-year project that ultimately established a mutated form of DAT that is cocaine-insensitive. But he encountered several surprising twists—and frustrating letdowns—along the way.

Chief among these, Dr. Gu was disappointed to find that the DAT from *Eloria* is not substantially less sensitive to cocaine than the DAT from other insects they tested, such as a silkworm that does not eat coca leaves. He quickly recognized that there was nothing unique about the *Eloria* caterpillar in this regard and was forced by that evidence to relinquish the elegant evolutionary theory he had held about how its insensitivity to the stimulating effects of the coca leaf might have developed.

But what he learned in the process was more important than a busted theory: Dr. Gu discovered that the DATs from a number of insect species are just 5 percent as sensitive to cocaine as is mouse DAT. "I seized on the difference to generate clues about how to alter the mouse DAT to be cocaine-insensitive like the insects'," he says.

As a first step, Dr. Gu switched fragments of insect DAT sequences with mouse DAT sequences and identified key regions that affect how tightly cocaine binds to the DAT protein. He then randomly generated a large number of alterations in these regions of the mouse DAT sequence. Working with cultured cells, he tested them one by one to see if the changes they introduced would desensitize mouse DAT to cocaine. Through this laborious process, he eventually identified the sequence changes that make the transporter cocaine-resistant.

Dr. Gu created mutant mice with the same DAT sequence changes. The mutant mice produced cocaine-resistant DAT. But were the animals truly immune to the rewarding sensations of the drug? Dr. Gu joined with colleagues at OSU and the

University of Tennessee College of Medicine to answer this question.

SELECTIVE INDIFFERENCE

When normal mice are exposed to cocaine in one compartment of a split cage, they demonstrate liking for the drug by later spending the bulk of their time in that compartment. The proportion of time the animals spend in the drug-associated compartment provides a quantitative behavioral measure of the intensity of the drug's rewarding effects. In Dr. Gu's trials, the mutant mice spent no more time in a cage area where they received the injections of cocaine (5 mg/kg or 20 mg/kg) than they did in a compartment where they were given saline injections—a clear demonstration that they were not experiencing cocaine's rewarding effects (see graph, left panel).

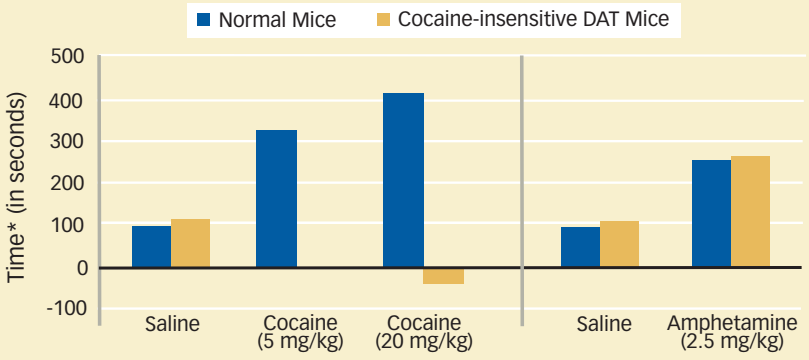
To ensure that the mutant mice retained normal responses to stimuli other than cocaine, the researchers gave them amphetamine. This stimulant triggers dopamine surges by mechanisms different from those that cocaine triggers. The researchers found that both mutant and normal mice developed elevated extracellular dopamine in the NAc after amphetamine exposure. In addition, the mutants exhibited as much behavioral evidence of amphetamine reward as did a comparison group of normal mice (see graph, right panel).

"The mutants' response to amphetamine demonstrated that the neural machinery works properly in these animals, and they are not generally deficient in drug-induced reward," says Dr. Gu.

Dr. Gu's team is now seeking to identify a chemical compound that will prevent human DATs—like the mouse's altered DAT—from responding to cocaine. Such a compound would eliminate the drug high and limit the frequency and length of relapses. Yet it would not interfere with the DAT's ability to regulate dopamine, which produces feelings of reward and motivation vital for life-promoting activities, such as eating. NIDA is supporting research to screen for such compounds with a protocol and cell lines provided by Dr. Gu.

MICE WITH MUTATED DOPAMINE TRANSPORTERS GET NO KICK FROM COCAINE

Normal mice spent more time in a chamber where they had received cocaine injections than in one where they had received saline. But mice with a cocaine-insensitive dopamine transporter (DAT) showed no preference (left panel). In contrast, both normal mice and those with an insensitive DAT lingered in the amphetamine-paired chamber longer than saline-treated animals (right panel).



*Time indicates preference for the chamber where mice received the injections.

A THEORY BOLSTERED

Beyond yielding leads for medication development, Dr. Gu's findings alleviate doubts that have arisen about the strategy of selective DAT desensitization to reduce cocaine reward. In some studies, animals continued to exhibit dopamine surges and behavioral responses to cocaine despite having been genetically altered to lack DAT.

"The results from mice without DAT represented a milestone in cocaine research—it was remarkable that these mice still experienced a high from cocaine," explains Dr. Gu. "In view of that observation, it is reasonable to question the approach of finding compounds that prevent cocaine from binding to the DAT as a therapeutic strategy for cocaine abuse. The results from our mutant mice, however, indicate that DAT altering can block cocaine reward."

In light of their work with the mutants, the researchers now attribute the persistence of cocaine response in DAT-less mice to adaptation. "The brains of DAT knock-out mice seem to undergo significant adaptive neurobiological changes that alter how cocaine produces its effects," says Dr. Gu.

"Dr. Gu and colleagues have verified decisively that cocaine's inhibition of DAT is necessary for its behavioral effects, answering an important question in addiction research," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. She notes, however, that the strong confirmation of DAT's role in cocaine reward does not rule out the idea of redundant systems. "If the dopamine system is damaged, as it is in the DAT-less mice, the brain may 'train' norepinephrine and serotonin neurons to take over reward and other functions," she says. ■

SOURCE

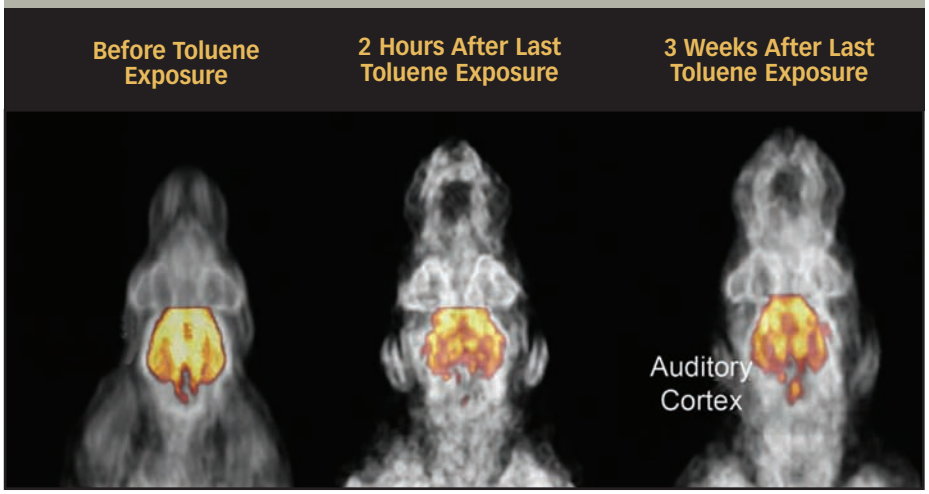
Chen, R., et al. Abolished cocaine reward in mice with a cocaine-insensitive dopamine transporter. *Proceedings of the National Academy of Sciences* 103(24):9333-9338, 2006.

Animal Studies Elaborate Toluene's Effects

Toluene abuse can harm the nervous system and body, yet scientists know relatively little about its specific actions.

BY LORI WHITTEN,
NIDA Notes Staff Writer

REPEATED TOLUENE EXPOSURE DEPRESSES BRAIN ACTIVITY Researchers used microPET imaging to compare brain activity of a rat before and after chronic toluene exposure. Yellow indicates high activity. Three weeks after the last exposure, the brain showed recovery, but activity in the auditory cortex and some other areas remained depressed throughout the 2-month study.



Toluene, a solvent found in paint removers, glues, and other common household products, is often the first substance abused by young people, who inhale its dangerous fumes. A recent NIDA-funded study has shown that toluene's behavioral and neurobiological effects bear similarities to those of both stimulants and depressants, while another study mapped the drug's impact on brain metabolism. The findings lay groundwork for new prevention strategies.

Various animal studies have indicated that abused inhalants have subjective effects like those of central nervous system depressants. Now, Dr. Scott E. Bowen at Wayne State University in Detroit has demonstrated that, in adult mice, the subjective experience of toluene also, in some ways, resembles that produced by amphetamine. Dr. Bowen injected mice alternately with amphetamine and saline and trained them to seek rewards by pressing the correct lever—one after amphetamine and the other after saline. He showed that under the influence of toluene, the animals pressed the drug-associated lever, indicating that the inhalant felt something like amphetamine to them (see chart, p. 15).

Dr. Bowen's findings add to emerging evidence that, in addition to its depressant effects, toluene induces stimulant-like behavioral effects (e.g., increased locomotor activity) by augmenting dopamine activity in the brain's reward pathway ("Dopamine Enhancement Underlies a Toluene Behavioral Effect," *NIDA Notes*, Vol. 19, No. 5).

After exposure to the highest concentration of toluene—6,000 parts per million (ppm)—the animals' lever-pressing responses indicated that they were still experiencing stimulant-like effects 15 to 20 minutes later, says Dr. Bowen. When tested again 30 minutes after exposure, the lever-pressing responses of the mice were similar to those after saline, suggesting that toluene's effects had worn off.

"Dr. Bowen's results indicate that toluene and amphetamine share, to some extent, similar subjective effects, which may reflect a common neurochemical action," says Dr. Minda Lynch of NIDA's Division of Basic Neuroscience and Behavioral Research. The finding is worrisome because, in animals, exposure to one stimulant often enhances the response to another stimulant experienced subsequently. "Young people who abuse inhalants may increase their risk for later drug abuse," says Dr. Lynch. "An important next step is to determine whether animals exposed to inhalants, particularly during adolescence, are then more prone to use stimulants upon exposure."

TOLUENE DEPRESSES BRAIN METABOLISM

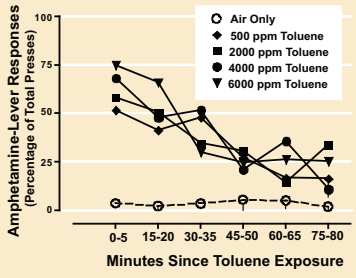
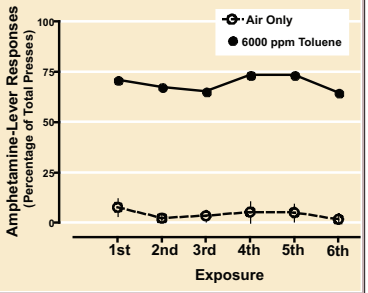
In a separate NIDA-funded study, Dr. Wynne K. Schiffer and colleagues at Brookhaven National Laboratory and New York University School of Medicine used positron emission tomography (PET) to measure brain metabolism in adolescent rats exposed to toluene.

During the 2-month study, the researchers tested the effects of repeated

exposure to toluene at a dose they previously established to be rewarding to adolescent animals. Two hours after the last toluene exposure, the animals' whole-brain metabolic activity had declined 20 percent compared with levels seen prior to exposure and with those of control animals. Metabolic activity in the brain continued to drop, reaching 40 percent below baseline after 24 hours; at this time, brain regions involved in movement coordination, memory, and learning showed the greatest effect.

The depression in overall brain activity persisted for a week. Two months after the last exposure, the now-mature rats showed recovery of overall brain metabolism. However, activity in the temporal cortex—an area involved in the processing of sounds and memories—remained about 10 percent below the baseline level.

TOLUENE HAS AMPHETAMINE-LIKE EFFECTS Mouse responses in the drug-discrimination protocol indicated that the animals experienced the commonly abused solvent toluene as if it were a stimulant.

Drug discrimination training	Toluene exposure and testing	Results
Adult mice in a training chamber learn to press levers for a milk reward. To receive the reward after a saline injection, they must press a certain lever; to receive the reward after an amphetamine injection, they must press a different lever. The trained mice thus signal, by their choice of levers, which substance they have just experienced. Scientists can find out if a test substance feels like amphetamine to the mice by injecting the test substance and determining whether mice respond to the amphetamine-linked lever or the saline-linked lever. If response to the drug-associated lever is high (around 80 percent of total lever presses), the scientists conclude that the test agent feels like the drug to the mice. An intermediate response (60 to 79 percent) indicates that the test agent feels somewhat like the drug.	To test a substance like toluene, which is not injectable, scientists let the mice inhale it and then return them to the lever-equipped chamber. A high level of responding on the drug-associated lever indicates that toluene exposure and amphetamine exposure feels similar to the mice. In the first experiment, mice received either air only or toluene vapors during a 10-minute exposure. Immediately after the exposure, mice were placed in the test cage for 5 minutes to measure their lever-press choices. They were then removed for a 10-minute break in a cage with no toluene and no levers. The animals experienced alternating assessments and breaks for 80 minutes.	 All concentrations of toluene elicited amphetamine-linked lever-pressing behavior, and similarity to amphetamine increased with toluene concentration. At the highest concentration of toluene, mice continued to feel its stimulant-like effects for at least 20 minutes.
	In a second experiment, mice received six 10-minute exposures to either toluene or air. After each exposure, the mice were placed into the test cage for 5 minutes.	 In repeated exposures, toluene continued to produce similar amphetamine-like responses.

"In humans, PET imaging has revealed a great deal about the characteristic metabolic signature of the addicted brain—that is, one can immediately see by the pattern of depressed activity in particular brain regions that a person has abused cocaine or alcohol. Our findings indicate that repeated toluene exposure has a similar signature, further linking its neurobiological effects to those of traditional drugs of abuse," says Dr. Schiffer.

"Dr. Schiffer's findings help shorten the list of brain areas we need to examine during future studies of toluene and may guide research on the drug's distribution in the brain and the changes that underlie its behavioral effects," says Dr. Rao Rapaka of NIDA's Division of Basic Neuroscience and Behavioral Research.

Toluene's toxicity with chronic exposure and its availability in household and industrial products drive scientists' efforts to identify the mechanisms that underlie its abuse. Clinical reports have linked chronic toluene abuse with a profound reduction in brain white matter, together with associated neurological problems such as impaired movement, cognition, hearing, and vision.

"Toluene appears typical of abused inhalants and may have the greatest potential for abuse and damaging effects," says Dr. Schiffer. Because of their usefulness as solvents and for other practical purposes, toluene and other abused inhalants are not likely to become less available, says Dr. Bowen. "Prevention efforts with youth and further research on the neurobiological and behavioral effects in animals, particularly during gestation and adolescence, are keys to countering the problem." ■

SOURCES

Bowen, S.E. Increases in amphetamine-like discriminative stimulus effects of the abused inhalant toluene in mice. *Psychopharmacology* 186(4):517-524, 2006.

Schiffer, W.K., et al. Metabolic correlates of toluene abuse: Decline and recovery of function in adolescent animals. *Psychopharmacology* 186(2):159-167, 2006.

Social Neuroscience Meeting Aims to Improve Prevention, Treatment

Scientists and clinicians gathered in Rockville, Maryland, on October 1–2, 2007, to review initial research results from the burgeoning field of social neuroscience—the study of how neurobiology and the social environment interact.

The NIDA-sponsored meeting, "Social Neuroscience: Developing More Powerful Behavioral Interventions," was part of the institute's ongoing efforts to advance knowledge about the neural underpinnings of interpersonal interactions, emotional responses, and social behaviors that relate to addiction prevention and treatment. The payoff could be great. For example, an understanding of how effective patient-counselor interactions modulate patients' brain function could be used to assess and improve therapeutic relationships. Charting the brain dynamics that occur in healthy, positive social relationships, which protect against drug abuse, could open the door to more effective prevention interventions.

The October meeting explored seven topics: empathy, disruption of social reward in drug abuse, self-monitoring and responding to cues from others, prejudice and self-stigmatization, parent-child interactions among substance abusers, social networks and decisionmaking in adolescents, and mirroring the behavior of others.

What are the interactions between drug abuse and companionship and other social rewards? The answer may rely on combining what is already known about how addiction usurps the reward system with research on less-studied brain circuits—including the interoceptive system, which is made up of neural circuits that monitor and process sensations including pain, temperature, hunger, thirst, and touch, and has been linked with emotion and motivation. NIDA-funded neuroscientist Dr. Martin Paulus reported that his team at the University of California, San Diego, is developing a method to assess interoceptive system functioning during brain imaging. The team plans to examine whether activity of the interoceptive circuit differs between drug abusers and nonabusers.

Dr. Michael Otto of Boston University envisioned one way such investigations might eventually find application in treatment. Noting that brain activity arising from disrupted interoceptive processing may underlie a heightened vulnerability to anxiety, he imagined counselors training substance abusers to use biofeedback—real-time brain scans—to reverse the abnormal activity. The benefits of such "weightlifting for the brain" could include reducing patients' risks of stress-induced relapses to substance abuse.

NIDA Renames Addiction Journal

NIDA's journal on addiction, formerly called *Science & Practice Perspectives*, is now being published as *Addiction Science & Clinical Practice*. The new name highlights the publication's goal of encouraging the exchange of ideas between researchers, clinicians, and others in the field of addiction science.

The first issue of the renamed journal—December 2007—introduced two other major changes: an increase in the number of issues from one to two per year and the journal's inclusion in the National Library of Medicine's MEDLINE (Medical Literature Analysis and Retrieval System Online) database. MEDLINE is the largest component of PubMed, an online database of biomedical journal citations and abstracts.

"Changing the name to *Addiction Science & Clinical Practice* reflects our ongoing commitment to bringing the latest in addiction science from the laboratory to the clinical field as quickly as possible," says NIDA Director Dr. Nora D. Volkow. "In addition, publishing the journal more frequently and broadening its access through MEDLINE will increase visibility and impact."

The journal promotes dialog between scientists and addiction treatment professionals with the aim of improving drug abuse treatment and research. It helps their programs keep pace with emerging knowledge and maximize treatment outcomes, while providing researchers with tools to construct new hypotheses and to design studies highly relevant to the needs of providers and patients. Each issue includes:

- Reviews by leading researchers of critical topics in the science of drug abuse prevention and treatment;
- Service providers' perspectives on what can and does work in diverse community treatment settings;
- Panel discussions on the practical implications of most articles; and
- Examples of successful addiction research-practice collaborations.

For more information and free subscriptions, go to: *www.drugabuse.gov/acsp/*. ■

Booklet Explains the Science of Addiction

Clearing up common misconceptions and reducing the stigma associated with drug addiction are the goals of a new book from NIDA. *Drugs, Brains, and Behavior: The Science of Addiction* explains in plain language what scientists know about how drug addiction alters the brain and affects behavior.

"Thanks to science, our views and our responses to drug abuse have changed dramatically, but many people today still do not understand why people become addicted to drugs or how drugs change the brain to foster compulsive drug abuse," says NIDA Director Dr. Nora D. Volkow. "This booklet aims to fill that knowledge gap by providing scientific information about the disease of drug addiction in language that everyone can understand."

The booklet discusses the reasons people take drugs, why some people become addicted while others do not, how drugs work in the brain, and how addiction can be prevented and treated. It also explains the consequences of abuse and addiction for substance abusers, their offspring, their sexual partners, and others.

Some of the key points made in the publication are:

- **Drug addiction is a disease, not a moral failing.** Drugs change the brain, disrupting and hijacking its normal functions. For most people, the initial decision to take drugs is voluntary, but over time, drug abuse can cause changes to the brain that impair a person's self-control and ability to make sound decisions, while generating intense impulses to take drugs.

- **Drug addiction is preventable.** Researchers have developed a broad range of programs that are effective in preventing early use of tobacco, alcohol, and illicit drugs and in curbing abuse that has already begun. Preventing substance abuse early in life, especially during adolescence, can reduce the chances of later abuse and addiction.

- **Drug addiction is treatable.** Like diabetes, asthma, and heart disease, drug addiction is a chronic disease that can be managed successfully. Relapse is not a sign of treatment failure, but rather an indication that treatment should be reinstated or adjusted to help addicted individuals fully recover.

NIDA hopes that a better understanding of the basics of addiction will empower substance abusers to make informed choices about their own lives and treatment providers to adopt science-based policies and programs to reduce abuse and addiction in their communities. The need is clear: In the United States, abuse of illicit drugs and alcohol annually contributes to more than 100,000 deaths, while tobacco is linked to an estimated 440,000 more.

Print copies of the 30-page, full-color booklet can be requested without charge, by sending an e-mail to *information@nida.nih.gov*. The publication is also available online at NIDA's Web site, *www.drugabuse.gov*. ■

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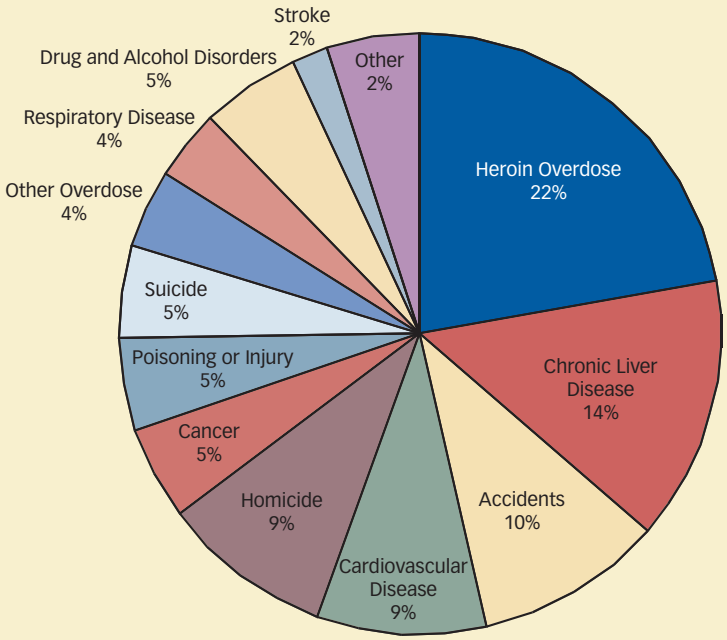
*Issue numbers appear in parentheses, followed by the page number(s).

WHAT THE NUMBERS SAY

Reduced Longevity Among Male Heroin Abusers, 1962–1997



Even before the era of HIV/AIDS, the lifespan of heroin abusers was drastically curtailed compared to that of the general U.S. population. A recent study looked at the fates of 581 California men who, from 1962 to 1964, were mandated by a court to enter heroin addiction treatment. Their average age was 25. By 1997, 282 of the men had died, at an average age of 47. Positing a hypothetical life expectancy of 65, the deceased men fell short by an average of 18 years. Heroin overdose caused 17 percent of the deaths, but—because it tends to occur at young ages—22 percent of the loss in life expectancy (see chart). Chronic liver disease, which is associated with hepatitis B, hepatitis C, and alcohol abuse, accounted for 15 percent of deaths and 14 percent of the reduction in longevity.

SOURCE: Smyth, B. et al. Years of potential life lost among heroin addicts 33 years after treatment. *Preventive Medicine* 44(4):369-374, 2007.

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