

A Collection of

NIDA NOTES

NATIONAL INSTITUTE
ON DRUG ABUSE

Articles That Address



WOMEN
AND
SEX/GENDER
DIFFERENCES
RESEARCH

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

NN0013

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Introduction

About NIDA

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic, behavioral, and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, behavior, and addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and research on effective messages to deter young people, in particular, from abusing drugs.

About NIDA Notes

This publication is a compilation of a sampling of articles focused specifically on Women and Sex/Gender Differences research reprinted from NIDA's research newsletter, *NIDA NOTES*. Published six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research in a format that specialists and lay readers alike can read and put to use. Selections such as those contained herein are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

For more information

To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit www.drugabuse.gov. For more information on NIDA's Women and Sex/Gender Differences Research Program, please visit www.drugabuse.gov/WHGD/WHGDHome.html, which includes a comprehensive list of publications and videos specific to this important research area.



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Prenatal Nicotine Exposure May Damage Receptors That Influence Auditory Processing

Tests correlate biochemical abnormality with deficits in rats' responses to sounds.

By *NIDA NOTES* Staff

Some children of women who smoked during pregnancy experience subtle difficulties processing auditory information; for example, they may have more than average problems recognizing slightly garbled words or understanding speech in a noisy environment. A recent series of animal experiments indicates that the cause of the problem is not in the ear but in the brain: Nicotine exposure during development damages a set of receptors in the brain's auditory processing center.

Hearing Versus Heeding

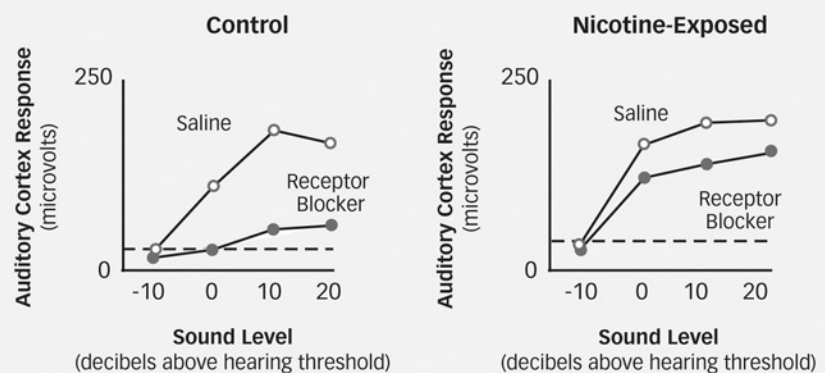
The NIDA-funded experiments first demonstrated a deficit in sound processing in rats that had been exposed to nicotine at a developmental stage corresponding to that of a human fetus in the third trimester of gestation. Dr. Raju Metherate and colleagues at the University of California, Irvine, began by injecting rat pups with nicotine twice daily for 5 days (postnatal days 8 to 12). The injections produced nicotine blood levels approximating those of smokers, and presumably of pregnant smokers' fetuses. A group of same-aged control rats received injections of saline.

When the rats were 2 months old, a researcher trained them to escape an electrical shock by crossing from one chamber of an experimental box to another. The next day, a 5-second tone preceded each shock. All the animals immediately turned their heads toward the tone, indicating that they had heard it. Over 4 days, the rats had the opportunity to learn that the tone signaled an impending shock.

By the end of the training, all but one of the 12 control animals had learned the lesson well enough to routinely avoid the shock by crossing into the safe chamber during the tone. These animals moved to the safe chamber more rapidly as time went on, and eventually, many went into the safe chamber as soon as the tone began. Just 6 of the

NICOTINE EXPOSURE DURING DEVELOPMENT ALTERS AUDITORY RESPONSE

Normal rats rely on nicotinic acetylcholine receptors in the auditory cortex to process auditory information. Rats exposed to nicotine shortly after birth have damaged nicotinic acetylcholine receptors and develop compensatory sound-processing mechanisms. As a result, blocking the receptors with mecamylamine reduces auditory cortex responsiveness dramatically in normal rats, but only slightly in rats exposed to the drug as pups.



11 rats exposed to nicotine, however, learned to associate the tone with the shock, and they responded more slowly than the control animals. The remaining 5 nicotine-exposed rats moved to the safe chamber only after receiving the shock.

A Less Responsive Cortex

The UC-Irvine researchers' next experiment linked the nicotine-exposed rats' poorer responses to warning tones to a difference in the animals' brains.

The auditory cortex is the brain's primary area for interpreting sounds. Normally, nicotine amplifies the cortex's responsiveness to auditory inputs. Researchers measure this effect by comparing electrical activity levels in the cortex before and after an injection of the drug.

Using this protocol when their rats were 2 to 3 months of age, Dr. Metherate's team documented smaller increases in cortical activity levels, on average, in the animals with early exposure to nicotine than in the control animals. Among adult rats not exposed to nicotine as pups, a

stronger auditory cortex response to nicotine at 2 to 3 months of age correlated with faster and more accurate learning to associate sound with electrical shocks. These observations may provide a hint why rats' early nicotine exposure leads to later difficulty using warning tones.

Underdeveloped Receptors

The researchers next investigated the underlying mechanism for their nicotine-exposed rats' diminished cortical responsiveness. The findings indicated that nicotine exposure during early development prevents a key receptor in the brain's acetylcholine signaling system from achieving full functionality.

Nicotine binds to the same receptors as acetylcholine, a chemical that neurons in the auditory cortex and elsewhere use to transmit electrical excitation to neighboring neurons. "When nicotine or acetylcholine binds to a receptor on the surface of a nerve cell, the binding process sets off chemical reactions inside the cell that help the cell function properly and fulfill its special physiological role," Dr. Metherate says.

The researchers measured electrical activity in the auditory cortex before and after injecting 2- to 3-month-old rats with mecamylamine, a compound that shuts down the nicotinic acetylcholine (nACh) receptors. The injection markedly reduced electrical activity in normal rats but made little difference in the rats that had been exposed to nicotine shortly after birth. This finding indicates that their nACh receptors were ineffective.

"Somehow, early nicotine exposure disconnects the receptors from the inside of the cell," Dr. Metherate says. "Acetylcholine and nicotine bind to the cell surface, but no chemical reactions take place in the interior."

A Clue and a Caution

Because human and rat brains process sounds similarly, the UC-Irvine findings may relate to the problems that people prenatally exposed to nicotine have interpreting sounds, and the experimental results may provide a clue to effective treatments as well. "If we can figure out how to reconnect the receptors to the activity inside the cells, we may be able to reverse these auditory-cognitive deficits in children, adolescents, or even adults," Dr. Metherate says.

He adds that nACh receptors also play a role in the development of other parts of the brain, including cortical areas that process vision and touch. So, prenatal nicotine exposure may undermine brain activity in those areas as well.

"Even though Dr. Metherate's rats were exposed to nicotine for only 5 days, the damage to their brains was long-lasting," says Dr. Thomas Aigner of NIDA's Division of Basic Neuroscience and Behavioral Research. "This is important information for women who think that smoking only intermittently during pregnancy is safe for the fetus. If they smoke during a critical period of brain development, in this case a few days into the third trimester, it looks as though the nicotine exposure can produce serious and long-lasting damage."

Sources

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Brain Activity Differs in Cocaine Abusers According to Gender

Cocaine abusers have reduced neural activity in the orbitofrontal cortex (OFC), a brain region that mediates decisionmaking. NIDA-funded researchers have discovered that gender determines where in the OFC the dampening occurs.

Dr. Bryon Adinoff and colleagues at the University of Texas Southwestern Medical Center and the Veterans Affairs North Texas Health Care System measured OFC neural activity, as indicated by blood flow, of 35 people who had used cocaine for 12 years, on average, but had been abstinent for 2 to 4 weeks. They compared the results with measurements from 37 people who had never used the drug. The researchers found that the OFC contributed a smaller portion of total brain activity in cocaine abusers than in nonabusers. However, the relative deficit was in the lateral OFC in men and in the medial OFC in women.

“One can hypothesize that sex differences in regional blood flow may give rise to contrasting behavioral responses,” says Dr. Adinoff. Such differences might arise because the areas most affected in each gender support different behaviors. For example, brain scans of people who do not use drugs have suggested that the lateral OFC is active when people refrain from doing something that they anticipate will have a bad outcome. In contrast, the medial OFC engages when people take action to try to achieve a desired result.

The depressed neural activity in the lateral OFC among men who abuse cocaine may lead to problems putting the brakes on behaviors with bad outcomes and so hinder their ability to abstain, says Dr. Adinoff. The less active medial area in women may reflect a blunted drug reward, he adds.

While his findings are likely to be relevant for individuals in early abstinence, Dr. Adinoff notes that they may not apply to individuals in later stages of recovery. “The participants in our study had only been abstinent 2 to 4 weeks,” he says. “Scientists need to examine whether the depressed neural activity we observed among cocaine abusers recovers with long-term abstinence.”

“Future research might examine whether regional differences influence treatment strategies and recovery success,” notes Dr. Harold Gordon of NIDA’s Division of Clinical Neuroscience and Behavioral Research.

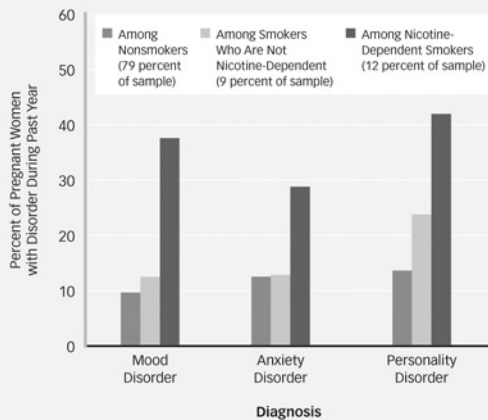
Dr. Adinoff concurs, suggesting that through understanding these differences, treatment providers may eventually be able to tailor gender-specific therapies that promote abstinence.

Source

- Adinoff, B., et al. Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Medicine* 3(3):206-222, 2006. **NN**

Nicotine Dependence is Linked With Mental Disorders in Pregnant Women

WHAT THE NUMBERS SAY



The link between mental disorders and nicotine dependence that had been previously observed in the general population also pertains to pregnant women, according to a U.S. survey that included 1,516 pregnant women. Taking into account important characteristics—including age, education, income, and marital status—associations appeared between nicotine dependence and having a mood, anxiety, or personality disorder. The presence of mental disorders may make smoking cessation particularly difficult. Smoking during pregnancy is of special concern because, according to prior research, it increases the risk of women having infants with low birth weight; such children subsequently face an elevated risk of health consequences and of learning and behavior problems.

SOURCE: An analysis of data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions reported in Goodwin, R.D., Keyes, K., and Simuro, N. Mental disorders and nicotine dependence among pregnant women in the United States. *Obstetrics and Gynecology* 109(4):875-883, 2007.

Reducing Postpartum Drug Use



In a recent clinical trial, a 20-minute computerized intervention reduced new mothers' drug abuse in the first 4 months postpartum. The computer software program, which was developed by Dr. Steven J. Ondersma and colleagues at Wayne State University in Detroit and Virginia Commonwealth University in Richmond, was administered in an urban obstetric hospital soon after each woman gave birth. The program features an animated narrator who asks questions, addresses ambivalence, provides feedback, and offers options. The intervention also included vouchers for an initial session of drug treatment and an easy-to-read brochure, mailed to the women after they took their babies home, that discussed infant and maternal health and briefly addressed drug abuse. The researchers estimated that the intervention had a "small to moderate" beneficial effect in their study population—107 mostly poor women who abused drugs. At a 4-month followup, those who received the intervention reported using cocaine, amphetamine, and opiates less frequently than before the birth, while the comparison group reported slightly increased abuse of these drugs. No definitive differences were observed between the two groups regarding marijuana use.

Source

- *American Journal of Preventive Medicine* 32(3):231-238, 2007. **NN**

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 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.

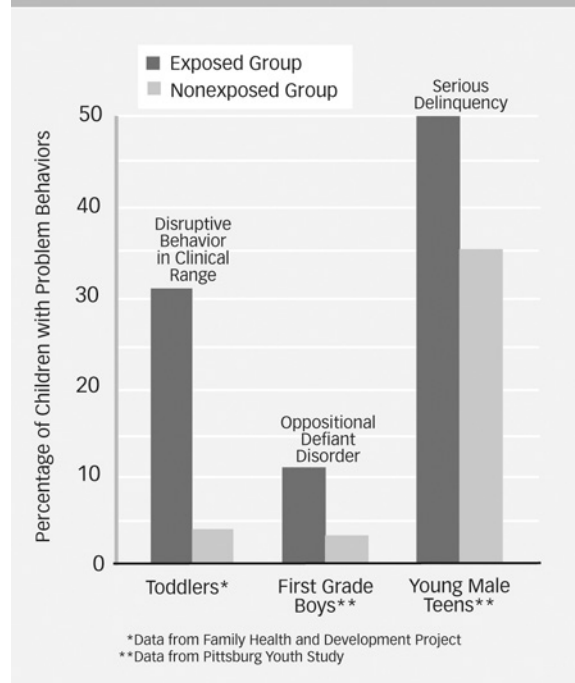
An Early Start to Disruptive Behavior

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

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.



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.”

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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- Wakschlag, L.S., et al. Elucidating early mechanisms of developmental psychopathology: The case of prenatal smoking and disruptive behavior. *Child Development* 77(4):893-906, 2006. **NI**

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. **NN**

Study Links Anabolic Steroids to Brain Changes in Adolescent Female Mice

Anabolic androgenic steroid (AAS) abuse, once largely limited to elite athletes, has spread to a wider population that includes adolescents along with adults, and girls as well as boys. While the psychological and behavioral consequences of AAS use presumably reflect its impact on a number of brain areas, a NIDA-funded study at Dartmouth Medical School has identified one neurobiological effect that has potentially important implications for the emotional stability and well-being of adolescent girls in particular.

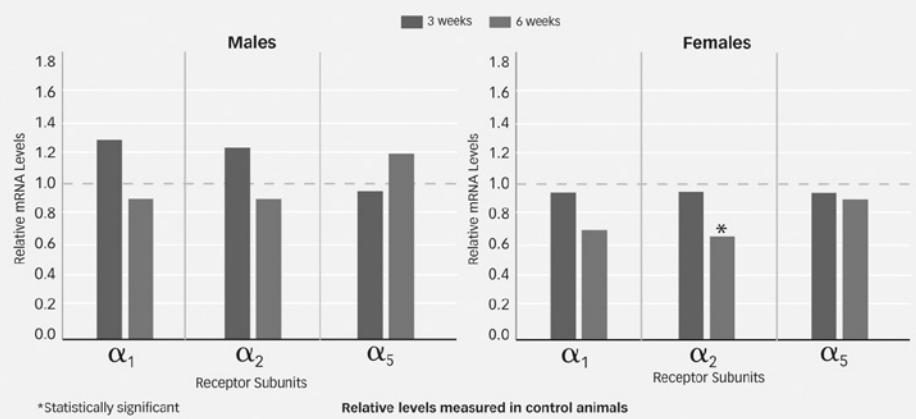
Principal investigator Dr. Leslie Henderson and colleagues studied the effect of the AAS, 17 α -methyltestosterone (17 α -MeT), on the activity of the neurotransmitter gamma-aminobutyric acid (GABA) in adolescent mice. Loosely speaking, GABA acts as a calming agent throughout the nervous system: It dampens activity of the neurons to which they are connected. Specifically, the researchers focused on the steroid's impact on GABA functioning in the medial preoptic area (MPOA) of the basal forebrain, a region that participates in the regulation of sexual behavior, anxiety, and aggression. They found that in female, but not male, animals the AAS interfered with GABA transmission in the area. Theoretically, this effect would reduce GABA's inhibitory influence and thus potentially contribute to the excessive emotions and behaviors seen in AAS abuse. Various studies have linked increased anxiety and aggression, and both increased and decreased libido to AAS use.

"The GABA system isn't the only target for the effects of AAS, but it is likely an important one," Dr. Henderson says. "Going into the experiment, we assumed we'd see an anabolic steroid effect on the GABA system in the MPOA and expected there would be differences between males and females." This area of the brain, particularly the cluster of neurons within it called the medial preoptic nucleus (MPN), is structurally different in the sexes.

Drug Targets Receptors

The researchers injected mice with a solution of 17 α -MeT in sesame oil, in doses (7.5 mg/kg/d) that would correspond to those taken by humans who are abusing

EFFECTS ON RELATIVE LEVELS OF GABA RECEPTOR mRNA The researchers measured the effects induced by anabolic androgenic steroids (AAS) on GABA_A receptor subunit mRNA levels for male and female mice treated with 17 α -MeT for 3 (blue) or 6 (purple) weeks. Six weeks of AAS exposure decreased the amount of one of the α subunits of the receptor α 2 only in female mice. No significant effects were observed in the treated male mice.



the drug heavily. They injected a control group of mice with the sesame oil vehicle alone. The researchers examined brain tissue from half the mice in each group after 3 weeks of treatment and from the other half after 6 weeks. They focused on the subunits that make up GABA type A receptors (GABA_A) in cells of the MPN and on the way that AAS exposure affected the function of these receptors. Each receptor contains five of these subunits, proteins that determine the receptor's sensitivity to drugs and hormones.

To test how the reduction in α 2 subunit production might affect GABA_A receptor function, the researchers measured the amplitude and frequency of inhibitory postsynaptic currents (IPSCs)—a measure of the receptor's efficacy in inhibiting the activity of neurons—in the MPN. Here, too, they found sex-based differences that were magnified by AAS. In untreated mice, the IPSCs were smaller in amplitude in females than in males. Female mice that received 3 to 4 weeks of AAS displayed smaller and less frequent currents than controls, suggesting that exposure to the drug had reduced GABA_A receptor function, thereby widening the gender gap. There was no comparable change in males.

The researchers concentrated on the α 2 subunit family, which earlier studies had shown that 17 α -MeT alters. Before treatment, levels of messenger RNA (mRNA) for the α 2 subunit were lower in female than in male mice in cells of the MPN. After 6 weeks, α 2 subunit mRNA—an

indicator of the quantity of the subunit being produced—had declined by 37 percent in female mice treated with the AAS compared with controls, but was essentially unchanged in males. When the researchers measured the actual protein that makes up the $\alpha 2$ subunit in female mice, they found a small but significant reduction (8 percent) in the number of neurons containing $\alpha 2$ protein.

Chronic exposure to the AAS augmented gender differences in both the structure and function of certain GABA receptors, Dr. Henderson says. “Overall, the effect was to decrease GABA transmission in the MPN of female, but not male, adolescent mice. This would presumably increase the level of activity or change the pattern of activity in postsynaptic neurons of the female mice.”

A Closer Look

How do these neurobiological changes contribute to the behavioral manifestations of AAS abuse? “It could be that an AAS that promotes aggression in males would promote it more in females, or have different effects on the expression of sexual behaviors, but this is something we are just beginning to explore,” Dr. Henderson says. “What’s more, there are 60 to 100 AAS, and their neurobiological effects are unlikely to be uniform. In time, we may be able to start parsing out whether certain commonly abused steroids are likely to amplify aggression and libido in women or in men while others affect both genders equally.”

Dr. Henderson notes that alterations in GABA_A receptor function could have other important effects as well. “The

GABA_A receptor is a major target of many drugs, including alcohol and benzodiazepines. Changing the subunit composition could alter the brain’s sensitivity to these chemicals.”

“Although this is a basic research study, its potential translation to humans, even if speculative, is striking,” says Dr. Pushpa Thadani, formerly of NIDA’s Division of Basic Neuroscience and Behavioral Research. “It demonstrates that AAS exposure in the adolescent period produces gender-specific changes at the molecular level that may be correlated with known behavioral outcomes.”

Although applying findings from this and similar studies in actual interventions remains a distant goal, “these studies advance our understanding of the actions of AAS on the brain and behavior, which can empower us to better educate the lay public on the harmful effects associated with abuse,” Dr. Thadani says. “The research is still in its infancy,” she observes. Other studies, now under way, are seeking to clarify the links between aggression in female mice and AAS-associated neurobiological changes. “When these findings are available, we’ll probably be in a better position to translate this information into the human arena.”

Source


- Penatti, C.A.A., et al. Sex-specific effects of chronic anabolic androgenic steroid treatment on GABA_A receptor expression and function in adolescent mice. *Neuroscience* 135(2):533-543, 2005. **NN**

Adolescent Inhalant Use Is Stable Overall, but Rising Among Girls

Almost 5 percent of girls between the ages of 12 and 17 used an inhalant to get high in 2005, an increase from 4.1 percent in 2002, according to a new report. Overall, inhalant use by boys and girls in this age group remained stable over the 4-year period, at an average annual rate of 4.5 percent, or an estimated 1.1 million adolescents.

The report, "Patterns and Trends in Inhalant Use by Adolescent Males and Females: 2002-2005," is based on an analysis of the 2002-2005 National Household Survey on Drug Use and Health, an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA, NIDA, and other federal agencies released the report at a March 15 press conference to kick off the 15th National Inhalants and Poisons Awareness Week, March 18-25.

"Young people who turn to inhalants may be completely unaware of the serious health risks," said NIDA Deputy Director Dr. Timothy P. Condon. "We know that inhalant abuse can start early, with research suggesting that even preadolescent children seek them out because they are easy to obtain. NIDA research also indicates that those who begin using inhalants at an early age are more likely to become dependent on them—and long-term inhalant abusers are among the most difficult drug abuse patients to treat."

The report is available at www.drugabusestatistics.samhsa.gov/2k7/inhalants/inhalants.pdf. 

Studies Focus on Acculturation and Hispanic Youth



U.S.-Born Hispanic Women Have More Drug Problems Than Immigrants: Among 19-to 21-year-old Hispanic women in South Florida, those born in the United States face a higher risk of drug addiction than immigrants, according to a recent study by Dr. R. Jay Turner and colleagues. The U.S.-

born women reported more acculturation, measured as preference for English over Spanish, and greater exposure to stressful events, both of which were associated with increased risk for addiction. The gap in acculturation between the two groups accounted for 40 percent of the risk difference; a high score on either acculturation or stress exposure was associated with a nearly three-fold increase in the odds of addiction, compared with low scores on those measures (evaluated at one standard deviation above and below average). The investigators speculate that cultural influences help protect foreign-born Hispanic young women from stress. Native-born and immigrant young men reported similar levels of stress exposure and had similar rates of addiction.

Source

- *Drug and Alcohol Dependence* 83(1):79-89, 2006.

Latino Parent Training: Men and women who completed a parent-training program adapted for Latino culture reported improvements in effective parenting practices and their children's (aged 13 years, on average) behavior compared with those who did not receive the intervention. Children whose parents received the program also reported that they were less likely to abuse tobacco, marijuana, and other drugs in the future. The parents also said their children's behavior improved.

Drs. Charles R. Martinez and J. Mark Eddy of the Oregon Social Learning Center randomly assigned 73 Spanish-speaking Latino parents (90 percent were of Mexican heritage) to participate in *Nuestras Familias: Andando Entre Culturas* (Our Families: Moving Between Cultures) or to receive no intervention. During each of 12 weekly 2.5-hour sessions, participants in the intervention group discussed developing effective family communication, bridging cultures, being positive, and encouraging success using appropriate discipline and limit setting, and practiced parenting techniques in role-play.

Source

- *Journal of Consulting and Clinical Psychology* 73(5):841-851, 2005. **NN**

Drugs Affect Men's and Women's Brains Differently

Gender appears to influence biological responses to nicotine, cocaine, and alcohol.

By Carl Sherman, *NIDA NOTES* Contributing Writer

Two recent NIDA-funded studies cast new light on men's and women's different responses to nicotine, cocaine, and alcohol. Dr. Steven G. Potkin and colleagues at the University of California (UC), Irvine, demonstrated that various brain regions are more strongly activated in women than in men while they perform certain tasks, and that nicotine equalizes the response. Dr. Elinore F. McCance-Katz and colleagues at the Medical College of Virginia found that women registered greater feelings of physical and mental well-being than men after receiving cocaine and had higher heart rates after drinking alcohol.

Brain Effects of Nicotine

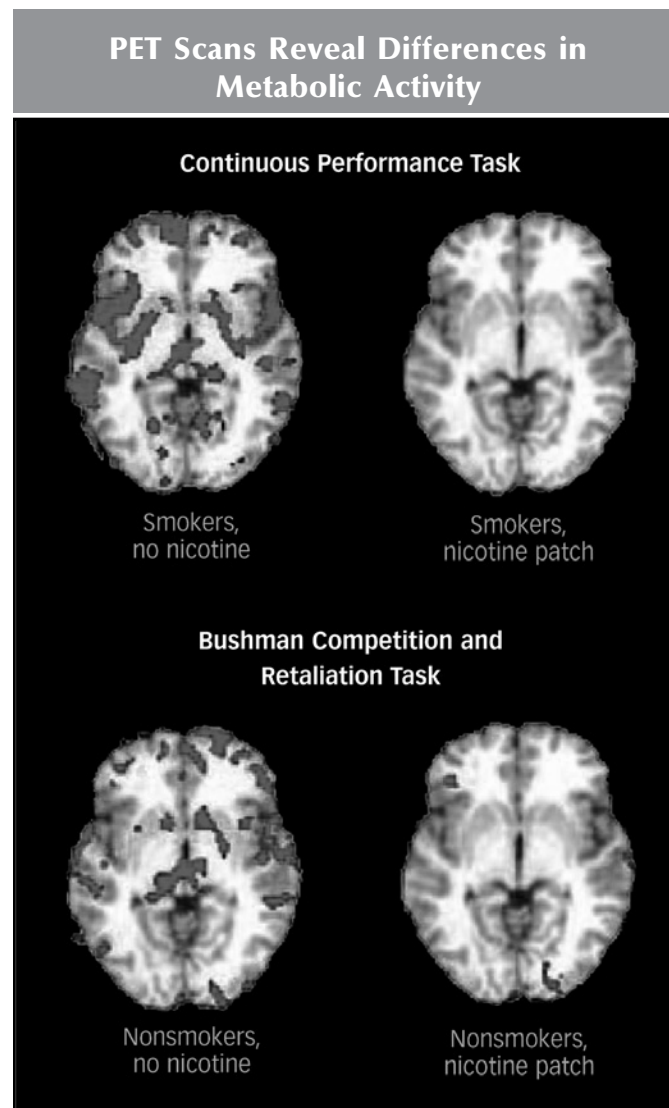
Men and women abuse the same drugs, but not always in the same ways. When women smoke cigarettes, they take shorter and fewer puffs and experience improvements in mood that men do not. Women generally are less successful in quitting. To the UC Irvine study team, these behavioral and experiential differences suggested that nicotine might affect men's and women's brains differently.

Using positron emission tomography (PET), the researchers tracked brain metabolism in 42 women and 77 men (55 smokers and 64 nonsmokers) while they performed two tasks. In the Continuous Performance Task (CPT), a test of vigilance, the study participant watched a series of numbers flashed on a screen and pressed a button when certain figures appeared. The objective of the Bushman Competition and Retaliation Task (BCRT) was to provoke an aggressive response: The participant and an unseen opponent (actually a computer) competed in a test of reaction time, with the loser receiving a blast of noise whose volume and duration were determined by the winner. When the participant lost, which was always the case in early rounds, he or she was shown the noise level that his or her opponent had set; when participants finally won, they could choose how loud and long to blast the opponent back. Participants performed each task once with a placebo patch and once with a transdermal nicotine patch.

When smokers performed the CPT wearing the placebo patch, women's brain metabolism was significantly higher than men's, particularly in the cortical and subcortical prefrontal systems—areas associated with choice, attention, executive function, mood, and memory. These differences largely disappeared when participants wore the nicotine patch: Brain metabolism increased for men and decreased

for women. Among nonsmokers, there was little difference in brain activity in men and women while performing the CPT, either with the nicotine patch or with placebo.

With the BCRT, in contrast, it was among nonsmokers that the male-female difference was most marked:



Red indicates brain areas where metabolic activity was higher in women than in men during the Continuous Performance Test and Bushman Competition and Retaliation Task. Exposure to nicotine greatly reduced the size of these areas, suggesting the drug's ability to neutralize gender differences in task-driven brain activity.

Reprinted from International Journal of Neuropsychopharmacology, Vol. 8(1): 511-528, Fallon, J. H., et al.: "Gender: A major determinant of brain response to nicotine," © 2005. Reprinted with the permission of Cambridge University Press.

Women's brain activity was higher in virtually all regions when the task was performed with placebo, but both sexes exhibited equal activity with nicotine. The gender disparity was smaller among smokers, and this, too, disappeared when they wore the nicotine patch.

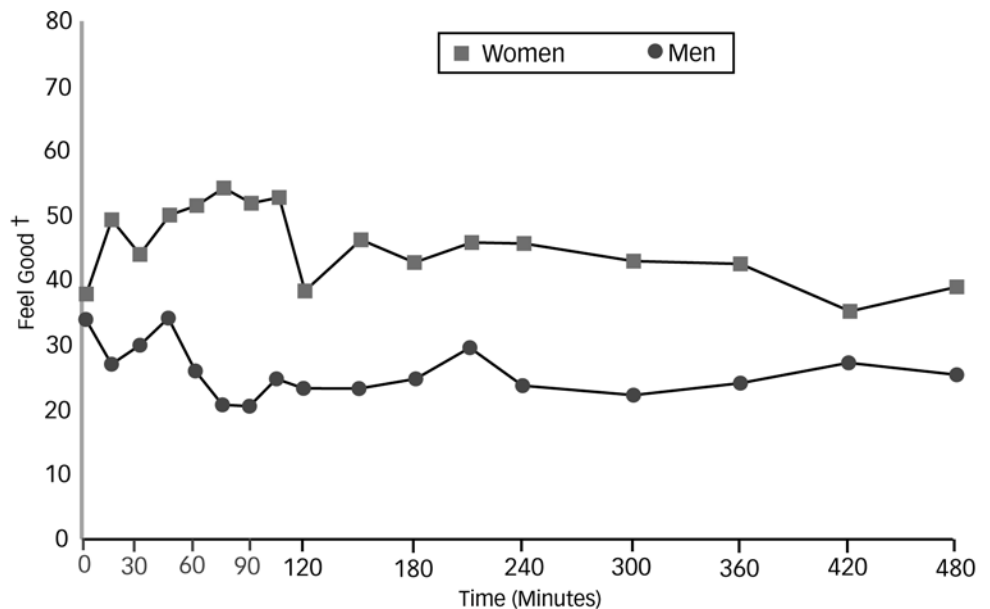
"Some effects of nicotine on brain metabolism was not due to the effects of chronic smoking, but rather a fundamental biological difference between men and women in their response to nicotine," Dr. Potkin says. "Everyone knew that there were differences in male and female smoking behavior and smoking rates, but assumed they were just cultural. Based on our findings, a more likely explanation is an interplay of cultural and biological differences. That provides an interesting starting point for devising gender specific interventions."

Effects of Alcohol, Cocaine, and Both Combined

Dr. McCance-Katz's study took as a starting point the observation that people frequently consume alcohol and cocaine simultaneously. "We wanted to understand why that might be and whether responses differed in men and women," says Dr. McCance-Katz.

In the double-blind study, nine men and eight women who were addicted to both cocaine and alcohol participated in three experiments performed on successive days. During the first, they received four 1 mg/kg intranasal doses of cocaine at 30-minute intervals, and two oral doses of alcohol 1 hour apart, in amounts calculated to maintain plasma alcohol concentrations of approximately 100 mg/dL; in the second, cocaine along with alcohol placebo; and in the third, alcohol along with cocaine placebo. The protocol was designed to approximate how cocaine and alcohol might be used together during a day-long binge, Dr. McCance-Katz says. The researchers monitored the participants' psychological and physiological status over an 8-hour period during and after the administration of the drugs.

"Feel Good" Ratings Differ by Gender



Women consistently rated their overall well-being higher than men after ingesting four 1 mg/kg doses of cocaine at half-hour intervals. The differences persisted long after the last dose.

By most measures, the men's and women's responses did not differ significantly. The researchers did note that women's hearts beat significantly faster than men's when given alcohol alone. Although men and women reported similar ratings of "rush," "any high," "cocaine high," "sad," "depressed," "nervous," or "paranoid" after taking cocaine, women consistently scored higher than men on "feel good"—a rating of combined mental and physical well-being—throughout an observation period starting with their first dose of cocaine and lasting until 6.5 hours after the last. On a scale from 0 to 100, the women's scores ranged from 36 to 54, whereas the men's ranged from a much lower 20 to 34, thus showing no overlap in scores. Gender differences in subjective response to cocaine and alcohol combined, or to alcohol alone, did not attain significance.

"We were a little surprised that women rated their well-being higher [after taking cocaine]," Dr. McCance-Katz says. In previous studies that involved single, somewhat larger doses, women had reported greater anxiety than men when they consumed cocaine. Although it is impossible to predict exactly how feelings of well-being might influence use of the drug, they could well increase the risk of toxicity, says Dr. McCance-Katz. "If you have a strong sense of good mental and physical well-being, you might not be attuned to the internal stimuli that signal

the need to stop.” Coupled with the fact that cocaine is the illicit drug most often cited by medical examiners in autopsies of female decedents, the finding underlines the importance of bringing more women into treatment and conducting further studies to explore which modalities are effective for women, she says.

Dr. Cora Lee Wetherington, Women and Gender Research Coordinator at NIDA, observes that Dr. McCance-Katz’s findings echo animal research showing that female rats exhibit higher levels of motivation for cocaine self-administration than male rats and may be particularly sensitive to the drug’s reinforcing effects. “The results of all these studies attest to the importance of not taking a unisex approach to the analysis of data,” comments Dr. Wetherington. “Otherwise, you could come up with averaged findings that don’t apply to men or women.”

Dr. Jamie Biswas, Chief of the Medications Research Grants Branch at NIDA, says that larger studies should explore why substances of abuse appear to elicit a greater perception of well-being among women. Future research might include women in diverse locales and situations and directly address whether they are more easily addicted or harder to treat than men.

Sources

- Fallon, J.H., et al. Gender: A major determinant of brain response to nicotine. *International Journal of Neuropsychopharmacology* 8(1):17–26, 2005.
- McCance-Katz, E.F., et al. Gender effects following repeated administration of cocaine and alcohol in humans. *Substance Use & Misuse* 40(4):511–528, 2005. **NN**

Community-Based Treatment Benefits Methamphetamine Abusers

A large California study finds favorable effects for inpatients and outpatients; women's gains are larger.

By Lori Whitten, *NIDA Notes* Staff Writer

Methamphetamine abusers can achieve long-term abstinence with the help of standard community-based drug abuse treatment. Nine months after beginning therapy, 87 percent of patients treated for heavy or long-term methamphetamine abuse in California outpatient and residential programs were abstinent from all drugs, according to a NIDA-supported analysis. "In the public dialogue, and even among professionals in the field, one sometimes hears that meth abuse is 'not treatable.' But that view is not borne out by recent clinical trials or our study, which shows that community-based treatment reduces drug abuse and other problems," says lead investigator Dr. Yih-Ing Hser.

Dr. Hser and colleagues at the University of California, Los Angeles analyzed data from the California Treatment Outcome Project (CalTOP), an ongoing study that has followed the progress of adult substance abusers treated at 43 outpatient and residential programs throughout the State since April 2000. The researchers focused on 1,073 patients who reported that methamphetamine abuse was their primary drug problem (572) or that they had abused the stimulant regularly for at least 1 year before beginning treatment (501). Most were in their 30s or younger, White or Latino, unemployed, and on public assistance; most had an arrest history. They had abused methamphetamine for about 9 years, on average, and nearly one-quarter (22 percent) reported injecting drugs at least once. Although 64 percent had children aged 18 or younger, one-third of parents did not live with their children in the month before beginning treatment. One parent in five reported that a child protection court had ordered that his or her children live with someone else, and 6.3 percent had their parental rights terminated by the State.

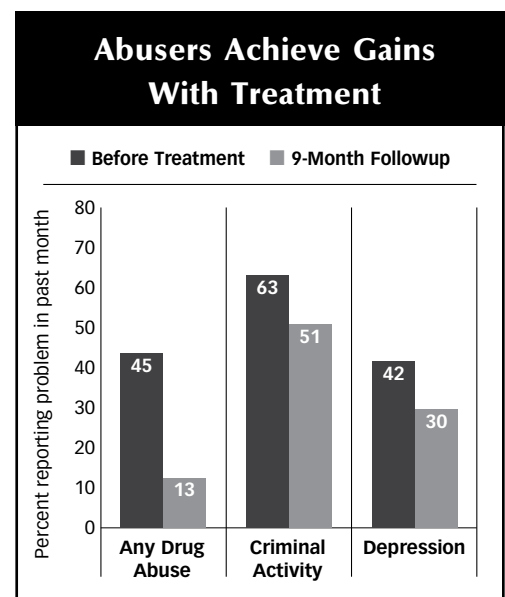
The patients received the addiction treatment services routinely provided by each program. These usually included group therapy, with an average of 69 drug-related and 51 alcohol-related sessions during the first 3 months of treatment. On average, the patients also received 22 sessions on dealing with mental health symptoms and 13 addressing psychosocial problems, including family, parenting, and employment.

More than 60 percent of the patients completed 3 months of treatment. Among all the patients in the study—those who finished 3 months and those who did not—the average reported frequency of methamphetamine abuse fell

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure."

from 2.7 to 0.5 days per month from the start of treatment to 9 months later. The portion who were abstinent from all drugs rose from 55 percent to 87 percent in the same interval, and 68 percent were abstinent and also not incarcerated. Patients improved in all areas—drug and alcohol abuse; mental health symptoms; and employment, family, and legal problems—except one: men's medical problems.

Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research says these findings should reassure professionals working in the



Nine months after methamphetamine abusers began addiction treatment, they had reduced past-month drug abuse and criminal activity, and fewer reported depression.

addiction, social services, and criminal justice fields that current therapies work for these troubled patients. “Dr. Hser’s findings suggest that treatments available in the community help meth abusers reduce drug abuse and start to get their lives back on track, echoing prior research,” he says.

Women’s Experiences

Dr. Hser’s findings confirm gender differences seen in other studies: Women began treatment with more severe psychosocial problems than men (see chart, right) and benefited more. Although treatment retention levels were similar for the two sexes, the women made greater gains in the areas of family relationships and medical problems, while achieving similar improvements in all other areas at the 9-month followup. The women’s better outcomes may have resulted in part from more intensive services (see chart below); as well, Dr. Hser says that many women in the study had a powerful motivator—family. “Many were trying to maintain or regain custody of their children by demonstrating improvement during treatment. Others had ‘hit bottom,’ saw how drug abuse was hurting their families, and decided to make a change,” she says.

“Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they

Men, Women Experience Different Problems			
Family and Social Circumstances	Women, % (n=567)	Men, % (n=506)	Total, % (N=1,073)
Children living with someone else by court order	29.3	9.9	20.1
Parental rights terminated	10.1	2.2	6.3
Family abused substances	21.7	10.5	16.4
Physically abused (past month)	5.5	1.8	3.7
Sexually abused (past month)	2.5	0.6	1.6
Employed	23.8	43.9	33.3
On public assistance	63.1	37.0	50.8
Criminal Justice System Involvement			
On parole	4.4	12.7	8.3
On probation	32.3	37.6	34.8
Ever arrested	76.7	88.3	82.2
Arrest in past year	36.7	45.1	40.6
Criminal activity (past month)	55.2	71.7	63.0
Psychiatric Symptoms (Past Month)			
Serious depression	38.8	29.8	34.6
Difficulties with understanding, concentrating, remembering	36.2	26.5	31.6
Suicidal thoughts	11.3	6.3	9.0
Prescribed psychiatric medicine	21.3	15.4	18.6

Women beginning treatment for methamphetamine abuse reported more psychosocial problems, while men reported more crime and criminal justice involvement.

may bear to the consequences of prenatal drug exposure,” says Dr. Hser. Dr. Hser and her colleagues continue to analyze CalTOP data, aiming to determine the longer-term impact of therapy and identify ways programs can improve outcomes. “Enhancing psychiatric, parenting, and employment services would better match patients’ needs, and my team plans to study the relationship between help for these problems and longer-term outcomes,” says Dr. Hser. They also plan to investigate whether women-only treatment is more effective for pregnant methamphetamine abusers than mixed-gender programs.

“The field needs more research following meth abusers over time to get a picture of the long-term outcomes of treatment, relapse episodes, and whether these patients require additional support to sustain gains made during therapy,” says Dr. Hilton. “Because the availability of community health and social services varies across States, we cannot generalize the findings from one State, such as California. We need data from across the country,” he adds.

Source

- Hser, Y.-I.; Evans, E.; and Huang, Y.-C. Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment* 28(1):77-85, 2005. **NN**

Women Receive More Services in Some Areas

Services	Women (No. of interventions [†])	Men (No. of interventions [†])
Employment*	4.6	2.3
Family [‡]	6.5	4.6
Mental Health [‡]	23.6	19.9
Parenting*	4.2	1.7

[†]Includes counseling sessions, medical appointments, and prescriptions. *Outpatients. [‡]Outpatient and residential.

For some problems, women received more services than men during the first 3 months of treatment.

Dr. Hser and her colleagues continue to analyze CalTOP data, aiming to determine the longer-term impact of therapy and identify ways programs can improve

Studies Identify Factors Surrounding Rise in Abuse of Prescription Drugs by College Students

By Lori Whitten, NIDA NOTES Staff Writer

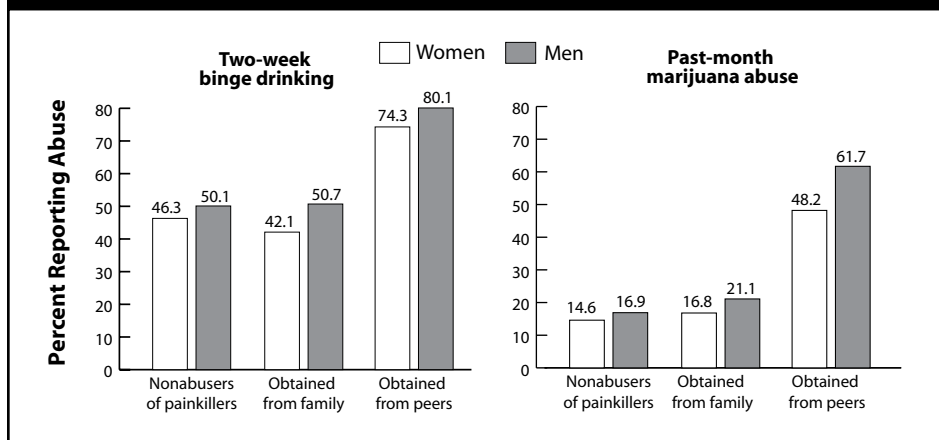
Prescription drug abuse among students in U.S. colleges and universities has been rising for several years. The 2004 Monitoring the Future (MTF) Survey of College Students and Adults—the most recent data available—estimated that 7.4 percent of college students used the painkiller hydrocodone (Vicodin) without a prescription in that year, up from 6.9 percent in 2002, with similar increases for other opioid medications, stimulants, and sedatives. Three new NIDA-funded studies reveal which students and campuses have the highest rates of abuse and connect such abuse to other unhealthy behaviors. According to the research, rates of collegiate prescription stimulant abuse are highest among men, Whites, fraternity/sorority members, and at schools in the Northeast.

Stimulant Abuse Nationwide

Dr. Sean Esteban McCabe and colleagues at the University of Michigan and Harvard University analyzed the answers from the Harvard School of Public Health College Alcohol Study, which in 2001 surveyed 10,904 randomly selected students enrolled at 119 colleges across the United States. Overall, 4 percent of the respondents reported having taken a stimulant medication without a prescription at least once during the previous year. Men were twice as likely as women (5.8 percent versus 2.9 percent) to have abused methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and amphetamine/dextroamphetamine (Adderall). Stimulant medication abuse was also more prevalent among students who were:

- White (4.9 percent versus 1.6 percent for African-Americans and 1.3 percent for Asians);
- Members of fraternities or sororities (8.6 percent versus 3.5 percent for nonmembers); and
- Earning lower grades (5.2 percent for grade point average of B or lower versus 3.3 percent for B+ or higher).

Binge Drinking, Marijuana Abuse Are Elevated Among Students Who Obtain Painkillers From Peers



At one university, students who obtained prescription painkillers from peers reported higher levels of binge drinking and marijuana abuse than nonabusers or those who received painkillers from family.

Students who abused prescription stimulants reported higher levels of cigarette smoking; heavy drinking; risky driving; and abuse of marijuana, MDMA (Ecstasy), and cocaine. Compared with other survey respondents, for example, they were 20 times as likely to report past-year cocaine abuse and 5 times as likely to report driving after heavy drinking.

The campus prevalence of past-year stimulant abuse ranged from 0 percent at 20 colleges—including the three historically African-American institutions included in the survey—to 25 percent. The prevalence was 10 percent or higher at 12 colleges. Students attending colleges in the Northeast, schools with more competitive admission standards, and noncommuter schools reported higher rates of abuse.

One University's Painkiller Picture

At a large Midwestern university, about 9 percent of 9,161 undergraduates surveyed had taken a prescription pain medication without a doctor's order at least once during the past year; 16 percent reported such abuse in their lifetime. Of the latter, 54 percent said they had obtained the drugs from peers, while 17 percent said their source was a family member. Dr. McCabe and colleagues

at the University of Michigan Substance Abuse Research Center found that students who obtained medications from peers were more likely to smoke and drink heavily and to have abused other substances—including marijuana, cocaine, and other illegal drugs—than those who obtained them from family members.

The researchers found that exposure to prescription pain medication early in life increased the likelihood of abuse in college. Women who had received prescriptions for pain relievers in elementary school were more than four times as likely as those with no prescribed use to report abuse in the past year. Men with early prescribed use were twice as likely as those without to report such abuse. In addition:

- Women students were more likely to be prescribed pain medication, while men were more likely to be approached to sell or give away prescribed medication.
- More men obtained the drugs from peers while more women obtained them from family members.
- Past-year prescription painkiller abuse was higher among fraternity members than nonmembers (17 percent versus 9 percent) and among sorority members compared with nonmembers (9.6 percent versus 8.6 percent).

“Students abuse prescription drugs to get high, to self-medicate for pain episodes, to help concentrate during exam time, and to try to relieve stress. Regardless of the motivation, people need to know the risks of abuse and the dangers of mixing drugs,” says Dr. Lynda Erinoff, formerly of NIDA’s Division of Epidemiology, Services and Prevention Research. Most people assume that if a medication is available on the market, it must be safe—even if it has not been prescribed for them, says Dr. Erinoff, “but a drug or dose that a doctor orders for one person is not necessarily appropriate for another, and prescription abusers are potentially taking a serious risk.” NIDA continues to work with doctors and pharmacists and to link prevention specialists with researchers focusing on the problem. “Educating the public remains a critical challenge,” says Dr. Erinoff.

Membership Matters

Based on responses from more than 5,000 young people who participated in the MTF when they were high school seniors in 1988 to 1997, and also when they were in college, Dr. McCabe and his Michigan colleagues found that active members of college fraternities or sororities engage in more heavy episodic, or “binge,” drinking, cigarette smoking, and marijuana abuse than nonmembers.

The students who joined fraternities or sororities in college were the same ones who reported the highest levels of substance abuse in high school. Moreover, cigarette smoking, binge drinking, and drug abuse increased for all survey participants as they progressed through college. Fraternity and sorority members showed greater elevations in binge drinking and marijuana abuse over time compared with nonmembers. The picture that emerges is of students who are already heavy drinkers when they come to college selecting fraternities and sororities with a reputation for “party-ing” and then, as members, further increasing their drinking in an environment that supports the behavior.

“It’s important for each student to explore, perhaps with counseling, a possible mismatch between his or her college environment and individual

needs. Some students benefit from settings that emphasize socialization outside of the party scene; these might include group living arrangements based on shared academic or extracurricular interests,” Dr. McCabe says.

Stimulant Abuse Varies by Campus Characteristics	
Selected Characteristics	Past-year Stimulant Abuse Rates, %
Admission criteria	
More competitive	5.9
Competitive	4.5
Less competitive	1.3
Geographical region	
Northeast	6.3
South	4.6
West	3.2
North Central	2.8
Commuter status	
Noncommuter school	4.6
Commuter school	1.2

Students enrolled in the most selective colleges reported relatively high levels of past-year stimulant abuse, as did those attending schools in the Northeast. Residential schools reported higher rates than commuter colleges.

Sources

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- McCabe, S.E., et al. Selection and socialization effects of fraternities and sororities on US college student substance use: A multi-cohort national longitudinal study. *Addiction* 100(4):512-524, 2005.
- McCabe, S.E.; Teter, C.J.; and Boyd, C.J. Illicit use of prescription pain medication among college students. *Drug and Alcohol Dependence* 77(1):37-47, 2005. **NN**

Weighing Nicotine Replacement



Postmenopausal women using the nicotine patch gained less weight during their first 2 weeks of abstinence from smoking than women on placebo, even though they consumed more total calories and fat and had the same level of physical activity. In one of the first studies to address the challenges older women face when they try to quit smoking, Dr. Sharon Allen and colleagues at the University of Minnesota also found that the simultaneous use of hormone replacement therapy by participants did not affect the results. One-third of women over age 45 smoke, and researchers are looking for strategies to help them quit. Fear of weight gain can be a serious barrier to quitting, particularly during the menopausal period when women typically gain a few pounds. **NN**

Source

- *Addictive Behaviors* 30(7):1273-1280, 2005.

Disulfiram May Work for Men, but Not Women

Researchers studying disulfiram, an “old” medication for alcoholism that has emerged as a potential “new” treatment for cocaine abuse, have found a possible sex difference in treatment response: Cocaine-addicted men who were treated with the medication had better outcomes than those who were not, whereas women showed no significant difference in outcome.

Dr. Kathleen Carroll of Yale University School of Medicine and her colleagues have conducted several studies on the medication’s effects on cocaine abuse and have moved on to the next step—determining which types of patients benefit from the treatment. There were not enough women in their recent study (see “Disulfiram Reduces Cocaine Abuse, *NIDA Notes*, Vol. 20, No. 2”) to analyze sex differences, so the investigators combined data from two of their other treatment studies to compare men’s and women’s responses to disulfiram. “We know that men and women react to cocaine differently. For example, women progress more quickly to cocaine addiction than men. Sex differences in treatment response seemed likely,” says Ms. Charla Nich, lead investigator of the study.

In one study, the investigators treated alcohol- and cocaine-addicted patients with disulfiram and various behavioral therapies; in the second, they tested disulfiram in opioid- and cocaine-addicted patients under treatment

with methadone. Altogether, 191 patients participated in the studies, which, when combined, had enough women (36 percent) to permit a valid comparison.

Both studies found that patient groups taking disulfiram reduced cocaine abuse compared with groups receiving placebo. But when the investigators combined and reanalyzed the data, they found that only the men in the groups responded to the medication. The reanalysis indicated that men treated with disulfiram produced a higher percentage of drug-free urine specimens than men in the placebo groups (49 versus 30 percent). Among women, however, the percentage of drug-free specimens was not significantly different with disulfiram or placebo (38 versus 39 percent).

“Our data don’t conclusively prove a sex difference in the response to disulfiram,” says Ms. Nich. “For that, we need studies that directly compare men and women taking the medication.” NIDA’s Dr. Dorynne Czechowicz agrees that researchers should follow up on these intriguing preliminary findings, which “highlight the importance of paying attention to sex differences in medication development and other drug abuse research.”

Source

- Nich, C., et al. Sex differences in cocaine-dependent individuals’ response to disulfiram treatment. *Addictive Behaviors* 29(6):1123-1128, 2004. **NN**

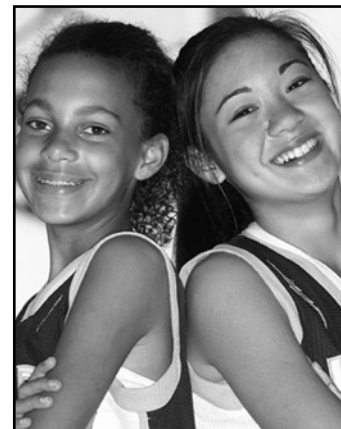
ATHENA Program Reduces Substance Abuse by Girls on High School Sports Teams

By Patrick Zickler, NIDA NOTES Staff Writer

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

In the ATHENA program, developed at the Oregon Health & Science University in Portland by Drs. Diane

Elliot and Linn Goldberg, selected team leaders receive a 90-minute orientation and then conduct discussion and activity sessions during scheduled team practices. Each team leader works with a squad of approximately six teammates, following a manual that is much like a playbook, with scripts for eight 45-minute sessions dealing with the harmful consequences of substance abuse and other unhealthy behaviors and the beneficial effects of good diet and exercise. Along with providing information, the workbook engages the girls in activities such as critiquing magazine advertising and other



media influences on self-image; classifying various foods according to carbohydrate, fat, and protein content; and determining the best balance of dietary fuels for athletic training and competition. Each ATHENA athlete uses a pocket-sized nutrition and training guide to monitor diet and exercise. Coaches and other staff members receive an orientation to assist the team leaders as timekeepers and facilitators for the sessions.

To evaluate ATHENA, the researchers recruited 40 girls' sports teams in 18 public high schools in northwest Oregon and southwest Washington. Teams from half the schools followed the ATHENA program. The other

ATHENA's Impact on Behavior and Nutrition

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

Data are significant differences expressed as the mean.

*Scored using a seven-item agreement scale ranging from 1 (strongly disagree) to 7 (strongly agree).

**Scored 0 to 4 for times occurred with 0 indicating none; 1, once; 2, two or three times; 3, four or five times; or 4, six or more times.

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

teams received printed information about eating disorders, substance abuse, and sports nutrition, but did not take part in discussion or group activities. Before the first practice of their sports season and again within 2 weeks after the season ended, each girl filled out a questionnaire about her eating patterns; nutritional awareness; use of diet pills, amphetamines, anabolic steroids, and muscle-building supplements; and other health-related behaviors.

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

Adolescent girls experience social and cultural pressure about body image, and they look to each other for role models more than they follow the guidance offered in classrooms, research has shown. The competitive environment of athletic programs may compound the pressure, leading to disordered eating and the use of body-shaping substances such as steroids, diuretics, laxatives, and even

tobacco, Dr. Elliot says. However, the athletic environment can exert positive peer pressure also. The researchers modeled ATHENA's use of sports teams as a forum to promote healthy lifestyles on a similar program they developed for male high school athletes (see "Like ATHENA, ATLAS Targets High School Athletes"). "We found that the team-based approach used in ATLAS [Athletes Training and Learning to Avoid Steroids] produced greater positive change than did a more conventional classroom-style approach," Dr. Elliot says.

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

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

Source

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

Like ATHENA, ATLAS Targets High School Athletes

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

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



Smoking Exposure *In Utero* Increases Risk of Later Addiction

By Arnold Mann, *NIDA NOTES* Contributing Writer

An expectant mother's smoking during pregnancy does not increase the likelihood that her child will later try smoking or become a regular smoker. Her pack-a-day smoking, however, doubles the risk that if her child does become a smoker, he or she will become addicted to tobacco, according to the first study to examine rates of tobacco addiction in adults who were prenatally exposed.

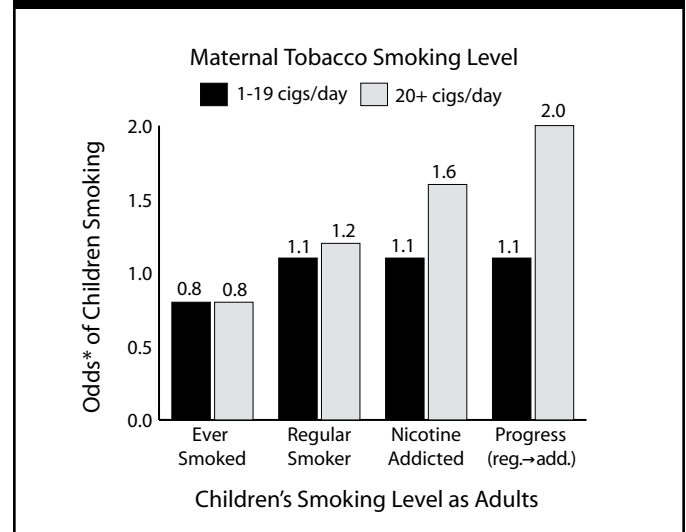
The study was led by Dr. Stephen L. Buka of the Harvard School of Public Health in Boston and cosponsored by the National Cancer Institute, the National Institute of Mental Health, the Robert Wood Johnson Foundation, and NIDA. Dr. Buka, together with Drs. Edmond D. Shenassa and Raymond Niaura, both of Brown Medical School in Providence, Rhode Island, collected data from 1,248 individuals aged 17 to 39. All the study subjects' mothers had participated in the Providence cohort of the National Collaborative Perinatal Project (NCP) between 1959 and 1966. As part of the NCP, pregnant women provided information about their smoking and gave blood samples for measuring nicotine levels.

Among the men and women in the new study, 62 percent had smoked regularly and 45 percent met the medical criteria for tobacco dependence at some time in their lives. The criteria, as defined by DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Revision III), include persistent, unsuccessful attempts to quit or control smoking, continued use despite smoking-related problems, and smoking to reduce withdrawal symptoms. Thirty-eight percent were born to mothers who did not smoke, 25.6 percent to mothers who smoked less than a pack a day, and 36.4 percent to mothers who smoked a pack or more per day at some point during pregnancy.

Among children who had smoked at least once, those whose mothers smoked up to a pack a day during pregnancy had a 20 percent higher, and those whose mothers smoked a pack a day or more had a 60 percent higher odds of having at some time been addicted to tobacco, compared with those whose mothers had not smoked. Among children who had at some time in their lives smoked daily for a month or more, those exposed *in utero* to a mother's pack-a-day smoking had double the odds of progressing to addiction.

"The evidence from this study, which reinforces the findings of experimental research with animals, is compel-

Heavier Maternal Smoking During Pregnancy Increased Children's Odds of Nicotine Addiction as Adults



Children of women who smoked at least 20 cigarettes a day during pregnancy were more likely to become addicted to nicotine or progress from regular smoking to nicotine addiction as adults compared with children of women who smoked fewer than 20 cigarettes a day. Children of heavier smokers were no more likely to try smoking or to smoke regularly than children of lighter smokers.

ling," says Dr. Buka. "Early exposure to tobacco during pregnancy apparently affects the individual's response to cigarettes in later adolescence and adulthood."

The researchers' statistical analyses indicated that the associations between maternal smoking during pregnancy and offspring's future smoking were independent of socioeconomic status, maternal age at pregnancy, offspring sex, and offspring age at the time of the interview. What's left, then, is a biological factor. "The most likely hypothesis is that the toxins in cigarettes cross the placental barrier and interact with the genes that control cell differentiation, permanently altering cells' responsiveness in ways that increase vulnerability to tobacco addiction," Dr. Buka says.

The cross-generational impetus to tobacco addiction documented by the study is a serious national health concern. Almost half of women who smoke continue to do so when they become pregnant, says Dr. Buka. The smoking mothers-to-be constitute about 12 percent of women who give birth—a national potential for 500,000 prenatal exposures every year.

The researchers also collected information about the study participants' marijuana abuse and found no tie to prenatal nicotine exposure. This suggests, the investigators say, that the “pathophysiological pathway” that promotes vulnerability to tobacco addiction among offspring differs from the pathway that leads to marijuana addiction.

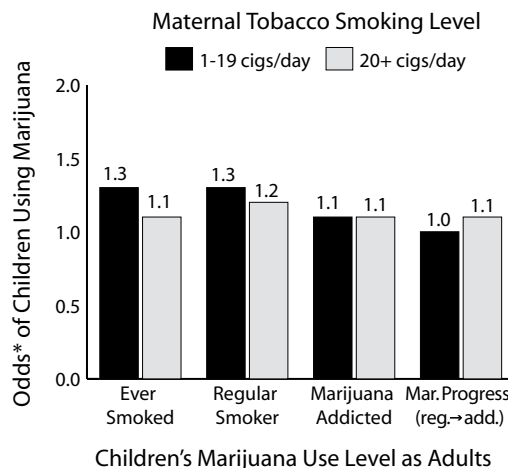
The study confirms the need for energetic efforts to deter women from smoking, especially during pregnancy, says Dr. Kevin Conway, deputy chief of NIDA's Epidemiology Research Branch. Preventing smoking by pregnant women will improve nicotine addiction rates of the next generation. “This study highlights opportunities for physicians to intervene with mothers who smoke, for the health of themselves and their children,” says Dr. Conway.

“Healthy-baby prenatal visits, labor and delivery, and postnatal-care visits are golden opportunities for providers to offer assistance to quit smoking and prevent relapse, thereby reducing the risk of children's progression to nicotine addiction,” says study coauthor Dr. Niaura. “Health care providers must take advantage of every opportunity to ask, advise, and assist patients in efforts to quit smoking.”

Source

- Buka, S.L.; Shenassa, E.D.; and Niaura, R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: A 30-year prospective study. *American Journal of Psychiatry* 160(11):1978-1984, 2003. **NN**

Maternal Tobacco Smoking During Pregnancy Did Not Affect Children's Odds of Marijuana Use as Adults



* Odds ratio, calculated by dividing the odds of the children in the maternal smoking group by the odds of those with nonsmoking mothers.

The finding that in utero exposure to tobacco did not affect later marijuana use indicates that the two drugs have different physiological pathways.

Men and Women May Process Cocaine Cues Differently

By Lori Whitten, NIDA NOTES Staff Writer

Some aspects of cocaine addiction and recovery are different for men and women—including the reasons for seeking drug rehabilitation, response to treatment, and vulnerability to relapse. Women are more likely to seek cocaine abuse treatment in response to co-occurring depression, remain abstinent after treatment, and relapse in response to interpersonal problems and negative feelings. Cocaine-addicted women also demonstrate greater craving than men in response to drug cues. In the first brain imaging study of cocaine craving by cocaine-addicted women, NIDA-funded researchers have made observations that, if borne out in larger studies, may point to neurological sources of these differences.

Dr. Clinton Kilts and colleagues at the Emory School of Medicine in Atlanta used positron emission tomography (PET) to measure drug-craving-related changes in regional cerebral blood flow—a correlate of neural activity—in eight cocaine-addicted African-American women aged 35 to 46. The women had abstained from cocaine use for 1 to 14 days and reported frequent periods of cocaine craving in the 30 days preceding the study. While lying in the PET scanner, each woman listened to a 1-minute recording of a script describing her personal experiences of acquiring the drug and anticipating sensations associated with taking cocaine. Each patient's script was derived from her own answers to an autobiographical questionnaire and narrated in the first person: "...I start thinking about how good it's going to feel to take that first hit...with my eyes wide open I take my lighter out of my pocket, put it to the stem, and get ready to take that first, good blast...."

The researchers injected each woman with a radiotracer and took pictures of the blood flow in her brain as she listened to the script and relived the scene in her mind. After each brain scan, the women rated the urge to use

Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People
(Cocaine-use imagery compared with neutral imagery)

Brain Region	Putative Role in Behavior	Activity Changes During Cocaine Craving	
		Men	Women
Right nucleus accumbens	Processes anticipated and attained rewards—probably contributes to the expectation of pleasure during craving	Increased activity	Increased activity
Amygdala	Generates and regulates emotional responses; assesses the positive or negative value of experiences and forms associations between experiences and emotional consequences	Increased activity	Decreased activity
Dorsal anterior cingulate cortex	Monitors competing options, inhibits goal-inappropriate behavior, and plans movements related to obtaining rewards; activity influenced by past experiences—possibly provides cognitive control of drug-seeking behavior	Increased activity	Increased activity, greater than that of men
Ventral anterior cingulate cortex	Regulates emotional response to cocaine cues; activation may precede craving onset	Increased activity	Increased activity, less than that of men
Frontal cortex	Monitors relationship of drug cue to drug availability; provides inhibition or control over actions; activity influenced by past experiences—possibly counter-regulates emotional input	Increased activity	Increased activity, greater than that of men

cocaine, vividness of the mental image, and their emotions. They repeated this process twice.

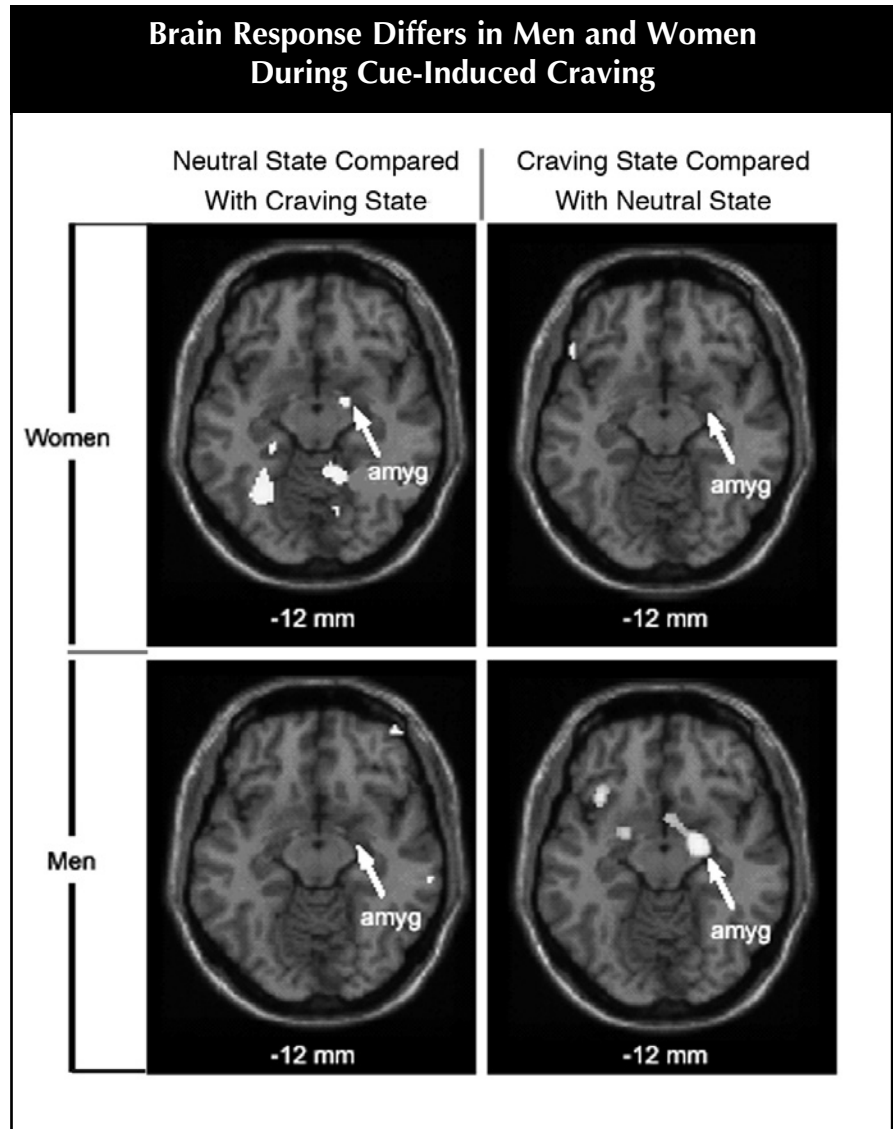
The women also underwent imaging in three control situations: resting, listening to a script of a personal experience in nature, and listening to a script designed to provoke anger. The researchers verified that the mental imagery of the cocaine-related script induced a greater urge to use cocaine than the nature or anger script. By comparing the brain scans produced in response to the different scripts, the researchers were able to evaluate cerebral blood flow while the women were craving cocaine versus when they were relaxed and not thinking of the drug. The procedure also distinguished changes related to craving from

those that might simply reflect strong general emotional reactions (as in the anger-inducing script). To examine possible sex differences in the neural representation of cocaine craving, the investigators compared the findings in women with results from eight cocaine-addicted men of similar ages and backgrounds who experienced the same process.

In both men and women, cue-induced cocaine craving activated several brain areas involved in determining a cue's reward value and controlling reward-related behaviors, including the right nucleus accumbens—a structure that seems to produce the expectation of pleasure during drug craving (see table, "Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People"). "These common activations suggest that both sexes may process cocaine-use memories—mental images that are associated with strong emotions—as cues that guide reward-based decisionmaking," says Dr. Kilts. However, men and women also showed some dissimilar neural responses to cocaine cues. Most notably, activity of the amygdala—a structure that assesses whether an experience is pleasurable or aversive and connects the experience with its consequences—fell in women during cocaine craving. "This finding is notable because our study and others have shown cue-induced amygdala activation in men," says Dr. Kilts. "Reduced neural responses in the amygdala may result from greater activation of the frontal cortex in women. The frontal cortex inhibits the activity of structures involved in emotional responding to drug cues, and our observations were consistent with previously reported sex differences in frontal cortical areas."

"As a field, we need more and better controlled studies of sex differences in factors that cause relapse," says Dr. Kilts. Combining imaging technologies in the same study—for example, PET with magnetoencephalography—would improve the localization of neural activity. "We could better define the neural responses that occur before, during, and after drug cues—illuminating the temporal sequence of the craving experience in men and women," he says.

"This research reveals that men and women differ in a critical brain area in their responses to cocaine craving," says Dr. Steven Grant of NIDA's Division of Clinical



These PET scans show differences in blood flow between a neutral state and a cocaine-craving state. White areas indicate an increase in blood flow. Most notable is the decrease in blood flow in the women's amygdala (top right panel) during craving; men show an increase in blood flow during craving (bottom right panel).

Neuroscience, Development, and Behavioral Treatments. "Differences in the amygdala may indicate that male and female abusers crave the drug for different reasons or hope to achieve different results from taking the drug. Imaging studies that examine gender differences in specific behavioral aspects of drug craving will provide insight on how to tailor treatment programs to meet the needs of men and women."

Source

- Kilts, C.D.; Gross, R.E.; Ely, T.D.; and Drexler, K.P.G. The neural correlates of cue-induced craving in cocaine-dependent women. *American Journal of Psychiatry* 161(2):223-241, 2004. **NN**

Conference Provides Overview of Consequences of Prenatal Drug Exposure

By Patrick Zickler, *NIDA NOTES* Staff Writer

On March 23 and 24, NIDA-supported investigators met in Bethesda, Maryland, to discuss long-term consequences of prenatal exposure to drugs. The conference, “Long Term Follow-up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities,” was cosponsored by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Health’s Office of Research on Women’s Health. The meeting brought together more than 100 researchers involved in studying the impact of prenatal exposure to drugs on children. Conference participants described recent findings and discussed research techniques and technology that can make the most effective use of the research cohorts recruited in the past two decades.

“NIDA has long recognized the importance of studies that can follow the development of children from before birth through adolescence and early adulthood,” said Dr. Vincent Smeriglio of NIDA’s Division of Clinical Neuroscience, Development, and Behavioral Treatment. “For example, NIDA supports the Ottawa Prenatal Prospective Study, which began in 1978 and has examined the impact of prenatal tobacco and marijuana use on offspring who are now in their early twenties,” continued Dr. Smeriglio. “Other research projects, such as those

designed to examine the effects of MDMA [Ecstasy] and methamphetamine over similarly long developmental periods, are just getting under way.” In all, NIDA’s prenatal drug research involves 24 studies and thousands of prenatally exposed offspring (see “Summary of Current Prenatal Studies”).

The largest longitudinal study of prenatal drug exposures is the Maternal Lifestyle Study (MLS), an interagency collaboration cosupported by NICHD. “This study involves more than 1,300 children who now are entering adolescence,” observed NICHD Director Dr. Duane Alexander. “MLS has allowed us to look at the effects of prenatal cocaine exposure as well as the longer term effects of a



postnatal environment involving drug abuse. The study has made significant contributions to the field of developmental science, and following these children even longer will help us assess more fully the impact of drugs on development.”

“To move forward in every aspect of prevention and treatment, we must build on our knowledge of what impact drugs have on development and on vulnerability,” said NIDA Director Dr. Nora Volkow. “That is why the focus of the research we’re discussing at these meetings is so important. It is crucial to study the effects of drugs at the earliest stages of brain development, while the fetus is still in the womb.” **NN**

Summary of Current Prenatal Studies

Studies	Total Sample (Range in Study Size)	Current Age Range
Cocaine 14 studies	5,936 (224-1,388)	1 month to 16 years
Tobacco 5 studies	1,108 (100-413)	Newborn to 24 years
Opiates 1 study	100	14 years (at final evaluation)
Marijuana 2 studies	719 (155-564)	18 to 24 years
Methamphetamine 1 study	508	Newborn to 12 months
MDMA (Ecstasy) 1 study	150	Newborn to 24 months

Researchers Adapt HIV Risk Prevention Program for African-American Women

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

The HIV/AIDS epidemic has taken a disproportionate toll on racial and ethnic minority populations, especially women. In its surveillance report on the number of Americans living with HIV/AIDS in 2002, the Centers for Disease Control and Prevention estimates that among women with HIV/AIDS, non-Hispanic African-American women outnumbered non-Hispanic white women by three to one—a racial disparity not found among men.

African-American drug-using women were addressed in two recent studies by NIDA-funded researchers in Atlanta. Dr. Claire E. Sterk of Emory University, Dr. Kirk W. Elifson of Georgia State University, and colleagues developed and tested gender-tailored, culturally specific adaptations of a standard NIDA HIV prevention intervention. They found that female African-American injecting drug users (IDUs) and crack cocaine users who received either of two targeted 4-week prevention programs reduced their risk behaviors related to drug taking

and sex more than did women who received the standard intervention.

“These studies are examples of research that is responsive to community needs,” says Dr. Dionne Jones of NIDA’s Center on AIDS and Other Medical Consequences of Drug Abuse. “When it comes to designing a prevention program, it’s not one-size-fits-all. You have to consider social context, be culturally sensitive and appropriate, and tailor your message to the group.”

The researchers’ goal was to develop culturally appropriate programs grounded in the reality of the daily lives of women most at risk and the difficulties they face in their individual, social, family, and sexual relations and activities. “We worked hard to develop interventions with input from this target population, deliver the interventions in a setting where they feel comfortable, and involve them in planning, implementing, and evaluating the interventions,” says Dr. Sterk.

Over 1 year, using one-on-one interviews and small focus groups, the researchers sought to define the key issues in the women’s lives and identify ways to address those issues, including such factors as gender dynamics, economic stressors, gender-specific norms and values, and power and control. Two interventions came out of this research phase. One, a motivation intervention, was designed to motivate the participants to change



Tailored Interventions Build on NIDA Intervention To Help Drug-Using Women Reduce HIV Risk

	Behavior in Past 30 days	NIDA Standard Intervention Group		Motivation Intervention Group		Negotiation Intervention Group	
		Baseline	Six-Month Followup	Baseline	Six-Month Followup	Baseline	Six-Month Followup
Injecting Drug Users	Number of days injected powder cocaine	8.2	3.1	6.4	0.1	4.7	0.2
	Number of days injected heroin	16.4	8.9	12.7	1.5	9.8	3.2
	Percentage who traded sex for drugs	70.4	40.7	50.0	20.0	42.9	10.0
Crack Cocaine Users	Mean number of days crack used	17.7	12.9	18.2	15.6	18.7	13.8
	Percentage who had vaginal sex with one or more paying partners	43.9	24.6	34.3	19.2	30.8	20.5

African-American drug-using women in three intervention groups reduced behaviors that heightened their risk of HIV infection. However, women receiving the culturally specific, gender-tailored motivation and negotiation interventions generally reported greater reductions in risky behaviors after their participation than women in the NIDA standard intervention.

their behavior. The other, a negotiation intervention, recognized that women may fear verbal or physical abuse if they propose safer sex or safer needle use and thus sought to strengthen their negotiation and conflict-resolution skills.

“Our goal in the motivation intervention was to reduce risk based on what’s realistic in the context of the participant’s life,” explains Dr. Sterk. “We worked with the women to set short- and long-term goals, celebrate successes, analyze failures, and identify and overcome barriers.” The negotiation intervention recognizes that many of the women’s challenges dealt with the need to resolve conflict and that negotiation skills are key to reducing risk.

Once the interventions were ready, more than 300 African-American women ages 18 to 59 years—68 IDUs and 265 crack cocaine users—were enrolled in the studies. All were HIV-negative and heterosexually active. The women were randomly assigned to one of the three interventions. The NIDA standard intervention was delivered in two one-on-one sessions; the motivation and negotiation interventions each involved four one-on-one sessions. (See textbox, below, for descriptions of each intervention.) At the 6-month followup, both IDUs and crack cocaine users in all three groups reported lower levels of drug-using behavior and risky sexual behaviors than they had reported before receiving the interventions. Reductions were greater among women who received the tailored interventions.

Injecting Drug Users. The motivation and negotiation interventions were equally effective in reducing the incidence of needle and injection-works sharing. At 6 months, there was no sharing of drug injection paraphernalia in these groups; in the standard intervention group, 13 percent reported sharing needles and 18 percent reported sharing injection works. Although women in all intervention groups reduced their number of injections over time, only those in the tailored interventions reported statistically significant decreases. Participants in the motivation intervention were most likely to attend drug treatment, whereas women in the negotiation intervention reported more changes in their sexual behavior than did women in other interventions.

Crack Cocaine Users. All three interventions were associated with a drop in crack use in the 30 days preceding followup. About 40 percent of the women in each group reported no use during that period. Among those still abusing crack at followup, women in the motivation intervention were more likely to have reduced their use of crack in risky settings, such as outside or in a crack house, hotel room, or car. Women in the standard and motivation intervention groups significantly decreased the number of paying partners for vaginal sex and the frequency of sex with paying partners.

Dr. Sterk suggests that the study’s results show it may be optimal to create an intervention that combines skills taught in both the negotiation and motivation

Protocols for Standard, Motivation, and Negotiation Interventions

All interventions include discussion of the local HIV epidemic, sex and drug-related risk behaviors, safer sex and drug use, and HIV risk-reduction strategies. The two tailored interventions also include a discussion of the impact of race and gender on HIV risk and protective behaviors.

The NIDA standard intervention is an HIV/AIDS education program that was developed in the early 1990s. It builds on standard HIV testing and counseling developed by CDC and adds discussion of the principles of HIV prevention for drug users and their sex partners. The intervention involves testing, counseling, and educating participants through use of cue cards on such topics as the definition of HIV/AIDS, who is at risk, and ways to reduce risk. Also offered are demonstrations on condom use and equipment-bleaching techniques for IDUs. Referrals to counseling and other services are provided.

The motivation intervention follows the format of the standard intervention for the first session but ends with asking participants to consider what they are motivated to change in their lives. During the second session, this list is reviewed and short- and long-term goals are set. The third and fourth sessions involve discussion of experiences with behavior change, including the woman’s sense of control and feelings of ambivalence about behavior change. Risk-reduction messages tailored to the participant’s level of readiness to change are also delivered in the fourth session.

The negotiation/conflict-resolution intervention also follows the NIDA standard intervention for the first session, but it ends with a discussion of intended behavior changes. The second session reviews the list of possible behavior changes and the level of control the participant believes she has and introduces general communication skills and strategies to develop assertiveness. Short-term goals are set for strengthening communication, gaining control, and developing assertiveness. Negotiation and conflict-resolution strategies are introduced during the third session and tailored to the individual during the final session.

interventions. While participants in the negotiation intervention were generally more successful at reducing sexual risk behaviors, including decreasing the number of paying partners and increasing condom use with steady partners, participants in the motivation intervention had more success at changing drug-use behaviors.

Efforts were also made to assist program participants in their lives outside of the program, with success extending well beyond the study's parameters, notes Dr. Sterk. "A lot of the women who received the one-on-one support available through the tailored interventions said the program served as a re-entry into society. For example, they were encouraged to obtain a photo ID. Many reported that this simple act made them feel more connected to society again, part of the larger world." Program graduates returned to school, earned their GED, found jobs, joined the project to become counselors or interviewers, and stopped using drugs.

"Over and over, researchers are finding that we need to take a more holistic approach to intervention programs," says NIDA's Dr. Jones. "We can't just focus on drugs and sex. We must look at the big picture. It involves child-care, education, employment, housing, and job training. Community stakeholders need to develop programs that address multiple needs."

The project maintained a high retention rate—96 percent of the women enrolled in the studies completed the 6-month followup interview. Dr. Sterk attributes this

success to the fact that the project was grounded in the community and to the value of involving community consultants—residents, both former drug users and others, who played key roles in recruiting, interviewing, and counseling participants.

In future research, Dr. Sterk intends to examine the cost-effectiveness of various intervention formats. "It appears that individual sessions may be more desirable and cost-effective," she predicts. Dr. Sterk would like to continue the research, assessing the long-term effects of specific interventions. She wants to develop an intervention that focuses on women's households, targeting both the woman and her main partner, and she is interested in capacity-building—translating her research into other settings and training people to develop similar programs in more communities.

Sources

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- Sterk, C.E.; Theall, K.P.; Elifson, K.W.; and Kidder, D. HIV risk reduction among African-American women who inject drugs: A randomized controlled trial. *AIDS and Behavior* 7(1):73-86, 2003. **NN**

Principles That Guide Format, Content of Interventions

The interventions used by Dr. Sterk and her colleagues in this study are firmly based in theoretical research. The researchers conducted a series of one-on-one interviews and focus groups with the target population. These interviews yielded the following key principles that guided both the format and the content of the interventions.

- **Offer counseling sessions on an individual basis.** "It was very clear that women wanted to start with one-on-one sessions," says Dr. Sterk. "HIV risk behaviors involve so many private, personal issues—previous abuse experiences, actions to support their drug habits, things they'd never before discussed. They found it easier to discuss these experiences with one person, not a group."
- **Adopt a holistic approach.** Along with this research project, a clothing fair was conducted and clothes made available to program participants. Food for breakfast was provided; daycare was close by; and ongoing services, such as help preparing for job interviews, were provided.
- **Make programs community-based.** The project was headquartered in a house in the community, which was key to participants' convenience and comfort. Researchers also found it important for the women to link participation in this project to local social and health services, including local drug treatment, daycare centers, health services, and other community-based organizations. Community consultants played a key role in the project.
- **Address women's multiple social roles in the intervention.** Participants insisted that they didn't want to be labeled simply as drug users. Instead, they wanted the social context of their daily lives to be addressed, including their roles as mothers and steady partners.

The Neurobehavioral Legacy of Prenatal Tobacco Exposure

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

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

Drs. Barry M. Lester and Karen L. Law and their colleagues at Brown Medical School in Providence, Rhode

Island, used the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) to document the effects of maternal smoking on 1- to 2-day-old infants. The researchers found significant differences in short-term neurobehavioral status in tobacco-exposed newborns compared with unexposed newborns and noted that neurobehavioral impact worsened as the mothers' smoking levels rose.

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

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

Tobacco-Exposed Infants Exhibit Significant Neurobehavioral Effects

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

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

see these very early behavioral differences in prenatally exposed children and consider them in light of effects in older children” (see below, “Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers”).

“This research is providing an important piece of the puzzle linking prenatal exposure to cigarette smoke and long-term behavioral outcomes,” Dr. Smeriglio says.

The researchers conducted their study with 56 new mothers, ages 18 to 35, and their newborns at a Providence hospital. Recruited shortly after they had given birth, the mothers—27 smokers and 29 nonsmokers—had not used any illegal drugs during their pregnancy and consumed

fewer than four alcoholic drinks per month. Mothers who smoked reported smoking fewer than seven cigarettes per day, with tobacco use confirmed by measuring saliva levels of cotinine, the primary metabolite of nicotine. Only healthy newborns whose weights were appropriate to their gestational ages were included in the study; the researchers controlled for birthweight so the effects they found on neurobehavior could not be attributed to the effects of maternal smoking on birthweight.

A certified examiner who was unaware of the mother’s smoking status administered the NNNS to each newborn within 48 hours of birth. The test examines an infant’s

Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers

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

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

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

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

Source

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

neurological state, considering muscle tone, reflexes, and integrity of the central nervous system (CNS); behavior, including attention, arousal, and excitability; and a checklist of 50 items shown by previous research to be markers of stress or—in high-risk babies—of drug withdrawal. Dose-response effects were determined by evaluating the relationship between measures of maternal smoking (cotinine and self-report) and NNNS scores.

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

“These infants’ higher scores in such areas as excitability and arousal reflect that nicotine is a stimulant,” says Dr. Lester. The researchers also found consistent dose-response relationships for both the cotinine bioassay

results and the self-reports of number of cigarettes smoked per day. “These results indicate that greater exposure to tobacco smoke is related to increasingly negative neurobehavioral effects,” he adds, “and that these children may be at increased risk for future neurobehavioral problems.”

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

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

Source

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

Gender and Ethnic Patterns in Drug Use Among High School Seniors

Although rates of marijuana, alcohol, and tobacco use by 12th-grade boys and girls declined over the 25-year period ending in 2000, the “gender gap” in use of these drugs remained largely unchanged. According to data compiled by the annual Monitoring the Future (MTF) survey, senior girls were 77 percent as likely as boys (compared with 78 percent in 1976) to have reported using marijuana in the past month. Girls in the 12th-grade class of 2000 were 64 percent as likely (up from 54 percent in 1976) to have had five or more drinks in a row during the past 2 weeks, and girls and boys were equally likely to be daily smokers.

Ethnic differences in drug use—for boys as well as girls—are much wider than are gender differences. A recently published review of MTF data reveals that these ethnic differences are significant and have persisted since MTF began collecting drug use data in 1976. Key substance use patterns among ethnic groups and gender differences within those groups are presented below.

Smoking

Daily smoking declined among all ethnic groups between 1976 and 1990, then leveled off before beginning to increase modestly between 1996 and 2000. Among ethnic groups, Native Americans were most likely to smoke and African Americans least likely. Within ethnic groups, African-American girls were less likely than boys to be daily smokers.

Alcohol

Girls were less likely than boys to report heavy alcohol use (five or more drinks in a row within the past 2 weeks), and the prevalence for girls and boys over the 25-year period ending in 2000 generally decreased. Among ethnic groups, Native Americans were most likely to report heavy drinking; Asian-American and African-American 12th-graders reported the lowest prevalence. No significant gender differences in alcohol use emerged within ethnic groups.

Substance Use Among High School Seniors, 1976-2000*

	12th-Grade Females					12th-Grade Males				
	'76-'80	'81-'85	'86-'90	'91-'95	'96-'00	'76-'80	'81-'85	'86-'90	'91-'95	'96-'00
Daily Cigarette Smoking										
White	28.8	23.6	22.6	22.2	27.2	24.4	18.6	19.2	22.3	26.3
Black	20.8	12.2	5.8	3.4	5.1	21.9	10.8	7.7	6.5	10.9
Mexican American	15.6	13.2	8.4	9.3	11.0	19.1	13.2	11.8	12.6	15.1
Puerto Rican/**				15.2	17.9				22.5	23.4
Other Latin American	18.0	15.0	12.4	10.8	9.8	18.7	13.7	12.4	8.9	15.3
Asian American	13.3	10.2	8.0	8.6	10.1	14.5	11.5	10.8	12.9	14.3
Native American	49.8	39.8	30.5	34.2	34.2	38.7	30.8	25.7	32.4	24.7
Heavy Alcohol Use Within Past 2 Weeks										
White	32.1	34.1	30.8	24.6	28.0	53.4	52.9	46.8	39.7	42.4
Black	12.1	11.1	8.6	7.6	8.3	27.5	24.8	22.9	19.9	18.0
Mexican American	25.0	26.8	21.4	19.6	23.4	52.0	48.3	44.1	38.8	40.6
Puerto Rican/**				16.2	18.0				34.2	27.0
Other Latin American	21.9	18.5	13.0	15.5	19.4	36.6	34.6	30.3	26.7	32.6
Asian American	14.7	11.4	9.0	8.2	11.1	28.4	22.4	19.4	15.2	18.9
Native American	40.9	38.3	30.8	26.9	32.5	62.8	57.6	46.8	46.2	41.5
Marijuana Use Within Past 30 Days										
White	30.8	24.6	17.9	15.0	20.8	40.4	31.6	22.5	19.7	26.0
Black	22.1	20.1	7.2	6.8	12.7	36.6	29.2	14.6	15.9	26.6
Mexican American	25.9	21.2	11.7	10.5	18.7	39.8	36.9	19.5	19.9	29.3
Puerto Rican/**				10.8	20.7				26.4	26.7
Other Latin American	19.5	14.4	8.7	11.0	12.9	34.7	22.7	17.2	13.7	19.6
Asian American	18.3	13.8	5.2	5.1	9.1	31.2	13.0	9.8	9.0	16.0
Native American	44.7	30.3	19.7	21.5	32.0	50.9	36.1	26.6	25.5	27.2

*Percentage prevalence shown as the mean for each 5-year span.

**Beginning in 1990, the data distinguish between Puerto Rican and Other Latin American.

Marijuana

Overall, 12th-grade boys in all ethnic groups were somewhat more likely than girls to have used marijuana within the past 30 days. Prevalence rates for girls and boys declined between 1976 and 1990, held steady until 1995, and increased between 1996 and 2000. Among ethnic groups, Native Americans were most likely and Asian Americans least likely to have used marijuana within the past month.

Source

- Wallace, J.M., et al. Gender and ethnic differences in smoking, drinking and illicit drug use among American 8th, 10th and 12th grade students, 1976-2000. *Addiction* 98(2):225-234, 2003. **NN**

Joint Treatment of PTSD and Cocaine Abuse May Reduce Severity of Both Disorders

By Robert Mathias, NIDA NOTES Staff Writer

Many individuals who abuse cocaine, alcohol, and other substances also suffer from posttraumatic stress disorder (PTSD) related to life-threatening or other traumatic events they have experienced or witnessed. Individuals with PTSD suffer recurring flashbacks, anxiety, and other symptoms that can impede substance abuse treatment. Similarly, substance abuse can make PTSD symptoms worse. Thus, integrated treatment is recommended as the way to treat patients with both disorders. Yet until recently, the most effective nonpharmacological treatment for PTSD, known as exposure therapy, was considered too risky to use with cocaine-dependent patients. The therapy seeks to desensitize patients to the distressing emotional effects of the trauma that triggered their PTSD by requiring them to repeatedly and graphically describe it.

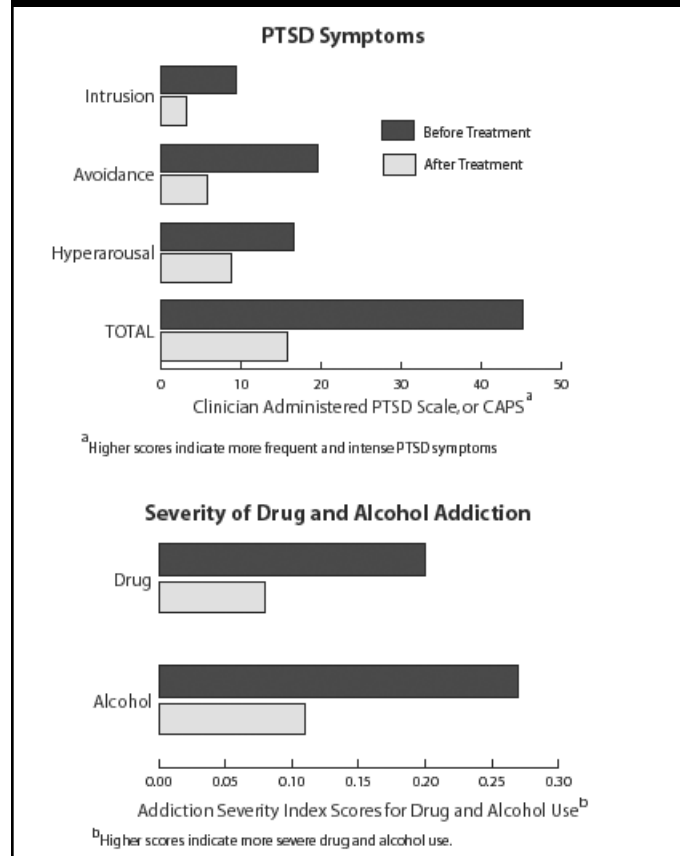
“Researchers and clinicians have been reluctant to use exposure therapy with cocaine-dependent patients,” says Dr. Kathleen Brady of the Medical University of South Carolina in Charleston. “Drug abuse patients were thought to be likely to turn to alcohol and drugs to cope with the emotional demands placed on them by recounting the fear-inducing experience.”

A preliminary study led by Dr. Brady suggests that the belief that exposure therapy would do these patients more harm than good may not be merited. In the study, instead of triggering emotional distress and relapse to substance abuse, treatment that combined exposure therapy for PTSD with substance abuse counseling produced substantial improvement in both disorders.

Thirty-nine cocaine-dependent individuals with PTSD, 32 of them women, participated in the outpatient study. The majority of participants had developed PTSD following such severe traumatic experiences as rape (74 percent), aggravated assault (89 percent), and other physical assault (95 percent). Individuals who feel intense fear and helplessness or horror during such terrifying events can later develop distressing symptoms that can impair their ability to live and work normally.

PTSD symptoms fall into three general categories: “intrusions,” such as flashbacks or nightmares in which the person reexperiences the traumatic event; “hyperarousal” or anxiety, which can be marked by extreme vigilance and jumpiness, difficulty sleeping or concentrating, and irritability; and “avoidance” of people, activities, and

Combination Psychotherapy Reduces Posttraumatic Stress Disorder (PTSD) Symptoms and Cocaine Use



Fifteen cocaine-dependent patients with PTSD who completed a psychotherapy that addressed both disorders significantly reduced cocaine use and had fewer and less intense PTSD symptoms, as assessed by physicians.

situations that might trigger memories of the incident. When symptoms persist for more than 3 months, PTSD is considered chronic. Chronic sufferers often have additional psychiatric disorders. An estimated 30 to 60 percent of individuals with substance abuse disorders have PTSD, according to studies cited by Dr. Brady.

The study used a psychotherapy developed by Dr. Brady and her colleagues that combines counseling for drug abuse with exposure therapy for PTSD. “We wanted to evaluate whether cocaine-dependent PTSD patients could

safely tolerate the therapy and whether it would be effective in reducing the severity of their PTSD symptoms and cocaine use,” Dr. Brady says. The combined therapy consists of 16 90-minute individual sessions. In the first 3 weeks, patients participate in two counseling sessions a week that concentrate solely on their drug abuse problems and developing relapse prevention skills. “The therapy in those first sessions gives people a chance to experience some sobriety and provides them the coping techniques and strategies they will need to deal with high-risk situations and the urges to use drugs they may experience when they get into the exposure therapy,” Dr. Brady says.

Once patients start to feel comfortable sharing their feelings with the therapist and are willing to engage in exposure therapy, a technique called imaginal exposure is used to address their PTSD symptoms. In imaginal sessions, patients describe in detail the circumstances and feelings they experienced during the traumatic event that triggered their disorder. They also develop a list of situations or places they have been avoiding because they associate them with the event. Between sessions, patients carry out assignments in which they gradually expose themselves to similar situations that are safe but fear-inducing. If, for example, they were abducted from a parking lot and assaulted, they may have become fearful of any parking lot or areas with cars in them. Assignments could involve going to such areas, first with a friend, then by themselves in the middle of the day.

“We are trying to get at the irrational fears and inappropriate avoidance of situations that are interfering with their lives,” Dr. Brady says. “By talking about their experience over and over in the imaginal sessions, they are basically reliving it. The point of the exposure is to desensitize them to the trauma, thereby reducing the fear, anxiety, and emotion from the memory itself. By the end of successful therapy, patients are able to go through their entire traumatic scenario and feel much less distressed because they are able to separate irrational fears from simply thinking about the event.”

The goal of the therapy is that the intrusion, arousal, and avoidance symptoms all recede. The exposure has done its job when someone can go through his or her detailed recalling of the event and score no higher than 5 on a 20-point scale that measures how much distress they are feeling, says Dr. Brady.

Fifteen of the 39 study participants completed the combined therapy, attending at least 10 of the 16 sessions, including a minimum of 3 exposure therapy sessions. Assessments by both patients and clinicians indicated that those who completed treatment experienced significant reductions in all three PTSD symptom categories and in cocaine use from study entry to treatment completion.

Using a self-administered Impact of Events Scale, patients reported a 53-percent reduction in “intrusion” symptoms and a 27-percent reduction in inappropriate avoidance behaviors. Over the same period, clinicians using a 30-item structured clinical interview tallied a 66-percent reduction in “intrusions,” a 70-percent reduction in “avoidances,” and a 47-percent reduction in hyperarousal symptoms. By the end of treatment, completers also had reduced cocaine use by 60 percent and reported experiencing significantly fewer substance-related problems. Followup assessments indicated that treatment completers had maintained these improvements in both PTSD symptoms and cocaine use 6 months after treatment ended. In contrast, no differences emerged in any PTSD or substance-abuse-related scores at treatment completion or 6 months later among noncompleters.

“This study provides promising preliminary evidence that exposure therapy can be used safely and effectively in treating PTSD in some cocaine-dependent individuals without increasing the risk of relapse,” says Dr. Brady. The improvements in PTSD symptoms were comparable to those reported by other studies that used exposure therapies to treat patients with no substance abuse disorder. Dropout rates, though high, also were similar to those in previous studies that used other psychotherapies to treat cocaine-dependent patients.

Nevertheless, the small number of patients in the study and the high dropout rates underscore the need for randomized controlled studies to replicate these results, Dr. Brady cautions. Such studies also could provide information that would help to identify patients who are likely to benefit from this treatment, as well as those who might need different approaches.

Source

- Brady, K.T., et al. Exposure therapy in the treatment of PTSD among cocaine-dependent individuals: Preliminary findings. *Journal of Substance Abuse Treatment* 21(1):47–54, 2001. **NN**

New Animal Model Simulates Human Exposure, Confirms Harm From Prenatal Cocaine

By Kimberly Martin, *NIDA NOTES* Contributing Writer

Research has shown that some children exposed in the womb to cocaine may have memory and attention deficits that hinder their ability to learn. These children also may have difficulties completing complex tasks or tests that involve distractions, and they tend to perform poorly on visual recognition memory and attention tasks.

Two-Object Recognition Test Mimics Test Used with Infants



Photo credit: Dorothy Cameron, the Johns Hopkins University Bloomberg School of Public Health.

This rat is exploring an object during the two-object recognition task. He was previously exposed to one object, whereas the other is new. The rat was considered to remember the former object if he spent more time exploring the new one. Rats exposed to cocaine before birth did not demonstrate a preference for the new object, indicating no memory of the familiar object.

Now, Dr. Bret Morrow and his colleagues at Yale University have demonstrated in rats that prenatal exposure to cocaine may cause long-term changes in an area of the brain responsible for short-term memory. Previous animal studies have reported negative effects of cocaine on cognitive performance, but doubts persisted about the applicability of study results to humans. The new findings help allay those doubts, which are based partly on differences in how people use cocaine and in how cocaine was administered to rats in earlier experiments. By designing an experiment that closely simulates the way humans use cocaine, the Yale team has enhanced the applicability of

cognitive impairment in rats prenatally exposed to cocaine to that observed in children.

“To more closely replicate the way human fetuses are exposed to cocaine, we administered the drug to the pregnant rats intravenously. This enabled us to use dosages similar to those taken by people. Also, the way cocaine is absorbed and metabolized when it is administered intravenously is much closer to what we see in humans,” says Dr. Morrow. “Additionally, tests commonly used in rat studies to assess cognitive deficits—maze and swimming tests—rely on artificial manipulation of the animal’s environment, such as food restriction, reward, or stress. Our test, a two-object recognition task that relied on the rat’s own motivation to complete the task, is comparable to one used with human infants to assess short-term memory.”

Cocaine was administered to pregnant rats twice a day for 11 days before they gave birth. At ages equivalent to human adolescence and adulthood, the male offspring were placed in a cage with two identical objects, allowed to explore the objects, then removed from the cage. After delays of 20 minutes, 1 hour, and 24 hours, the rats were returned to the cage with one of the former objects and a new object. The time a rat spent actively exploring the new and former objects was recorded. If he spent more time exploring the new object, the rat was considered to remember the former object. To count as “exploring” time, the rat had to be actively exploring the object, with his nose within about 2 cm of the object.

“The rats that were not exposed to cocaine spent more time exploring the novel object than the familiar object after 20-minute and 1-hour delays, but not after 24 hours,” says Dr. Morrow. “We interpreted this behavior as memory of the familiar object from the previous exposure. The rats that were prenatally exposed to cocaine did not demonstrate a preference for the novel object over the familiar object at any time. This behavior was interpreted as their having no memory of the familiar object. These findings indicate that in the rat model, prenatal exposure to cocaine may result in long-lasting deficits in short-term memory.”

In a separate study, the researchers found that adolescent rats prenatally exposed to cocaine as described above had

long-term changes in the frontal cortex. They showed excess activation of neurons in the prefrontal cortex, the brain area governing short-term memory. Activation was measured by the concentration of Fos, a protein produced by excited neurons. “Fos activation during development can change the way a neuron responds in the future; in other words, it undergoes a long-term adaptation,” says Dr. Morrow. “In some cases, this may indicate important adaptations that help the animal meet new challenges. However, in cocaine-exposed animals, we believe that the excessive Fos activation may lead to deficits in attention and memory.”

“This type of animal model is valuable in guiding research into the possible mechanisms and consequences of exposure to drugs of abuse during human development,” says Dr. Laurence Stanford of NIDA’s Division of Treatment Research and Development. “Animal models allow us to reduce the number of variables and confounding factors that are present when pregnant women abuse drugs. Research with children strongly suggests a significant dose effect, with the severity and presence of deficits linked to the extent of exposure. Maternal health may also play a role in the effects of prenatal drug exposure. For example,

the appetite-suppressing effects of cocaine and resulting nutritional deficits can contribute to growth retardation in the womb. For the purposes of reducing the number of variables, and thus attempting to isolate the effects of prenatal cocaine exposure, this research is a valuable experiment.”

“This animal model may prove valuable not only for probing neurological and cognitive deficits caused by prenatal cocaine exposure, but also for testing potential therapies,” says Dr. Susan Volman of NIDA’s Division of Neuroscience and Behavioral Research.

Sources

- Morrow, B.A., et al. Prenatal cocaine exposure disrupts nonspatial, short-term memory in adolescent and adult male rats. *Behavioral Brain Research* 129 (1-2):217–223, 2002.
- Morrow, B.A., et al. Male rats exposed to cocaine in utero demonstrate elevated expression of Fos in the prefrontal cortex in response to environment. *Neuropsychopharmacology* 26(3):275–285, 2002. **NN**

Substance-Abusing Adolescents Show Ethnic and Gender Differences in Psychiatric Disorders

By Kimberly Martin, *NIDA NOTES* Contributing Writer

NIDA researchers have found that the patterns of co-occurring psychiatric disorders in adolescent substance abusers differ between ethnic groups and between boys and girls. This information may help clinicians be particularly alert to symptoms of the most common psychiatric disorders when interviewing patients from each group. Eventually, it may aid in the development of tailored screening, assessment, and treatment interventions for different groups.

avoidance of interaction with others, and loss of interest in activities.

“Studies have consistently documented high rates of psychiatric disorders among adolescent substance abusers. They also have found that certain co-occurring disorders are associated with certain treatment outcomes. For example, depression or attention-deficit/hyperactivity disorder (ADHD) may contribute to early dropout and poor treatment outcomes,” says Dr. Robbins. “Therefore, treating

substance abuse alone may not be enough. Treatment providers need to address the constellation of emotional and behavioral problems presented by each individual.”

The researchers recruited 167 Hispanic and African-American 12- to 17-year-olds referred for outpatient treatment for substance abuse between October 1997 and March 2000. Participants’ substance use was assessed before treatment with the Adolescent Drug Abuse Diagnosis, a standard assessment tool that provides information on the frequency of use of alcohol, marijuana, cocaine, and other drugs during the preceding month. The youths also completed the Diagnostic Interview Schedule for Children—

Predictive Scales, a questionnaire that screens for nine psychiatric disorders, including social phobias, panic, anxiety, major depression, ADHD, oppositional defiant disorder (ODD), and conduct disorders (CD).

Dr. Robbins and colleagues found that Hispanic and African-American youths were similar in the drugs they used and their overall prevalence of co-occurring psychiatric disorders. More than 80 percent of the participants reported using marijuana, and about 17 percent and 35 percent reported using cocaine and alcohol, respectively.

Typical Behaviors in Adolescent Psychiatric Disorders

Externalizing Behaviors	Internalizing Behaviors
<ul style="list-style-type: none"> • Recurring patterns of aggression • Excessive arguing • Use of physical or verbal coercion • Noncompliance with reasonable requests • Persistent pattern of tantrums • Persistent pattern of lying or stealing • Lack of self-control, acting-out behavior • Behaviors that prevent development or maintenance of relationships 	<ul style="list-style-type: none"> • Sad affect, depression, feelings of worthlessness • Auditory or visual hallucinations • Constant repetition of certain thoughts, ideas, or situations • Repetitive and useless actions • Frequent crying, atypical affect • Severe headaches or other somatic problems • Talk of suicide • Decreased interest in activities • Restricted activity levels • Withdrawal, avoidance of interactions, lack of personal care

Ethnic Differences

Dr. Michael Robbins and colleagues from Florida’s University of Miami found high rates of psychiatric disorders among Hispanic and African-American adolescent substance abusers referred for outpatient therapy. Their study distinguished externalizing disorders—characterized by lack of self-control and acting-out behaviors, recurring patterns of aggression, and behaviors that prevent the development and maintenance of relationships—from internalizing disorders, typified by sadness, withdrawal,

Overall, 87 percent of the youths reported symptoms of at least one co-occurring psychiatric disorder. Of these, about 19 percent reported symptoms for only one disorder, while more than 54 percent reported symptoms of three or more disorders.

Hispanic youths had significantly more symptoms of externalizing psychiatric disorders, such as ADHD and ODD, than did African-American youths. More than 78 percent of Hispanics reported symptoms of at least one externalizing disorder, compared with about 65 percent of African-American youths. However, about twice as many African-American adolescents reported symptoms for agoraphobia, an internalizing psychiatric disorder that finds the sufferer severely anxious about going outside the home. The researchers note, though, that the high rates of symptoms associated with agoraphobia may instead reflect legitimate fears about being in very dangerous public settings.

“Our findings suggest that substance abuse among Hispanic youths may occur more often within a larger context of problem behaviors,” says Dr. Robbins. “In addition to enhancing Hispanic youths’ emotional and behavioral functioning, interventions need to address problems with their families, schools, peer group, and other areas where co-occurring externalizing behaviors often have severe and profound consequences.”

Dr. Robbins observes that his findings may be relevant primarily to youths referred for outpatient treatment, rather than all Hispanic and African-American substance-abusing youths. “We believe substance abuse among African-American youths may be related to problem behaviors as well. Our sample drew from community outpatient referrals. Further research is warranted to determine if there is a basic difference between ethnic groups in the constellation of behavior problem symptoms or if our numbers reflect a bias in the way youths are referred to outpatient treatment. African-American youths may

be more likely to be referred to other types of treatment providers or sent to jail or detention.”

Co-Occurring Psychiatric Disorders Vary by Ethnicity and Gender in Adolescent Substance Abusers (by Percent)

Psychiatric Disorder	African American ^a	Hispanic ^a N=90	Female ^b N=34	Male ^b N=101
Externalizing Behaviors				
Attention-deficit/hyperactivity disorder	N=77	41.4%	23.5%	45.5%
Oppositional defiant disorder	20.8%	60.5	26.5	18.8
Conduct disorder	41.6	56.6	47.1	72.3
Any disruptive behavior disorder	53.6	NA ^c	76.5	94.1
Agoraphobia	NA ^c	19.5	NA ^c	NA ^c
Internalizing Behaviors				
Major depressive disorder	40.3	33.3	44.1	16.8
Any mood disorder	26.0	NA ^c	50.0	36.6
	NA ^c			

^a Robbins et al., Journal of the American Academy of Child and Adolescent Psychiatry, 2002. Percentages indicate a probability estimate of the presence of psychiatric disorders.

^b Latimer et al., Experimental and Clinical Psychopharmacology, 2002.

^c Data not available.

Among substance-abusing youths referred for outpatient substance abuse treatment, Hispanics reported higher rates of externalizing disorders than did African Americans, while African Americans reported higher rates of the internalizing disorder agoraphobia. In a separate study of adolescent substance abusers, boys were more likely to be diagnosed with externalizing disorders, while young women were more likely to be diagnosed with depression, an internalizing disorder.

Gender Differences

Dr. William Latimer and colleagues at the Johns Hopkins University, Bloomberg School of Public Health, in Baltimore, and the University of Minnesota, Twin Cities, Minneapolis, examined gender differences in rates of co-occurring psychiatric disorders in substance-abusing adolescents. They found that more male teenage substance abusers also had disruptive disorders, whereas females had higher rates of depression.

“Gender may be useful in helping clinicians who assess youths referred to drug treatment by signaling the likely presence of certain psychiatric disorders for males and females. However, clinicians should not rule out the possibility of a disorder based on the patient’s gender,” says Dr. Latimer. “For example, although co-occurring disruptive disorders are more common among males than females, this shouldn’t obscure

the equally important finding that high rates of these disorders are also present among substance-abusing females.”

The researchers recruited 135 adolescents (ages 12 to 19) who met the Diagnostic and Statistical Manual of Mental Disorders criteria for one or more psychoactive substance use disorders (PSUD), including alcohol abuse or dependence, marijuana abuse or dependence, and abuse or dependence on drugs other than alcohol and marijuana. Adolescents and their parents completed the Diagnostic Interview of Children and Adolescents, which provided information about PSUDs and symptoms of ADHD, ODD, CD, and mood disorders. Adolescents also completed the Personal Experience Inventory, which provided information about 3-month, 12-month, and lifetime alcohol and other drug use frequencies and related consequences. Adolescents’ reports of substance abuse were verified by urine tests.

About 68 percent of the girls and 75 percent of the boys were diagnosed with alcohol abuse or dependence, while about 85 percent of the girls and 93 percent of the boys were diagnosed with marijuana use disorders. More than 17 percent of the girls and 21 percent of the boys were diagnosed with abuse or dependence on some other drug or drugs. The patterns of single-substance versus polysubstance use also varied with gender. Girls were more likely to be diagnosed with abuse or dependence on only one drug, while boys were more likely to be diagnosed with simultaneous abuse or dependence on more than one drug.

The researchers found that nearly twice the percentage of teenage male substance abusers had co-occurring ADHD or CD compared with female teen abusers, whereas roughly three times the percentage of females had a co-occurring major depressive disorder. However, both genders had similar rates of mild depression (dysthymia), double depression (chronic depression with episodes of major depression), and bipolar disorders.

“Drug abuse and psychiatric disorders co-occur at extremely high rates in adolescents,” says Dr. Latimer. “Therefore, drug treatment programs may be more effective if strategies that address multiple patterns of simultaneously occurring disorders are included. Those geared toward adolescent boys may benefit by incorporating strategies that address psychiatric problems related to behavioral dysfunctions, while those intended for adolescent girls may need to include therapies that address major depression.” Further examination of how simultaneously

occurring psychiatric and substance abuse disorders interact is needed, he notes.

“When a group of patients shares a characteristic, such as age or gender, it seems reasonable to expect that they might require a treatment sensitive to that characteristic,” says Dr. Melissa Racioppo of NIDA’s Behavioral Treatment

Development Branch. “But it is also possible that a characteristic may be irrelevant to treatment outcome. Drs. Robbins’ and Latimer’s studies help identify characteristics of groups of substance abusers, which lays the groundwork for testing the relevance of these characteristics to treatment interventions. In the future, we may have effective behavioral treatments that appropriately attend to gender and racial/ethnic differences among adolescent substance abusers.”

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Girls were more likely to be diagnosed with abuse or dependence on only one drug, while boys were more likely to be diagnosed with simultaneous abuse or dependence on more than one drug.

Animal Studies Show Sex Differences in Impact of Efforts To Reduce Drug Seeking

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

In recent studies, Dr. Marilyn Carroll and her colleagues at the University of Minnesota looked at the impact of two interventions on self-administration of heroin and cocaine by rats and found that, in each case, the intervention produced a greater effect on the female rats studied than on the male rats. These findings and the results of other studies looking at sex differences suggest that the most effective drug abuse treatments for men and women may be quite different.

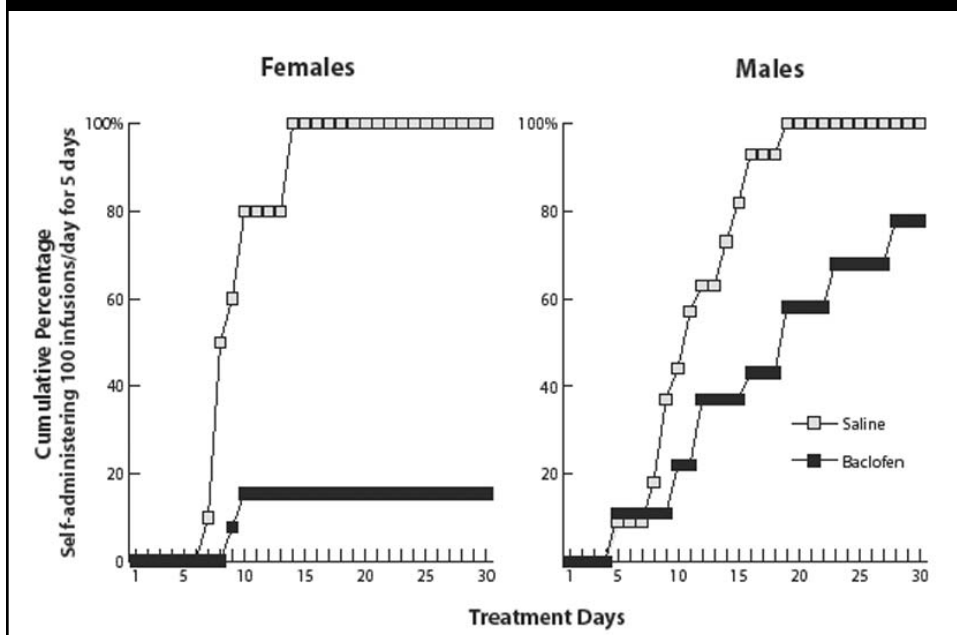
In one study, Dr. Carroll found that administering baclofen, a muscle relaxer, suppressed the establishment of cocaine use significantly more in female rats than in males. The other study looked at the effect of offering wheel-running as an alternative to drug-seeking behavior; again, the result was that only female rats significantly decreased their levels of drug self-administration—in this case, cocaine.

“These studies highlight the importance of paying attention to sex differences in the development of pharmacotherapies and in other drug abuse research,” says Dr. Cora Lee Wetherington, NIDA’s women and gender research coordinator. “For example, some smoking cessation medications seem to work better for men; others work better for women. As new medications are developed for other forms of drug abuse, the story may be similar. Treatment effects may not be the same in males and females.”

“We are increasingly finding that sex and hormonal status are important determinants of drug abuse at all phases of addiction—acquisition, maintenance, escalation/dysregulation, and reinstatement,” says Dr. Carroll, whose previous animal research has consistently found that females tend to use more drugs, more quickly. Recent epidemiological data indicate that in humans, females also tend to progress to dependence at a faster rate than males.

In the first study, Dr. Carroll and her colleagues examined the effects of baclofen on 44 rats that had never been exposed to cocaine. Previous animal studies have demonstrated the promise of baclofen, which modulates several neurotransmitter systems, as a potential treatment medication. Each rat participated in 30 daily sessions. During the first six hours of each session, the rats were given repeated, random infusions of baclofen at a relatively low dose of 0.2 mg/kg. For each infusion, a lever extended into the cage where it stayed for 15 seconds, after which the cocaine was administered and the lever retracted. If the animal touched the lever during the 15-second latency period, cocaine was administered immediately. In this manner, the rats learned within a few days to associate the lever with drug

Baclofen Slows Establishment of Cocaine Use in Females More Than Males



Pretreatment with baclofen has been shown to slow the establishment of cocaine use in rats. Among rats pretreated with baclofen, only 15.4 percent of females self-administered an average of 100 cocaine infusions for 5 consecutive days during a 30-day trial, compared to 77.7 percent of males. Under saline pretreatment, all of the animals tested reached this injection frequency and consistency within 30 days.

infusions and to push the lever to self-administer cocaine. A second 6-hour component each day allowed the rats to freely self-administer cocaine; the lever remained extended into the cage and a dose of cocaine was delivered each time the lever was pressed.

To test the effects of baclofen on the rate of acquisition of a habit of regular drug-taking, investigators divided the rats into four groups. One male and one female group were injected with baclofen prior to each session; another male and another female group were pretreated with saline. Researchers measured the number of infusions each rat received during the self-administration session until it reached the acquisition criterion or level at which it was considered to have developed a habit of cocaine use, defined as an average of 100 infusions per day for 5 days.

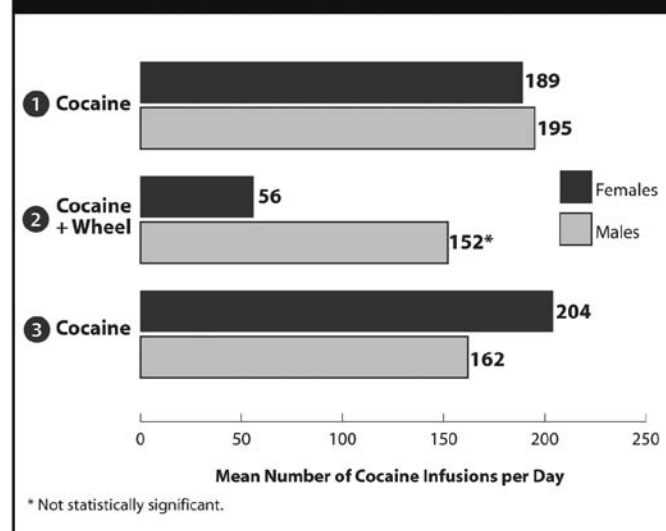
All of the female rats pretreated with saline reached the acquisition criterion by day 14. All males pretreated with saline met the criterion by day 19. In the group of female rats pretreated with baclofen, only 15.4 percent met the acquisition criterion within the 30-day limit. In contrast, 77.7 percent of males pretreated with baclofen met the criterion within the 30-day limit. When baclofen treatment was discontinued, all of the females who initially did not meet the acquisition criterion did so within 11 days.

“Pretreatment with baclofen slowed the rate at which the rats reached the specified level of cocaine self-administration and reduced the percentage of rats reaching that level to a greater extent in females than in males,” says Dr. Carroll. “The propensity of the female rats to use cocaine at the specified levels was no different than that of the males, because they all acquired a habit of cocaine use without baclofen. It was just that the baclofen had a different effect on the females.”

The next study looked at sex differences identified as a result of a behavioral intervention to reducing drug use. “Enriching the environment is a promising approach to reducing the initiation, maintenance, and reinstatement of drug abuse,” says Dr. Carroll. (See also, “Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction,” *NIDA NOTES*, Vol. 17, No. 5.) In this study, rats were offered access to a running wheel as an alternative to self-administering cocaine. Wheel-running is an activity rats enjoy, and research has shown that when given a choice between food and running wheels, rats often chose running over eating.

Seventeen rats were initially given access to a running wheel alone until their average daily number of wheel rotations stabilized. Next, rats were trained to self-administer cocaine (0.2 mg/kg) until they reached an average of 100 infusions a day for 5 consecutive days. The rats were then given concurrent access to cocaine and the running wheel. Researchers calculated the mean number of wheel rotations and mean number of cocaine infusions during the last five sessions of each phase.

Access to Wheel-Running Decreased Cocaine Self-Administration in Females



Having access to a running wheel as an alternative to drug-seeking behavior caused a 70-percent reduction in cocaine self-administration among females. The difference for males was not statistically significant. In succession, the rats studied were given access to (1) cocaine only; (2) cocaine and the wheel; and (3) cocaine only.

Under cocaine-only conditions, both males and females averaged 30 infusions per hour. Females saw a reduction of 70.6 percent in infusions to fewer than 10 per hour when there was concurrent access to the running wheel. In males, while infusions decreased slightly (21.9 percent) to an average of 25 infusions per hour, the reduction was not statistically significant.

“Taken together, these studies suggest that females rats are more responsive than males to treatments for drug abuse,” says Dr. Carroll. Although few data exist on sex differences regarding treatment of drug abuse in humans, research is beginning to point to hormones as one cause of sex differences in drug abuse. “A growing body of research indicates that ovarian hormones, such as estrogen, may account for many of the sex differences in drug abuse, increasing the subjective effects of drugs and their reinforcing potential.” More studies are needed, both in animals and humans, to better understand these sex differences and to use this knowledge to improve treatment options.

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Study Finds Significant Mental Deficits in Toddlers Exposed to Cocaine Before Birth

By Robert Mathias, NIDA NOTES Staff Writer

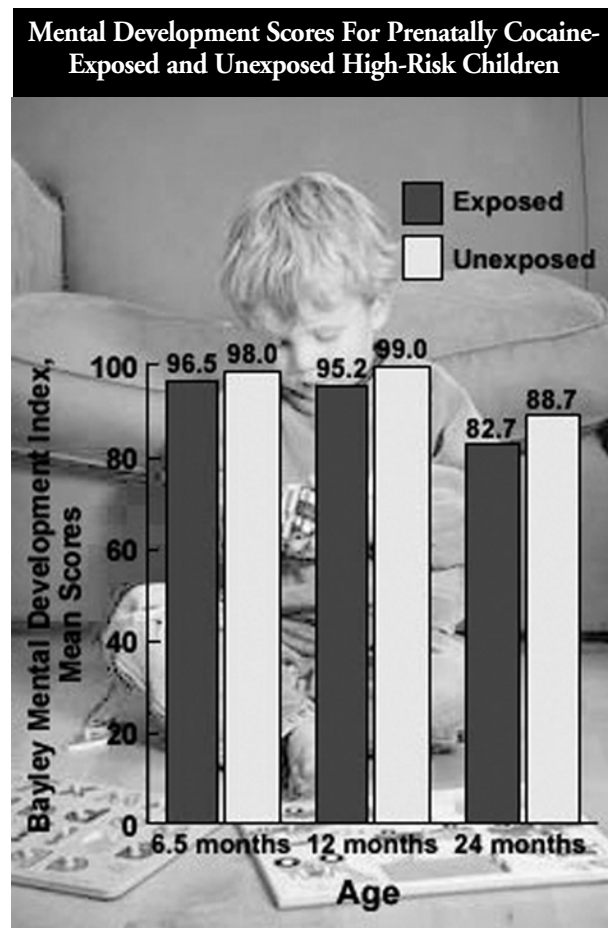
Since the mid-1980s, up to 1 million children born in the United States are estimated to have been exposed to cocaine in the womb. Determining cocaine's impact on these children's development has been difficult because there often are other possible explanations for physical and mental problems the children may have, such as the mother's use of other substances during pregnancy and poor prenatal care. Now, a NIDA-supported study that was able to separate the effects of cocaine from those of

many other such factors has found that children born to poor, urban women who used cocaine throughout pregnancy were nearly twice as likely as children with similar backgrounds but no prenatal cocaine exposure to have significant cognitive deficits during their first 2 years of life.

The study, led by Dr. Lynn Singer of Case Western Reserve University in Cleveland, Ohio, is the first to show a clear association between prenatal cocaine exposure and cognitive impairment in 2-year-olds. "Since cognitive performance at this age is indicative of later performance, these children may continue to have learning difficulties that need to be addressed when they reach school age," Dr. Singer says.

"The findings of this well-controlled study make an important contribution to a growing body of knowledge about the effects of prenatal cocaine exposure that may help us to identify those exposed children who are at increased risk of developmental harm," says Dr. Vince Smeriglio of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. Previous findings from other NIDA-supported studies that have been following cocaine-exposed children from birth have produced conflicting results about cocaine's impact on developmental outcomes at this age, he notes. "Comparing and contrasting the circumstances in this study with those found in other studies of cocaine-exposed children may enable us to identify specific biological and environmental factors that increase or reduce the developmental risk from cocaine exposure," Dr. Smeriglio says.

The study followed a group of 415 infants born at a large urban teaching hospital from 1994 through 1996 to mothers from low socioeconomic backgrounds who had been identified by the hospital staff as being at high risk of drug abuse. Women who participated in the study were given urine tests for drug use immediately before or after delivery and interviewed shortly after they gave birth to produce estimates of the type, frequency, and amounts of drugs they had used during pregnancy. Each baby's first stool, known as meconium, also was analyzed for the presence of cocaine and its metabolites to help establish the level of drug exposure. Of the 415 babies in the study, 218 had been exposed to cocaine and 197 had not. Both groups of infants also had been exposed to tobacco, alcohol, and marijuana during pregnancy.



Tests of mental development at 6.5, 12, and 24 months showed average scores of cocaine-exposed and unexposed children from comparable backgrounds were below the normative score of 100 for children in the general population. At age 2, cocaine-exposed children did significantly poorer in mental development than children in the comparison group.

Researchers measured the children's developmental progress at 6.5, 12, and 24 months of age with the Bayley Scales of Infant Mental and Motor Development. Motor tests assessed the infants' ability to control and coordinate their movements. Mental tests assessed language, memory, and ability to solve problems at 12 and 24 months. For example, children were asked to describe objects in pictures, remember where an object had been hidden, and put shaped objects into the correct spaces cut out on form boards.

To isolate cocaine's effect, researchers adjusted test results for the effect of other risk factors, such as other drugs used during pregnancy; characteristics of biological mothers and alternative caregivers; the infants' head size, weight, length, and gestational age at birth; and the quality of their postnatal home environments. The analysis showed that while prenatal cocaine exposure had not affected the infants' motor development, it was clearly linked to significant deficits in their cognitive performance at age 2. Cocaine-exposed children scored 6 points lower on the Mental Development Index (MDI), averaging 82.7 percent compared to 88.7 percent for unexposed children and an average general population score of 100. Other findings include the following:

- From 6.5 to 24 months, MDI scores declined for both groups, but cocaine-exposed children had a greater decline—14 points compared to a 9-point decline for unexposed children.
- Almost 14 percent (13.7 percent) of cocaine-exposed children had scores in the mental retardation range, below 70 on the MDI, nearly twice the 7.1-percent rate found in the unexposed children and almost five times the rate (about 2.8 percent) expected in the general population.
- Nearly 38 percent (37.8 percent) of cocaine-exposed children had developmental delays requiring remedial intervention, nearly double the 20.9 percent rate for unexposed children.

The study found that other influences, including the mother's intelligence scores and educational level, exposure to other substances, and the quality of the postnatal home environment, also played significant roles in poor outcomes for cocaine-exposed children. "However, after controlling for these factors in our analysis, we found that cocaine still has a harmful effect on cognitive

performance," Dr. Singer says. Additional support for this conclusion comes from mothers' self-reports and biological data from mothers and infants that established a direct link between cocaine dose and toddlers' cognitive performance. These data showed that children of mothers who used more cocaine and used it more frequently during pregnancy performed worse on the MDI than children of mothers who used less of the drug.

"The only risk factor we couldn't completely control for is the effect of other drugs used during pregnancy," Dr. Singer says, "because it is nearly impossible to find children who have been exposed only to cocaine." The study partially adjusted for this influence by including children who had been heavily exposed to alcohol, tobacco, and marijuana in both groups. "Animal studies suggest there are possible synergistic effects of these drugs in combination, and the study may not have been large enough to control for these effects," she notes.

"We believe that cocaine exposure is a neurologic risk factor that may take a poor child who has a lower IQ potential because of maternal and other risk factors and push him or her over the edge to mental retardation," Dr. Singer says. For example, average IQ scores for both cocaine-exposed and unexposed toddlers in the study were well below the average score for the general population. "In effect, cocaine lowered the range of IQ scores and that means more children may require early stimulation and educational programs," she says.

"While many children in this study may require special educational services when they enter school, it is important not to assume that the findings from a single study, with its unique characteristics, necessarily apply to all cocaine-exposed children," cautions NIDA's Dr. Smeriglio. Ultimately, NIDA's extensive portfolio of research on groups of cocaine-exposed children being raised in a variety of settings should provide detailed information about mother, child, environment, and drug-use characteristics that can be used to develop interventions that reduce risk of harm and guide clinical care for cocaine-exposed children.

Source

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Women and Smoking: Sensory Factors, Attitudes About Weight, Phase of Menstrual Cycle All Key To Quitting

By Jill S. Williams, NIDA NOTES Contributing Writer

NIDA-funded researchers are studying gender differences in smoking behavior and working to develop treatment plans that will help more women end their nicotine addiction. Three recent studies headed by Dr. Kenneth Perkins of the University of Pittsburgh add to this knowledge and test new treatment approaches for women.

In one set of studies, Dr. Perkins has found that the smell and taste of cigarettes play a greater role in women's smoking behavior than in that of men. Another study found that cognitive-behavioral therapy aimed at changing attitudes about weight promotes smoking cessation by women. Additionally, Dr. Perkins found that menstrual cycle phase has an effect on both mood and tobacco withdrawal symptoms for women trying to quit smoking—a finding that suggests that women could improve their success rate simply by starting their quit attempt during certain days of their cycle.

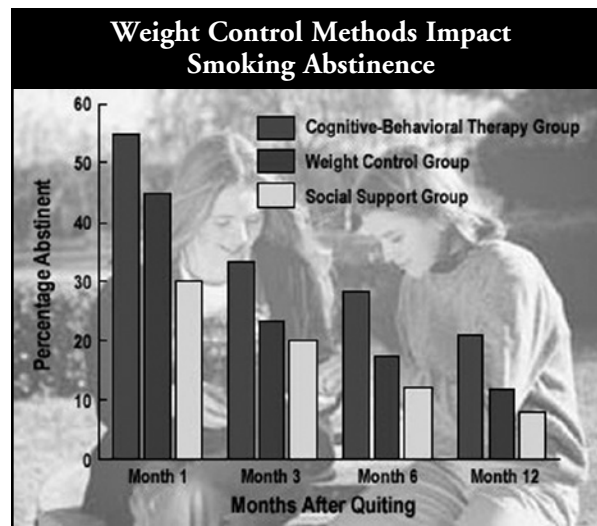
Sensory Factors in Smoking

Dr. Perkins and his colleagues used a set of laboratory studies to examine the effects of sensory cues—seeing a lit cigarette and smelling and tasting smoke—on smoking behavior of women versus men. In one of the studies, researchers recruited 51 young smokers (21 men, 30 women) from the nearby community for what subjects were told was a test of different kinds of cigarettes. The smokers wore opaque goggles or swimmers' noseclips while smoking to test the roles that visual and olfactory cues—that is, cues related to seeing and smelling—play in smoking pleasure and reinforcement. Researchers measured smoking reinforcement—the number of puffs taken in different situations—and pleasure—using subjective measures such as the Rose Sensory Questionnaire—to assess the extent that sensory cues reinforce smoking.

They found that blocking olfactory stimuli made a greater difference to women than to men. While pleasure in smoking was reduced for both women and men when visual and olfactory cues were blocked, women found significantly less pleasure in smoking and also smoked less than men under the blockade conditions. This study

shows that sensory cues play a larger role in smoking for women than for men and further demonstrates that the olfactory cues, not the visual, were the cause of the difference.

Dr. Perkins has recently tested the effects of nicotine "dose" in cigarettes on smoking pleasure and reinforcement in 30 men and women smokers. The smokers sampled, rated, and then smoked their regular brand of cigarette or an ultra-low-nicotine cigarette, both of which were presented with brand markings concealed. The nicotine dose of cigarettes had less effect on self-reported pleasure and reinforcement in women compared to men, consistent with the notion that nicotine may be a less important influence on smoking behavior in women than in men.



Women who participated in cognitive-behavioral therapy, learning to accept a modest weight gain while trying to quit smoking, achieved greater abstinence levels than those in the weight control group, who were given daily calorie goals, or the social support group, who received counseling that did not focus on weight issues.

“Because women pay more attention to cues related to smell than do men,” says Dr. Perkins, “they could benefit from counseling to avoid those cues and could learn cognitive coping strategies to reduce the urge to smoke.” Such behavioral counseling is not now used widely or effectively, he says. He suggests that future research could focus on other conditioned reinforcers of smoking, such as brand markings, “hand-mouth” activity, environmental contexts, and consumption of other drugs (such as caffeine or alcohol), with the goal of finding ways to extinguish the reinforcing effects of these stimuli or finding sensory substitutes.

Dr. Cora Lee Wetherington, NIDA's Women and Gender Research Coordinator, points out that this study is consistent with other research showing that women may benefit less from the nicotine patch or gum but more from the nicotine inhaler than do men. "Women lose both the sensory cues and the nicotine when they quit smoking," she says. "Therefore, replacing those cues—something the inhaler can do, but not the patch or gum—and learning ways to avoid or cope with those cues may help more women succeed in quitting."

Attitudes About Weight Gain

Previous smoking cessation trials have found that more than half of women smokers have a hard time quitting, at least partly because of concerns about weight gain. The average postquit weight gain of 10 pounds sabotages many attempts to quit smoking early on and causes some women to resist even trying to quit, to drop out of treatment, or to relapse after quitting. Research has found that dieting to prevent this weight gain is ineffective and may actually interfere with quit efforts. Now, a new study has shown that cognitive-behavioral therapy (CBT) aimed at reducing dietary restraint and changing attitudes about weight proved more successful at both controlling weight gain and promoting smoking cessation.

Dr. Perkins and his colleagues studied 219 women between the ages of 18 and 65 who wanted to quit smoking but were significantly concerned about gaining weight, as determined by telephone interviews during subject recruitment. The women, divided into three treatment groups, all received standard smoking cessation counseling. Each group also received either behavioral weight-control counseling, CBT to reduce weight concerns, or social support not focused on weight issues.

Members of the weight-control group were given daily calorie goals and instructed to track food intake in a diary, with the goal of reducing between-meal snacking (the primary source of excess calorie intake after quitting smoking). These women successfully prevented any weight gain in the month after quitting, as expected.

The CBT group received therapy to help them accept a modest weight gain in light of the benefits of quitting smoking. In putting together a CBT approach for smokers, Dr. Perkins turned to his colleague Dr. Marsha Marcus, who is an expert on eating disorders. "We wanted to help women accept the likelihood that they may gain 5 to 10 pounds, and we used CBT to modify their attitude toward that weight gain," she says. "We identified unrealistic thoughts or beliefs about weight gain and smoking, and we developed cognitive approaches to counteract those thoughts. Our key message was, 'adopt moderation

in eating, reduce stress levels, and exercise more during an attempt to quit smoking.'"

At 1-year followup, 21 percent of the CBT group had successfully quit smoking, compared with 13 percent of the weight-control group and 9 percent of the social support group. Weight gain for those continuously abstinent at 1 year averaged 6 pounds for the CBT group, 12 pounds for the weight-control group, and 17 pounds for the social support group.

"Health care providers and smokers should be aware that the CBT approach has more promise than the diet approach," says Dr. Perkins. He suggests that future research can distill the key elements of the CBT intervention so it can be delivered concisely and test a combination of CBT with medication to further improve outcomes.

Today, researchers are paying more attention to the possibility of sex differences and analyzing those differences in their own data. "Both women and health care providers should recognize the obstacles women face and consider how to approach them to maximize their chances of success at quitting smoking," says Dr. Perkins.

Dr. Wetherington sees great value in this type of research: "Because of the gender-based approach Dr. Perkins has taken, we are beginning to see that what works best for males may not work best for females, and vice versa. We are beginning to develop better treatment strategies."

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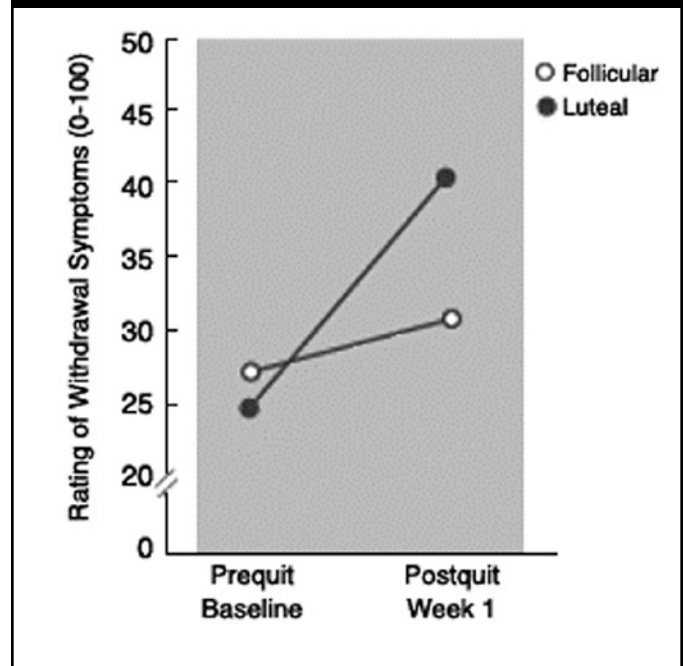
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Timing Quit Date May Help Women Smokers

Women trying to quit smoking may be able to improve their success rate by starting their quit attempt on certain days of their cycle. In the course of the larger smoking cessation trial focused on weight issues, Dr. Perkins also examined tobacco withdrawal and mood measures for 78 premenopausal women who maintained smoking abstinence for 1 week after quitting. Half of the women quit during the follicular phase of their menstrual cycle (days 1 through 14) and half quit during the luteal phase (day 15 or later). He found that women quitting during the luteal phase reported significantly more tobacco withdrawal symptoms and depression than those who quit during the follicular phase.

“This research suggests a clear behavioral prescription for increasing the odds of success in quitting,” says Dr. Perkins. “Women should set a quit date early in the follicular phase. Withdrawal symptoms and depression may be less intense. If withdrawal is blunted, quitting should be easier. And this simple strategy for timing the quit day costs nothing.” **NN**

Tobacco Withdrawal Symptoms, Luteal Versus Follicular Phase



Withdrawal symptoms for luteal-phase women 1 week after quitting smoking were significantly higher than those of follicular-phase women. Symptoms of irritability, anxiety, difficulty concentrating, restlessness, impatience, hunger, and depression were rated by participants on a scale ranging from 0 (none) to 100 (extremely intense). The graph illustrates mean values for all symptoms combined.

Prenatal Exposure to Ecstasy May Impair Memory and Cognition

By Jill S. Williams, NIDA NOTES Contributing Writer

Dr. Harry Broening, Dr. Charles Vorhees, and colleagues at the Cincinnati Children's Research Foundation and the University of Cincinnati have demonstrated that rats exposed to MDMA—ecstasy—during the developmental period corresponding to the third trimester of human pregnancy suffer memory and learning deficiencies that persist into adulthood.

Scientific studies have already established that ecstasy users are at risk for dehydration, hypertension, hyperthermia, and heart or kidney failure. The drug also has been shown to damage nerves in the brain's serotonin system and appears to produce long-term deficits in memory and cognition. The new study suggests that unborn children of ecstasy users may suffer deleterious effects that last into adulthood. "The possibility that these findings in rats may also apply to humans raises a concern because this drug, which is incorrectly perceived as safe by many of its proponents, is sometimes being used by young women who are pregnant," says Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research.

Timing and Vulnerability

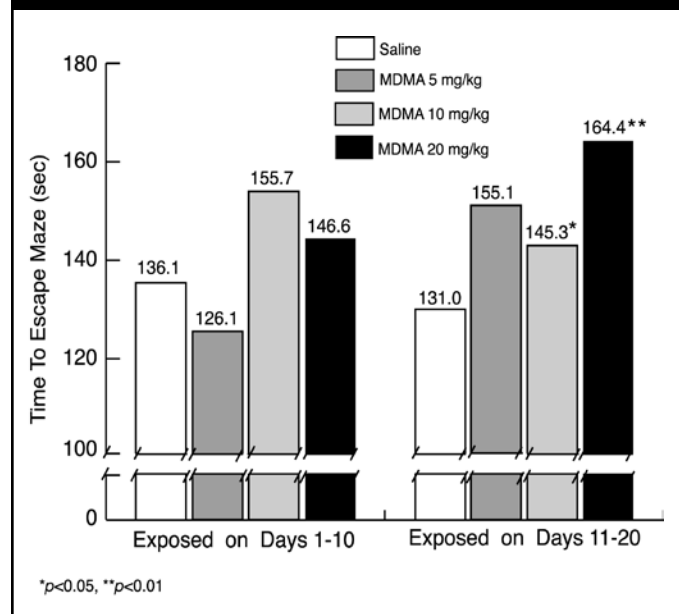
In designing the current study, the researchers drew on previous studies by Dr. Vorhees on the effects of methamphetamine exposure on rodent brain development. These studies identified specific periods late in rodent brain development—days 11 to 20 after birth, which are analogous to late third-trimester human fetal brain development—in which the brain is quite vulnerable to methamphetamine-induced impairments of spatial learning and memory. The question became, can related drugs, such as MDMA and other synthetic stimulants, also cause such impairments?

Dr. Vorhees and his colleagues decided to test the effects of MDMA administered to rats at this same crucial 11 to 20 days postnatal developmental period and to a comparison group of rats on days 1 to 10 after birth (comparable to early third trimester of human pregnancy). According to Dr. Vorhees, the dosages given to rats in the study are equivalent to a 110-lb woman taking 25 mg, a common dose for MDMA users, up to 250 mg, an amount sometimes reached or exceeded by chronic abusers.

Testing for Learning, Memory

When the rats reached young adulthood, the researchers put them through a series of maze and swimming trials

Animals Exposed to MDMA Take Longer To Escape Multiple-T Water Maze



Adult rats that had been exposed to MDMA doses of 10 or 20 mg/kg body weight (comparable to doses used by human MDMA abusers) on days 11 to 20 after birth (a period comparable to late in the third trimester of human pregnancy) took significantly longer to escape the multiple-T water maze than did animals exposed to saline solution. No statistically significant increase in escape times was observed among rats exposed on days 1 to 10 after birth.

to assess the effects of MDMA exposure on learning and memory. An initial test revealed no significant differences between the MDMA-exposed rats and the controls in terms of swimming performance or motivation to escape from the water. Next, animals were evaluated in a test of sequential learning called the multiple-T (Cincinnati) water maze. The rats had to search through nine decision points to find their way through the maze and out of the water. The researchers found that the rats exposed to MDMA on days 11 to 20 after birth made significantly more errors and took significantly longer to escape the maze than did either the MDMA-unexposed animals or those exposed to MDMA on days 1 to 10 after birth.

"The animals exposed to MDMA during the critical 11 to 20 days postnatal brain development period cannot seem to eliminate errors the way normal animals do," says Dr. Vorhees. "The difference is the rate at which they learn.

All of the animals eventually learned how to navigate the maze, but it took the MDMA-exposed animals significantly longer to do so.”

The Morris hidden platform maze was used to further evaluate the animals’ spatial memory and cognitive abilities. A 6-foot diameter swimming pool was constructed and a small clear acrylic platform was placed so that the animals could escape if they found it. In increasingly difficult phases the rats had to find the platform when it was above the water, below the water, moved to a new location, or below the water and reduced in size. Memory trials were also performed with the platform removed. Animals exposed to MDMA on days 1 to 10 after birth performed as well as unexposed animals on the trials. However, the animals exposed to MDMA on days 11 to 20 after birth showed significant impairment of memory and spatial learning when the platform was submerged and on memory trials when the platform was removed, but no differences when the platform was above the water.

“These later trials test the animals’ ability to remember something in space,” explains Dr. Vorhees. “We found that as we made the task harder, MDMA-exposed animals had a disproportionately harder time finding the platform. The harder the task was, the more their learning disability was revealed.”

Comparing Infant Versus Adult Exposure

Upon completion of the trials, the rats were sacrificed and their brains were preserved for later analysis. The researchers wanted to know if animals exposed to MDMA during early brain development would show the same pattern of damage to neurotransmitters that has been shown in adult animals exposed to MDMA. They did not. “This was a surprise because we didn’t find the same damage to neu-

rotransmitters as was found in previous studies of animals exposed to MDMA as adults,” says Dr. Vorhees. “Yet, the animals in the current study still show cognitive impairment, as demonstrated by their performance on the learning and memory trials.” He hypothesizes that a different mechanism is at work in animals exposed to MDMA during brain development that later affects their memory and learning ability. Future research will focus on identifying this mechanism.

Dr. Frankenheim points out that this research is a warning that what is happening in animals may also happen with people. “The work of determining what drugs of abuse do to fetuses when the mother takes them is very difficult. It is not yet known whether human fetuses exposed to MDMA will develop persistent memory and learning problems. However, these findings in rats raise the concern that MDMA may pose a previously unrecognized risk to the developing human brain,” he says.

Future research will involve determining whether there are effects of MDMA exposure at earlier points in fetal development, such as during the period corresponding to the first trimester in humans, when drug exposure is more likely for women who may not yet be aware that they are pregnant. The first trimester is also the developmental period when humans are most sensitive to neurotoxins.

Source

- Broening, H.W.; Morford, L.L.; Inman-Wood, S.L.; Fukumura, M.; and Vorhees, C.V. 3,4-methylenedioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. *Journal of Neuroscience* 21(9):3228–3235, 2001. **NN**

In Drug Abuse, Gender Matters

By NIDA Acting Director Glen R. Hanson, Ph.D., D.D.S.

Recent decades have seen a marked increase in awareness of the importance of gender in medical treatment and research. In the complex field of drug abuse research, scientists have helped us understand that there are genetic, physiological, psychosocial, and environmental dimensions to drug abuse and addiction. Male and female differences in any of these dimensions can give rise to gender differences in the causes, effects, and consequences of drug abuse. Researchers and clinicians have developed a repertoire of effective treatment and prevention principles that can now be enhanced through their adaptation for the differing needs of men and women and boys and girls.

NIDA's National Drug Abuse Treatment Clinical Trials Network adheres to the overall National Institutes of Health requirement for analysis of data by gender and supports gender-specific protocol development. NIDA recently issued a Program Announcement for support of dissertation research in five areas, one of which is women and gender. A new Program Announcement on Women and Gender Differences will be issued soon to fund research specifically in the areas of epidemiology, prevention, and treatment.

These efforts will build on NIDA-sponsored research that has established that important gender effects exist in biological and behavioral responses to drugs, risk for drug abuse, and treatment response.

Response to drugs: The neurobiological basis of drug abuse and addiction is essentially the same, regardless of the drug taken or the person taking it. Still, males and females may differ in their biological and behavioral responses to drugs. Laboratory studies have revealed sex-related differences in the ways that male and female animals metabolize drugs, the amount of drug they will self-administer, how soon after their first exposure they begin to administer drugs, and their vulnerability to

relapse after abstinence. Preliminary results from studies of human drug abusers appear to be consistent with the findings from animal studies of gender differences in the patterns and the biological impact of drug use. For example, women typically progress from first use of cocaine, heroin, or marijuana to dependence more quickly than men. Additionally, cocaine-induced cognitive impairments and risk for stroke have been found to be more severe in men than in women.



Researchers and clinicians have developed a repertoire of effective treatment and prevention principles that can now be enhanced through their adaptation for the differing needs of men and women and boys and girls.

Risk for drug abuse: While risk factors related to drug abuse vulnerability in males and females largely overlap, a variety of differences exist. Depression is much more common among women than men in the general public. This gender difference is much less pronounced among drug abusers. Possible explanations are that depression is a more potent risk factor for drug abuse among men than among women, or that drug abuse itself is more likely to cause depression among men than among women. Other risk factors that appear to be stronger for one gender than the other include conduct disorders, which correlate more with drug abuse by adolescent females, and aggression, which correlates with drug abuse by adolescent males.

Along with these differences, studies of gender and risk have revealed an unexpected and important similarity between males and females. Most experts long assumed that females were less attracted to or more wary of drug abuse than were males. That seemed a straightforward conclusion based on the fact that the percentage of women who abuse drugs is lower than the percentage of men who abuse drugs. However, the conclusion turns out to be not true. A recent study found that the lower rate of drug abuse for females is largely a matter of opportunity. (See "Gender Differences in Prevalence of Drug Abuse Traced to Opportunities to Use.") During the youthful ages when most drug abuse initiation occurs, more boys than girls receive offers of drugs. When drug offers are made, both genders are equally likely to accept. Once hav-

ing accepted, males and females generally are equally likely to become dependent. This underscores the importance of drug refusal skills in prevention efforts with both genders.

Although the focus on gender is relatively new in drug abuse science, we already know that gender's impact is far reaching and complex.

Response to treatment: Success in drug treatment is directly associated with the length of time spent in treatment: The more time in treatment, the better the outcome. Science-based drug treatments are equally effective for men and women, but women often spend less time than men in treatment. In part, this could reflect differences in social and economic circumstances. Women entering treatment are more likely than men to be custodial parents and to have fewer economic resources; they are less likely than men to have graduated from high school, to be employed, or to have sufficient supportive social networks. Studies also indicate that males and females tend to relapse to drug use for different reasons. For example, among men relapse is more likely to be associated with anxiety and positive feelings, while among women depression and negative feelings appear to be more

common triggers. All these differences suggest that it may be possible to enhance the effectiveness of treatment by tailoring it for the patient's gender.

The area of nicotine addiction is one in which our understanding of gender effects is relatively advanced, although still far from complete. Research has shown that different aspects of smoking more strongly influence addiction to nicotine in men and women. For men, the compulsion to smoke is driven more strongly by nicotine's pharmacological effects on the brain, while women's addiction owes more to the visual, tactile, taste, and olfactory sensations involved in smoking. Because of these differences, men tend to get more relief overall from nicotine replacement therapy, and women who use nicotine replacement do better with nicotine inhalers than the nicotine patch. Recent NIDA research also suggests that women can increase their chances for quitting by timing their attempt to coincide with the first half of their menstrual cycles, since nicotine craving and withdrawal symptoms are generally more severe during the second half of their cycles.

Although the focus on gender is relatively new in drug abuse science, we already know that gender's impact is far reaching and complex. A comprehensive and detailed picture of gender-related effects can lead to improvements in treatment and prevention efforts that bring us closer to the goal of individualized interventions that best meet the distinct needs of each patient. When it comes to reducing the tremendous burden of drug abuse and addiction, gender most certainly matters. **NN**

Prenatal Exposure to Methamphetamine Increases Vulnerability to the Drug's Neurotoxic Effects in Adult Male Mice

By Kimberly R. Martin, NIDA NOTES Contributing Writer

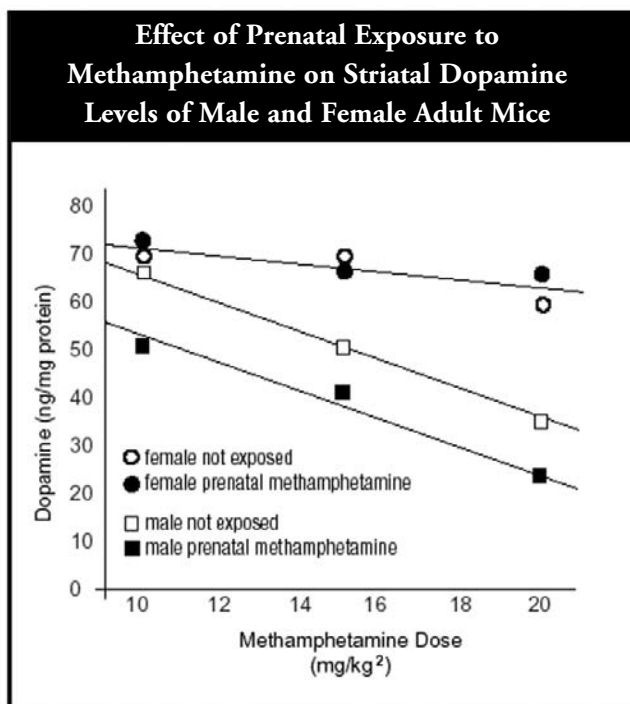
A NIDA-funded study has shown that exposure to methamphetamine before birth results in more severe neurotoxic effects in male mice given the drug as adults than in females. These findings raise concerns regarding the long-term health consequences of methamphetamine use, particularly for men who were exposed to the drug *in utero*.

"Many young people using club drugs such as methamphetamine are cavalier about its dangers. They mistakenly believe that they can use these drugs with no consequences," says Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research. "Although this study was conducted in mice, these findings suggest that the children, especially sons, of pregnant women who abuse methamphetamine may suffer the consequences of their mothers' actions later in life."

To investigate the effects of methamphetamine exposure *in utero*, Drs. Alfred Heller and Lisa Won at the University of Chicago injected pregnant female mice with neurotoxic doses of methamphetamine or saline twice daily from gestational days 7 through 18. At 11 weeks of age (equivalent to young adulthood), the offspring received two injections of either saline or methamphetamine in a range of doses. Rectal temperatures were measured hourly from just before the first injection to at least 4 hours after the second injection. Seven days later, the mouse brains were analyzed for dopamine and its metabolites in the striatum, ventral and dorsal brainstem, cortex, and cerebellum.

Fetal exposure to methamphetamine alone did not affect dopamine or its metabolite levels, but after methamphetamine exposure of the adults, considerable differences were observed between the adult male and female offspring. Adult males had lower levels of dopamine and its metabolites in the striatum and cortex than did females. In addition, the prenatally methamphetamine-exposed males had greater reductions than any other group. A 20 mg/kg dose of the drug in an adult produced a 70-percent reduction of striatal dopamine in prenatally methamphetamine-exposed males, compared to a 55-percent reduction in unexposed males. Females showed a 14- to 25-percent reduction in striatal dopamine. In the brainstem, only the prenatally methamphetamine-exposed males suffered a reduction of dopamine from exposure to the drug as an adult. Effects of methamphetamine on cortical dopamine were not enhanced by prenatal exposure to the drug.

"The increased dopamine losses observed in prenatally exposed males in response to adult exposure to the drug occurred in the regions of the brain that are affected by neurological disorders such as Parkinson's disease," says Dr. Heller. "If similar neurological effects are occurring



Adult mice were given two doses of methamphetamine 2 hours apart. One week after the drug injections, their brains were analyzed for dopamine. Males that had been prenatally exposed to methamphetamine had a greater reduction in striatal dopamine levels compared with females and unexposed males.

Methamphetamine is known to be a neurotoxic agent that damages the endings of brain cells containing dopamine, a brain chemical that regulates movement, emotion, motivation, and feelings of pleasure. Previous research in animals has indicated that methamphetamine causes damage to cells in the striatal and cortical regions of the brain. In humans, these regions are associated with memory, cognitive function, and movement.

in humans, males whose mothers used methamphetamine during pregnancy may be at a greater risk for developing these ailments.”

Previous research has indicated that the neurotoxic effects of methamphetamine are associated, in part, with its ability to raise body temperature. Hyperthermia, however, did not account for the increased susceptibility of prenatally methamphetamine-exposed males compared to other males. Adult males exhibited the same rise in body temperature whether or not they had been exposed to methamphetamine *in utero*.

The hyperthermic effects of methamphetamine were a contributing factor to the differences in neurotoxicity observed between males and females. Adult females did not exhibit a change in body temperature in response to methamphetamine exposure, while adult males did exhibit a rise in body temperature.

“The finding that the female mice in this study did not experience the same degree of neurotoxicity or hyperthermic effects when given methamphetamine as adults does not mean that female offspring are safe from harm,” cautioned Dr. Heller. “Other research indicates that the age of adult exposure to methamphetamine may play a role in susceptibility to the drug’s effects. This study was conducted in animals that were equivalent to young adults. The same findings may not hold true for younger or more mature female mice.”

Source

- Heller, A.; Bubula, N.; Lew, R.; Heller, B.; and Won, L. Gender-dependent enhanced adult neurotoxic response to methamphetamine following fetal exposure to the drug. *Journal of Pharmacology and Experimental Therapeutics* 298:769–779, 2001. **NN**

High-Risk Sex Is Main Factor in HIV Infection for Men and Women Who Inject Drugs

By Robert Mathias, NIDA NOTES Staff Writer

A 10-year study has found that the biggest predictor of HIV infection for both male and female injecting drug users (IDUs) is high-risk sexual behavior, not sharing needles used to inject drugs. High-risk homosexual activity was the most important factor in HIV transmission for men; high-risk heterosexual activity was most significant for women. Risky drug-use behaviors also were strong predictors of HIV transmission for men but were less significant for women, the study found.

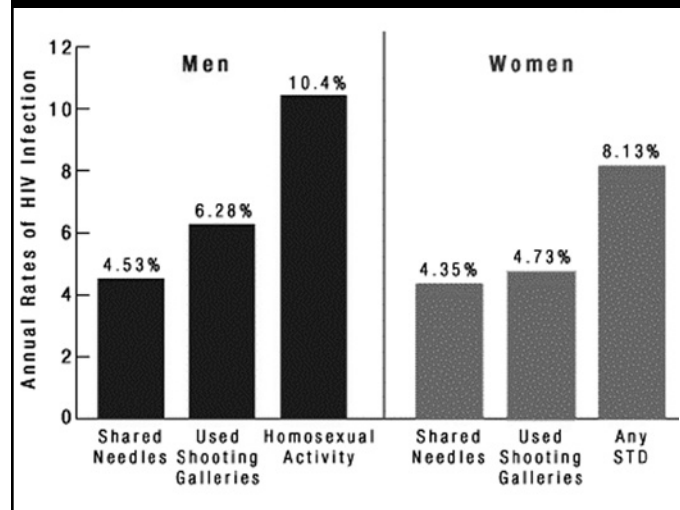
“In the past, we assumed that IDUs who were HIV-positive had been infected with the virus through needle-sharing,” says Dr. Steffanie Strathdee of the Johns Hopkins University Bloomberg School of Public Health in Baltimore, who conducted the NIDA-funded study. “Our analysis indicates that sexual behaviors, which we thought were less important among IDUs, really carry a heavy weight in terms of risks for HIV seroconversion for both men and women.”

In the study, Dr. Strathdee led a team of researchers who analyzed data collected every 6 months from 1,800 IDUs in Baltimore from 1988 to 1998. Participants had to be at least 18 years of age when they entered the study, have a history of injection drug use within the previous 10 years, and not have HIV infection or AIDS. More than 90 percent of the participants said they had injected drugs in the 6 months prior to enrolling in the study. In their semi-annual interviews, study participants reported their recent drug use and sexual behavior and submitted blood samples to determine if they had become HIV-positive since their last visit.

Researchers analyzed the role of homosexual activity in HIV seroconversions among male IDUs in the study, after taking into account other factors that increased their risk of acquiring HIV, such as their drug injection practices. This analysis revealed that the incidence of HIV infection among male IDUs who had engaged in homosexual activity within the previous 6 months was 10.44 percent a year, compared to 3.01 percent among men who did not report having homosexual sex.

Visiting “shooting galleries,” where drug abusers gather to obtain and inject drugs, sharing needles used to inject drugs with multiple partners, and injecting drugs daily also were independently linked to significantly higher rates of HIV infection among men in the study. Men who said they had used shooting galleries had an HIV incidence

High-Risk Sexual Behavior Leading Cause of HIV Infection Among Injection Drug Users in 10-Year Study



High-risk sexual behavior played the biggest role in HIV infection for both male and female injection drug users (IDUs) in this study of 1,800 IDUs. Significant risk factors for men were high-risk homosexual activity, using shooting galleries, and sharing needles used to inject drugs with multiple partners. For women, high-risk heterosexual activity, as indicated by reporting a recent sexually transmitted disease (STD), was the most significant cause of HIV infection.

rate of 6.28 percent per year, and men who shared needles with more than one partner had a rate of 5.52 percent per year. These infection rates were more than double those found among men who had not engaged in these behaviors. Men who injected drugs at least once a day had HIV infection rates of 4.68 percent, more than one and one-half times the rate among men who had injected less than once a day.

Sharing needles also increased risk of HIV infection among women IDUs. However, high-risk heterosexual activity was a much more important risk factor for these women, the study found. In fact, other than being younger than 30 years—which independently predicted HIV infection for both sexes—high-risk heterosexual activity was the main predictor of HIV seroconversion among women. Women who reported having a recent sexually transmitted disease (STD), an indicator of

unprotected sex, had more than 2.5 times the rate of HIV infection of women who did not have an STD.


“Both homosexual men and heterosexual women IDUs appear to be at dual risk for becoming infected with HIV,” Dr. Strathdee says. “In previous studies by our group, being a gay male IDU was closely linked to visiting shooting galleries and sharing needles. Heterosexual women IDUs tend to have more of an overlap in their sexual partners and their drug use than men do. This puts them at increased HIV risk because they are sharing needles and having unprotected sex with a partner who is more likely to be infected with the virus.

“HIV prevention programs have done a good job in reducing needle-sharing and other drug-use behaviors that spread the virus among IDUs,” Dr. Strathdee says. “However, our study indicates that HIV prevention programs can achieve better results by also addressing sexual risk behaviors among IDUs. A multifaceted approach is needed that screens both men and women IDUs for STDs at places where they go, such as needle-exchange programs

and methadone treatment programs, and provides comprehensive treatment at those sites.

“HIV prevention efforts also should be gender-specific, targeting the important differences we have found in sexual and drug-use behaviors among men and women that increase their risk of acquiring and transmitting HIV,” Dr. Strathdee says. “For example, women IDUs in stable relationships could be shown how to negotiate condom use with their partners and offered couple counseling to educate both partners about HIV risks associated with their drug use and sexual behaviors. We need more research to identify and evaluate HIV prevention approaches for male IDUs who have sex with men to determine what kinds of interventions might work.”

Source

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Cocaine's Effects on Cerebral Blood Flow Differ Between Men and Women

By Jill S. Williams, NIDA NOTES Contributing Writer

Researchers studying the effects of cocaine on the brain have found that men and women with comparable drug use histories do not exhibit comparable damage. One study showed that women suffered less neuronal injury than men; another, that cocaine-dependent women have fewer abnormalities in blood flow to the brain than do cocaine-dependent men. Now, a recent NIDA-funded study has taken an important step toward explaining these differences between the sexes.

Cocaine constricts blood vessels, temporarily narrowing arteries and reducing blood flow to the brain, heart, and other areas of the body. Repeated exposure to cocaine can lead to blood-flow deficits in the brain that persist long after cocaine use has ended, causing permanent damage.

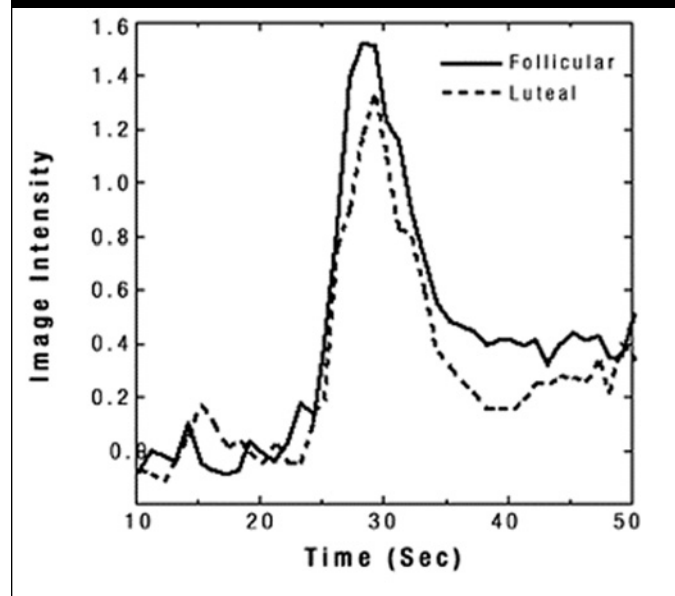
Dr. Marc J. Kaufman and colleagues at McLean Hospital, Harvard Medical School, in Belmont, Massachusetts, found that cerebral blood flow during the follicular phase of women's menstrual cycles (days 1 through 14, prior to ovulation) is not affected by exposure to cocaine. In women during their luteal phase (after ovulation, typically days 15 through 28) and in men, cocaine restricts cerebral blood flow.

"We hypothesized that the differences in blood flow might be caused by sex hormones," says Dr. Kaufman. "We decided to investigate whether women with high levels of estrogen, which improves blood-vessel elasticity, are more resistant to the vasoconstrictive effects of cocaine."

Dr. Kaufman and his colleagues used dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) to study cocaine-induced changes in cerebral blood volume in 13 healthy young women (average age 28) with histories of occasional cocaine use. The women's self-reported lifetime cocaine use averaged 13 exposures (ranging from 1 to 40).

Each woman was given a dose of cocaine and underwent a DSC MRI scan of cerebral blood volume during both phases of her menstrual cycle. During the first part of the menstrual cycle, estrogen levels are high and progesterone levels are low; during the second part, progesterone levels rise. In each imaging session, two brain images were collected: one as a baseline measure of cerebral blood volume and the second 10 minutes after cocaine administration.

Cocaine's Effect on Cerebral Blood Volume Varies Throughout Menstrual Cycle



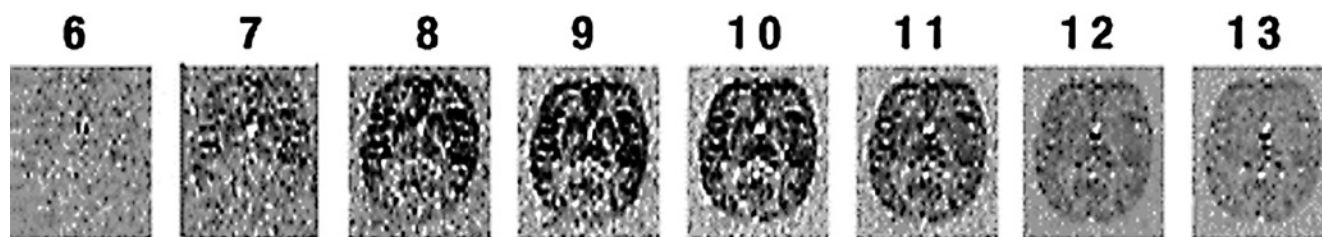
Magnetic resonance (MR) image intensity was measured to compare the hemodynamic effects of cocaine during two phases of a woman's menstrual cycle. Following cocaine administration during the follicular phase, image intensity was relatively high, reflecting cerebral blood flow at 97 percent of its pre-cocaine baseline. When the drug was given during the luteal phase, lower image intensity reflected a fall in blood flow to 82 percent of baseline. The MR technique is illustrated on the next page.

The study found no significant changes in cerebral blood volume after cocaine administration during the women's follicular phase. During the luteal phase, when progesterone levels are highest, the women's cerebral blood flow fell approximately 10 percent after cocaine administration. These data compare to Dr. Kaufman's findings in a similar 1998 study, that men experience, on average, a 20-percent reduction in cerebral blood volume after cocaine administration.

"We found what we were expecting," says Dr. Kaufman. "There was a minimal change in follicular cerebral blood volume, attributable, we believe, to the protective effects

Using Magnetic Resonance Imaging (MRI) To Track Cerebral Blood Volume

Seconds After Contrast Injection



A sequence of magnetic resonance images taken at 1-second intervals after a woman received an intravenous blood marker progresses from light to dark to light as her cerebral blood flow carries the marker into her brain and washes it back out again. The total marker present in all the images, measured as their intensity (darkness), reflects total cerebral blood volume. To study the hemodynamic effects of cocaine, investigators compared two such sequences, obtained before and after administration of the drug, during each menstrual period.

of estrogen. The greater vasoconstrictive effect of cocaine in luteal-phase women may be attributable to the progesterone, which has been shown to increase cocaine's vascular toxicity."

Dr. Kaufman's next step will be to administer estrogen or progesterone to men and luteal-phase women and measure the effects on cerebral blood volume after cocaine administration. The ultimate goal will be to develop a hormone-like medication to counteract the vascular effects of cocaine.

"Beyond confirming that cocaine does have a damaging effect on the brain and is not safe to use, this research contributes to our understanding of the drug's deleterious effects," says Dr. Steven Grant, of NIDA's Division of Treatment Research and Development. "Additionally, the

research points out that we've got to stop thinking of both sexes as the same when it comes to the effects of drugs. Dr. Kaufman has shown that cocaine affects men and women differently."

Sources

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Childhood Sex Abuse Increases Risk for Drug Dependence in Adult Women

By Patrick Zickler, NIDA NOTES Staff Writer

Women who are sexually abused during childhood are at increased risk for drug abuse as adults, according to NIDA-supported research conducted at the Medical College of Virginia Commonwealth University in Richmond. Using data gathered from interviews of 1,411 adult twins, Dr. Kenneth Kendler and his colleagues assessed the association between three levels of childhood sex abuse (nongenital, genital, and intercourse) and six adult disorders—major depression, generalized anxiety disorder, panic disorder, bulimia nervosa, alcohol dependence, and drug dependence. Women who experienced any type of sexual abuse in childhood were roughly three times more likely than unabused girls to report drug dependence as adults.

“Overall, childhood sexual abuse was more strongly associated with drug or alcohol dependence than with any of the psychiatric disorders,” Dr. Kendler says. “Only drug and alcohol dependence were significantly associated with all levels of abuse.”

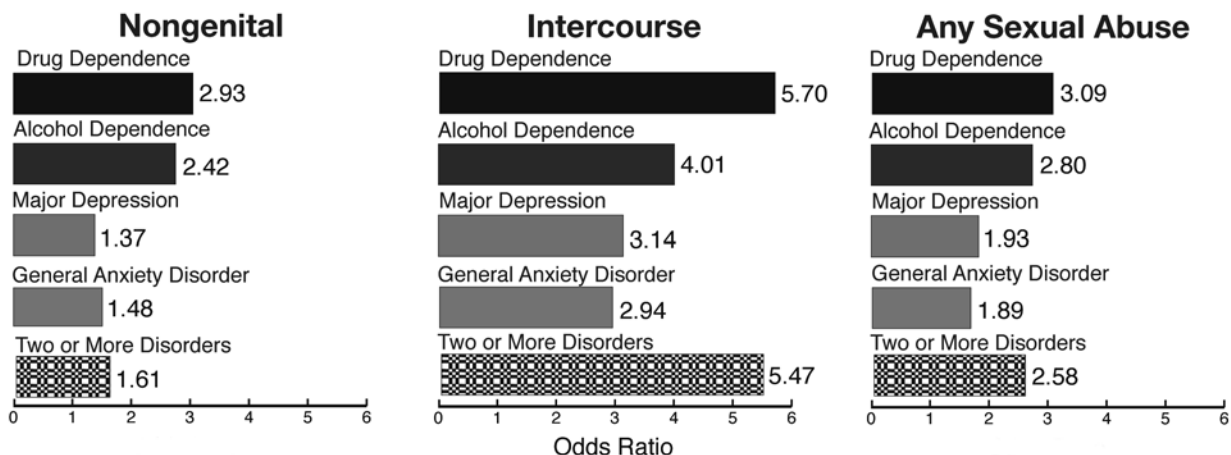
In this study, 1,411 women born between 1934 and 1974 responded to written questionnaires that asked them if,

before they reached age 16, any adult or person older than they had ever (“never,” “once,” or “more than once”):

- involved them in an incident that included an invitation or request to do something sexual;
- kissed or hugged them in a sexual way;
- subjected them to genital display or exposure;
- touched or fondled them in a sexual way;
- made them touch the older person or adult in a sexual way; or
- attempted intercourse.

In addition, the researchers conducted written interviews with 90 percent of the twins’ parents to assess family environment and parental psychopathology. The parental interviews did not mention possible sexual abuse of the children, but did provide data on family financial status; parents’ disciplinary practices, including spanking, slapping, or hitting; church attendance; and measures of harmony, discord, authoritarianism, and protectiveness.

Association of Childhood Sex Abuse With Drug Dependence And Psychiatric Disorders in Adult Women



Among more than 1,400 adult females, childhood sexual abuse was associated with increased likelihood of drug dependence, alcohol dependence, and psychiatric disorders. The associations are expressed as odds ratios: for example, women who experienced nongenital sexual abuse in childhood were 2.93 times more likely to suffer drug dependence as adults than were women who were not abused.

“Controlling for family factors and parental psychopathology produced a small change in some of the associations, but the increased odds of reporting drug or alcohol dependence in adulthood after suffering sexual abuse as a child can’t be explained by these background factors,” Dr. Kendler says.

The women who participated in the research are part of an ongoing research investigation of female twins included in the Virginia Twin Registry, which represents a large cross-section of the population and includes data on a broad range of research topics, including psychiatric and substance abuse disorders.

“This study has particular significance because it is based on data from women in the general population,” says

Dr. Cora Lee Wetherington of NIDA’s Division of Neuroscience and Behavioral Research. “Numerous clinical studies have documented high rates of childhood sexual abuse among women in treatment. This study, the first to document it in a nonclinical population, is particularly important in addressing questions concerning the relationship between sexual abuse and patterns of drug abuse and addiction.”

Source

- Kendler, K.S., et al. Childhood sexual abuse and adult psychiatric and substance use disorders in women: An epidemiological and co-twin control analysis. *Archives of General Psychiatry* 57(10):953–959, 2000. **NN**

Biochemical Brain Abnormality Found in School-Age Children Prenatally Exposed to Cocaine

By Robert Mathias, NIDA NOTES Staff Writer

Exposure to cocaine before birth may affect the way a child's brain functions many years later, according to a recent NIDA-funded study. The brain-imaging study found a chemical abnormality in the brains of 8-year-old children that may reflect alterations in metabolic processes that enable brain cells to use energy and function properly, the researchers say.

"These children were exposed to cocaine only during gestation and their brains have had 8 years to recover from that exposure," says Dr. Joseph Frascella of NIDA's Division of Treatment Research and Development. "It is surprising that they are still showing these deficits so many years later." The new finding suggests that early exposure to drugs has more long-lasting effects on the brain than previously thought, he notes.

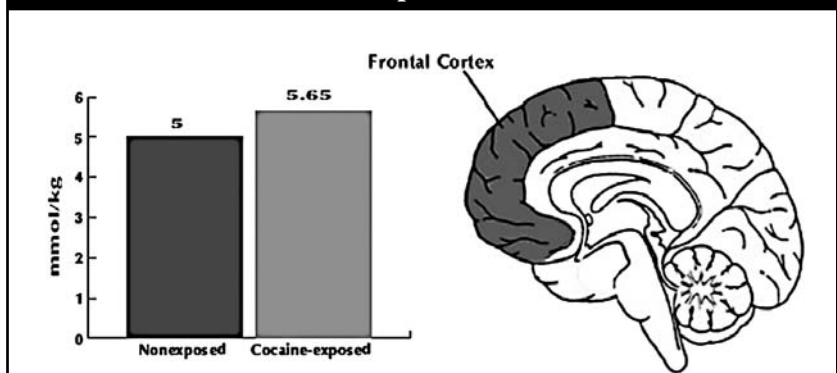
The nature and extent of possible developmental damage to infants and children from prenatal exposure to cocaine has been the subject of much apprehension and scientific study. In the 1980s, anecdotal reports of abnormalities among cocaine-exposed children contributed to fears that these children were irreparably damaged and would never be able to function in society. Subsequent scientific research has dispelled such exaggerated concerns for the vast majority of prenatally exposed children. NIDA-funded studies that have been tracking the development of groups of cocaine-exposed babies through adolescence now indicate that most seem to function normally, but some may have subtle impairments in their ability to control emotions and focus attention that could put them at risk of behavioral and learning difficulties.

Previous brain-imaging studies of children prenatally exposed to cocaine have yielded conflicting information about the drug's effects on the developing central nervous system. Some studies have found abnormalities in brain structure, while others have not. Studies in abstinent adult cocaine abusers, using an imaging technique called magnetic resonance spectroscopy (MRS), have suggested that chronic cocaine use may cause persistent damage to neurons in the frontal lobes of males and that brain metabolic abnormali-

ties also could exist despite a normal-appearing brain structure. Dr. Lynne Smith of the Harbor-UCLA Medical Center in Torrance, California, and Dr. Linda Chang of Brookhaven National Laboratory, in Upton, New York, used this MRS technique to see if similar biochemical abnormalities might be present in the brains of children who had been prenatally exposed to cocaine, even if they appeared to have no structural damage.

The researchers used magnetic resonance imaging (MRI) to assess brain structure and MRS to examine brain biochemistry in 14 8-year-old children who had been exposed to cocaine in the womb. They administered the same brain scans to a control group of 12 age-matched, nonexposed children. The MRS scans measured levels of various chemicals in different brain regions. Increased or reduced concentrations of these chemicals can indicate either damage to nerve cells or alterations in brain cell function in these regions. The researchers assessed a frontal area of the brain, made up of "white matter," which consists mainly of nerve fibers and specialized support cells. They also looked at an area deep in the brain called the basal ganglia, which contains clusters of nerve cell bodies, or "gray matter."

Creatine Level Alterations in Frontal White Matter of Cocaine-Exposed Children



MRS scans suggest cocaine-exposed children did not have significant nerve damage or loss in the brain regions that were examined. However, cocaine-exposed children had significantly higher levels of the brain metabolite creatine than nonexposed children in a frontal area of the brain made up of "white matter," which consists mainly of nerve fibers and specialized support cells. The abnormality may reflect alterations in metabolic processes that enable brain cells to use energy and function properly.

The study found no difference between the exposed and nonexposed children in concentrations of N-acetyl-aspartate (NAA), a nerve cell metabolite, in either the frontal area or the basal ganglia. Because NAA levels are markers for the density and integrity of nerve cells, the normal NAA found in children prenatally exposed to cocaine suggests they did not have significant nerve damage or loss in the two brain regions that were examined. The MRI evaluations also showed no brain structure abnormalities in children in either group. However, cocaine-exposed children had significantly higher levels of creatine in the white matter of the frontal lobes than nonexposed children. Elevated creatine levels indicate that the brain cells of cocaine-exposed children use energy differently in this region.

“All brain cells require creatine for all functions,” says Dr. Chang. “The altered creatine levels we found could affect how both nerve cells and support cells are functioning in the brain. We also have found the same abnormal creatine levels in frontal white matter in adult cocaine abusers more than a year after they have stopped using cocaine. The drug seems to have a particularly long-lasting effect on energy metabolism in this brain area that merits further investigation.”

“The frontal area of the brain is involved in our ability to control impulses and sustain attention on a task,” notes Dr. Frascella. Thus, it is possible that the altered brain function found in this area could be a biological basis for findings from other research that some cocaine-exposed children are more impulsive and easily distracted than their peers. However, additional research is needed to make this determination, he says.

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Similar Long-Term Effects Seen From Prenatal Methamphetamine Exposure

Dr. Linda Chang of Brookhaven National Laboratory in Upton, New York, and her colleagues at UCLA-Harbor Medical Center in Torrance, California, have followed up their brain-imaging study of cocaine-exposed children with a preliminary study of school-age children who were prenatally exposed to methamphetamine. The researchers assessed the same chemical metabolites that they had assessed in the brains of cocaine-exposed children.

“The findings in methamphetamine-exposed children were very similar to what we saw with cocaine-exposed children,” Dr. Chang says. “We found the same abnormalities in creatine levels in the frontal white matter, which indicate altered energy metabolism. Unlike the cocaine-exposed children, methamphetamine-exposed children also showed abnormalities of N-acetyl-aspartate (NAA), a marker of nerve cell integrity, simi-

lar to those seen in adult methamphetamine and male cocaine abusers,” she says. In the adult studies, the researchers were able to conclude that such NAA levels suggested methamphetamine abuse and cocaine abuse by males could result in damaged or destroyed nerve cells. In the prenatal methamphetamine study, too few children were assessed for the researchers to determine whether the differences in NAA levels between methamphetamine-exposed and nonexposed children were statistically significant.

Source

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Adolescents, Women, and Whites More Vulnerable Than Others to Becoming Nicotine Dependent

By Patrick Zickler, NIDA NOTES Staff Writer

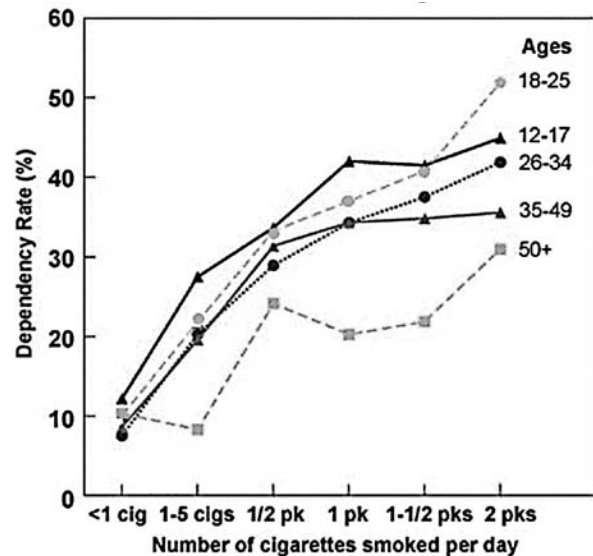
Rates of drug dependence—the percentage of users who experience symptoms that reinforce their drug use and have trouble quitting—are higher for nicotine than for marijuana, cocaine, or alcohol. Rates of dependence also vary among different groups of smokers, according to NIDA-supported research. A new study suggests that differences in sensitivity to nicotine make some smokers more likely than others to develop nicotine dependence. Age, sex, and race all appear to make a difference.

Dr. Denise Kandel and Dr. Kevin Chen of Columbia University in New York City analyzed data collected between 1991 and 1993 as part of the National Household Survey of Drug Abuse, which surveys a representative sample of the U.S. population 12 years and older. In examining data from 22,292 respondents who had smoked cigarettes during the preceding month, Dr. Kandel and her colleagues determined rates of nicotine dependence symptoms based on respondents' reports of tolerance (needing to smoke more to feel the effects), withdrawal symptoms, smoking more than intended, failed efforts to cut down, negative social and job-related consequences, and persistent health problems.

The researchers found that among persons who smoke one-half pack of cigarettes each day, nicotine dependence rates are higher among females than males (31.6 percent compared with 27.4 percent) and higher among whites (31.3 percent) than among blacks (25 percent) and Hispanics (27.6 percent). Adolescents smoke fewer cigarettes than adults but experience significantly higher rates of dependence than adults at the same level of use. Dependence rates are lowest among adults older than 50. Overall, the researchers say, dependence rates increase sharply as consumption moves up to 10 cigarettes per day. The rates level off with higher consumption, although dependent smokers need to smoke more to feel the physical effects of nicotine.

“Understanding the differences among groups in their vulnerability to developing nicotine dependence will be valuable in developing targeted strategies for prevention,” Dr. Kandel says. “The higher rates at which adolescent, women, and white smokers develop symptoms of nicotine dependence given the same quantity smoked daily seem to reflect differences in sensitivity to nicotine. Increased sensitivity may also account for the fact that adolescents develop symptoms of dependence at lower doses of nicotine than adults.”

Rates of Nicotine Dependence Are Greater for Young Smokers



Data from the National Household Survey on Drug Abuse show that the rate of nicotine dependence is higher in people younger than 25 than in other age groups and that the dependence develops with less exposure to nicotine.

Adolescents appear to be particularly vulnerable to becoming nicotine dependent, especially at low levels of cigarette consumption and when they continue to smoke on a regular daily basis, according to the researchers. Adolescents' nicotine dependence rates were associated with the length of time that they had been daily smokers, in contrast with adults, in whom dependence rates were associated with the amount of tobacco smoked. “Once regular smoking has been established, quantity smoked may become a more important determinant of dependence than duration of daily smoking,” Dr. Kandel says. “This possible connection suggests that with adolescents we should focus not only on preventing the uptake of smoking but on shortening smoking careers as soon as possible.”

Source

- Kandel, D.B., and Chen, K. Extent of smoking and nicotine dependence in the United States: 1991–1993. *Nicotine and Tobacco Research* 2(3):263–274, 2000.



Maternal Smoking During Pregnancy Associated With Negative Toddler Behavior and Early Smoking Experimentation

By Josephine Thomas, *NIDA NOTES* Contributing Writer

NIDA-funded researchers have added to the accumulating scientific evidence that women's smoking during pregnancy adversely affects their children's health and development. Two new studies have linked prenatal tobacco exposure to negative behavior in toddlers and smoking experimentation by pre-adolescents.

In a study conducted by Dr. Judith Brook, Dr. David Brook, and Dr. Martin Whiteman of the Mount Sinai School of Medicine in New York City, mothers who smoked during pregnancy indicated that their toddlers exhibited more negative behaviors—impulsiveness, risk-taking, and rebelliousness—than mothers who did not smoke during pregnancy reported among their children.

A study conducted by NIDA-funded researchers Dr. Marie Cornelius and Dr. Nancy Day demonstrates that, even more than growing up in a home where the mother smokes, prenatal exposure to smoke may predispose children to early smoking experimentation. Dr. Cornelius, Dr. Day, and their colleagues at the University of Pittsburgh School of Medicine found that not only does such exposure to maternal smoking predict early experimentation, it also appears linked to child anxiety, depression, and behaviors such as hitting and biting others.

Previous studies have supported a link between prenatal smoking exposure and behavioral problems in later childhood and adolescence. Combined with earlier results, the new studies suggest that prenatal smoking contributes to a train of developmental difficulties and health risks that begin at an early age.

Toddler Negativity

The Mount Sinai study included 99 mothers who smoked and their 2-year-old children. The mothers are participants in a large community study that Dr. Judith Brook has been conducting with Dr. Patricia Cohen of Columbia University in New York City for the past 25 years. In the new study, the mothers answered a questionnaire that elicited information about their children's behaviors

and their own smoking histories, alcohol and drug use, personalities and attitudes, styles of child-rearing, and socioeconomic characteristics.

Fifty-two of the women reported that they had smoked while pregnant, and 47 said they either stopped smoking during pregnancy or did not begin to smoke until after they had given birth. The mothers who smoked during pregnancy scored their children higher on the questions that measured toddler negativity.

The mother's disciplinary style also was strongly linked to a toddler's negative behavior. However, when the researchers adjusted for this factor in the analysis, they determined that a mother's smoking during pregnancy independently increased the estimated risk of negativity at age 2 by fourfold.

"We found three major maternal risk factors related to toddler negativity," says Dr. Brook. "They are maternal smoking during pregnancy, conflicts between the mother and child, and the mother's use of power-assertive

discipline, such as hitting the child. We can speculate that maternal smoking during pregnancy causes disturbances in the neurophysiological functioning of the fetus," says Dr. Brook. "This, in turn, could precipitate the toddler's negative behavior."

The potential implications of these findings reach beyond early childhood. Previous studies have demonstrated that toddlers who display negative behaviors are more likely to use drugs, exhibit delinquent behaviors, and achieve less as adolescents and to develop severe mental health problems later in life.

Early Experimentation With Tobacco

Although the effects of maternal smoking on childhood behaviors have been studied, few studies have investigated the connection between maternal smoking and childhood



experimentation with tobacco. The connection is important because the earlier a person starts smoking, the more likely he or she is to become a regular smoker, become addicted, and suffer the long-term adverse health effects of smoking.

Dr. Cornelius and her colleagues interviewed 589 10-year-olds. Six percent of the children said they had tried cigarettes, smokeless tobacco, or both. Most of the reported tobacco use was experimental; only a few children had used tobacco more than a few times.

In this prospective study, begun by Dr. Day in 1982, the children's mothers have been providing researchers with information about themselves, and they reported on their smoking at the time they were pregnant with the children who are now 10. Putting data from the children together with those reports, the researchers estimated that maternal smoking of at least a half-pack of cigarettes per day during pregnancy increased by fivefold the likelihood that a child would have tried tobacco by age 10. The only factor that produced a greater risk of early experimentation was exposure to smoking within the child's peer group.

It is not yet clear exactly why these factors are related to early experimentation. "Perhaps the nervous system damage caused by maternal smoking may later be

expressed as impulsivity, inattention, aggression, depression, and/or anxiety and may create a vulnerability in the child that could contribute to poorer adjustment and an increased likelihood of early initiation of tobacco use," Dr. Cornelius says.

Dr. Cornelius notes that in her study, the 10-year-olds who were exposed prenatally to tobacco were more likely to have experimented than those whose mothers were current smokers. This finding reinforces the hypothesis that a physiological effect of prenatal exposure to smoking, rather than a genetic vulnerability affecting both mother and child, may be an important link between mothers' smoking during pregnancy and early childhood experimentation.

Sources

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- Cornelius, M.D.; Leech, S.L.; Goldschmidt, L.; and Day, N.L. Prenatal tobacco exposure: Is it a risk factor for early tobacco experimentation? *Nicotine & Tobacco Research* 2:45–52, 2000. **NN**

Women and Smokeless Tobacco Use

Although more than 90 percent of smokeless tobacco users in the United States are male, a substantial number of women also use smokeless tobacco products. In 1998, 0.5 percent of females over the age of 12, about 573,000, were current users of smokeless tobacco products, according to the National Household Survey on Drug Abuse.

The comparatively small percentage of women who use smokeless tobacco accounts in part for the lack of research on the patterns of smokeless tobacco use among women, says Dr. Dorothy Hatsukami of the University of Minnesota School of Medicine. In addition, "women rarely respond to our advertisements to participate in smokeless tobacco treatment studies," she says. For example, Dr. Hatsukami recently reported that 99.8 percent of 402 people who responded to advertisements for participation in a smokeless tobacco treatment study with the nicotine patch were male.

"Women may be embarrassed about admitting smokeless tobacco use because the general perception is that smokeless tobacco use is socially undesirable, and women don't use it," Dr. Hatsukami speculates. Among the unattractive features of smokeless tobacco use is the need to spit tobacco juice from time to time and dislodge particles of loose tobacco that get trapped between the teeth. This disadvantage of smokeless tobacco use was the one most frequently cited by women who participated in a study of female smokeless tobacco users who weren't seeking treatment, conducted by Dr. Hatsukami and her colleagues.

In the study, 20 female smokeless tobacco users from the upper Midwest completed a questionnaire and brief interview. The study revealed some similarities between females' smokeless tobacco use and what research has shown about males' smokeless tobacco use. For example, on average, both sexes began using smokeless tobacco between 16 and 18, and friends played a major role in their initiating use. About 25 percent of men and women also indicated they used smokeless tobacco to help them stop smoking.

The study also revealed some differences in patterns of smokeless tobacco use by females and the patterns of use reported in a previous study that assessed features of smokeless tobacco use among males who weren't seeking treatment. For example, on average, the women said they

used 3.6 dips of moist snuff daily, compared to the 6.3 dips reported by males, and women held the tobacco in their mouths about 22.5 minutes, compared to 39.9 minutes for men. A tin of snuff lasted women anywhere from 2 days to 3 months with a median duration of 6 days per tin. In contrast, men used approximately 2.8 tins per week.

The women in this study may have used less smokeless tobacco than men because they had used smokeless tobacco for less than 4 years, Dr. Hatsukami says. This contrasts with the men, who averaged more than 5 years of smokeless tobacco use. Perceived social disapproval of women using smokeless tobacco also may contribute to lower patterns of use in women. In fact, 38 percent of the women in Dr. Hatsukami's study said they could not use smokeless tobacco in the presence of certain people, and another 25 percent cited social disapproval as a drawback to smokeless tobacco use. These social concerns may reduce opportunities for women to use smokeless tobacco and lead to lower levels of use, Dr. Hatsukami says. In spite of these drawbacks, a significant percentage of women in the study said the relaxing and calming effects and pleasure they associate with smokeless tobacco use are advantages of using these products.

Identifying factors associated with smokeless tobacco use by women and their current patterns of use could generate ways to prevent and treat smokeless tobacco use among women, Dr. Hatsukami says. "The data from this research could help target some of the educational and prevention messages that we should be giving to women," she says. "However, first we have to make women smokeless tobacco users aware that other women use smokeless tobacco products and that they are not abnormal, so they are willing to seek help," she says.

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Drug Abuse and Conduct Disorder Linked to Maternal Smoking During Pregnancy

By Raymond Varisco, *NIDA NOTES* Contributing Writer

Researchers at Columbia University in New York City have found new evidence that children whose mothers smoke during pregnancy are at much greater risk than other children for drug abuse and conduct disorder. The findings reinforce those of other studies spanning more than 25 years that have shown similar problems associated with prenatal exposure to smoke in children ranging from toddlers through teens. The study also revealed marked gender differences, with girls at significantly increased risk for drug abuse and boys at significantly increased risk for conduct disorder.

The investigators interviewed 147 mother-child pairs 3 times over 10 years, with the children ranging from ages 6 to 23 at the start of the study. Both mothers and children were interviewed on entry into the study, again 2 years after the initial interview, and, finally, about 10 years after the initial interview. Because the researchers followed the children through either adolescence or young adulthood—something few studies have done before—they were able to collect data about whether and when the children began to abuse drugs, says Dr. Myrna Weissman, the study's principal investigator.

Data were gathered on psychiatric and substance abuse disorders of parents; family environmental factors, such as divorce and family discord; and maternal factors, such as alcohol and coffee consumption and postnatal smoking, to rule out other explanations for the presence of drug abuse and conduct disorder.

The researchers found that maternal smoking during pregnancy has long-term effects on children's behavior and health that cannot be explained by any other factor included in the study. Risk for adolescent drug abuse in girls was more than 5-fold higher if their mothers smoked more than 10 cigarettes a day during pregnancy. Among boys whose mothers smoked more than 10 cigarettes a day, risk for the onset of conduct disorder was greater than 4-fold that of boys whose mothers did not smoke, with the increase appearing in boys younger than 13. The drug most frequently abused by both boys and girls was marijuana, and the most frequent combination of drugs abused was marijuana and cocaine. Of the females who abused drugs, 70 percent abused more than one.

Why boys exposed to smoking before birth should be at risk for conduct disorder and girls at risk for drug abuse remains to be understood, Dr. Weissman says. She speculates that the differences may be related to sex differences in prenatal brain development.

Many of the findings of this study are consistent with those of related studies, she notes. Researchers at the University of Chicago also have found a link between maternal smoking during pregnancy and conduct disorder in boys, she says. Likewise, a 1994 study conducted by Dr. Weissman's coinvestigator Dr. Denise Kandel found that maternal smoking during pregnancy increases risk for adolescent-onset smoking in girls. Studies also have found other behavioral problems in children exposed prenatally to smoke. For example, scientists at Massachusetts General Hospital found an association between prenatal exposure to smoke and attention deficit hyperactivity disorder. Similarly, a recent study by Dr. Judith Brook and her colleagues at Mount Sinai School of Medicine in New York City has found negative behavior in 2-year-olds of mothers who smoked during pregnancy.

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Boys and Girls Encounter Different Drug Offers, Use Different Refusal Strategies

NIDA-funded researchers at the Arizona State University in Phoenix found that among 12-year-olds who have been offered drugs, boys are most likely to have received those offers from other males or their parents. Girls are most likely to have been offered drugs by a female friend or family member. Although the most common strategy for rejecting these offers is a simple refusal, boys are more likely than girls to explain their refusal.

Dr. Drea Moon (now at California State University, San Marcos) and Dr. Michael Hecht (now at Pennsylvania State University) interviewed 2,622 7th-graders in the metropolitan Phoenix area to determine patterns of exposure to and use of illicit drugs—alcohol, tobacco, marijuana, or “hard drugs” (described in the interviews as hallucinogens, cocaine, or crack cocaine), and inhalants.

“Boys are more at risk than girls for offers at a younger age, and more likely to be offered alcohol, marijuana, and ‘hard’ drugs by their parents or by other males—relatives, acquaintances, and strangers,” Dr. Moon says. “On the other hand, girls tend to be at risk for offers from other girls—acquaintances or family members of roughly the same age—or, to a lesser extent, from older boyfriends.”

The social settings and nature of drug offers also differ by gender, the researchers say. Boys are more likely to receive offers in a public setting, such as on the street or in a park, and the offers to males typically emphasize the

“benefits”—improved status or self-image—of drug use. Girls are more likely to receive a straightforward “do you want some?” offer or one that minimizes the risks of drug use. For girls, these offers are usually made in a private setting such as a friend’s home.

The strategies used to resist drug offers appear to have gender-based influences, Dr. Moon notes. “Boys are often socialized in a way that makes a simple ‘no’ unacceptable. They are more likely to explain their refusal,” she says. Girls, on the other hand, are less likely to use an “explain” strategy because it leads to a counter explanation. “If this continues through two or three cycles of explain-and-counter, girls may be susceptible to use,” according to Dr. Moon. “Understanding the different ways in which boys and girls experience and refuse offers of drugs is crucial to the design of more effective intervention or prevention programs,” she says.

Source

- Moon, D.G.; Hecht, M.L.; Jackson, K.M.; and Spellers, R.E. Ethnic and gender differences and similarities in adolescent drug use and refusals of drug offers. *Substance Use & Misuse* 34(8):1059–1083, 1999. **NN**

Gender Differences in Drug Abuse Risks and Treatment

By Patrick Zickler, NIDA NOTES Staff Writer

Over the past few years NIDA has made a major research commitment to identifying and understanding differences in the ways that women and men—or girls and boys—are first exposed to drugs, in their risks of abuse and addiction, and in the effectiveness of drug treatment. Understanding these differences, and incorporating that understanding into drug abuse prevention and treatment, can reduce the dangers and improve outcomes. NIDA-supported research has shown that gender differences play a role from the very earliest opportunity to use drugs, that women and men tend to abuse different drugs, that the effects of drugs are different for women and men, and that some approaches to treatment are more successful for women than for men.

Are Women Less Likely Than Men to Abuse Drugs?

Men are more likely than women to have opportunities to use drugs, but men and women given an opportunity to use drugs for the first time are equally likely to do so and to progress from initial use to addiction. However, women and men appear to differ in their vulnerability to some drugs. Both are equally likely to become addicted to or dependent on cocaine, heroin, hallucinogens, tobacco, and inhalants. Women are more likely than men to become addicted to or dependent on sedatives and drugs designed to treat anxiety or sleeplessness, and less likely than men to abuse alcohol and marijuana. There are also differences between men and women who seek treatment for drug abuse. Women in treatment programs are less likely than men to have graduated from high school and to be employed and are more likely than men to have other health problems, to have sought previous drug treatment, to have attempted suicide, and to have suffered sexual abuse or other physical abuse.

Are There Gender Differences In the Biological Effects of Drugs?

Animal research and human studies have revealed that males and females may differ in their biological responses to drugs. In studies of animals given the opportunity to self-administer intravenous doses of cocaine or heroin, females began self-administration sooner than males and administered larger amounts of the drugs. Women may be more sensitive than men to the cardiovascular effects of cocaine. In human studies, women and men given equal doses of cocaine experienced the same cardiovascular response despite the fact that blood concentrations of cocaine did not rise as high in women as in men. In

studies involving long-term cocaine users, women and men showed similar impairment in tests of concentration, memory, and academic achievement following sustained abstinence, even though women in the study had substantially greater exposure to cocaine. Women cocaine users also were less likely than men to exhibit abnormalities of blood flow in the brain's frontal lobes. These findings suggest a sex-related mechanism that may protect women from some of the damage cocaine inflicts on the brain.


Does Gender Play a Role in Nicotine Addiction?

Women and men are equally likely to become addicted to nicotine, yet women typically smoke cigarettes with lower nicotine content than those smoked by men, smoke fewer cigarettes per day, and inhale less deeply than men. Overall, however, women are less successful than men in quitting smoking and have higher relapse rates after they do quit. Treatment involving nicotine replacement therapy—nicotine gum or patch—works better for men than for women.

What Are Women's Risks for HIV/AIDS?

Research suggests that there are sex-related differences in some fundamental aspects of the HIV/AIDS disease process. For example, an HIV-infected woman with half the amount of virus circulating in the bloodstream as an infected man will progress to a diagnosis of AIDS in about the same time. And, according to the Centers for Disease Control and Prevention, among cases that progress to a diagnosis of AIDS, drug abuse accounts for a greater percentage of cases among women than among men. Nearly half (47 percent) of all women diagnosed with AIDS are injecting drug users (IDUs), whereas among men, IDUs account for 32 percent of AIDS cases. An additional 19 percent of women, compared with 2 percent of men, with AIDS report having sex with users who inject drugs. In all, drug abuse is nearly twice as likely to be directly or indirectly associated with AIDS in women (66 percent) as in men (34 percent).

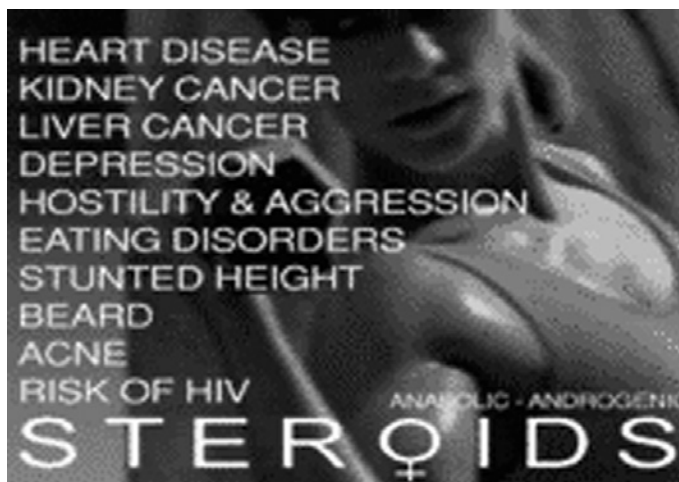
For More Information

- NIDA's gender-related research is discussed in *Drug Addiction Research and the Health of Women*, available on NIDA's home page on the World Wide Web: www.drugabuse.gov. 

NIDA Initiative Targets Increasing Teen Use of Anabolic Steroids

By Patrick Zickler, NIDA NOTES Staff Writer

To reverse the rising use of anabolic steroids by high school-age children, NIDA and seven national partners have launched an initiative designed to alert the public about the risks associated with anabolic steroid use.



As part of NIDA's anabolic steroids initiative, the Institute has distributed more than 500,000 "art" cards—colorful postcards with messages about the harmful effects of steroid abuse—in gyms, restaurants, bookstores, and clubs.

"The most recent data from our Monitoring the Future survey tell us that the trends in use of these drugs and in teenagers' attitudes about them are going in the wrong direction," said NIDA Director Dr. Alan I. Leshner at a Washington, DC, press conference to announce the initiative. "More than a half million 8th- and 10th-grade students are now using these dangerous drugs, and increasing numbers of high school seniors say they don't believe the drugs are risky."

Anabolic steroids are synthetic compounds that mimic the action of the male sex hormone testosterone. The drugs have some medical uses, but they

also are abused by some athletes and sports enthusiasts who want to increase muscle mass and improve performance. Some teens use them because of concern about body image.

In adolescents, anabolic steroid abuse can halt bone growth and has been associated with damage to the heart, kidneys, and liver. In males, steroid abuse can lead to impotence, shrunken testicles, and breast enlargement. In females, the drugs' effects include menstrual irregularities, growth of body hair and loss of scalp hair, a deepened voice, and reduction in breast size. Some of these biological effects are irreversible. Use of anabolic steroids also has been linked to increased and unpredictable levels of aggression in human and animal studies.

NIDA's initiative includes a new Web site—www.steroidabuse.org—that provides science-based information about the risks and prevention of steroid abuse. NIDA has also released an updated Research Report on anabolic steroids as part of the nationwide multimedia initiative. NIDA and its partners will distribute 250,000 copies of a special Community Drug Alert Bulletin on anabolic steroid abuse and will place 500,000 "art cards"—colorful postcards with messages about the harmful effects of steroid abuse—in gyms, bookstores, restaurants, and clubs in Washington, DC, Los Angeles, Miami, Baltimore, Seattle, and Indianapolis.

The Institute's partners in the initiative include the National Collegiate Athletic Association, the American Academy of Pediatrics, the American College of Sports Medicine, the National Association of School Nurses, the National Federation of High Schools, International Students in Action, and Dr. Drew Pinsky, a physician who hosts discussions about relationships and sexual behavior on MTV's "Loveline" and the Web site www.drDrew.com.

The press conference announcing the initiative was followed by a scientific session at which NIDA-supported scientists presented summaries of research on anabolic steroids. Dr. Charles Yesalis of Pennsylvania

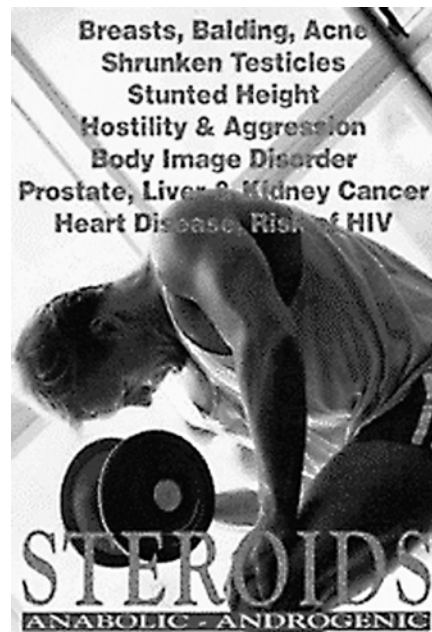


Dr. Linn Goldberg (left) of Oregon Health Sciences University, explains the Adolescent Training and Learning to Avoid Steroids (ATLAS) program to reporters at a science session following the NIDA press conference.

“More than a half million 8th- and 10th-grade students are now using these dangerous drugs, and increasing numbers of high school seniors say they don’t believe the drugs are risky.”

State University discussed the history and social context of steroid use and abuse. Dr. Linn Goldberg and Dr. Diane Elliot of the Oregon Health Sciences University in Portland described the Adolescent Training and Learning to Avoid Steroids (ATLAS) program, a science-based prevention program that uses a team-centered approach to educate young male athletes about the risk and protective factors associated with steroid use. The researchers are currently developing a similar program—Athletes Targeting Healthy Exercise and Nutrition Alternatives (ATHENA)—to prevent eating disorders and abuse of steroids and other body-shaping drugs by young women on school-sponsored athletic, dance and drill, and rally teams.

Dr. Harrison Pope of the McLean Hospital in Belmont, Massachusetts, discussed results of a study designed to examine the effects of steroids on mood and increased aggression, a phenomenon referred to as “roid rage.” The research, which involved 56 men who regularly work out at gyms and health clubs, revealed increased aggressive behavior in some participants who received testosterone in dosages smaller than those typically used by athletes or body-builders. Dr. Marilyn McGinnis of Mount Sinai School of Medicine in New York City provided additional



“Art” cards like this and the one on the previous page help spread the word about the harmful effects of steroids.

evidence that steroid use can result in aggressive behavior. She described recently-completed laboratory studies in which rats with elevated levels of steroids exhibited unprovoked aggression toward passive, nonthreatening rats as well as intensely aggressive responses to provocation.

For More Information

- The report and other information about anabolic steroids can be found at the special NIDA Web site: www.steroidabuse.org. **NN**

Marijuana-Like Compound in Womb May Influence Early Pregnancy

By Steven Stocker, NIDA NOTES Contributing Writer

Ever since scientists began discovering in the early 1990s that marijuana-like compounds are normally produced in various parts of the body, they have been investigating the function of these compounds. Research has suggested that in the brain, the compounds, called endocannabinoids, inhibit pain perception and help to regulate movement. In the spleen and blood, endocannabinoids seem to be partly involved in suppressing inflammation and other responses of the immune system. Now NIDA-funded researchers have discovered that in the female mouse reproductive tract, one of these endocannabinoids, called anandamide, appears to help regulate the early stages of pregnancy.

Dr. Sudhansu K. Dey and his colleagues at the University of Kansas Medical Center in Kansas City, Kansas, have found that the mouse uterus contains the highest anandamide levels yet discovered in any mammalian tissue. At times, parts of the uterus contain anandamide levels that are more than 100 times higher than those in the brain. The researchers have also found that mouse embryos contain cannabinoid receptors—proteins on the cell surfaces that latch on to endocannabinoids in the vicinity—again, at levels that exceed those of the brain.

To find out why the uterus contains anandamide and the embryo contains cannabinoid receptors, the scientists first examined the effects of anandamide on embryo development. When they placed embryos from mice in cell culture, about 90 percent proceeded to the next stage of embryonic development, the blastocyst, which normally implants into the wall of the uterus and eventually becomes a fetus. With the addition of anandamide, only 36 percent proceeded to the blastocyst stage. However, if these embryos were then placed in cell culture without anandamide, most started developing again.

In addition to inhibiting the growth of embryos prior to implantation, anandamide probably also inhibits implantation itself, the researchers found. They determined that administering compounds similar to anandamide prevented blastocysts from implanting in the uterine wall.

Functions of Anandamide

Anandamide may be serving at least three functions before and during implantation, suggests Dr. Dey. First, the compound may be involved in synchronizing the development of the embryo with the preparation of the uterus for receiving it. For example, anandamide secreted into the fluid of the uterus is ready to receive the implanting blastocyst and to sustain it once it has implanted.

Second, anandamide may be involved in embryo selection. “In the mouse, about 15 percent of embryos never implant, and in humans, as many as 60 percent either don’t implant or don’t survive after implantation,” says Dr. Dey. “Perhaps these rejected embryos are inferior in some way, and high anandamide levels in the uterine wall may prevent them from implanting or surviving after implantation.”

Finally, Dr. Dey suggests, anandamide may prevent a second blastocyst from implanting nearby one that has already implanted. After the first one implants, the anandamide level in the surrounding area increases again, which prevents other blastocysts from implanting at the same site.

Understanding how anandamide acts in the female reproductive tract may lead to an explanation for some cases of infertility in women, if anandamide is found to exist in the human uterus, suggests Dr. Dey. In these infertile women, excessive uterine levels of anandamide may be disrupting embryo development and implantation, says Dr. Dey.

This research may also lead to the development of new contraceptives that can inhibit embryo development and implantation in the same manner as anandamide. Conversely, it could also lead to the development of fertility agents that act in ways opposite to those of anandamide.

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UCLA Study Looks at Women in Treatment

Women in women-only drug abuse treatment programs were more than twice as likely to complete treatment as women in mixed-gender programs, according to a NIDA-funded study conducted by Dr. Christine E. Grella of the University of California, Los Angeles. The study also found that, on average, pregnant women had used their primary drug for less time than nonpregnant women; and pregnant women in women-only drug abuse treatment programs averaged more days in treatment than did those in mixed-gender programs, 87.4 days vs. 74 days. Overall, pregnant women spent about 15 percent less time in treatment than nonpregnant women.

Dr. Grella's study compared the characteristics of 4,117 women through data reported from 1987 to 1994 by all publicly funded drug abuse treatment programs in Los Angeles County. The statistical analyses of the treatment program data by pregnancy status and gender composition support the premise that women in drug abuse treatment programs have different needs than men in treatment, and a successful program for women often depends on meeting those different needs, Dr. Grella says. **NN**

Female Rats Progress Quickly to Drug Abuse

In a study conducted by Dr. Wendy Lynch and Dr. Marilyn Carroll of the University of Minnesota in Minneapolis, female rats gave themselves more cocaine and heroin sooner than male rats, a finding consistent with human studies suggesting that women progress faster than men to drug addiction.

The experiment consisted of a series of 6-hour sessions in which rats could administer the drugs to themselves freely by pushing a lever. Seventy percent of the females, but only 30 percent of the males, progressed to a predetermined level

of cocaine use. For heroin, 90 percent of the females and 91.7 percent of the males reached that level.

The female rats reached the predetermined level of cocaine use in a mean of 7.57 sessions compared to 16.67 sessions for males. They reached the level for heroin use in a mean of 8.7 sessions compared to 13 sessions for males. Among the rats that reached that level of use, both cocaine and heroin use were higher in females than in males, and cocaine use was significantly higher. **NN**

Support Group Improves Outcomes for Pregnant Drug Users

Participation in a support group while pregnant can improve maternal and infant outcomes among drug-dependent women, according to a NIDA-supported study. Researchers from The Johns Hopkins University School of Medicine in Baltimore, the University of Maryland in Baltimore, Emory University in Atlanta, and the University of Kansas in Lawrence found that women who participated in a drug abuse support group had more prenatal care visits than drug-abusing women who did not attend the support group, and their infants had higher birthweights. The study also found that support group participation resulted in lower medical care costs for mothers and their infants.

The researchers studied 121 drug-dependent pregnant women registered for prenatal care during a 16-month period at a high-risk obstetric clinic in a poor urban neighborhood. A total of 54 women attended the weekly support group meetings held at the clinic, and 67 did not attend. The groups were led by a drug abuse counselor and discussed how drugs affect the developing fetus, how

to avoid drug-related situations, and the benefits of staying in touch with each other outside of the weekly meetings.

Average maternal medical care costs were almost \$1,000 less for support group attenders than nonattenders. Costs were derived from review of Medicaid claims data and calculated from 1 week before delivery through 3 weeks after. For infants of support group attenders, average medical costs were about \$1,500 less in their first 3 weeks than for those whose mothers did not attend.

The researchers believe that locating the support group at the prenatal clinic provides a cost-effective way to deliver drug abuse treatment. They conclude that this type of “low-intensity intervention” may be an effective way for some women to reduce or eliminate their drug use during pregnancy. For other women, the support group may lead to more intensive drug abuse treatment, the researchers suggest. **NN**

Twin Studies Help Define the Role of Genes in Vulnerability to Drug Abuse

By Patrick Zickler, NIDA NOTES Staff Writer

Some individuals who use drugs become drug abusers—they continue taking drugs even though doing so causes serious problems in their lives. Others avoid abuse or addiction. By studying patterns of drug use in pairs of twins, NIDA-supported researchers are beginning to clarify the role that genes play in predisposing individuals to drug abuse.

“Twin studies explore the roles and interrelationship of genetic and environmental risk factors in the development of drug use, abuse, and dependence,” says Dr. Naimah Weinberg of NIDA’s Division of Epidemiology, Services, and Prevention Research.

In twin studies, researchers interview both members of identical (monozygotic) and fraternal (dizygotic) twin pairs, who typically are exposed to common environmental influences. If genes influence their risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or not abuse drugs. Fraternal twin pairs, on the other hand, are no more similar genetically than non-twin siblings, and so will be less concordant—there will be more pairs in which one twin abuses drugs and the other does not. By comparing the degree of concordance in identical and fraternal twins, researchers can estimate the extent to which genes influence vulnerability to drug abuse.

Marijuana and Cocaine Abuse Among Female Twins

NIDA-supported researchers Dr. Kenneth Kendler and Dr. Carol Prescott at the Medical College of Virginia in Richmond have examined the patterns of marijuana and cocaine use by female twins and found that genetic factors play a major role in the progression from drug use to abuse and dependence. The researchers interviewed 1,934 twins, ranging in age from 22 to 62, recruited from the Virginia Twin Registry, a database compiled from Commonwealth birth records.

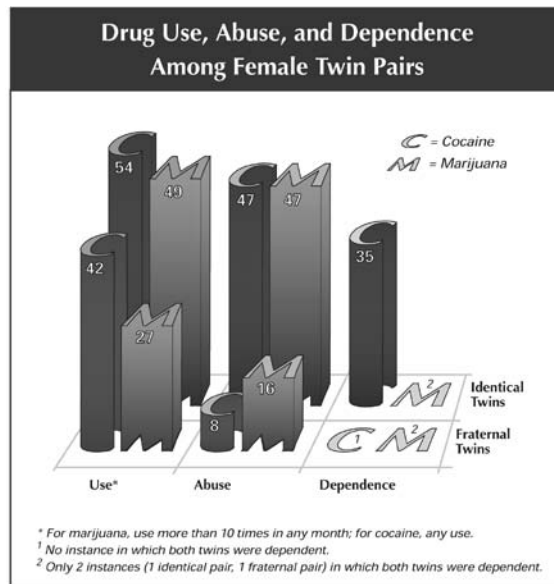


Illustration © 1998 by Richard Liles

If genes influence the risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or both will not abuse drugs.

In the study, drug “use” involved at least one nonprescribed use of a drug; “abuse” was based on the definition provided in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), which includes symptoms such as recurrent use in situations where it presents a physical danger, failure to meet obligations at work or school, or recurrent social or interpersonal problems caused by effects of the drug; and “dependence” was based on the DSM-IV definition and included characteristics such as physical symptoms of tolerance or withdrawal, taking larger amounts of the drug or using it over a longer period than intended, or spending large amounts of time seeking, obtaining, and recovering from the effects of the drug.

“Our research supports other studies that indicate family and social environmental factors are influential in determining whether an individual begins using these drugs,” Dr. Kendler says. “But our findings suggest that the progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors.”



Percentages of pairs in which both twins used, abused, or were dependent on marijuana or cocaine were higher in identical twins than in fraternal twins.

In addition, Dr. Kendler says, the study found that concordance rates—both twins using, abusing, or being dependent on drugs—were higher for identical than fraternal twins (see chart). For cocaine use, concordance was 54 percent in identical twins and 42 percent in fraternal twins; for abuse, 47 percent in identical twins and 8 percent in fraternal twins; and for dependence, 35 percent in identical twins and zero for fraternal twins.

“Abuse and dependence are highly heritable,” Dr. Kendler says. “For both cocaine and marijuana, genetic factors are responsible for roughly 60 to 80 percent of the differences in abuse and dependence between fraternal and identical twin pairs.”

Genetic Risk Factors Differ Among Drugs and Between Males and Females

Dr. Ming Tsuang, a NIDA-supported researcher at Harvard University in Cambridge, Massachusetts, has found that, in males, genetic influences are stronger for abuse of some drugs than for others. Dr. Tsuang and his colleagues studied drug use in 1,874 identical male twin pairs and 1,498 fraternal male twin pairs recruited from the Vietnam Era Twin Registry, a database compiled from Department of Defense records. The average age of participants was 45.

The researchers found evidence to suggest that genetic influences contribute to a common vulnerability for abusing marijuana, sedatives, stimulants, heroin or opiates, and psychedelics. “There is some characteristic of the individual that imparts vulnerability to the abuse of all categories of drugs. Abusing any category of drugs was associated with a marked increase in the probability of abusing every other category of drugs,” Dr. Tsuang says. In addition to this shared vulnerability, the researchers found different vulnerabilities for different drugs. “Each category of drugs we looked at, except psychedelics, had unique genetic influences,” Dr. Tsuang says. “The genetic influence for abuse was greater for heroin than for any other drug.”

NIDA-supported studies involving male and female twins suggest that genetic factors for drug abuse are stronger in males than in females. Dr. Marianne van den Bree and Dr. Roy Pickens of NIDA’s Intramural Research Program and their colleagues studied 188 twin pairs in which at least 1 twin was recruited through a drug treatment program. The sample included 56 identical male pairs, 66 fraternal male pairs, 38 identical female pairs, and 28 fraternal female pairs. Participants were interviewed to determine drug use (five times or more) and clinical diagnosis

(according to DSM criteria) of drug abuse, dependence, or both for sedatives, stimulants, opiates, marijuana, or cocaine. For most drugs, clinical diagnosis of abuse, dependence, or both was more strongly influenced by genetic factors than was drug use. In addition, for most drugs, genetic influences for abuse or dependence were greater for males than for females.

“For females, genetic influences accounted for 47 percent of the differences between identical and fraternal twins in abuse, dependence, or both for any drug, compared with 79 percent for males,” Dr. van den Bree says.

The impact of genetic factors also seems to differ for specific drugs, she notes. The researchers found no evidence for genetic influence for opiate or sedative abuse, dependence, or both in females, but in males genetic influences were generally larger than environmental influences.

“The results we see from these twin studies are making important advances in our understanding of the role of genetic influences in drug abuse,” observes NIDA’s Dr. Weinberg. “Although the studies can’t tell us anything about the risk for a particular individual, they are of enormous value in helping define the variations in drug abuse vulnerability in the population.”

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“The progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors.”

Gender Differences in Progression to AIDS

NIDA-funded research on injecting drug users (IDUs) conducted by Dr. Homayoon Farzadegan and his colleagues at The Johns Hopkins University School of Hygiene and Public Health in Baltimore has shown that the course of HIV infection differs in women and men, so that gender-specific treatment may be needed. This study of 2,960 adult IDUs, begun in 1988 with followup in 1992 and 1997, revealed that although women progressed to AIDS as rapidly as men, they had approximately half the viral load in their bloodstreams when they developed AIDS. Initiation of AIDS treatment is based on HIV viral

load, and current treatment guidelines are derived mainly from studies with men.

The researchers speculate that physiological factors such as hormones may account, in part, for their findings. Dr. Farzadegan and the research team believe that these gender differences must be explored further, and the possibility that women are being under-treated based on current guidelines warrants considering a change in when women start therapy. The study was published in *Lancet* in 1998. **NN**

Study Shows How Genes Can Help Protect From Addiction

By Robert Mathias, *NIDA NOTES* Staff Writer

A recent NIDA-funded study illustrates how genetic differences can contribute to or help protect individuals from drug addiction. The study shows that people with a gene variant in a particular enzyme metabolize or break down nicotine in the body more slowly and are significantly less likely to become addicted to nicotine than people without the variant. In addition, people with the genetic variant who do become tobacco-dependent smoke fewer cigarettes than individuals without the variant, the study indicates.

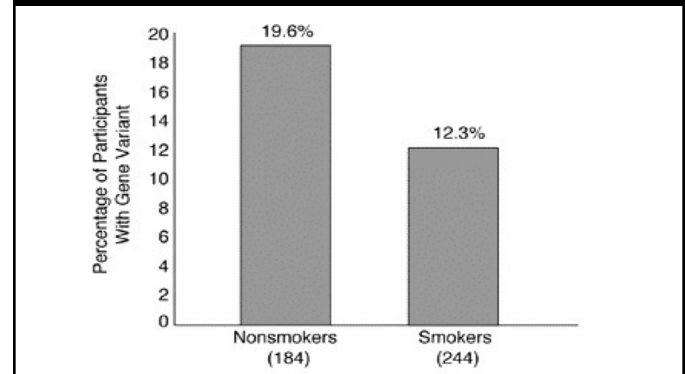
"This study shows the importance of looking at the role of genetics in drug addiction and treatment," says Dr. Jonathan Pollock of NIDA's Division of Basic Research. Ultimately, increased knowledge about underlying genetic vulnerability might lead to more effective treatments for nicotine addiction that are tailored to particular types of smokers, Dr. Pollock says.

In the study, Dr. Edward Sellers and coinvestigator Dr. Rachel Tyndale of the University of Toronto examined the role that a gene for an enzyme called CYP2A6 plays in nicotine dependence and smoking behavior. CYP2A6 metabolizes nicotine, the addictive substance in tobacco products. Three different gene types, or alleles, for CYP2A6 have been identified by previous research—one fully functional allele and two inactive or defective alleles. Each person has a paternal and maternal copy of the gene. Therefore, a person can have two active forms of the gene and normal nicotine metabolism; one active and one inactive copy and impaired nicotine metabolism; or two inactive copies, which would further impair nicotine metabolism.

The study found that people in a group who had tried smoking but had never become addicted to tobacco were much more likely than tobacco-dependent individuals in the study to carry one or two defective copies of the gene and have impaired nicotine metabolism. The researchers theorize that the unpleasant effects experienced by people learning to smoke, such as nausea and dizziness, last longer in people whose bodies break down nicotine more slowly. These longer lasting aversive effects would make it more difficult for new smokers to persist in smoking, thus protecting them from becoming addicted to nicotine.

"We have proven that the risk of becoming a smoker significantly decreases if you have one of the inactive alleles for this enzyme," Dr. Sellers says. Individuals who have two defective copies of the gene would have an even lower risk of becoming a smoker, he predicts. Although only 1 to 2 percent of the general population may carry two defective alleles, individuals with at least one defective allele constitute about 16 to 25

Percentages of Smokers and Nonsmokers With Gene Variant That Slows Nicotine Metabolism



Nonsmokers in a study at the University of Toronto were more likely than smokers to carry a copy of the CYP2A6 gene variant, which slows nicotine metabolism.

percent of the general population, Dr. Sellers says. "We've calculated that the frequency of defective alleles that we've found would be protecting about 7 million North Americans from becoming smokers," he says.

The study also found that individuals with impaired nicotine metabolism who do go on to become addicted to nicotine are afforded a measure of protection from the harmful effects of nicotine addiction. The study shows that smokers with at least one inactive allele smoked significantly fewer cigarettes daily and weekly than smokers with two active copies of the allele. Generally, smokers with slower nicotine metabolism do not need to smoke as many cigarettes to maintain constant blood and brain concentrations of nicotine, the researchers explain. However, this slower nicotine metabolism had a greater impact on reducing smoking among men than women in the study. This is probably because women's smoking is controlled less by nicotine dependence than is men's, the researchers suggest.

In addition to illustrating the role genetics can play in vulnerability to addiction, identification of the effect of the defective gene on smoking has prevention and treatment implications, Dr. Sellers says. "If you could find a chemical or some other way of causing the same effect, such as blocking the enzyme, you might be able to prevent people from becoming smokers," he says. "If you did the same kind of thing in people who were already smokers, they would be likely to smoke less, which could lead to smoking cessation," Dr. Sellers concludes.

Source

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Men and Women in Drug Abuse Treatment Relapse at Different Rates and for Different Reasons

By Steven Stocker, *NIDA NOTES* Contributing Writer

Recent NIDA-funded studies have found that women in drug abuse treatment relapse less frequently than men do, at least partly because women are more likely to engage in group counseling. Other NIDA-supported researchers have found that cocaine-addicted women and men differ in the factors that cause them to relapse, indicating that males and females might benefit from different relapse prevention strategies.

Likelihood of Relapse

In a study conducted at the University of California, Los Angeles, Dr. Robert Fiorentine and his colleagues have found that women drug abusers are less likely than men drug abusers to relapse after entering treatment because women participate more frequently in group counseling and that this more intensive level of treatment engagement helps them to remain drug-free.

The researchers followed 182 women and 148 men in 26 public outpatient drug abuse treatment programs in Los Angeles County. The programs provided group, individual, and family counseling; educational activities; and referrals to other health and social services. The treatment lasted 6 months.

About half the patients regularly used just one drug—primarily crack cocaine, marijuana, or powder cocaine, and about half used more than one drug. Regular use was defined as three or more times per week. The patients were interviewed while in treatment and approximately 6 months after the first interview.

The scientists found that the women in their sample were less likely than the men to relapse: only 22 percent of the women compared to 32 percent of the men relapsed to drug use in the 6 months between interviews. The researchers considered several theories to account for this finding.

One possibility was that the women used drugs less than the men, so abstaining from drug use was easier for them. However, the study findings showed otherwise. In the year preceding treatment, more women had used crack cocaine than men, and about the same percentages of women and men had used powder cocaine, marijuana, and other drugs. In addition, women used all drugs as frequently as men, except for crack and heroin, which women used more frequently. Finally, about the same percentage of women and men used two or more drugs.

Another possibility the researchers considered was that the women received more social support than the men from a variety of sources, such as families, friends, and coworkers. The investigators found that, although the women were more likely than the men to maintain a social network, they were no more likely than men to receive emotional support for their problems and encouragement to stop using drugs.

What did appear to explain the difference in relapse was the fact that the women were more likely to engage in treatment, particularly group counseling, says Dr. Fiorentine. In his study, the women engaged in an average of 10.9 sessions of group counseling per month compared to 7.9 sessions a month for the men. Research has shown that more intense participation in treatment is associated with lower rates of relapse.

The women did not seem to be attending group counseling sessions more often than men because the sessions were somehow oriented more toward women. The sessions dealt with the problems of both genders more or less equally and were usually attended by both men and women, Dr. Fiorentine says.

The reason that women attended group counseling sessions more than men may stem from women's greater willingness to seek professional help for their health problems, speculates Dr. Fiorentine. "Women appear to be more willing to seek help for their problems, including their substance abuse problems," he says. "Men, on the other hand, are more likely to say, I'm OK. I don't need help. I can take care of this. It's just a little problem." He recommends that treatment providers discuss with male drug abusers the possibility that their reluctance to seek help may be hampering their recovery.

Even though the women attended more group counseling sessions than men, they did not attend more individual counseling or family counseling sessions than men did. If women are more likely to use services in general, why did they not engage more often in these other types of therapies? The explanation seems to be that these other therapies are not offered as frequently as group counseling in Los Angeles County, primarily because of the county's budget constraints, Dr. Fiorentine suggests. "Individual counseling, for example, is expensive and there are only so many counselors to go around, so treatment programs ration individual counseling," he says.

“Both women and men already may be attending the maximum number of individual counseling sessions they can attend. If patients could attend as many of these sessions as they desired, you might see more women than men in these sessions, just as you see more women than men in group counseling sessions.”

In a related study, Dr. Roger Weiss and his colleagues at McLean Hospital in Belmont, Massachusetts, also found less likelihood of relapse for women than for men among patients who were hospitalized for cocaine addiction. When 74 patients were interviewed 6 months after the hospitalization, 51 percent of the women had remained abstinent compared to 25 percent of the men.

Like Dr. Fiorentine, Dr. Weiss theorizes that the women in his sample were more motivated for therapy than the men were. “Studies have identified barriers to entering drug abuse treatment programs that exist for women but not for men,” says Dr. Weiss. “These include childcare difficulties and the predominance of male patients and staff. There is also more social stigma for women in being labeled an addict. Women who come to these treatment facilities must be willing to overcome these barriers, which could lead to a higher percentage of women who are motivated to change.”

Reasons for Relapse

In addition to identifying gender differences in the likelihood that drug abusers relapse, scientists also have identified gender differences in drug abusers’ experiences before and during relapse. Dr. James McKay and his colleagues at the University of Pennsylvania in Philadelphia found that women in treatment for cocaine addiction were more likely than men to report negative emotions and interpersonal problems before they relapsed. The men, on the other hand, were more likely to report positive experiences prior to relapsing and were more likely to engage in self-justification and rationalizing afterward. They reported, for example, that they felt entitled to use cocaine or that they believed they could control their cocaine use. The women also were much more likely to be impulsive in their return to cocaine use. Fifty-six percent of the women, compared with only 17 percent of the men, reported that they relapsed immediately after the thought of using cocaine occurred to them.

These gender differences in relapse factors suggest that different relapse prevention strategies might be emphasized for women and men, says Dr. McKay. For example, women might benefit more from techniques that enable them to deal more effectively with unpleasant emotions and interpersonal problems. “One strategy is to take action quickly as your mood starts to deteriorate rather than waiting until you are in a really bad mood and then trying to do something about it,” he says. “If it’s a small

problem, planning an enjoyable activity might be all that is needed. If, however, it’s a serious depression, medication or psychotherapy might be necessary.”

In contrast, men might benefit more from strategies that counter their tendency to let down their guard when feeling good, Dr. McKay says. “These strategies are derived from concepts taught in 12-step programs, such as not getting too cocky or confident when your mood improves,” he says. “Patients are told to be on the lookout for warning signs that might be present when they’re feeling good, such as thinking to themselves, ‘I’m feeling great today. I don’t need to go to that meeting. I can go hang out with this friend of mine. I know he uses, but I’m feeling good today, and I’m not vulnerable to using.’”

More Research

Gender differences in drug abuse are of intense interest to NIDA, says Carol Cowell of NIDA’s Division of Clinical and Services Research. “Researchers are finding gender differences across the broad spectrum of drug abuse research—from basic research to studies such as these on treatment and services—and we would like to encourage more study of these differences,” she says. She occasionally suggests that NIDA-funded researchers analyze their data in terms of gender differences. “This sometimes results in a study that increases our knowledge of the role of gender in treatment outcomes,” she says.

“Performing gender analyses is simply a matter of doing good science,” says Dr. Cora Lee Wetherington, NIDA’s women’s health coordinator. When gender differences exist but investigators fail to test for them, flawed conclusions may be drawn, either for males or females or both, she says.

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Researchers Find Gender Differences In How Drug Abusers Respond To HIV Prevention Strategies

By Steven Stocker, NIDA NOTES Contributing Writer

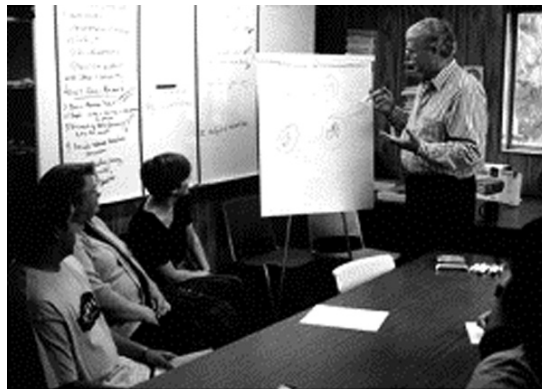
Men who abuse drugs are more likely to reduce their sexual risks of HIV infection if they are given risk-reduction information on the street, while women drug abusers respond better if they are given this information in an office with counseling. This is one of the findings of a NIDA-funded study on the effectiveness of HIV risk-reduction programs tested in two towns in Arizona.

Dr. Robert Trotter and his colleagues at Northern Arizona University in Flagstaff developed two enhanced programs for reducing drug-related and sexual risks for HIV transmission and added the programs to a standard program developed by the Centers for Disease Control and Prevention and modified by NIDA. The standard program recruits drug abusers on the street and then provides HIV risk-reduction information at the project office. In the office, counselors provide information on proper condom use and bleach disinfection of drug injection equipment. Drug abusers also are offered testing for HIV infection.

One of the enhanced programs developed by the researchers, called the active outreach intervention, provides the HIV risk-reduction information on the street rather than in the office. Later, the entire network of people who use drugs together and share drug use equipment is invited into the office for a group discussion of HIV transmission risks.

The other enhanced intervention, called the office-based intervention, involves the same recruitment procedure as the standard intervention, but additional counseling techniques are used when the drug abuser visits the office. In the office, the person is first asked to identify at least one HIV risk in his or her life. The person is then asked how this risk might be reduced and is encouraged to do

so. Like the active outreach intervention, the office-based intervention also involves a subsequent group session with the network of drug abusers.



Dr. Robert Trotter of Northern Arizona University discusses with his staff possible strategies for reducing HIV transmission risks among drug abusers who use drugs together and share drug injection equipment.

All three interventions, both the standard and the two enhanced, reduced HIV risk behaviors; however, for reducing sexual risks, the researchers found that the active outreach intervention worked better for men, and the office-based intervention worked better for women. The men seemed to respond well to being taught about HIV risk-reduction on the street because that was the environment in which HIV risks often occurred, Dr. Trotter speculates. "Some pretty solid social science theory states that, for certain kinds of behavior, providing the behavior reduction intervention in the context in which the behavior occurs is more effective," he says.

However, this theory did not apply to the women in the study. The women told the researchers that they felt safe discussing sensitive matters in the office, where they were not under pressure from family and other drug abusers. "If we had conducted the interventions with these women on the street or in their homes, people would be around who might hear what they were saying, and the women were afraid of the repercussions. In the office, the women felt emotionally and physically protected," Dr. Trotter says.

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NN

Gender Affects Relationships Between Drug Abuse and Psychiatric Disorders

By Neil Swan, NIDA NOTES Staff Writer

In the general population, women are more than twice as likely as men to suffer depression. But among cocaine and alcohol abusers, men are as likely to be diagnosed with depression as women, a NIDA-funded study indicates.

Why? Is cocaine more likely to trigger depression among men than among women? Perhaps.

Researchers have long been aware that many drug abusers also have serious mental disorders, a status referred to as dual diagnosis or comorbidity. Does the psychiatric disorder precede and perhaps contribute to the onset of drug abuse? Or, conversely, do drug abuse and addiction develop first, perhaps contributing to the development of the mental disorder?

A study conducted by Dr. Kathleen T. Brady and her colleagues at the Medical University of South Carolina provides insights into these questions. The researchers examined gender differences in psychiatric disorders among 100 treatment-seeking cocaine and alcohol abusers. Among these substance abusers, comorbidity with mental disorders was substantive. Some 48 percent of the men and 70 percent of the women had a comorbid affective or anxiety disorder. In addition, a substantial number were also dually diagnosed with other mental disorders including passive-aggressive, obsessive-compulsive, and antisocial

personality disorders. Some 56 percent of the men and 68 percent of the women abusers had one or more of these additional disorders, either alone or with an affective or anxiety disorder.

The study's preliminary findings suggest that both onset scenarios—drug abuse first or mental disorder first—sometimes may occur. It is possible that the sex of the drug abuser may be a factor in determining which comes first, depending on the comorbid psychiatric disorder involved.

In the case of depressive episodes, Dr. Brady's study suggests that for women, depression comes first more often; for men, drug abuse appears to come first more often. Because cocaine has such powerful effects on the brain, it may be that in many people cocaine use activates depressive episodes that linger after the period of euphoria and withdrawal, she says. "Perhaps men are at greater risk for this response to cocaine, which would help explain the lack of gender differences in depression rates among cocaine abusers we studied compared to rates in the general population," explains Dr. Brady. Also, men typically consume more alcohol and use more cocaine, which would increase the damaging effects of these substances, which, in turn, might lead to depression, she adds.

The study shows that women more often than men were diagnosed with not just depression but with other psychiatric disorders as well before they began using drugs (see table on following page). For example, as with depression, women are significantly more likely than are men to have a diagnosis of panic disorder before the onset of drug abuse, says Dr. Brady, a psychiatrist. Panic disorder is manifested in sudden attacks of acute anxiety or terror that may be uncontrollable.

The most dramatic gender difference in prevalence rates found by the South Carolina researchers was in the diagnosis of posttraumatic stress disorder (PTSD)—emotional shock ignited by the threat of death or actual or threatened injury resulting in

Percentage of 100 Cocaine and Alcohol Abusers Who Were Ever Diagnosed With Comorbid Psychiatric Disorders

	Men (50)	Women (50)
Any affective or anxiety disorder	48%	70%
Major depressive episode	36%	40%
Bipolar disorder (severe mood swings)	6%	4%
Panic disorder	10%	18%
Social phobia	14%	10%
Posttraumatic stress disorder (PTSD)	24%	46%

Individuals may have been diagnosed with more than one psychiatric disorder during their lifetimes.

Cocaine and Alcohol Abusers Who Had Psychiatric Disorders *Before* the Onset of Substance Dependence

	Men (50)		Women (50)	
	Total with Disorder	No. with Disorder First	Total with Disorder	No. with Disorder First
Major depressive episode	18	4	20	10
Bipolar disorder (severe mood swings)	3	1	5	2
Panic disorder	5	1	9	8
Social phobia	7	7	5	5
Posttraumatic stress disorder (PTSD)	11	8	23	18

severe fear, feelings of helplessness or horror, and recurrent memories. Of the 50 men and 50 women whom Dr. Brady studied, some 46 percent of women were diagnosed with lifetime PTSD, compared to only 24 percent of the men (see table on previous page).

Social phobia—extreme shyness and fear of embarrassment and humiliation or performance anxiety such as stage fright—was found in 12 percent of the study group compared to only 2.8 percent of the population at large, which other studies have shown. The onset of social phobia predated drug abuse in 100 percent of both women and men diagnosed with the disorder in this study. This suggests that patients may use drugs to self-medicate their social phobia, says Dr. Brady.

Other epidemiologic studies have shown that social phobia is 1.5 times more common in women than men. “But we found little gender difference in the prevalence of social phobia in the group of substance abusers,” she says. “This means that while social phobia is a risk factor for substance abuse in both sexes, it appears that it may be a greater risk factor for men. Perhaps cultural expectations for men to be more socially aggressive prompt men more to use drugs or alcohol to overcome shyness and other aspects of social phobia.”

The study found no gender differences in the study group in prevalence of other psychiatric disorders such as antisocial personality disorder, paranoid or schizoid personality disorders, or obsessive-compulsive disorder. In general, the study demonstrates important gender differences in some psychiatric disorders, but not in others, among the substance abusers and compared to the population at large.

Dr. Brady’s data on these disorders show similar rates of prevalence for these diagnoses in men and women. Particularly for antisocial personality disorder, these similar rates are in contrast to several earlier studies, she notes. In the general population, as well as in alcoholics and opiate abusers, a higher prevalence of antisocial personality disorder in men than in women has been reported. But in one earlier study of psychopathology in cocaine abusers, no significant gender differences in antisocial personality disorder rates were noted. The majority of the women in


her study were cocaine-dependent, which may partially explain the discrepancy between her data and some of the other studies, Dr. Brady says.

Her study results imply that different psychiatric factors may have differing roles prior to—or in response to—drug abuse in women compared to men, says Dr. Brady. These preliminary findings are important indicators for designing research to develop and implement improved gender-specific drug abuse treatment strategies, says Dr. Cora Lee Wetherington, NIDA’s Women’s Health Coordinator.

In another study, Dr. Brady examined cocaine-abusing men and women who also were diagnosed with PTSD, dividing them by order of onset of diagnosis—cocaine first or PTSD first. In the cocaine-first group, the PTSD-causing trauma was generally related to the dangers involved in procuring and using cocaine and was more common among men. In the PTSD-first group, the trauma was generally childhood abuse and was more common among women, the study found. For women, PTSD preceded cocaine dependence in 77 percent of the cases; for men, this figure was 38 percent.

“Because much of the PTSD in substance-abusing women appears to be closely related to the sexual and physical victimization of women, my colleagues and I are now investigating this relationship in hopes of finding new treatments for PTSD and drug abuse that would address important gender differences,” Dr. Brady says.

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Women's Dependence on Smoking Affected By Something in Addition to Nicotine

By Neil Swan, NIDA NOTES Staff Writer

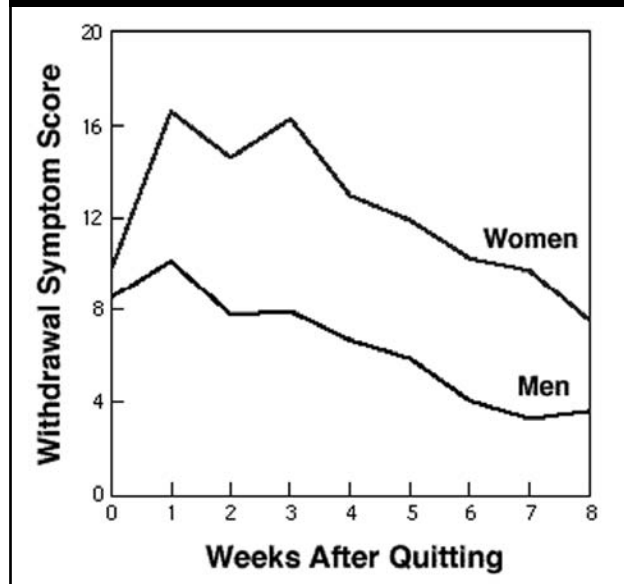
A number of studies have shown that women find it more difficult than do men to quit smoking cigarettes. This is especially evident in studies of nicotine replacement therapies that use nicotine patches or nicotine gum. Now two separate NIDA-funded studies examining gender differences related to smoking suggest that something in addition to nicotine is involved in women's dependence on smoking tobacco.

"It appears that, compared to men, women may smoke less for nicotine and more for non-nicotine effects of smoking," says Dr. Kenneth A. Perkins, a psychologist at the University of Pittsburgh Medical Center. These nonnicotine influences might include nondrug-induced sensory effects like seeing and smelling tobacco smoke, conditioned responses to these smoke stimuli, or social pleasures involved in smoking rituals, he suggests.

For example, one observer has noted that smokers may exhibit gender differences in the way they gather outside buildings to smoke, Dr. Perkins says. Male smokers tend to be loners; females tend to gather in social groups. These behaviors may indicate critical gender-based differences relating to tobacco smoking that may have little to do with nicotine, observers theorize. Dr. Perkins calls these nonnicotine influences "external stimuli."

If further research supports this view of gender differences in external and behavioral influences related to smoking, says Dr. Perkins, it will be important to revise smoking cessation treatments for women trying to quit. This would mean tailoring therapy for women to increase behavioral

Withdrawal Is Different for Women—Appetite, Craving Greater Than Men's



*Women using nicotine gum therapy to quit smoking reported greater withdrawal symptoms than men did. The withdrawal Symptom Score was calculated from self reports of the degree to which study participants experienced symptoms such as craving for a cigarette, irritability, anxiety and tenseness, and excessive hunger. A high score represented greater symptoms. Source: D. Hatsukami in *Experimental and Clinical Psychopharmacology*, 1995, American Psychological Association. Reprinted by permission of the author.*

support and rely less on nicotine replacement.

Dr. Perkins reviewed scores of studies of smoking and its addictive properties and smoking cessation programs. He found that these epidemiological and clinical studies consistently show that while smoking is declining among Americans, it is not decreasing as rapidly among women as among men. If present trends continue, women smokers will outnumber men by the next decade, says Dr. Perkins. The research suggests that this is at least partly because of the greater difficulty women have in quitting. Women in the studies tend to be less successful in smoking cessation trials, especially those using nicotine replacement therapy.

Lower cessation rates for women could be expected if women smoked more cigarettes or inhaled more nicotine than did men. Both are indicative of nicotine dependence, and smokers who are more strongly nicotine-dependent often have greater difficulty quitting. But just the opposite appears to be the case, says Dr. Perkins. Women tend to smoke fewer cigarettes per day, to smoke brands with lower nicotine yields, and to be less likely to inhale deeply, compared to men, according to his research review. Thus, evidence indicates women smokers are less, not more, nicotine-dependent than are men.

Further support for the notion of additional, nonnicotine addiction factors comes from a study of gender differences in the effects of different doses of nicotine gum on tobacco withdrawal symptoms. Dr. Dorothy Hatsukami, a psychiatry professor at the University of Minnesota, found that nicotine gum did not work as well to ease withdrawal

symptoms for women trying to quit smoking as it did for men trying to quit. As in Dr. Perkins' review, her results seemed contrary to expectations. If women are more sensitive to or dependent on the effects of nicotine than are men, as their lower smoking cessation rates would suggest, then women should be more responsive than are men to nicotine replacement, she reasoned. But this was not shown in her data, which paralleled Dr. Perkins' findings. Women were less sensitive to the effects of nicotine, she says.

The lower cessation success with nicotine replacements in women compared to men may in part be attributed to this reduced effectiveness of the replacement therapy in relieving nicotine withdrawal symptoms. It also may indicate that something else is involved besides nicotine dependence, says Dr. Hatsukami. Like Dr. Perkins, she concluded that women may be more affected by other aspects of smoking.

What is the "something else?" In his review, Dr. Perkins examines alternative possibilities such as gender variations related to body weight or physiological effects of the 4,000 compounds found in cigarettes in addition to nicotine. He finds no strong evidence to support these or other alternative explanations for gender differences in responses to smoking or attempts to quit smoking, leading to his speculation on the role of nondrug, or external, factors.

One answer might lie in psychophysiology studies that compare men's and women's abilities to detect changes within their bodies, such as heart-beat rate fluctuations, explains Dr. Perkins. Women are consistently less able than are men to detect changes in heart rate when no external clues are provided, according to a research review published in 1995 by Southern Methodist University scientists. But this gender difference narrows significantly when subjects are provided with an external context, or clue, for the internal changes, such as viewing a horror film.

Thus, external stimuli appear to be more important to women than to men. It can be theorized, then, that

women may be less responsive to internal stimuli such as nicotine and more responsive to external stimuli such as the sight and smell of tobacco and its smoke, he says.


Dr. Perkins emphasizes that it is wrong to conclude that nicotine is not important in reinforcing tobacco smoking among women. Women clearly experience nicotine withdrawal symptoms, he says. "The point is that there may be relatively subtle—but very important—differences in the sources of reinforcement [reward] that tobacco smoking provides to women relative to men," he says.

Some observers have speculated on the role of external influences in gender differences related to the use of other abused drugs. Research with users of cocaine, heroin, and other drugs points up the significance of external drug-craving "cues" such as persons,

activities, or locations associated with prior drug use. Are there critical gender differences in responses to these powerful craving cues?

More research is essential, says Dr. Perkins. For tobacco, more study is called for because studies of nonnicotine reinforcement may help develop more effective smoking cessation therapies for women, he says.

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Compared to men, women may smoke less for nicotine and more for nonnicotine effects of smoking.

Cocaine Affects Men and Women Differently, NIDA Study Shows

By John A. Bowersox, *NIDA NOTES* Contributing Writer

A recent NIDA-funded study suggests that gender differences will become an increasingly important consideration in drug abuse treatment strategies. The study by researchers affiliated with Harvard Medical School found that cocaine affects men and women differently and that hormonal fluctuations play an important role in women's responses to the drug.

In the study, Dr. Scott E. Lukas and his colleagues at the Alcohol and Drug Abuse Research Center in Belmont, Massachusetts, measured a variety of responses to cocaine in six male and six female volunteers. On separate days, the volunteers snorted single doses of cocaine and placebo powder in equal amounts relative to their body weights. The men were tested once, but the women were tested at two different times during their menstrual cycle: once during their follicular phase and again during their luteal phase. The follicular and luteal phases, respectively, correspond to the times before and after ovulation. The researchers calculated the phases of each woman's cycle from the onset of menstruation:

- Dose 1 (midfollicular phase) was given 5 to 9 days after the onset of menstruation;
- Dose 2 (midluteal phase) was given 18 to 22 days after onset of menstruation.

The researchers found that at both points in the menstrual cycle the women were much less sensitive to the drug than the men were. The men in the study had significantly more episodes of euphoria, or good feelings, and dysphoria, or bad feelings. When asked to rate the severity of their dysphoria, the men judged the bad feelings to be more unpleasant than the women did. The men also experienced greater heart rate and blood pressure increases and detected cocaine's effects sooner than the women did. Although the men and women received equivalent doses of cocaine, women had lower levels of the drug in their blood than the men; their cocaine blood levels were even lower when they took the drug during the luteal phase of their menstrual cycle.

Dr. Lukas says that differences in the speed with which cocaine is metabolized may account for the drug's different effects in men and women. In the body, cocaine is broken down into inactive metabolites by enzymes known as cholinesterases. Although men have higher levels of

these enzymes in their blood plasma, women have higher levels of a type of cholinesterase enzyme found in red blood cells, Dr. Lukas explains. The red blood cell enzyme metabolizes cocaine much more actively than the plasma enzyme does.

Physical changes that occur during the menstrual cycle also may contribute to women's decreased sensitivity to intranasal cocaine, says Dr. Lukas. The increase in certain hormone levels during the luteal phase causes women's mucous membranes, including those that line the nasal passages, to secrete more mucus. Dr. Lukas says that the increased mucus may act as a barrier to the absorption of cocaine when women snort the drug during the luteal phase of their menstrual cycle.

"We believe that the gender differences in cocaine's effects that we observed are due to a combination of metabolic differences and the greater physical barrier to cocaine absorption created by the increase in mucosity," says Dr. Lukas. He adds that other as yet unknown factors could also help produce cocaine's differing effects.

Dr. Lukas says the findings, which he presented at the 1994 meeting of the College on Problems of Drug Dependence, might help explain, at least from a physiological perspective, why the prevalence of cocaine use among women has traditionally been much lower than it has been among men. According to the National Household Survey on Drug Abuse, approximately 3.1 million men and 1.4 million women used cocaine at least once during 1993. Women also appear to take cocaine less frequently than men do. The 1993 survey, which was conducted by the Substance Abuse and Mental Health Services Administration, estimates that about 365,000 men compared with 111,000 women used cocaine at least once a week.

Many women have reported that they did not get high when they first tried cocaine, says Dr. Lukas, adding that women's low sensitivity to the drug combined with its high price create a strong disincentive to its continued use. On the other hand, he says, some women may become heavy users because they need to take more cocaine to get the same effect as men.

If further studies substantiate Dr. Lukas' findings, they could have important implications for the treatment of cocaine

abusers, says Dr. Elizabeth Rahdert, a research psychologist in NIDA's Division of Clinical and Services Research.

"Therapists would have to realize that for women, the response to cocaine will be different at different times of the month and not a steady state as it is for men," she says.

Presumably, she adds, patterns of craving and response to withdrawal could also fluctuate with a woman's menstrual cycle, and treatment professionals would have to recognize that women could be more vulnerable to relapse at different points in their cycle. Furthermore, treatment strategies designed to address male usage patterns would have to be modified in accordance with women's usage patterns.

Dr. Lukas' work reflects NIDA's increased interest in examining the gender-specific effects of drug abuse. Basic research findings such as the discovery that sex hormones can interact with neurotransmitters during normal brain functioning have fueled this interest.

"Previously, drug abuse research on women focused mainly on issues related to pregnancy and the effects of

drug abuse on the developing fetus," says Dr. Cora Lee Wetherington, a psychologist in NIDA's Division of Basic Research.

"More recently, we've seen a shift with the realization that the treatment needs of women may be different from those of men. Although issues related to childbearing and child-rearing are still important areas of drug abuse research, researchers are questioning whether treatment strategies that were developed through research conducted largely on male subjects are appropriate for women," says Dr. Wetherington.

Source

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Daughters of Mothers Who Smoked During Pregnancy are More Likely to Smoke, Study Says

By Robert Mathias, NIDA NOTES Staff Writer

Researchers have long wondered about the impact of prenatal exposure to drugs on a child's vulnerability to drug abuse. Now, NIDA-funded studies have documented a relationship between prenatal exposure to nicotine and adolescents' use of tobacco. Dr. Denise Kandel of Columbia University found that daughters of women who smoked cigarettes while they were pregnant are four times more likely to begin smoking during adolescence and to continue smoking than daughters of women who did not smoke during pregnancy.

"The clearest message from the study is that mothers should not smoke during pregnancy," says Dr. Kandel. The study suggests that nicotine, which crosses the placental barrier, may affect the female fetus during an important period of development so as to predispose the brain to the addictive influence of nicotine more than a decade later, she says.

Prenatal smoking by these mothers did not have a strong effect on their sons' smoking, but it is not clear why, says Dr. Kandel. Male hormones or structural differences of male and female brains may protect the developing male fetus from the nicotine entering the brain, she says, but notes, "That is all very speculative."

Prenatal exposure to smoking has previously been linked with impairments in memory, learning, cognition, and perception in the growing child, says Dr. Jagjitsing Khalsa of NIDA's Division of Clinical and Services Research. The results of Dr. Kandel's study suggest that smoking during pregnancy may create a risk of early and continued smoking among these women's children, he says. Noting that other NIDA researchers are looking at the possible intergenerational transmission of a tendency to use mari-

juana through prenatal exposure, Dr. Khalsa says, "We need to let women know that if they take drugs during pregnancy they may put their offspring at risk for future drug use."

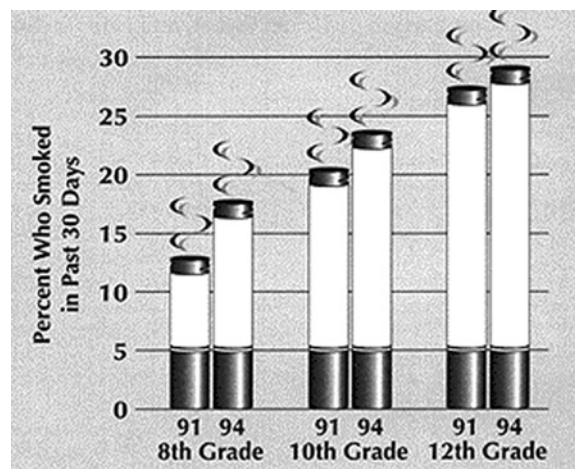
In previous research, Dr. Kandel had examined the intergenerational effects of drug use by following a cohort of New York State adolescents who were periodically reinterviewed over the course of 19 years. That research indicated that a mother's cigarette smoking had a greater effect than a father's on smoking among both sons and daughters. When analyses of different social influences could not identify the reason for this maternal effect, Dr. Kandel focused on one factor that differentiated mothers from fathers—a mother's smoking during pregnancy.

In her most recent study, Dr. Kandel analyzed follow-up interview data on 192 mothers and their first-born adolescents from the New York State study. The children's mean age was 12 1/2. The analysis revealed that 26.4 percent of girls whose mothers smoked while pregnant had smoked in the last year. By comparison, only 4.3 percent of girls who were not prenatally exposed to nicotine had smoked in the last year. While more prenatally exposed boys had also smoked in the last year compared with boys whose mothers had not smoked during pregnancy, the difference was not statistically significant.

ence was not statistically significant.

Subsequently, Dr. Kandel replicated her New York State analysis with pre- and postnatal smoking data on 797 mothers and their children drawn from the National Longitudinal Survey of the Work Experience of Youth Cohort, a Bureau of Labor Statistics survey that has been conducted annually since 1979. The second analysis

Trends in Adolescent Girls' Current Use of Cigarettes



Source: NIDA's Monitoring the Future Studies, 1991-94

According to NIDA's Monitoring the Future Study, the percent of adolescent girls who smoke cigarettes has increased in the last 4 years. Although smoking among adolescent girls has been linked to many different factors, Dr. Kandel's study is the first to document a possible link between prenatal exposure to nicotine and an adolescent girl's tendency to smoke cigarettes.

confirmed the findings from the New York State survey, says Dr. Kandel. The combined data from both surveys indicated a fourfold greater risk of smoking for girls whose mothers smoked during pregnancy.

To ensure that it was a mother's prenatal smoking and not her postnatal smoking that affected her daughter's smoking, the researchers analyzed the impact of those mothers' smoking both during and after pregnancy. They found that, regardless of the amount or duration of current or past maternal smoking, the strongest correlation between maternal smoking and a daughter's smoking occurred when the mother smoked during pregnancy.

Smoking activates several brain neurotransmitter systems including the dopamine system, which is involved in the reinforcing effects of addictive drugs in general, points out Dr. Kandel. Since this study raises the possibility that

nicotine may modify the developing fetus's dopamine system, making it more susceptible to the effects of nicotine at a later time in life, "The children whose mothers smoked during pregnancy are not only going to be more likely to smoke, but also may be more likely to use and become dependent on other drugs," she predicts. Dr. Kandel hopes to research this issue by following the adolescents in her study for another 6 years.

Source

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Early Childhood Behavior and Temperament Predict Later Substance Use

By Neil Swan, *NIDA NOTES* Contributing Writer

By the first grade, or earlier, children show temperament and behavior traits that are powerful indicators of their inclination to use and abuse drugs in their teenage and adult years. Researchers have identified not only common childhood risk factors and behaviors that predict drug abuse potential but also protective factors that shield some children from influences to use drugs.

A number of long-range NIDA-funded studies have traced at-risk children into adulthood and parenthood, trying to determine why some children are able to resist persistent influences to use substances of abuse. Studies have zeroed in on several important factors in predicting a first-grader's subsequent use of substances: shyness, aggressiveness, rebelliousness, and gender. External risk factors include substance use among peers, drug use by parents, and troubles with the police. Protective factors include achievement in school or after-school activities and close family ties. The researchers are now designing drug abuse prevention and intervention strategies based on these findings made over 20 or more years.

Some of the earliest studies, by Dr. Margaret E. Ensminger and Dr. Sheppard G. Kellam and colleagues of The Johns Hopkins University, started in the 1960s with first-graders and their families in Woodlawn, a poor, urban African-American community on the South Side of Chicago.

Today the researchers are following about 1,000 of the 1,242 original first-graders to continue to identify and monitor early childhood factors affecting later drug use and symptoms of psychiatric problems. These first-graders are now 32 or 33 years old.

Interviews in 1993 show that key risk factors such as aggressive behavior and shy-aggressive behavior identified 26 years ago continue to hold and are valid predictors of the subjects' current levels of cocaine use as adults.

During their studies, Dr. Ensminger and her colleagues rated each first-grader's mental health using two criteria: social adaptation and psychological health. To measure pupils' social adaptation to school, researchers used teachers' ratings of children's classroom social performance

and intelligence as well as the results of standardized tests. Psychological health was determined by a number of criteria, including psychological symptoms, abnormal behavior, and level of self-esteem.

For both sexes, higher scores on first-grade IQ and readiness-for-school tests were associated with higher levels of beer or wine, hard liquor, and marijuana use 10 years later.

Two important risk factors identified as predictors of later drug use are shy behavior—described by the teachers as sitting alone, having few friends, and not speaking up in class—and aggression—described as fighting with others or breaking rules. Shyness and aggression are types of poor social adaptation distinct from symptoms of anxiety or depression, which are internal feelings, noted the researchers.

While shyness and aggressiveness are key predictors of drug use, a complex relationship exists between the two factors. Among boys, aggressive behavior in the first grade leads to increased

teenage substance abuse, while first-grade shyness alone without aggressiveness leads to lower levels of substance abuse as teenagers. However, the combination of shyness and aggressiveness leads to even higher levels of adolescent substance use among boys than aggressiveness without shyness does, the studies found.

Boys whose teachers said they had problems concentrating in class had higher levels of later substance abuse because concentration problems appear to be closely related to aggressiveness, the studies reported. By contrast, neither aggressiveness, nor shyness, nor concentration problems in the first grade were associated with later substance use among girls.

Understanding Gender Differences

Shyness and aggressiveness may be less important predictors of substance use among females than among males because girls' peer groups are smaller and less important to them, she adds. These gender-based considerations are now being studied in drug abuse prevention programs, says Dr. Ensminger, who was among the first researchers to urge colleagues to stop dismissing gender as a possible key consideration in predicting children's subsequent drug use.

When the first-graders reached age 16 or 17, girls used smaller amounts of beer, wine, liquor, and marijuana and other illicit drugs but not cigarettes than boys did. For both sexes, higher scores on first-grade IQ and readiness-for-school tests were associated with higher levels of beer or wine, hard liquor, and marijuana use 10 years later, the researchers found. "This tells us that the children who are most ready for school are also those most ready to experiment with drugs," says Dr. Ensminger.

Psychological well-being and family relationships in the first grade seemed more important to girls than to boys in terms of influencing psychiatric symptoms 10 years later. Mothers had an important effect on the psychological status of their daughters but not of their sons. Mothers' expectations of how far daughters would go in school and mothers' own psychological health were positive factors in their daughters' psychological well-being 10 years later, the study found. Girls with strong family bonds tend to use drugs less than other girls do, but the same family influence is not so apparent with boys, said Dr. Ensminger.

Results from the Woodlawn study served as the basis for prevention programs started in Baltimore in the 1980s by Dr. Kellam and colleagues. That prevention effort focused on aggressive behavior because of its relationship to later drug use and on underachievement because of its relationship to depressed feelings.

Recent data gathered on the Woodlawn study subjects show that early childhood aggression is still a valid predictor of drug abuse when measured against the now-adult subjects' levels of use of cocaine, Dr. Ensminger reports. Those data are now being prepared for publication.

Examining Protective Factors

Another long-term study of drug-use predictors focuses on children in Northeastern States. For 20 years, Dr. Judith S. Brook of Mt. Sinai School of Medicine has studied risk factors identified in early childhood and in adolescence that are related to drug use during adolescence. She is conducting a study of 1,000 children and their mothers that began in 1975 in two communities representative of the population of the Northeastern United States. In the continuing research, Dr. Brook is examining not only risk factors but also protective factors that help shield children and adolescents from these risk factors. Dr. Brook and



A number of long range NIDA-funded studies have traced at-risk children into adolescence and beyond trying to determine why some of them are able to resist influences to use substances of abuse.

her colleagues have identified a number of risk factors for subsequent drug use such as childhood aggression, which includes anger, aggression toward siblings, noncompliance, temper, and nonconforming behavior. Other risk factors are unconventionality—an attitude of deviance, rebelliousness, and evasion of responsibility—the extent of drug use among peers, and parental sociopathy, that is, parents' problems with drinking, drugs, or the police.

Dr. Brook's group examined the risk factors and their implications during childhood,

ages 5 to 10; middle adolescence, ages 13 to 18; and late adolescence, ages 15 to 20. They found that childhood aggression and parental sociopathy predicted increased levels of drug use in late adolescence. They also determined that unconventionality during the early years of adolescence had an "important and pervasive impact on all aspects of middle and late adolescent functioning," including increased drug use.

The research team is now observing the original subjects' children, beginning at age 2, and interviewing both parents of these children to collect data on the new generation. "So we're now studying the third generation—the grandchildren of the mothers [of the original subjects] initially studied in 1975," says Dr. Brook. "And we're finding a great deal of consistency down through the generations in regards to personality and family characteristics," including traits that are drug-use risk factors.

The researchers also have studied interactions among risk factors and their implications for subsequent drug use as the children grow older. In addition to childhood aggression, they found three additional factors that influence late-adolescent drug use—unconventionality and drug use in middle adolescence and parental sociopathy during childhood. They found that little or no drug use in middle adolescence when combined with conventionality during the same age span resulted in the least amount of subsequent drug use.

As expected, parental sociopathy is related to late-teen drug use. Parents who drink or use drugs or both may be the most strict with their children, telling them, "Do as I say, not as I do," according to Dr. Brook's study. These admonitions might be effective in middle adolescence, when children are more likely to be influenced by parental demands, but not in later adolescence, when the family

has less control and the parents' own display of negative behaviors becomes a drug-use risk factor, she says.

Dr. Brook agrees with other researchers that there are childhood protective factors that can be very powerful shields to safeguard children and adolescents from the recognized risk factors. These protective factors include achievement, religious commitment, strong family bonds, and a solid attachment to and emulation of a wholesome role model, she says.

"Some of these children are remarkably resilient," says Dr. Brook. Among those who become successful, she found evidence of protective factors such as church attendance, childhood achievement in school or in extracurricular activities, or close ties to brothers and sisters.

"Many of these kids go on to lead successful, productive lives, yet we tend to focus on the ones that don't," says Dr. Brook. "I want to learn more about what makes those that do well do so."

Family Relationships Critical

Still another continuing study of predictive factors for drug use focuses on a different population segment—at-risk children of white families living in small and medium-sized communities in Oregon. The study by Dr. Hyman Hops and colleagues of the Oregon Research Institute examines family and peer-group influences on adolescent substance use and is now in its 10th year. About 500 subjects were ages 11 through 15 at their first assessment in 1984 and will be 21 through 25 at their last assessment this year.

Among those studied, 90 percent of subjects who progressed from one substance of abuse to another did so in the following sequence—abstinence, alcohol, cigarettes, marijuana, and hard drugs. The most dramatic increase in drug use occurred between the ages of 13 and 14, when adolescents are going from middle to high school.

Parents' use of substances, including cigarettes, is an important predictive factor influencing their children's drug use. Within two-parent families, Dr. Hops found that fathers' drinking appears to have a greater impact than mothers' drinking on both girls and boys, while mothers' drinking has an effect only on adolescents under 14, before they enter high school. Parents who use cigarettes and alcohol may influence not only their children's use of the same substances but illicit substances as well, he says.

Family conflict and strife are strongly associated with increased substance abuse, based on the researchers' direct observations of problem-solving scenarios between parents and adolescents. Their findings suggest that families with

substance-abusing children typically are unable to easily resolve problems and that the resulting confrontations negatively affect drug use.

In examining peer influences, the Oregon researchers balanced each study subject's self-reports of levels of substance use against reports of his or her substance use level from the child's best friend. The scientists reported that the amount of both family cohesion and peer encouragement to use drugs was predictive of initial levels of substance abuse. A good family relationship may play a powerful role as a protective factor in middle and late adolescence, they say. On the other hand, peer encouragement to use substances plays a stronger role across the age range and also suggests that early peer influences may encourage higher levels of drug use at later ages.

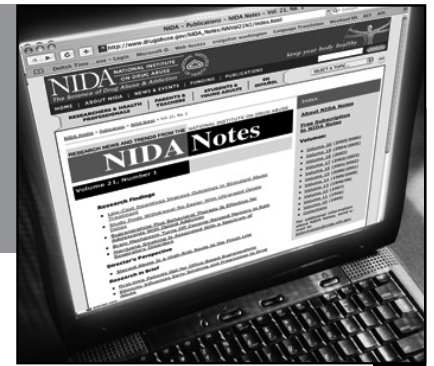
"These findings underscore the importance of family influences on substance abuse throughout adolescence and suggest greater attention to the family, as well as the peer group, in designing prevention strategies," says Dr. Hops. "You've got to have a healthy family relationship to counter the very powerful peer influences that kids face today."

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Revised July 2009
Revised July 2008
Revised September 2006
Revised April 2004
Printed May 2002