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NOTES**

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1974-2004

Articles That Address



WOMEN

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GENDER

DIFFERENCES

RESEARCH

**U.S. Department of Health and Human Services
National Institutes of Health
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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.

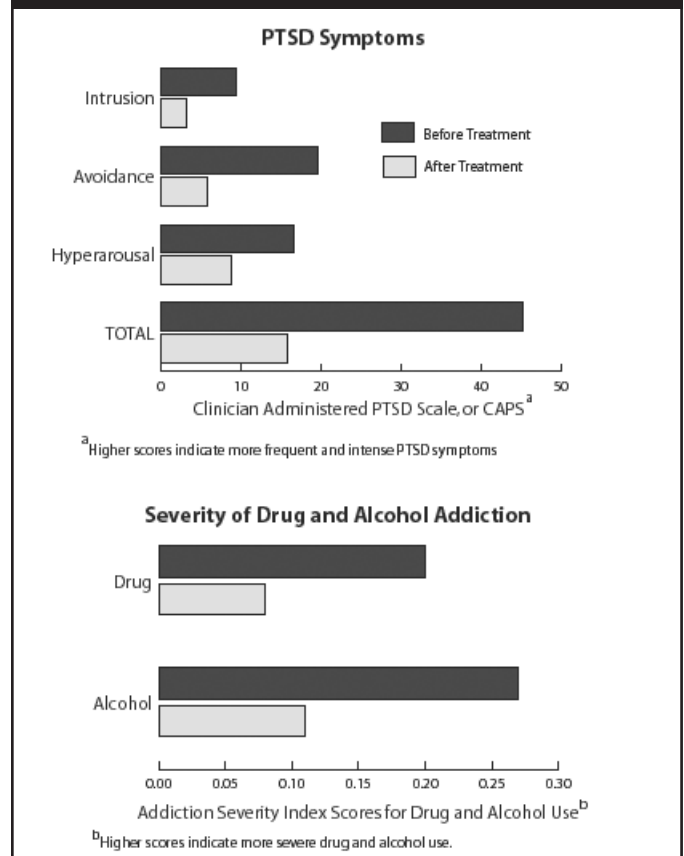
“Researchers and clinicians have been reluctant to use exposure therapy with cocaine-dependent patients,” says Dr. Kathleen Brady of the Medical University of South Carolina in Charleston. “Drug abuse patients were thought to be likely to turn to alcohol and drugs to cope with the emotional demands placed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

internalizing disorders, typified by sadness, withdrawal, 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

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

percent reported using cocaine and alcohol, respectively. 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.”

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

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

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

^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.

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."

Sources

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- Robbins, M.S., et al. Ethnic differences in comorbidity among substance-abusing adolescents referred to outpatient therapy. *Journal of the American Academy of Child and Adolescent Psychiatry* 41(4):394–401, 2002. **NN**

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

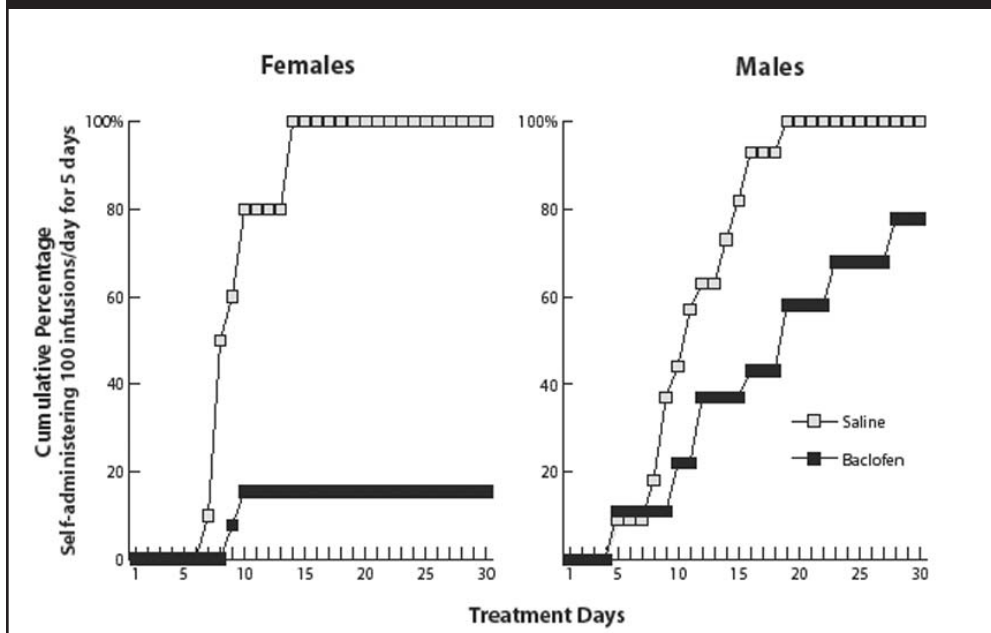
In recent studies, Dr. Marilyn Carroll and her colleagues at the University of Minnesota looked at the impact of two interventions on self-administration of heroin and cocaine by rats and found that, in each case, the intervention produced a greater effect on the female rats studied than on the male 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.

Baclofen Slows Establishment of Cocaine Use in Females More 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

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.

lever with drug 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.

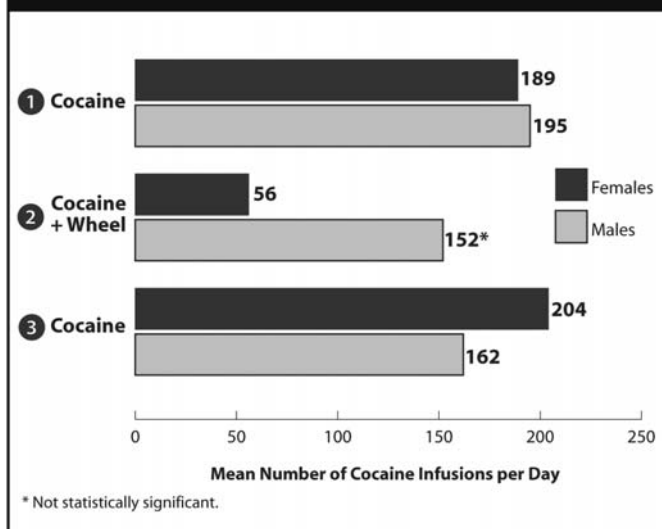
All of the female rats pretreated with saline reached the acquisition criterion by day 14. All males pretreated with saline met the criterion by day 19. In the group of female rats pretreated with baclofen, only 15.4 percent met the acquisition criterion within the 30-day limit. In contrast, 77.7 percent 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 female 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

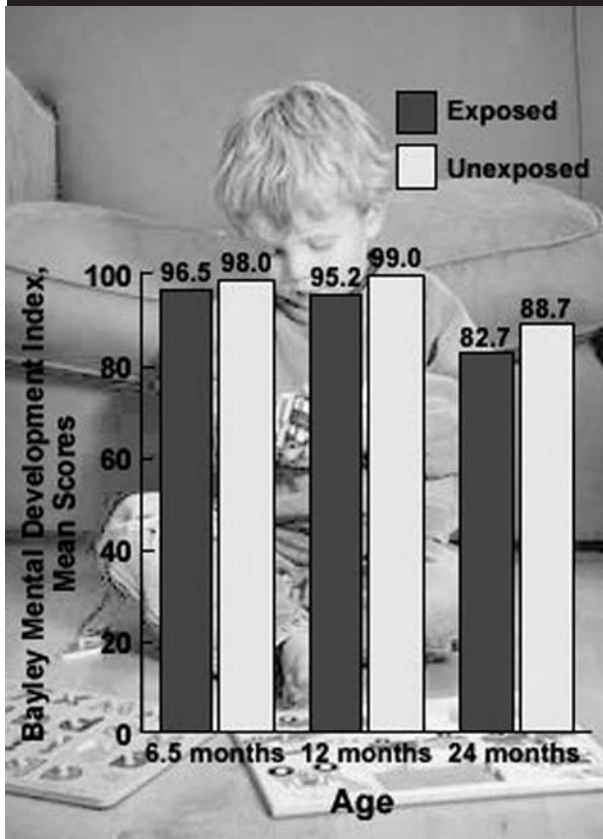
many other such factors has found that children born to poor, urban women who used cocaine throughout pregnancy were nearly twice as likely as children with similar backgrounds but no prenatal cocaine exposure to have significant cognitive deficits during their first 2 years of life.

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.

Mental Development Scores For Prenatally Cocaine-Exposed and Unexposed High-Risk Children



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.

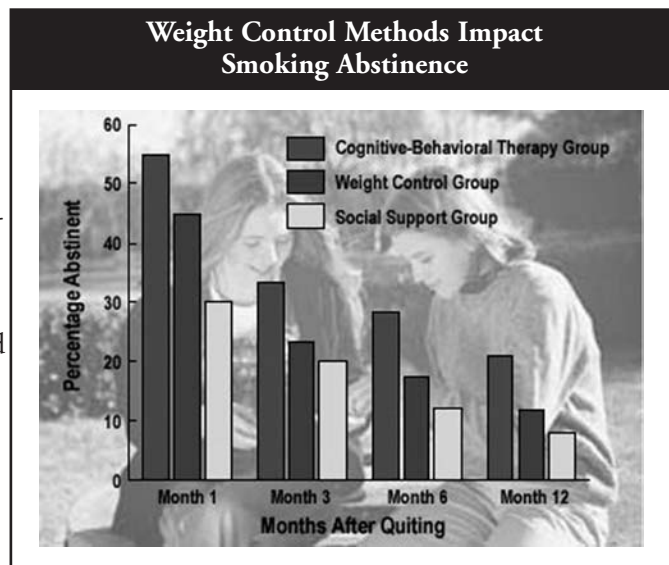
They found that blocking olfactory stimuli made a greater difference to women than to men. While pleasure in smoking was reduced for both women and men when

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.

“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



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.

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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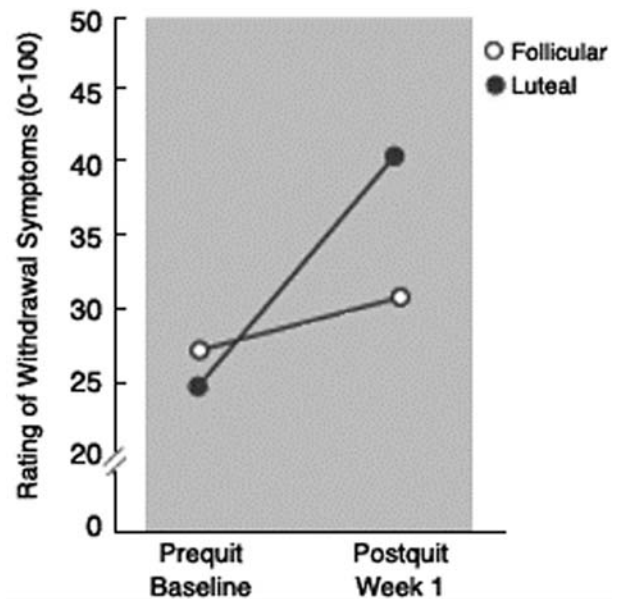
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Timing Quit Date May Help Women Smokers

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.

Inhalant Abuse Among Young People

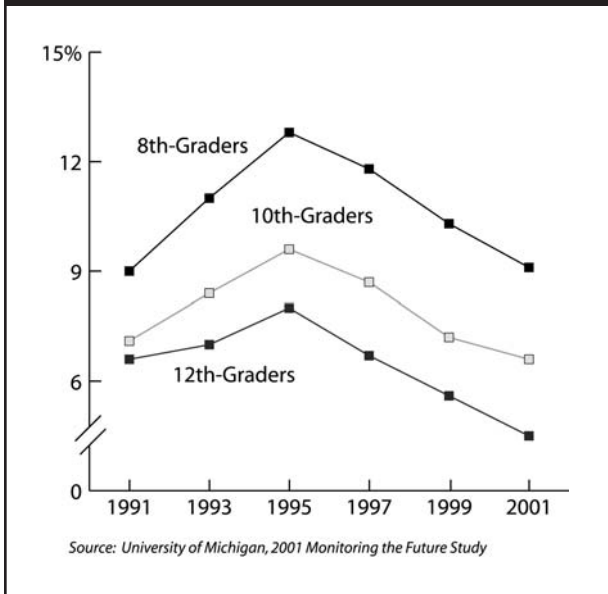
Inhalant abuse is a public health problem that disproportionately affects young people. This page provides graphic representation of recent trends in use, attitudes about inhalants among U.S. schoolchildren, and current levels of inhalant use in the United States, distributed by gender, ethnicity, and age. The source of the data is NIDA's annual Monitoring the Future survey of adolescents in grades 8, 10, and 12.

Current trends are positive in two respects. Increasingly, young people surveyed see "great risk" in trying inhalants.

At the same time, the percentage reporting inhalant abuse is declining.

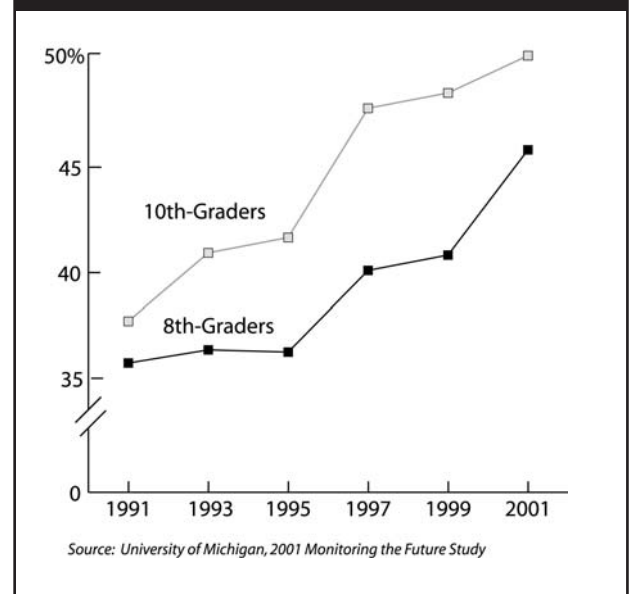
Although the percentages of U.S. male and female students reporting past-year use of inhalants are virtually identical among 8th- to 12th-graders, use by males is more likely among older youths. Inhalant use is reported by a greater percentage of Whites and Hispanics than by Blacks. **NIJ**

Percentage of Students Reporting Past-Year Use of Inhalants, by Grade



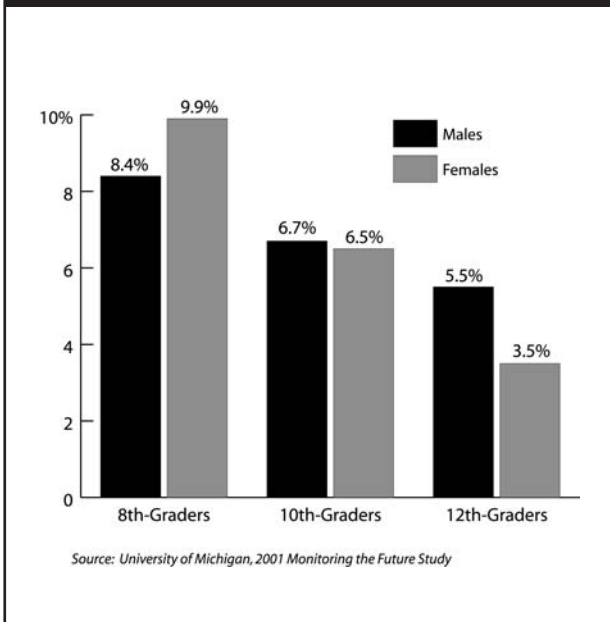
A consistent pattern shows higher rates of inhalant use in earlier grades, with levels of use in all three grades peaking in 1995 and declining from 1996 through 2001. The decline in inhalant use that began in 1996 may be linked to an increase in perception of inhalant risk, a trend that began in 1995–1996.

Percentage of 8th- and 10th-Graders Seeing "Great Risk" in Trying Inhalants Once or Twice



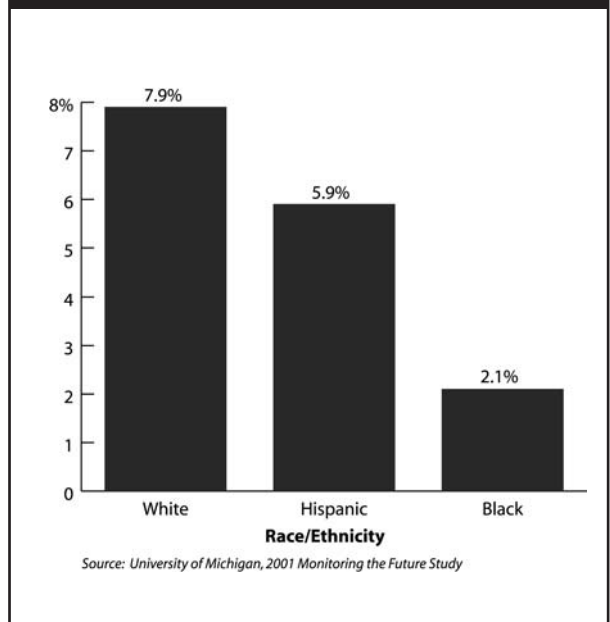
From 1991 to 1993 roughly 40 percent of 8th- and 10th-graders perceived any experimentation with inhalants to be very risky. Between 1995 and 2001, significant increases in perceived risk were reported by both groups.

U.S. Male and Female Students Who Reported Past-Year Use of Inhalants, 2001



A slightly higher percentage of 8th-grade girls than boys reported inhalant use. Among 12th-graders, a greater percentage of boys report past-year use of inhalants.

U.S. Students Who Reported Past-Year Use of Inhalants, 2001, by Race/Ethnicity



Higher rates of past-year inhalant use were found among Whites and Hispanics, lower rates among Blacks.

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.

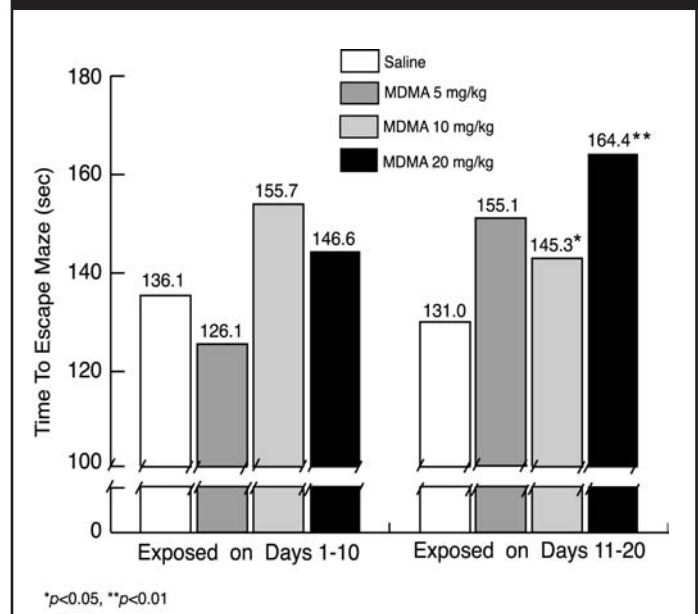
Scientific studies have already established that ecstasy users are at risk for dehydration, hypertension, hyperthermia, and heart or kidney failure. The drug also has been shown to damage nerves in the brain's serotonin system and appears to produce long-term deficits in memory and cognition. The new 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.

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.

Testing for Learning, Memory

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

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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.

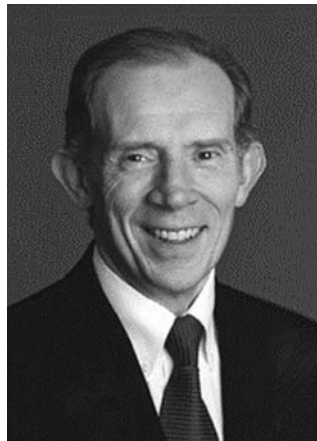
NIDA's National Drug Abuse Treatment Clinical Trials Network adheres to the overall National Institutes of Health requirement for analysis of data by gender and supports gender-specific protocol development. NIDA recently issued a Program Announcement for support of dissertation research in five areas, 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.

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



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.

having 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*.

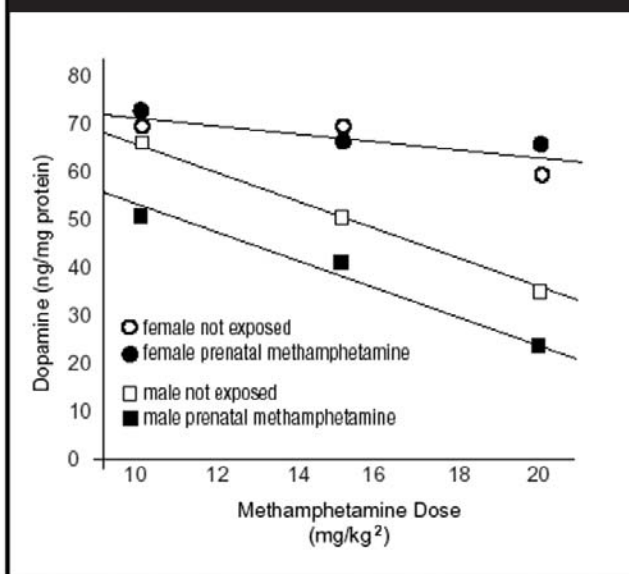
"Many young people using club drugs such as methamphetamine are cavalier about its dangers. They mistakenly believe that they can use these drugs with no consequences," says Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research. "Although this study was conducted in mice, these 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 in

Effect of Prenatal Exposure to Methamphetamine on Striatal Dopamine Levels of Male and Female Adult Mice



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.

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.

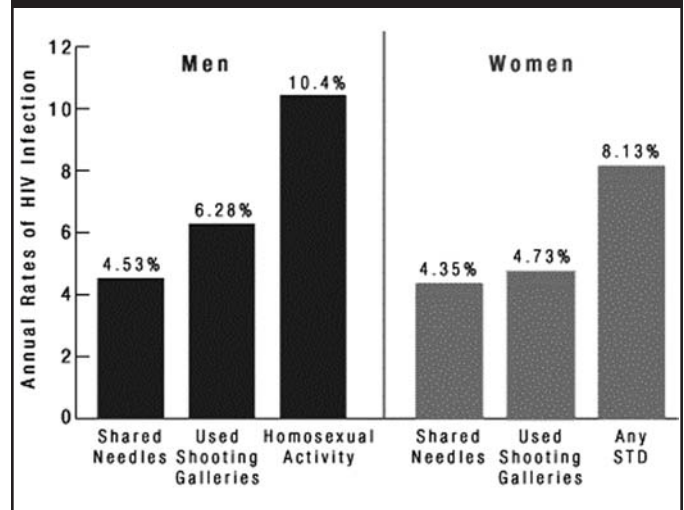
“In the past, we assumed that IDUs who were HIV-positive had been infected with the virus through needle-sharing,” says Dr. Steffanie Strathdee of the Johns Hopkins University Bloomberg School of Public Health in Baltimore, who conducted the NIDA-funded study. “Our analysis indicates that sexual behaviors, 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

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.

they had used shooting galleries had an HIV incidence 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 sex-

ually 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

- Strathdee, S.A., et al. Sex differences in risk factors for HIV seroconversion among injection drug users. *Archives of Internal Medicine* 161:1281–1288, 2001.



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.

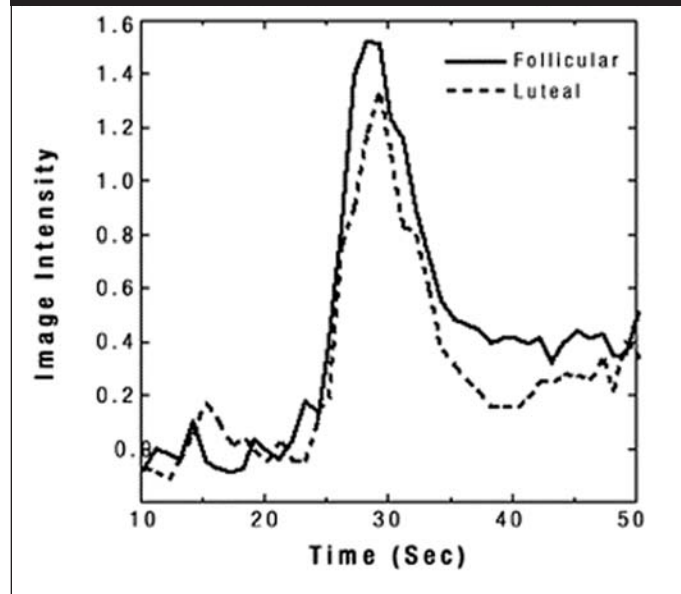
Dr. Marc J. Kaufman and colleagues at McLean Hospital, Harvard Medical School, in Belmont, Massachusetts, found that cerebral blood flow during the follicular phase of women's menstrual cycles (days 1 through 14, prior to ovulation) is not affected by exposure to cocaine. In women during their luteal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

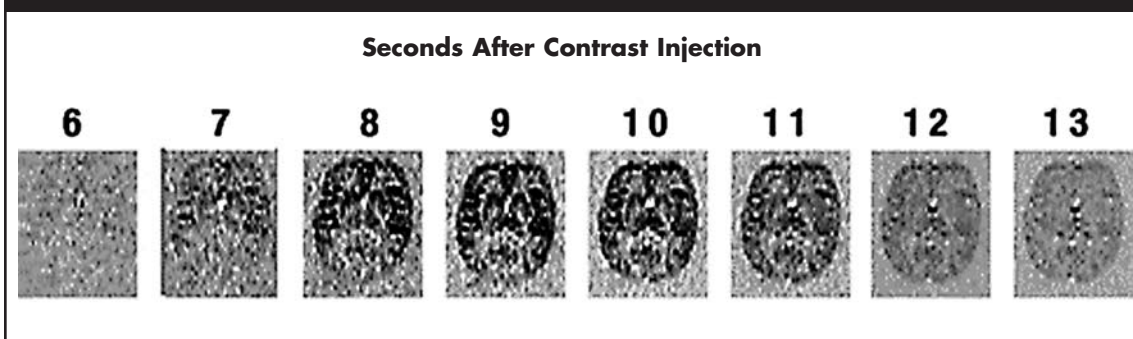


Magnetic resonance (MR) image intensity was measured to compare the hemodynamic effects of cocaine during two phases of a woman's menstrual cycle. Following cocaine administration during the follicular phase, image intensity was relatively high, reflecting cerebral blood flow at 97 percent of its pre-cocaine 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 of estrogen. The greater vasoconstrictive effect of cocaine

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



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.

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

- Kaufman, M., et al. Cocaine-induced cerebral vasoconstriction differs as a function of sex and menstrual cycle phase. *Biological Psychiatry* 49(9):774–781, 2001.
- Kaufman, M., et al. Cocaine decreases relative cerebral blood volume in humans: A dynamic susceptibility contrast magnetic resonance imaging study. *Psychopharmacology* 138:76–81, 1998. **NN**

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.”

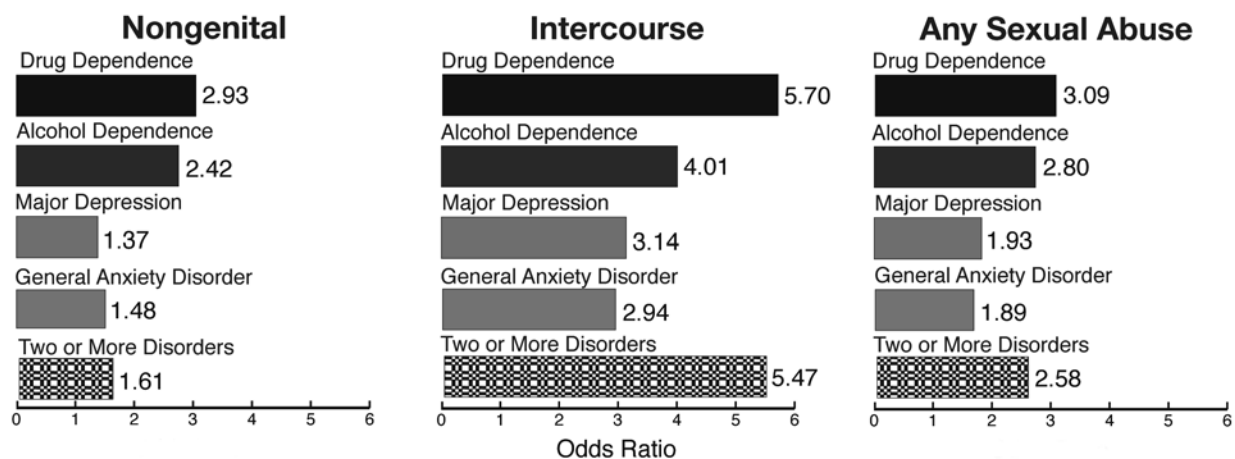
In this study, 1,411 women born between 1934 and 1974 responded to written questionnaires that asked them if,

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.

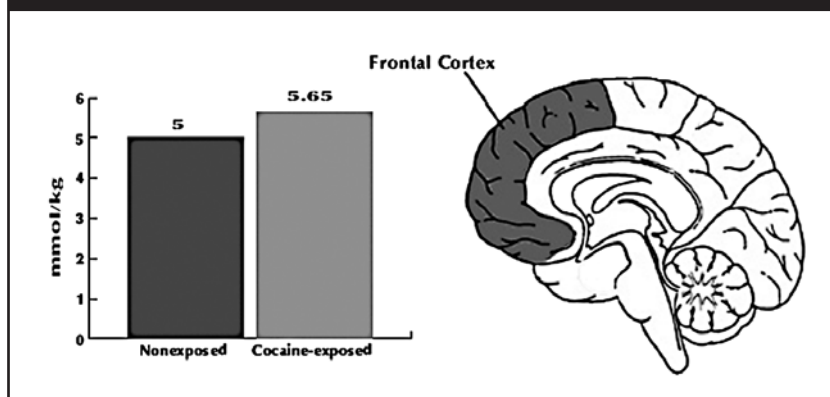
The nature and extent of possible developmental damage to infants and children from prenatal exposure to cocaine has been the subject of much apprehension and scientific study. In the 1980s, anecdotal reports of abnormalities among cocaine-exposed children contributed to fears that these children were 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 abnormalities

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.

Sources

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- Chang, L., et al. Neurochemical alterations in asymptomatic abstinent cocaine users: A proton magnetic resonance spectroscopy study. *Biological Psychiatry* 42(12):1105–1114, 1997.
- Smith, L.M.; Chang, L.; et al. Brain proton magnetic resonance spectroscopy and imaging in children exposed to cocaine *in utero*. *Pediatrics* 107(2):227–231, 2001. **NN**

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, similar 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

- Smith, L.M.; Chang, L.; Yonekura, M.L.; Grob, C.; Osborn, D.; and Ernst, T. Brain proton magnetic resonance spectroscopy in children exposed to methamphetamine in utero. *Neurology* 57(2):255–260, 2001. **NN**

Pathological Obesity and Drug Addiction Share Common Brain Characteristics

By Robert Mathias, NIDA NOTES Staff Writer

Reduced brain activity of dopamine, a naturally occurring substance that modulates feelings of pleasure, may contribute to obesity as well as drug addiction, a NIDA-funded study suggests. The study found that the brains of obese individuals have relatively few of the nerve cell components called D2 receptors through which dopamine acts to stimulate pleasurable feelings from basic activities such as eating and sex. Individuals with this deficiency may need to overeat to get feelings of gratification from food, the researchers say. Because a deficit of the same receptor has been implicated in addiction to cocaine, heroin, and other drugs of abuse, the researchers suggest that it may be linked to a range of compulsive behaviors.

“Although many complex factors may be involved in excessive behaviors such as compulsive drug abuse, overeating, and gambling, they are all similar in that the brain is changed, reward circuits are disrupted, and the behavior eventually becomes involuntary,” says Dr. Joseph Frascella of NIDA’s Division of Treatment Research and Development. “Finding low D2 receptors across various drugs of abuse and now obesity suggests a common brain mechanism that could contribute to such disorders,” he says.

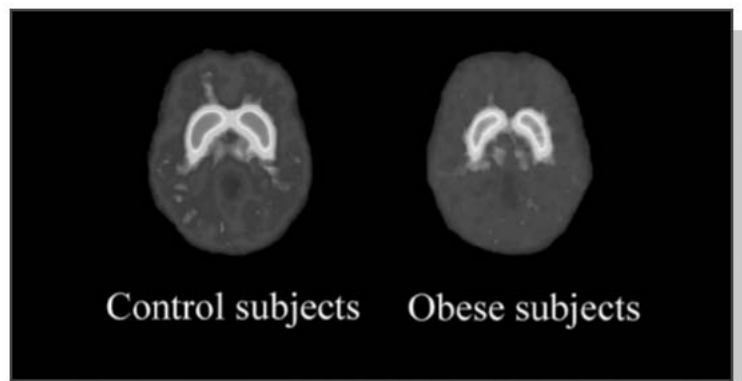
In the study, Dr. Gene-Jack Wang and Dr. Nora Volkow of Brookhaven National Laboratory in Upton, New York, used positron emission tomography (PET) to assess metabolic activity and dopamine D2 receptor levels in the brains of 10 severely obese and 10 nonobese subjects. The obese group included five men and five women and the control group had seven men and three women. Obese subjects had an average body mass index (BMI) of 51.2. Controls had an average BMI of 24.7. BMI is a measure of weight in relation to height. An index of 25 or greater is considered overweight and an index of 30 or above is considered obese.

The PET scans showed that, compared to controls, obese individuals had significantly fewer dopamine D2 receptors in the striatum, an area of the brain where dopamine receptors are particularly concentrated. Data analyses showed that neither gender nor brain metabolism was related to the differences in receptor availability

between the two groups. The best direct relationship to receptor levels was BMI—the greater an individual’s BMI, the fewer available dopamine D2 receptors.

The brain area the researchers imaged includes the nucleus accumbens (NAc), the central structure in the brain’s reward system. Eating increases extracellular levels of dopamine in the NAc, producing feelings of satisfaction and pleasure, the researchers explain. Previous research has shown that drugs that increase dopamine concentrations in this area decrease appetite. Conversely, drugs that block dopamine receptors increase appetite and lead to significant weight gain. “Thus, low D2 receptor levels in obese individuals may contribute to continued overeating to compensate for reduced stimulation of their brain reward circuits,” Dr. Wang says.

“It is through activation of these circuits that we are motivated to do the things we perceive as pleasurable,” Dr. Volkow says. “If you have a decrease in dopamine receptors that transmit pleasurable feelings, you become less responsive to the stimuli, such as food or sex, that normally activate them,” she says. “When these activities don’t reward you enough, your brain signals you to do something that will stimulate the circuits sufficiently to



These composite brain scan images show that obese individuals have significantly fewer dopamine receptors in the outlined area than control subjects. These receptors transmit pleasurable feelings from basic activities such as eating and sex. Low levels of these receptors also have been found in people addicted to drugs of abuse. The reduced reward experienced by people with this deficiency may make them more likely to engage in addictive behaviors.

create a sense of well-being. Thus, an individual who has low sensitivity to normal stimuli learns behaviors, such as abusing drugs or overeating, that will activate them.”

It remains unclear whether low D2 brain receptor levels are a cause or a consequence of addictive behaviors—or both. “This deficiency could be a double-edged sword that cuts both ways,” says NIDA’s Dr. Frascella. First, the reduced reward experienced by people with this deficiency may make them more likely to engage in addictive behaviors. Then, the addictive behavior itself could make the deficit worse as the brain further lowers D2 levels in response to constant overstimulation of the reward pathway. “In the end, they could be much worse off biologically than when they started,” he says.

“This phenomenon has important implications for drug abuse treatment,” Dr. Volkow says. “If the only behavior that will activate reward centers is taking drugs, then people are going to take drugs. However, if treatment can help drug abuse patients to develop alternative behaviors that can activate these centers, they can start to replace drug use with these behaviors.”

Source

- Wang, G-J.; Volkow, N.D.; et al. Brain dopamine and obesity. *Lancet* 357(9253):354–357, 2001. **NN**

NIDA Scientific Panel Reports on Prescription Drug Misuse and Abuse

By Patrick Zickler, NIDA NOTES Staff Writer

NIDA launched a new initiative on prescription drug abuse, misuse, and addiction at a press conference in Washington, DC, in April. NIDA developed the initiative in response to reports of increased abuse of prescription pain relievers and concern over abuse of other prescription drugs. A scientific program following the press conference provided an overview of current research into issues associated with prescription opioid drugs used in pain relief, central nervous system depressants prescribed for anxiety and sleep disorders, and stimulants used to treat attention-deficit/hyperactivity disorder (ADHD) and obesity. Dr. Alice Young, a NIDA-supported researcher at Wayne State University in Detroit, presented a discussion of the neurobiology of addiction. In subsequent presentations, researchers focused on investigations into specific aspects of prescription drug abuse.

Dr. Howard Chilcoat of The Johns Hopkins University School of Public Health and Hygiene in Baltimore discussed research into the epidemiology of prescription drug abuse. Overall, he said, the number of people who abuse prescription drugs each year roughly equals the number who abuse cocaine—about 2 to 4 percent of the population. Whites are more likely than other racial or ethnic groups to abuse prescription drugs, and many people who abuse these drugs also have psychiatric disorders. Persons age 18 to 25 are more likely than persons in other age groups to begin abusing prescription drugs. Between the ages of 12 and 17, girls are more likely than boys to begin prescription drug abuse and are more likely to abuse stimulants and sedatives than other prescription drugs.

Dr. Kenneth Schmader of Duke University in Durham, North Carolina, said that the elderly (persons age 65 or older) represent about 13 percent of the U.S. population but consume one-third of all prescription drugs. These patients are generally less healthy than younger persons and often suffer from multiple diseases for which they take multiple drugs, Dr. Schmader said, and are therefore more vulnerable than are younger patients to unintentionally misusing and becoming habituated to prescription medications. In one study of more than 1,500 elderly patients, 50 patients, roughly 3 percent, were abusing prescription drugs. In a study of consecutive admissions to a treatment program, 70 of 100 elderly patients admitted for prescription drug abuse were women. Eighty were



As part of its initiative on prescription drug misuse and addiction, NIDA is distributing 400,000 postcards with messages about the dangers of prescription drugs. The cards are available in restaurants, book stores, clubs, record stores, coffee shops, gyms, and other locations in several major cities.

dependent (that is, they experienced withdrawal symptoms if they tried to stop taking the drugs) on sedatives, 49 on opioids, and 3 on stimulants. Thirty-six were dependent on 2 drugs and 8 were dependent on 3.

Dr. Timothy Wilens of Massachusetts General Hospital in Boston discussed prospective studies designed to determine whether children treated for ADHD with the stimulant methylphenidate (Ritalin) are at risk for abuse of

other stimulant drugs. The research involved two groups of patients diagnosed with ADHD of similar severity: one group was treated with methylphenidate and the other received treatment that did not include stimulants. Dr. Wilens reported that those who were treated with methylphenidate were less likely to abuse drugs, including prescribed or unprescribed stimulants, during treatment and throughout youth and adolescence.

Dr. Richard Brown of the University of Wisconsin Medical School in Madison said that physicians' misunderstanding of the risks associated with prescription drugs can lead to inadequate treatment of some illnesses. Dr. Brown based his statement on research in which he and his colleagues asked physicians how they would treat a set of hypothetical patients who suffered anxiety disorders, pain associated with cancer, or back pain. The researchers gave the clinicians detailed profiles of the hypothetical patients that included a treatment history and characteristics, such as use of alcohol and history of substance abuse, related to possible misuse of prescription medication. The researchers compared the physicians' treatment plans with a plan developed by a panel of experts. Compared to the experts, the 2,000 physicians who participated in the study were more reluctant to provide opioids and less cautious about prescribing sedatives. For example, 5 percent of the respondents would not prescribe opioids for severe cancer pain and nearly 80 percent would avoid opioids for severe, chronic back pain that had not responded to other treatments. About 25 percent of the physicians would prescribe benzodiazepines (sedatives such as Valium or Xanax) for a hypothetical patient with an adjustment disorder (anxiety or sadness associated with a particular situation), even though they showed several signs and symptoms of a current alcohol use disorder.

Dr. Steven Passik of Community Cancer Care, Inc., in Indianapolis, Indiana, discussed a study designed to evaluate the risks of misuse or abuse of drugs prescribed for management of chronic pain and to compare the risks with the drugs' benefits. The research involved 264 patients being treated with opioids for chronic pain not associated with cancer. On average, patients reported that



In 1998 roughly 1.6 million people used prescription pain relievers nonmedically for the first time—four times as many as in 1980.

the drugs relieved nearly 60 percent of their pain, and more than 90 percent said the pain relief made a significant improvement in their quality of life. Nearly 80 percent reported improvement in overall aspects of daily life such as mood, physical functioning, relationships, and sleep patterns. More than 60 percent of patients reported some adverse side effects from their medication, but only 1.2 percent described the side effects as intolerable. Overall, roughly 6 percent of patients (or their physicians) reported abuse or misuse of prescribed drugs. Drug abuse issues in pain management are complex, Dr. Passik said, but his study results suggest that the risk of opioid abuse is low compared with the benefits of the drugs in chronic pain management. **NN**

Annual Survey Finds Increasing Teen Use of Ecstasy, Steroids

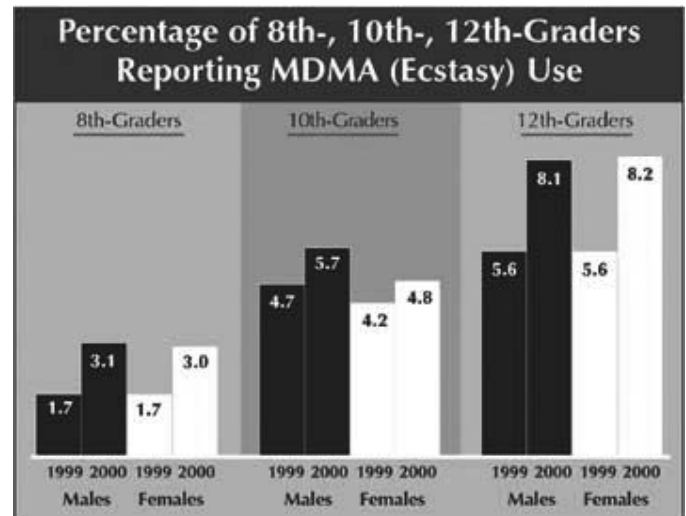
By Patrick Zickler, NIDA NOTES Staff Writer

For the fourth year in a row, the percentages of 8th-, 10th-, and 12th-graders avoiding all use of illicit drugs remained level or increased in 2000, according to the 26th annual Monitoring the Future study. However, the nationwide survey of drug use among teenagers found that use of MDMA (ecstasy) has increased in all age groups and that use of steroids has risen among 10th-graders.

The findings marked the second consecutive year of increased MDMA use among 10th- and 12th-graders and the first increase among 8th-graders. In 2000, 8.3 percent of 12th-graders reported that they had used MDMA at least once in the past year, up from 5.6 percent in 1999 and 3.6 percent in 1998. Eighth-graders' use of the drug increased from 1.7 percent in 1999 to 3.1 percent in 2000. Among 10th-graders, past-year MDMA use remained statistically unchanged, at 5.4 percent in 2000, but use in the past month increased from 1.8 percent in 1999 to 2.6 percent last year, according to the study's principal investigator, Dr. Lloyd Johnston of the University of Michigan in Ann Arbor.

Use of steroids during the year prior to the survey rose from 1.7 percent in 1999 to 2.2 percent in 2000 among 10th-graders but remained stable at 1.7 percent among 8th- and 12th-graders. Among teenage males, where most steroid use is concentrated, past-year use was reported by 2.2 percent of 8th-graders, 3.6 percent of 10th-graders, and 2.5 percent of 12th-graders, Dr. Johnston said at a December 2000 press conference announcing the most recent findings.

The Monitoring the Future study, conducted by the University of Michigan's Institute for Social Research and funded by NIDA, has tracked high school seniors' illicit drug use and attitudes toward drugs since 1975. Younger teens, in grades 8 and 10, were added to the survey in 1991. Data for the 2000 survey represent responses of more than 45,000 students in 435 schools across the Nation to questions about lifetime use, use during the past year, use during the past month, and daily use of various illicit drugs, alcohol, cigarettes, and smokeless tobacco.



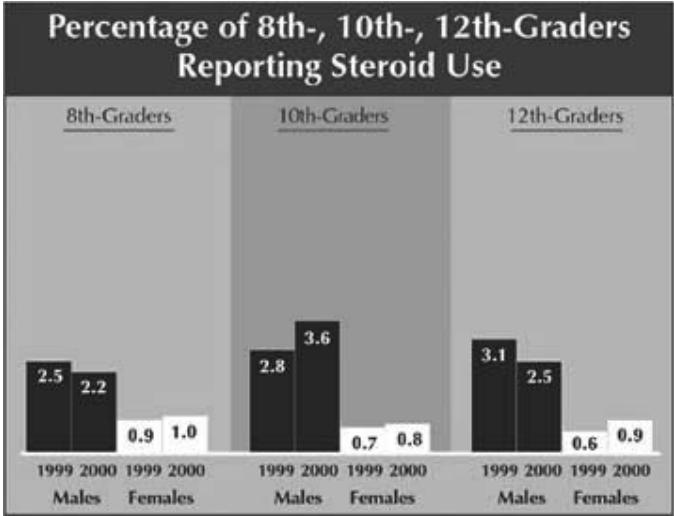
Past-month use of MDMA increased for all teenagers from 1999 to 2000.

“This survey provides crucial information on the real-world experience of young people with drugs.”

“This survey provides crucial information on the real-world experience of young people with drugs, and the recent increases in MDMA use are a major concern,” said NIDA Director Dr. Alan I. Leshner. “Ecstasy is not a ‘fun’ drug. It is neurotoxic—it severely damages brain cells and has consequences that include dehydration, hypertension, hyperthermia, and heart or kidney failure.”

The number of 8th-graders having used an illicit drug during the past year has declined steadily from 22.1 percent in 1997 to 19.5 percent in 2000. Among 10th-graders, use of an illicit drug was reported by 38.5 percent in 1997 and 36.4 percent in 2000. For seniors, past-year use of an illicit drug was reported by 42.4 percent in 1997 and by 40.9 percent in 2000.

Tenth-graders' past-month use of cigarettes was 23.9 percent in 2000, roughly the same as in 1999; however, daily cigarette smoking decreased significantly in this group, from 15.9 percent to 14.0 percent. Daily smoking among 12th-graders declined from 23.1 percent in 1999 to 20.6 percent in 2000.



Steroid use rose among 10th-grade boys and among girls in grades 8, 10, and 12.

Reductions in other measures of smoking also occurred among 8th-, 10th-, and 12th-graders. “For cigarettes, and for smokeless tobacco as well, the overall declines from peak levels of the mid-90s have been substantial,” Dr. Johnston says. Alcohol use by teens remained largely unchanged in 2000.

For More Information

- Additional information about the Monitoring the Future study can be obtained from NIDA Infobox at 1-888-NIH-NIDA (644-6432) or from NIDA’s home page at www.drugabuse.gov. Information is also available from the Monitoring the Future home page at the Institute for Social Research at the University of Michigan: www.monitoringthefuture.org. Information about MDMA (ecstasy) is available at the NIDA club drugs Web site, www.clubdrugs.org. Information about steroids is available at NIDA’s steroids Web site, www.steroidabuse.org. **NN**

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

By Patrick Zickler, NIDA NOTES Staff Writer

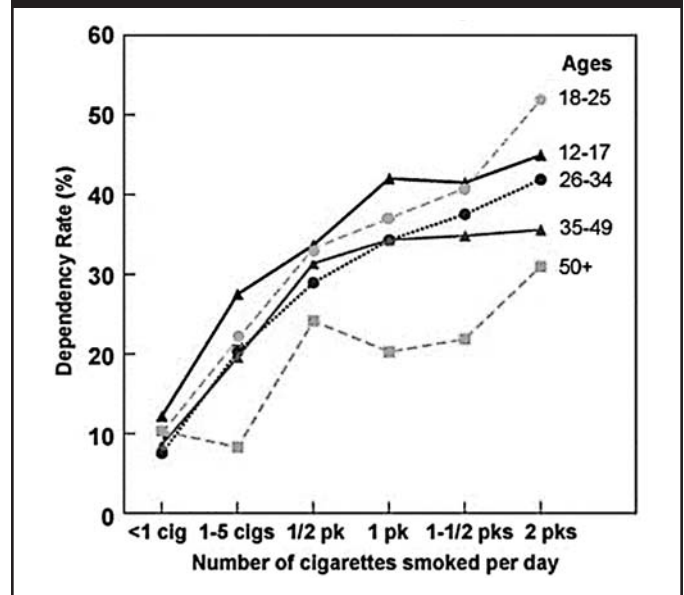
Rates of drug dependence—the percentage of users who experience symptoms that reinforce their drug use and have trouble quitting—are higher for nicotine than for marijuana, cocaine, or alcohol. Rates of dependence also vary among different groups of smokers, according to NIDA-supported research. A new 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. **NN**

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.

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Meeting the Challenge of Reducing Health Disparities

NIDA Director Dr. Alan I. Leshner

Through more than 25 years of scientific research, NIDA has dramatically advanced our understanding of the ways that drugs act on cells, in the brain, and in the lives of individuals. We have also learned how groups of individuals—populations distinguished by race, ethnicity, gender, or other characteristics—are affected by drug abuse.

NIDA research shows that, contrary to a common stereotype, overall rates of drug abuse among racial and ethnic minorities are similar to rates in the general population, although some aspects of drug abuse may differ. For example, the initiation and progression of drug use appear to differ among populations. White youth begin using drugs at a younger age than do minority youth, but evidence suggests young African Americans who begin using drugs are more likely to continue use than are whites.

We also know that some populations suffer disproportionately from consequences of drug abuse. Since the AIDS epidemic began, injection drug use has been directly or indirectly responsible for more than a third of all cases overall, but women with HIV are twice as likely as men to have been infected through injection drug use or through sexual activity with an injecting drug user. Minority populations are disproportionately affected by the relationship between drug abuse and HIV/AIDS. For example, between 1985 and 1999 more than twice as many blacks (94,700) as whites (36,800) developed AIDS through injection drug abuse, even though there are only one-fourth as many black injection drug users. Roughly the same number of Hispanics (35,100) and whites developed AIDS through injection drug abuse, even though there are only one-eighth as many Hispanic injection drug users. Of the drug-related AIDS cases in women reported through June 2000, 56 percent were among African-American women, 21 percent among Hispanic women, and 22 percent among white women.

NIDA is committed to building scientific understanding of the environmental, social, and biological factors that influence the different patterns and disproportionate consequences of drug abuse among various populations. To coordinate and accelerate research into the health disparities that complicate efforts to prevent and treat drug abuse among populations, NIDA has developed a Strategic Plan on Reducing Health Disparities that will:

- improve our understanding of the incidence and causes of drug abuse and addiction in racial and ethnic populations, including Native Americans, Asians, and Pacific Islanders;

- strengthen and expand the community and institutional infrastructure for conducting research within racial and ethnic populations;
- provide the scientific foundation for improved prevention and treatment for racial and ethnic groups at highest risk for addiction and medical consequences of drug abuse and addiction; and
- widely disseminate information that identifies the best approaches to prevention and treatment of drug abuse and the disease of addiction in racial and ethnic communities.

To reach the goals established in the Strategic Plan, NIDA has developed a Health Disparities Initiative, which is directed

by the Institute's Special Populations Office and includes activities in each of the Institute's program divisions and offices. The initiative will focus on four major research areas: epidemiology, prevention, treatment, and basic and clinical research. In some cases, these efforts will represent an expanded commitment to existing programs, but the initiative also will include important

new activities. For example, NIDA will expand training opportunities to increase the capacity of minority institutions—and the number of minority scientists—involved in drug abuse research. The Center on AIDS and Other Medical Consequences of Drug Abuse and the Division of Epidemiology, Services and Prevention Research have jointly issued a Request for Applications for research projects that will encourage cross-disciplinary biomedical, epidemiological, developmental, and social science research to develop more effective interventions to reduce the impact of HIV/AIDS and other disease consequences of drug abuse in minority populations. NIDA also will convene a national conference on health disparities and drug abuse, to be held in the fall, that will bring together scientists, policymakers, and educators with expertise on minority populations. These experts will explore the underlying reasons for health disparities related to drug abuse and develop insights about prevention and treatment strategies that can be effective in specific minority populations.

These efforts are part of a concerted and comprehensive program of research that will help us fill significant gaps in knowledge about the effects of drug abuse and addiction in minority populations and will allow us to develop and verify effective prevention and treatment services that reduce the disproportionate suffering of these communities. **NN**

***“Some populations
suffer disproportionately
from consequences of
drug abuse.”***

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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Update on Nicotine Addiction And Tobacco Research

What makes nicotine addictive? Why do some children decide to smoke, while others never light up? What makes quitting smoking so difficult, and how can we make it easier? NIDA-funded researchers are seeking answers to questions like these in nicotine- and tobacco-related studies. Following are highlights of recent gains in our knowledge about nicotine and tobacco.

Teen Smokers

The NIDA-funded Monitoring the Future survey of students in grades 8, 10, and 12 shows that the number of current teenage smokers has declined since 1997. Still, nearly one in four high school seniors smokes every day, and more than one in eight smokes a half-pack or more each day.

Peer pressure, parental smoking, and family conflicts are the most significant predictors of whether a child makes the transition from occasional smoking to regular cigarette use. In a study of 11- to 13-year-olds, researchers found that 75 percent of the children who smoked had one or two smoking parents. Researchers also found that the earlier teens start to smoke, the more severe their addiction will be. Depression and delinquency also have been shown to be powerful predictors of smoking urges and behavior.

Genetic Influences

Researchers have found that they can prevent nicotine dependence in mice genetically altered so that they lack a portion of one of the brain receptors at which nicotine binds to produce its rewarding effects. While normal mice self-administered nicotine in laboratory tests, the altered mice did not. Similarly, a natural genetic mutation has been found in humans that inhibits nicotine metabolism. Male smokers with this mutation are less likely to become addicted to nicotine and more likely to find it easier to quit smoking; however, the presence or absence of the defective gene does not affect women's smoking.

Gender Differences

In addition to the genetic difference described above, a number of other gender differences have been found among smokers. For example, accumulating evidence shows that, for women, nicotine intake may be less important in smoking behavior than it is for men. Studies have shown that women take fewer and shorter puffs from cigarettes and are less sensitive to some of nicotine's effects, but they may be more sensitive to external stimuli, such as the presence of a lit cigarette or the smell of smoke.

Women also have been less successful than men with nicotine replacement therapy for smoking cessation.

Treatment Approaches

In addition to nicotine replacements in the form of gum, skin patches, aerosol spray, and inhalers, medications to aid smoking cessation include the non-nicotine compound bupropion (marketed as Zyban). Bupropion is a prescription antidepressant that also blocks nicotine's pleasurable effects. Other medications used in the treatment of nicotine addiction include clonidine, mecamylamine, and buspirone.

To date, medication combined with behavioral treatment has been the most effective approach to treating nicotine addiction. Behavioral therapies such as relapse prevention/skills training approaches, motivational enhancement, and group or individual counseling are designed to support both short-term and long-term abstinence from nicotine.

On the Horizon

NIDA has defined new areas of nicotine research to include studies of regional brain metabolism, the role of multiple nicotine receptors, genetic contributions to smoking initiation and persistence, and the phenomenon of craving.

NIDA's Teen Tobacco Addiction Treatment Research Clinic in Baltimore, a new outpatient research program for treatment of nicotine-addicted adolescents, has implemented a 6-month controlled clinical trial addressing the safety, tolerability, and efficacy of two nicotine replacement therapies—gum and patch—in combination with either counseling or group support.

At Washington University in St. Louis, a large-scale gene mapping study is under way to identify candidate genes for risk of nicotine addiction. Researchers are examining adult twins to learn more about the relative contributions of genetic and environmental factors in both smoking initiation and continuing cigarette use.

New medications being studied for treating nicotine addiction include methoxsalen, an approved treatment for psoriasis, and NicVAX, a vaccine that can immunize smokers against nicotine's effects. Methoxsalen reduces the action of an enzyme that metabolizes nicotine and so may help smokers quit more easily. NicVAX has been successful in animal studies and soon will be tested in clinical trials. The vaccine, if successful with current smokers, also might be effective in protecting children from the risk of nicotine addiction. **NN**

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. Dreama 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

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 or from the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686. **NN**

NIDA's Epidemiological Compasses

NIDA Director Dr. Alan I. Leshner

Epidemiology is the science of identifying trends and patterns in the occurrence of health problems. Epidemiological studies advance NIDA's mission by gauging the scope and nature of the Nation's drug problems and providing information fundamental to improving treatment and prevention.

NIDA sponsors two major epidemiological tracking programs. The Monitoring the Future study (MTF), now in its 25th year, asks 50,000 students in a representative sample of the Nation's middle and high schools to report on their use of drugs and attitudes toward drug use. MTF provides a sensitive register of trends and patterns of drug use among youth. The other program, NIDA's Community Epidemiology Work Group (CEWG), has tracked drug abuse in 20 of the Nation's largest cities and the State of Texas for 24 years. CEWG gathers information from State and local law enforcement agencies, survey data, and a variety of public health services. The researchers review data on drug-related deaths and emergency department visits, admissions to drug abuse treatment programs, drug arrests, and drug test results among arrestees. CEWG investigators also conduct focus groups and interviews with community members. CEWG is particularly attuned to the harmful impacts of drug abuse and has given early warning of every emerging major drug trend in recent decades.

NIDA uses MTF and CEWG to document the size of the drug abuse problem, spot trends, pinpoint the groups in the Nation's population that are most in need of prevention and treatment, and assess the effectiveness of interventions. Epidemiological estimates of the number of people abusing a particular drug are also used to set NIDA's research agenda. These estimates may be weighed, along with what is known or suspected about the health and social consequences of abusing the drug and evaluations of technical feasibility, in determining directions for research.

NIDA's epidemiology programs also enable us to respond rapidly to new trends in drug use. This is critical because, when a new drug of abuse comes on the scene, young people tend to hear first about its attractive properties. They also need to hear—and hear quickly—about the drug's health and social consequences in order to quell the trend at an early stage.

Within the past year alone, NIDA has twice mobilized rapid responses to epidemiological evidence of new trends.



“NIDA uses two epidemiological tracking programs to document the size of the drug abuse problem, spot trends, pinpoint the groups in the Nation's population that are most in need of prevention and treatment, and assess the effectiveness of interventions.”

First, the latest MTF recorded a leveling off of students' overall drug use, but a sharp rise in their use of anabolic-androgenic steroids from 1998 to 1999. The results also showed a decrease in the percentage of 12th-graders reporting that they believed these drugs are harmful. NIDA immediately mobilized a campaign to alert parents and potential users that steroids are anything but safe. Steroid abusers are at risk for stunted growth, increased aggression, and (although this is rare) fatal liver disease.

Males may experience testicular shrinkage and breast enlargement, while females may experience masculinization and menstrual irregularity. To date, NIDA has spread this message via a Research Report, a Community Drug Alert Bulletin, a fact sheet and press releases, two eye-catching postcards, and a special Web site, www.steroidabuse.org. In mid-April, NIDA and influential partners from

the worlds of sports and medicine held a press conference that drew media attention to the dangers of these drugs and announced the first successful program to prevent steroid abuse among high school athletes. One register of the timeliness of this effort is the strong response from the public. More than 1,000 individuals viewed the Web site daily during the first days of its operation.

In a second example of epidemiology findings galvanizing a rapid NIDA response, last winter NIDA mounted a similarly comprehensive public information campaign in response to a CEWG finding that use of MDMA (ecstasy), Rohypnol, ketamine, and other so-called club drugs was increasing. Clearly, drug dealers and the reports of some users had convinced many young people that these drugs offered low-risk pleasure. NIDA's continuing campaign emphasizes case reports of acute side effects including heart attacks, strokes, coma, and death from respiratory depression, as well as research findings of long-term neurotoxicity and memory loss following exposure to some of these drugs. (For more on NIDA's research on club drugs, see www.clubdrugs.org.)

Public information campaigns are among NIDA's most immediate responses to new trends revealed by MTF and CEWG. For the longer term, epidemiological findings highlight questions for research. Thus, NIDA has joined with a number of institutional partners to earmark \$54 million to investigate club drugs. As another recent striking example of epidemiological findings leading to a research response, in the 1990s NIDA studies disclosed

that most new heroin use was occurring in suburbia rather than—as previously—in urban centers. In addition, many new users were inhaling rather than injecting the drug, often lulled by beliefs that inhalation would not lead to addiction or exposure to blood-borne diseases such as HIV/AIDS and hepatitis C. To examine these beliefs, NIDA sponsored a study of transition from heroin inhalation to injection. Not only did the results show that transition was often rapid, they also documented very high rates of hepatitis C infection among new injecting drug users. NIDA is now disseminating this information as a deterrent to the myth of safe heroin use.

Drug abuse in the Nation is never static. The availability of new illicit drugs, changing circumstances in our communities, even generational shifts fuel new problems and create new opportunities for interventions. By tracing the complex patterns of drug abuse, MTF and CEWG help to identify where prevention and treatment are most needed and can be most effective. They also provide us the measure of our success in curbing the growth in drug abuse that occurred in the 1990s, and of the challenge still remaining. **■**

About Anabolic Steroid Abuse

NIDA has issued an updated research report that summarizes the latest scientific information on anabolic steroids. The eight-page Research Report, *Anabolic Steroid Abuse*, is part of a nationwide education initiative launched by NIDA and several national organizations to counter a significant rise in anabolic steroid abuse among adolescents. Highlights from the report are:

What are anabolic steroids?

Anabolic steroids are synthetic substances related to the male sex hormones, called androgens. They have a number of physiological effects, most notably an anabolic effect that promotes the growth of skeletal muscle and androgenic effects that foster the development of male sexual characteristics. Although the proper term for these compounds is anabolic-androgenic steroids, they commonly are called anabolic steroids.

Anabolic steroids are legally available only by prescription in the United States. Doctors use these drugs to treat delayed puberty, impotence, and body wasting in patients with AIDS and other diseases. Abused steroids most often are obtained from clandestine laboratories, smuggled, or illegally diverted.

What is the scope of steroid abuse?

Steroid abuse is higher among males than females but is growing most rapidly among young women. An estimated 2.7 percent of 8th- and 10th-graders and 2.9 percent of 12th-graders have taken anabolic steroids at least once in their lives, according to the 1999 Monitoring the Future study, a NIDA-funded survey of drug abuse among adolescents. These figures represent increases since 1991 of approximately 50 percent among 8th- and 10th-graders and 38 percent among 12th-graders.

Why do people abuse anabolic steroids?

Abuse of anabolic steroids is motivated in most cases by a desire to build muscles, reduce body fat, and improve sports performance. Abuse is estimated to be very high among competitive bodybuilders and may also be widespread among other athletes. Some men who abuse steroids perceive their own bodies to be small and weak, even if they are large and muscular. Some women who abuse these drugs think they look obese or flabby, even though they are actually lean and muscular. Other

individuals abuse steroids because they are trying to become bigger and stronger to protect themselves from recurrence of physical or sexual assaults.

How are anabolic steroids used?

Anabolic steroids are taken orally as tablets or capsules, by injection into muscles, or as gels or creams that are rubbed into the skin. Doses taken by abusers can be up to 100 times greater than doses used for treating medical conditions.

Anabolic steroids often are taken in combination in a practice called "stacking," in which the abuser mixes oral and/or injectable types of anabolic steroids. Steroid abusers often also "pyramid" stacked compounds in cycles of 6 to 12 weeks, meaning that they gradually increase doses then slowly decrease them to zero. The belief that these practices produce bigger muscles and allow the body to adjust to and recuperate from high doses of steroids has

not been substantiated scientifically.

What are the potential health consequences of steroid abuse?

Health consequences associated with anabolic steroid abuse include:

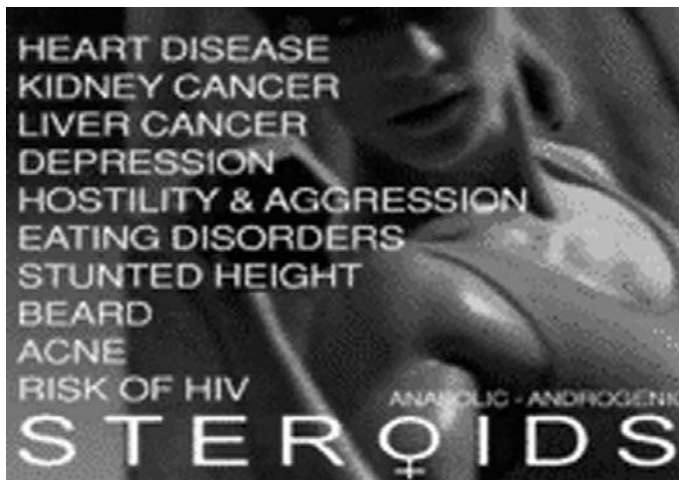
- *Hormonal system disruptions.* Reduced sperm production, shrinking of the testicles, impotence, and irreversible breast enlargement in boys and men. Decreased body fat and breast size, deepening of the voice, growth of excessive body hair, loss of scalp hair, and clitoral enlargement in girls and women.
- *Musculoskeletal system effects.* Premature and permanent termination of growth among adolescents of both sexes.
- *Cardiovascular diseases.* Heart attacks and strokes.
- *Liver diseases.* Potentially fatal cysts and cancer.
- *Skin diseases.* Acne and cysts.
- *Infections.* In injecting steroid abusers, HIV/AIDS, hepatitis B and C, and infective endocarditis, a potentially fatal inflammation of the inner lining of the heart.
- *Behavioral effects.* Increased aggressive behavior, particularly when high doses are taken. Depression, mood swings, fatigue, restlessness, loss of appetite, and reduced sex drive when steroid abuse is stopped. **NN**

"Doses taken by abusers can be up to 100 times greater than doses used for treating medical conditions."

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.

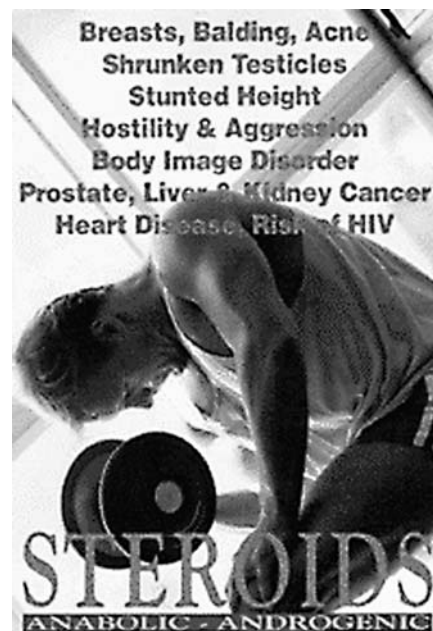
The Institute's partners in the initiative include the National Collegiate Athletic Association, the American Academy of Pediatrics, the American College of Sports Medicine, the National Association of School Nurses, the National Federation of High Schools, International Students in Action, and Dr. Drew 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 State University discussed the history and social context of steroid use and abuse. Dr. Linn Goldberg and



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.”



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

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 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 NIDA Research Report “*Anabolic Steroid Abuse*” (NCADI publication #PHD561) can be obtained from the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847; phone 800-729-6686; fax 301-294-5516; e-mail info@health.org. The report and other information about anabolic steroids can be found at the special NIDA Web site: www.steroidabuse.org. **NN**

Evidence Builds That Genes Influence Cigarette Smoking

By Patrick Zickler, NIDA NOTES Staff Writer

More than one in four Americans older than 17 regularly smokes cigarettes despite increasing public awareness of tobacco's severe health risks. Some start younger than others and, among those who try to quit, some are more successful than others. NIDA-supported scientists are finding increasing evidence that these differences may be due in part to an inherited vulnerability to nicotine addiction.

At the St. Louis University Health Sciences Center, Dr.

William True and Dr. Hong Xian interviewed male twin pairs to assess genetic influences on smoking. In twin studies, researchers compare patterns of tobacco use in fraternal and identical twin pairs, who typically are exposed to common environmental influences. If genes play a role in determining tobacco use, identical twins—who share the same genes—will be more similar in their use of tobacco than fraternal twins, who share roughly half of their genes. The St. Louis University researchers found that among the 3,356 twin pairs studied, genetic factors make a stronger contribution to nicotine dependence (61 percent) than do environmental factors (39 percent) and also play a more prominent role (55 percent) than environmental factors (45 percent) in alcohol dependence. In another study, Dr. Kenneth Kendler and his colleagues at the Medical College of Virginia in Richmond interviewed 949 female twin pairs and found that genetic factors play a more important role (78 percent) than do environmental factors (22 percent) in smoking initiation and in nicotine dependence (72 percent vs. 28 percent).

“These studies emphasize the importance of understanding the role of genetic influences in smoking,” says Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences Research Branch. “The more we understand about

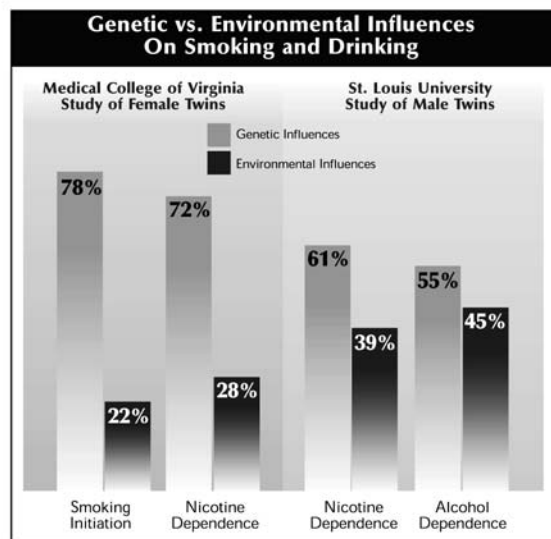
vulnerabilities, risks, and possible protective factors, the better able we will be to tailor treatments that help people stop smoking.”

Other NIDA-supported scientists are studying genes that are polymorphic—that is, in different individuals the same gene has slight variations called alleles—and have found that individuals with one type of allele are more likely to begin smoking or to have greater success quitting than are individuals with another type.

For example, researchers at the University of Toronto have found that different alleles in a gene that helps regulate nicotine metabolism may protect some smokers from becoming dependent on nicotine.

Dr. Caryn Lerman, principal investigator of the NIDA-supported Transdisciplinary Tobacco Use Research Center at Georgetown University in Washington, DC, and her colleagues studied two genes, designated SLC6A3 and DRD2, that may influence smoking behavior by affecting the action of the brain chemical dopamine. In a study involving 289 smokers and 233 nonsmokers (42 percent male, 58 percent female, average age 43), the researchers found that smokers were less likely to have an allele designated SLC6A3-9 (46.7 percent) than were nonsmokers (55.8 percent).

The likelihood of smoking was even lower if the individual had both the SLC6A3-9 allele and the DRD2-A2 allele. In addition, Dr. Lerman observed that smokers with the SLC6A3-9 allele were more likely to have started smoking later and to have had longer periods of smoking cessation than those without the allele. These findings imply that the allele may impart a protective effect. Therefore, Dr. Lerman suggests, smokers without the SLC6A3-9 allele may be better able to quit smoking if their treatment incorporates a medication



A Medical College of Virginia study involving 949 female twin pairs found genetic factors to be more influential than environmental factors in smoking initiation and nicotine dependence. Likewise, a St. Louis University study of 3,356 male twin pairs found genetic factors to be more influential for dependence on nicotine and alcohol.

such as bupropion that acts on the brain's dopamine pathway. This hypothesis is currently being tested in a randomized trial.

Dr. Lerman and her colleagues also studied a polymorphism in a gene, designated 5-HTTLPR, that helps regulate the brain chemical serotonin to determine the gene's possible role in smoking. The polymorphism has two alleles, one designated the short, or S, allele, the other the long, or L allele. In previous studies the S allele has been linked to neuroticism—an anxiety-related personality trait. Dr. Lerman and her colleagues studied 185 smokers (46 percent male, 54 percent female, and average age 45) to investigate the possible relationship between genetically influenced neuroticism and smoking behavior. They found that neuroticism was associated with increased nicotine dependence, smoking for stimulation, and smoking to relieve negative mood in the group of smokers who had the S allele. Among smokers with the L allele, neuroticism was not associated with these smoking patterns. “Anxious persons tend to smoke more and have more difficulty quitting,” Dr. Lerman says. The new findings suggest that among smokers with neuroticism, determining the 5-HTTLPR genotype may help identify who will be more responsive to a particular type of treatment. “Once validated, these results may lead to targeted pharmacotherapy for smoking cessation,” says Dr. Lerman.

“The more we understand about vulnerabilities, risks, and protective factors, the better able we will be to help people stop smoking.”

“This area of research represents our first small steps along a very complicated path to understanding the role that genes play in drug abuse,” notes Dr. Harold Gordon of NIDA's Clinical Neurobiology Branch. “Many genes interact with each other and with other biological and environmental factors. Defining these interactions and understanding their influence on nicotine addiction will be crucial to development of treatments for smoking and for other addictions.”

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Antibody May Treat PCP Overdose and Abuse, Also Block Prenatal Harm

By Robert Mathias, NIDA NOTES Staff Writer

A monoclonal antibody being developed by NIDA-supported scientists may treat PCP (phencyclidine) overdose and abuse and also may block or reduce the fetal brain damage that can result from prenatal exposure to PCP. The antibody, which like other monoclonal antibodies is derived from a single cell and then produced in large quantities, reduces PCP's psychoactive and toxic effects by attaching itself to PCP in the bloodstream and blocking or reversing its chemical actions in the brain.

Researchers led by Dr. Michael Owens, who directs the Center for Alcohol and Drug Abuse Studies at the University of Arkansas Medical Center in Little Rock, have been testing the PCP antibody in an extensive series of studies aimed at increasing understanding of how such antibodies work in the body to counter the harmful effects of abused drugs. These studies have shown that a fragment of the PCP antibody, called "Fab," can rapidly remove PCP from the brains of rats. The full antibody, immunoglobulin G (IgG), can provide significant long-term reductions in PCP brain concentrations and reduce PCP's behavioral effects in rats given repeated doses of the drug.

Treating PCP Overdose

Every year, many PCP abusers are treated in hospital emergency rooms for psychotic symptoms, such as delusions and paranoia, or for overdose of the drug. PCP alone or in combination with other drugs prompted 2,287 visits to hospital emergency departments across the United States in the first 6 months of 1997, according to Drug Abuse Warning Network data compiled by the

Substance Abuse and Mental Health Services Administration. People under the influence of PCP often become violent or suicidal. Thus, a treatment that could quickly detoxify PCP abusers with a single injection would be valuable in reducing the harm that PCP abusers can cause to themselves or others. It could also shorten hospital stays and reduce the long-term costs associated with their recovery.

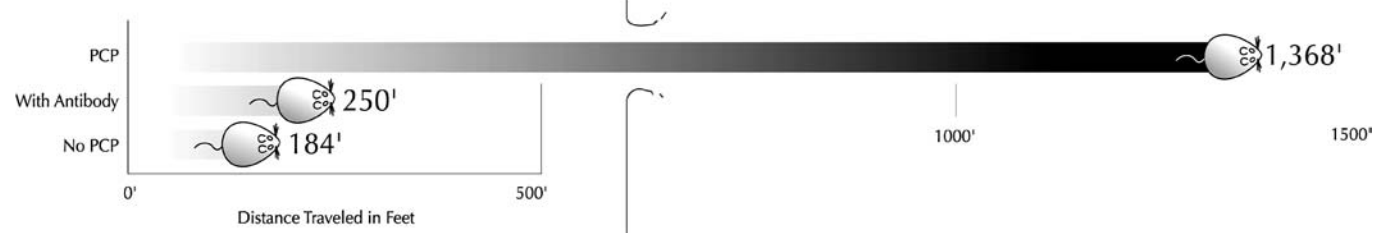
In their studies, the researchers showed that a single large dose of "Fab" completely removed PCP within 15 minutes from the brains of living rats whose bodies had been saturated with PCP. The body processes "Fab" more quickly than it does the whole antibody and can eliminate it rapidly through the kidneys along with the PCP that is bound to it, Dr. Owens explains. "Fab's fast-in/fast-out action makes it perfect for treating the acute toxic effects of drug overdose in hospital emergency rooms," he says.

With NIDA's support, Dr. Owens plans to complete the necessary preclinical research and apply for approval from the Federal Food and Drug Administration (FDA) to begin clinical trials of "Fab" in humans.

Long-Term Treatment for PCP Abuse

The researchers found that, in contrast to the short-term effects of "Fab," a single, large dose of IgG, given 24 hours after they started infusing rats with PCP, significantly reduced PCP brain concentrations during 27 days of continuous high-dose PCP infusion. In other studies, a single injection of IgG greatly reduced such PCP-induced effects as hyperactivity and distance traveled by rats given escalating doses of PCP every 90 minutes, on every third day, over 2 weeks. Measurements of these behavioral effects

Antibody Lessens Effect of PCP in Lab Rat Distance Tests



Measurements of rats' movement showed that administering the PCP antibody, "Fab," dramatically reduced the distance PCP-treated rats traveled during the experiment. The antibody reduced PCP's behavioral effects almost immediately to levels of rats that were not given PCP.

during the experiment showed that IgG-treated rats had significant decreases in PCP-induced responses for the entire 2-week period compared to rats that had been treated with an inactive saline solution.

Although many details must be worked out before IgG and similar antibodies can be used in long-term treatment of drug abuse, the results from these animal studies are encouraging, Dr. Owens says. If, as these studies suggest, a single injection of IgG can significantly reduce PCP brain concentrations and behavioral effects in rats for extended periods, antibody-based medications might be able to block or significantly blunt the rewarding effects of the drug for a month or more in humans, he says. Thus, if someone in treatment relapsed to drug use, the PCP antibody would diminish the drug's pleasurable effects and reduce the incentive to use it again. "Therefore, this might make a good medication to combine with behavioral approaches in a comprehensive treatment plan to give people a better chance of recovery," Dr. Owens says.

Prenatal Protection From PCP Exposure

Because the PCP antibody would remove the drug from the bloodstream of a pregnant woman, theoretically it would be possible to use it to block the fetal brain damage that prenatal PCP exposure has been shown to cause in rats, Dr. Owens says. "We have no reason to believe that if the antibody were used properly it wouldn't work to pull PCP out of the placenta in the same way it pulls it out of other organs that we have tested, such as the brain and testes," he says.

Pregnant women with deficient immune responses have been given massive doses of antibodies to supplement their immune systems with no ill effects, Dr. Owens

points out. "Therefore, it may be possible to give pregnant women the large doses we use in our animal studies," he says. Furthermore, "if the antibody does not harm the mother, it is unlikely that it will harm the fetus." The key is to use forms of the antibody that do not trigger an allergic reaction in the mother or fetus, he says.

"The potential for the PCP antibody to block harmful prenatal effects certainly would be worth examining," says Dr. Jamie Biswas of NIDA's Division of Treatment Research and Development. However, considerable research would be needed to establish the risks to both the mother and fetus of using the antibody versus the potential benefits of blocking PCP's possible fetal brain damage, she says.

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A Smithsonian Institution Seminar on Gender

By Raymond Varisco, *NIDA NOTES* Contributing Writer

Dr. Leshner delivered the opening remarks and NIDA-supported investigators discussed specific areas of research during an all-day seminar, "Gender Differences in Addiction and Recovery," at the Smithsonian Institution in Washington, DC "This forum gives us an excellent chance to help disseminate some of the important information our research has revealed about the biological, psychological, and social differences between the patterns of drug use and the effects that drugs have on women and men," Dr. Leshner said.

The event, cosponsored by NIDA and the Society for Women's Health Research (SWHR) was held January 29. Nearly 200 attendees heard Dr. Mary McCaul of The Johns Hopkins University in Baltimore provide an overview of gender differences in drug abuse and alcoholism; Dr. Kathleen Brady of the Medical University of South Carolina in Charleston discuss issues associated with comorbidity in women being treated for substance abuse; Dr. David Vlahov of the New York Academy of Medicine in New York City describe health consequences of drug abuse; Dr. Dace Svikis of The Johns Hopkins University discuss treatment issues for pregnant or HIV-positive women; and Dr. Brenda Miller of the University of Buffalo, New York, discuss drug-abusing women's increased risks for violence and victimization. In addition to these NIDA-supported scientists, Dr. Florence Haseltine, founder of the SWHR, and Dr. Neil Grunberg of the Uniformed Services University of Health Sciences, Bethesda, Maryland, made presentations on aspects of gender differences in drug abuse, treatment, and recovery. **NN**



Left: NIDA Director Dr. Alan I. Leshner delivers opening remarks at the Smithsonian Institution seminar. Right: Dr. Neil Grunberg presents information on gender differences in tobacco use and cessation at the Smithsonian seminar.



At the Smithsonian Institution's seminar, Dr. Mary McCaul discusses gender differences in drug abuse and alcoholism.

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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Facts About Drug Abuse and Hepatitis C

What is Hepatitis C?

Hepatitis C, a viral disease that destroys liver cells, is the most common blood-borne infection in the United States. Approximately 36,000 new cases of acute hepatitis C infection occur each year in the United States, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. People with acute HCV infection may exhibit such symptoms as jaundice, abdominal pain, loss of appetite, nausea, and diarrhea. However, most infected people exhibit mild or no symptoms.

About 85 percent of people with acute hepatitis C develop a chronic infection. Chronic hepatitis is an insidious disease whose barely discernible symptoms can mask progressive injury to liver cells over 2 to 4 decades. An estimated 4 million Americans are infected with chronic hepatitis C, according to CDC.

Chronic hepatitis C often leads to cirrhosis of the liver and liver cancer and causes between 8,000 and 10,000 deaths a year in the United States. It is now the leading cause of liver cancer in this country and results in more liver transplants than any other disease.

How Is HCV Transmitted?

People become infected with the hepatitis C virus (HCV) through direct contact with an infected person's blood. Although this contact can occur in a number of ways, injection drug use now accounts for at least 60 percent of HCV transmission in the United States, according to CDC. This estimate may be conservative because about 10 percent of people newly diagnosed with HCV do not report an identifiable risk factor. Some of these cases may represent people who are reluctant to identify injection drug use as a risk factor. Because HCV is highly transmissible through the blood, anyone who has ever injected drugs is at risk for liver disease and should be tested for the virus.

Injecting drug users (IDUs) contract hepatitis C by sharing contaminated needles and other drug injection paraphernalia. One recent study found that 64.7 percent of IDUs who had been injecting for 1 year or less were already infected with the virus. Overall prevalence of HCV was 76.5 percent among IDUs who had been injecting drugs for 6 years or less.

Additional research indicates that rates of hepatitis C among past or current IDUs are extremely high in a number of cities in the United States. For example, last year a NIDA- and CDC-funded study detected HCV infection in approximately 85 percent of 3,000 IDUs in Seattle. Researchers in Texas reported similar percentages in several Texas cities and

noted that many recovering IDUs who tested positive for HCV reportedly had not injected for 5 to 15 years.

Hepatitis C, HIV/AIDS, and hepatitis B share common risk factors for infection. IDUs have a high prevalence of coinfection with the viruses that cause these diseases. It is important to test IDUs for all three viruses.

Prior to the development of sophisticated HCV blood screening tests in the early 1990s, blood transfusions accounted for a substantial proportion of HCV infections. Now, there is only 1 chance in 100,000 that someone will get HCV from transfused blood or blood products. However, people who received blood transfusions prior to July 1992 should be tested for HCV.

The risk of perinatal transmission of hepatitis C is relatively low. About 5 of every 100 infants born to HCV-infected women become infected. However, about 17 out of every 100 infants born to HCV-infected women who are also infected with HIV become infected with HCV. HCV infection among women with HIV also is associated with increased maternal-infant transmission of HIV.

Can HCV Infection Be Prevented?

Although there are vaccines for other forms of hepatitis, none exists to protect against HCV. However, prevention of illegal drug injection would eliminate the greatest risk factor for HCV infection in the United States, according to CDC. Therefore, drug addiction treatment can play a major role in reducing HCV transmission. Research shows that drug users who enter and remain in treatment reduce high-risk activities, such as sharing needles and other drug injection paraphernalia, that are responsible for spreading HCV. AIDS outreach and HIV prevention programs for out-of-treatment drug users that reduce HIV risk also reduce the risk of HCV transmission.

How Can HCV Infection Be Treated?

Available antiviral drugs to eliminate the virus and reduce liver injury are not highly effective for patients with chronic hepatitis C. Side effects can be severe and the treatment is costly, lengthy, and effective for only 30 to 40 percent of those with the disease.

For More Information

- Patients and health care providers can obtain information on hepatitis C from the Centers for Disease Control and Prevention, Hepatitis Branch: Mailstop G-37, 1600 Clifton Road, NE, Atlanta, GA 30333, 1-888-443-7232. CDC's hepatitis Web site at www.cdc.gov/ncidod/diseases/hepatitis contains a variety of educational materials on HCV and links to additional sources of information. **NN**

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**

NIDA Science Education Program Reaches Out to Young Rural Women

By Patrick Zickler, NIDA NOTES Staff Writer

A program developed by NIDA-supported researchers at the University of Kentucky in Lexington has begun introducing young women from rural Appalachia to the excitement of hands-on science—and to the possibility of pursuing a career in drug abuse research. The program—Young Women in Science—brings high school students to the university for intensive 3-week sessions each summer and five weekend sessions during the school year.

During the first summer session, completed last August, a group of 26 ninth-grade girls worked with researchers to learn basic concepts of physiology and biology and to understand the methods of scientific research.

A second group of at least 26 young women will begin the program next summer.

“Very few opportunities exist for young women from rural areas to learn about scientific research. This program offers them a chance to work with university professors during a summer session and to stay involved by working with women mentors back in their communities,” says Dr. Carl Leukefeld, Director of the Center for Drug and Alcohol Research at the University of Kentucky College of Medicine. “Our hope is that it will attract more women to the field of drug abuse research, but an equally important goal is to get more young women exposed to and involved in male-dominated scientific fields.”



Above: Learning about drug abuse research begins with lessons in anatomy and physiology for students selected for the Young Women in Science program at the University of Kentucky. Here the teenagers study structure and function of the lungs and heart. From left, Carter Florence, Amanda Melvin, Christina Davis, Samantha Prater, and Megan Howard. Photo by Jahi Chikwendiu, Lexington Herald-Leader.

During their second year in the program, the young women will concentrate on behavioral aspects of drug abuse and traditional treatment interventions. The third year will involve research that matches the young women with successful women scientists. Dr. Leukefeld developed the program curriculum in cooperation with colleagues at the University of Kentucky Center for Science and Health Careers.

The program includes a stipend for each summer session, and will provide a \$1,000 college scholarship to each young woman who completes the 3-year program, whether they choose to major in science or some other subject.

“One of NIDA’s goals has always been to attract young students, and in particular young women, to careers in drug abuse research,” says Dr. Cathrine Sasek of NIDA’s Office of

Science Policy and Communications. “This program reaches out to rural areas of Appalachia to encourage young women to become involved in science and nurtures their interests by linking them with local community leaders, educators, or researchers who can serve as mentors.”

The young women in the program were selected based on academic achievement in math and science, involvement in school and community volunteer activities, personal references, and their interest in pursuing a career in science. **NN**

High-Dose Methadone Improves Treatment Outcomes

By Patrick Zickler, NIDA NOTES Staff Writer

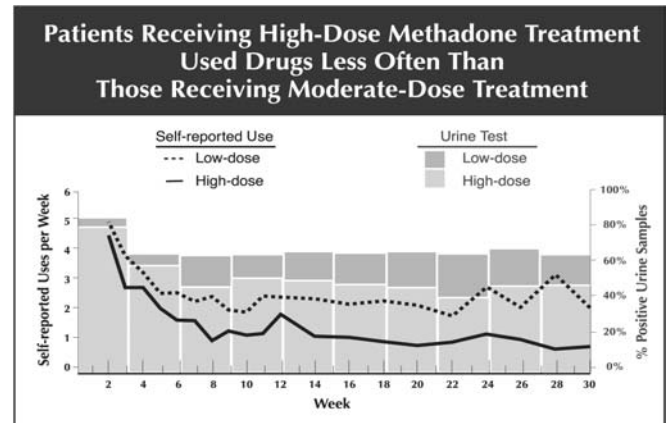
Methadone has been used effectively for more than 30 years as a treatment for heroin addiction. The medication blocks heroin's narcotic effects without creating a drug "high," eliminates withdrawal symptoms, and relieves the craving associated with addiction. Methadone is administered orally in licensed clinics and its effects typically last 24 to 36 hours.

Although methadone has been used for decades, no clinical consensus has been reached about the most effective daily dose. Many clinics do not adjust dosages according to the needs of individual patients. Instead, they administer fixed doses. One clinic might use doses of 25 milligrams (mgs) per day for all patients; others may administer daily doses of 60 mg. "Federal regulations require that a clinic receive a special exemption in order to provide patients with doses greater than 100 mg per day, but no contemporary studies have examined the effectiveness of daily doses greater than 80 mg," says Dr. Eric Strain, a NIDA-supported researcher at The Johns Hopkins University Medical Center in Baltimore.

Dr. Strain and his colleagues investigated the effectiveness of high-dose—80 to 100 mg per day—methadone treatment and found this dosage to be more effective in reducing heroin use than treatment with a moderate dose of 40 to 50 mg per day. The study involved 192 patients. Sixty-five percent of participants were male; pregnant women were excluded from the study group.

During the first week of treatment all patients received 30 mg daily methadone doses. Daily doses were increased until, by the 8th week, half the patients were receiving a moderate dose of 40 to 50 mg per day and the other half were receiving a high dose of 80-to-100 mg per day. These doses were maintained through the study's 30th week. Dosages were then decreased by 10 percent each week during the final 10 weeks of the program. Patients were encouraged to enroll in long-term community-based treatment programs following completion of the 40-week study.

Dr. Strain and his colleagues evaluated the effectiveness of treatment through analysis of twice-weekly observed urine testing, weekly patient reports of heroin use, and the length of time patients remained in treatment. "The high-dose group used opiates significantly less during treatment than did the moderate-dose group on average," Dr. Strain says. "Patients in the high-dose group reported using opiates no more than once a week. The moderate-dose group reported using drugs two to three times per week on average." Among patients who completed the 30-week active phase, 33 percent of high-dose patients remained in treatment throughout a 10-week methadone phase-out, compared



Following a 1-week orientation period, patients receiving high-dose (80-100 mg) methadone treatment had less self-reported heroin use and lower rates of drug-positive urine samples than patients on moderate-dose (40-50 mg) treatment. Urine results are shown as 3-week averages of twice-weekly samples.

with 20 percent of moderate-dose patients. There were no gender-related differences in outcome for high- or moderate-dose groups, and no difference was reported between the high- and moderate-dose patients for side effects such as grogginess or constipation.

In an earlier study, the researchers found that moderate-dose treatment of 50 mg per day was more effective than low-dose treatment of 20 mg per day. "The current study provides strong evidence that we can achieve much better outcomes at dose rates much higher than 50 mg per day," Dr. Strain says.

Dosages exceeding the currently regulated ceiling of 100 mg per day may provide the best result for some patients, Dr. Strain says, but he notes that clinical trials would be needed to support changing this regulation. "The most important aspect of our research from a therapeutic and public health perspective is that methadone treatment over a broad range of doses results in significant clinical improvement for opioid-addicted patients," he says.

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The State of the Art in Drug Addiction Treatment

NIDA Director Dr. Alan I. Leshner

NIDA's recent publication, *Principles of Drug Addiction Treatment: A Research-Based Guide*, distills the lessons of 25 years of scientific investigation. Principles is written for health care providers, to stimulate their awareness of the variety of effective approaches to drug treatment. It is also for patients and potential patients and their families, to help them understand the nature of addiction and to tell them about scientifically based treatments and what to expect if they enter treatment. And it serves planners and policymakers as well, enabling them to make informed decisions concerning treatment programs.

In short, this book is for you. That is why NIDA mailed a copy in October to every *NIDA NOTES* reader in the United States. If you have not yet read yours, I urge you to do so. If you did not receive a copy or want additional copies to pass on to friends or colleagues, the Tearoff on page 15 of this issue of *NIDA NOTES* gives ordering information.

Based on a yearlong review of treatment research, *Principles* describes where we stand today in our quest for the most effective, replicable treatments for drug abuse. The book contains many important messages, but one is central.

Treatment is effective. Scientifically based drug addiction treatments typically reduce drug abuse by 40 percent to 60 percent. These rates are not ideal, of course, but they are comparable to compliance rates seen with treatments for other chronic diseases such as asthma, hypertension, and diabetes. Moreover, treatment markedly reduces undesirable consequences of drug abuse and addiction—such as unemployment, criminal activity, and HIV/AIDS and other infectious diseases—whether or not patients achieve complete abstinence. Research has shown that every \$1 invested in treatment saves \$4 to \$7 in costs related to drug abuse.

That treatment is effective will not be news to treatment providers or to the tens of thousands of individuals and families who have benefited from treatment. Unfortunately, many members of the public still mistakenly doubt that treatment can help someone overcome addiction,

perhaps because—as *Principles* explains—recovery from addiction can be a long-term process and frequently requires multiple episodes of treatment. To these people, the message of *Principles* is: We have the tools, let's do the job.

By describing the current state of the art, *Principles* also clarifies the many challenging research pathways that remain to be traversed on the way to our goal of fully effective treatment for every patient. To cite just a few of the more pressing objectives, we need to:

- Understand the complete behavioral and biological mechanisms of addiction;
- Obtain a full picture of the transition from drug use to drug addiction and the stages of recovery in order to fashion optimal treatments for patients at every point along that trajectory;
- Understand better how gender affects vulnerability to drug addiction and the response to treatment in order to more appropriately tailor treatments for men and women;
- Develop additional medications for treating opiate addiction and effective medications for addiction to stimulants such as cocaine and methamphetamine;
- Continue to test the effectiveness of treatments in real-life community-based settings.



“Based on a year-long review of treatment research, Principles describes where we stand today in our quest for the most effective, replicable treatments for drug abuse.”

NIDA is adjusting its organizational structure and has instituted key procedures to expedite the next stage of our treatment research journey. As I write, the Institute is completing the creation of a new Division of Treatment Research and Development (DTRD). The new Division will facilitate research on combined medication and behavioral treatments, which appears to be an essential strategy for improving many patients' chances of successful treatment outcomes.

With the support of its Medications Development Division, one of DTRD's predecessors, NIDA has developed cooperative links with the pharmaceutical industry that enable NIDA-supported researchers to obtain

proprietary chemical compounds for testing as possible medications for drug abuse. As a first fruit of these partnerships, a new cocaine “vaccine” is currently being tested in a large-scale clinical trial. Based on NIDA-supported basic studies, this new medication appears to reduce the desire to use cocaine by blocking the drug’s euphoric effects. NIDA also is exploring ways for new medications to reach more of those in need. The demonstrated effectiveness of buprenorphine and naloxone in treating opiate addiction, for example, suggests that these drugs may be safely dispensed by physicians in controlled settings.

With respect to behavioral therapies, NIDA has established a three-stage process for developing, evaluating, and introducing new approaches into mainstream clinical use. The potential of each proposed new behavioral treatment is first explored in a small pilot study. If the preliminary data are promising, the treatment is tested in a full-scale clinical trial. If the trial demonstrates efficacy, clinicians take the treatment out of the research setting and adapt it as necessary for mainstream use. This new model establishes the first clear benchmarks for testing, comparing, and implementing behavioral treatments. To date, two new treatments have passed the preliminary stage of testing and moved on to the clinical trials stage.

As regular readers of *NIDA NOTES* are aware, the largest initiative in NIDA’s history is focused on treatment. This is the National Drug Abuse Treatment Clinical Trials Network (CTN), in which research centers ally with nearby community treatment programs to set research goals and participate in large-scale multisite clinical trials. NIDA recently announced the establishment of the first five CTN locations. Ultimately, the CTN will provide a nationwide coordinating infrastructure with sufficient patient numbers and diversity to enable scientists to optimize treatment effectiveness by matching treatments with appropriate patient groups.

There is a pattern in scientific research in which knowledge and techniques are slowly, painstakingly developed until they reach a critical mass that makes possible a more rapid and direct approach to problem solving. This first edition of *Principles* reflects the power of this pattern of progress to produce epochal advances in public health and welfare. With well-defined questions and powerful new technologies and research techniques coming on line every year, we do not expect to wait very long before publishing the second edition of *Principles*. **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.



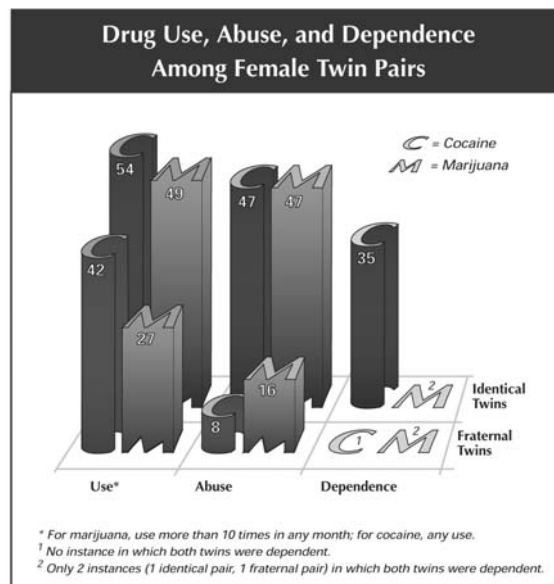
Illustration © 1998 by Richard Lillash

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.”

In addition, Dr. Kendler says, the study found that concordance



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.

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.”

Drug Abuse and Mental Disorders: Comorbidity Is Reality

NIDA Director Dr. Alan I. Leshner

A quarter century of basic and clinical research has provided us with a substantial number of scientifically developed and tested pharmacological and behavioral techniques for treating drug abuse and addiction. A main thrust of NIDA's current research is to discover which combinations of treatments and services work best for individual patients with particular constellations of problems. The goal is to customize treatment for every patient, including those with coexisting problems such as multiple drug abuse, drug abuse-related infectious diseases, histories of sexual abuse, or homelessness.

Drug abusers who have concurrent, or comorbid, mental health problems are at the top of the list of those who will benefit from this research, for two reasons. First, they are numerous. Recent epidemiologic studies have shown that between 30 percent and 60 percent of drug abusers have concurrent mental health diagnoses including personality disorders, major depression, schizophrenia, and bipolar disorder. Second, drug abusers with mental illness comorbidity are more likely to engage in behaviors that increase risk for HIV/AIDS. For example, two studies of injecting drug abusers have found that antisocial personality disorder (APD) is associated with a higher frequency of needle sharing.

In order to direct treatment and services research to where it is most needed, NIDA supports epidemiologic studies of mental health comorbidities. The results to date suggest that the most common are personality disorders including APD and borderline personality disorder; anxiety disorders including post-traumatic stress disorder (PTSD); and depression. Some evidence suggests that men who use drugs are more likely to have APD, while women and minorities are more likely to have depression or PTSD. While people with schizophrenia do not constitute a large portion of the drug-abusing population, an extraordinarily high percentage of people with this disease abuse drugs.



A concurrent mental disorder can complicate drug abuse treatment in a multitude of ways. For example, research suggests that clinically depressed individuals have an exceptionally hard time resisting environmental cues to relapse—that is, urges to resume drug taking that commonly occur when abstinent addicts encounter people, places, or things associated with their previous drug use. In some cases, treatment for mental disorders must be adjusted because of concurrent drug abuse. For example, opiate users with anxiety disorders are considered poor candidates for standard therapy with anti-anxiety drugs of the benzodiazepine class because these drugs can cause a second addiction.

“Recent epidemiologic studies have shown that between 30 percent and 60 percent of drug abusers have concurrent mental health diagnoses including personality disorders, major depression, schizophrenia, and bipolar disorder.”

NIDA-supported researchers have identified effective ways to tailor treatment for some patients with dual diagnoses. In one study, opiate addicts with APD responded better when standard contingency management therapy was modified. In the standard type of this therapy, patients receive small rewards for abstinence that become progressively greater the longer abstinence is maintained. In the modified version, treatment professionals gave more frequent rewards for desirable behaviors, such as attending scheduled counseling sessions and testing clean for drugs. *NIDA NOTES* Vol. 11, No. 4, p.10. In another study, drug craving was reduced among teenage cocaine abusers with bipolar disorder who receive lithium, and in depressed heroin abusers who were treated with imipramine. In this issue of *NIDA NOTES*, we report on promising results with methylphenidate and antidepressants in children with attention-deficit/hyperactivity disorder (ADHD) and with methylphenidate in adult cocaine abusers with ADHD.

Just as the co-occurrence of drug abuse and mental health problems presents special problems for treatment, so does it also for research. The problems arise in part because drug abuse and other mental health disorders can intertwine in several ways. For example, successful treatment of cocaine addiction often also dispels concurrent depression, while nicotine addicts' depression commonly persists after successful smoking cessation treatment. Such variations make it difficult to generalize treatment research findings across large patient groups. As a result, progress has been made in relatively small increments.

Another problem facing researchers is that a study population that is ostensibly uniform because all individuals have the same drug abuse and mental health disorders may actually be nonuniform. The reason is that the relationship between the two disorders may vary in different patients. For example, some people with a mental disorder may initiate drug use as an inappropriate form of self-medication, some people who take drugs may develop mental disorders as a consequence of their drug use, and a third group may simply have the two disorders at the same time. If an intervention is evaluated in a study population where some patients have drug abuse as a primary disorder and others as a secondary disorder, the treatment may appear to be ineffective even though it works well for one of these subgroups.

A structural difficulty that complicates research on drug abuse and mental illness comorbidity is that few drug abuse treatment programs treat enough patients with a particular mental health disorder to easily generate the preliminary data necessary to justify a full-scale study of a treatment for the disorder. To overcome this difficulty and accelerate the pace of discovery, NIDA's Behavioral Therapy Development Program places special emphasis on pilot studies in drug abuse and mental illness comorbidity. The program represents a kind of research "venture capital,"

making possible the rapid initial testing of many ideas, the best of which will then proceed rapidly to further, more definitive testing. Starting next year, NIDA's Clinical Trials Network will accelerate this wider testing by facilitating the recruitment of large numbers of patients with the drug abuse and comorbidity characteristics that treatments are designed to address.

Drug abuse and mental health professionals both confront the difficulty of providing effective care to patients whose problems overlap two health care specialties that share much, but are also in many ways very distinct. In response to this situation, NIDA and the National Institute of Mental Health have been actively collaborating on epidemiologic and treatment research on comorbidity. For example, the two

Institutes are examining the problem of treating the relatively small population of patients who abuse drugs and also have severe mental disorders, such as schizophrenia or bipolar disorder. These patients require integrated specialty treatments.

In drug abuse as in other areas of health care, isolated disorders are simplest to study and treat, but comorbidity is reality for many individuals. NIDA research has laid the foundation for successful investigations of these complex realities. **NN**

“Drug abusers who have concurrent, or comorbid, mental health problems are at the top of the list of those who will benefit from this research.”

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**

Ethnic Identification and Cultural Ties May Help Prevent Drug Use

By Patrick Zickler, NIDA NOTES Staff Writer

Among Puerto Ricans, African Americans, and Asians, cultural influences and ethnic identification may significantly influence drug use. Studies conducted by NIDA researchers in New York City suggest that Puerto Rican and African-American adolescents who strongly identify with their communities and cultures are less vulnerable to risk factors for drug use and benefit more from protective factors than do adolescents without this identification. In San Francisco, NIDA-supported research demonstrated different patterns of drug use among different subgroups of the Asian community.

These findings suggest that incorporating ethnic and cultural components into drug abuse prevention programs can make these programs more effective.

In one study, Dr. Judith Brook at the Mount Sinai School of Medicine in New York City examined the extent to which ethnic and cultural factors influenced drug-related behavior in Puerto Rican adolescents. She and her colleagues interviewed 275 males and 280 females aged 16 to 24. The researchers asked the participants to describe the importance in their lives of cultural and ethnic factors such as observation of Hispanic holidays and customs, preference for speaking Spanish or English, feelings of attachment to their ethnic group, ethnic affiliation of their friends, and the value placed on the family. The participants also answered questions designed to assess their personal risk for drug use; these risk factors included the use of drugs by parents or siblings, peer use or tolerance of drug use, perception of the riskiness of drug use, and the availability of illegal drugs in their environment. The participants were categorized into stages of drug use: no reported drug use, used alcohol or tobacco only, used marijuana but no other illicit drug, or used illicit drugs other than or in addition to marijuana.

“Other studies have looked at ethnic identification in isolation, not as an interactive part of a young person’s cultural and social context,” Dr. Brook says. “We wanted to determine the extent to which ethnic and cultural factors might mitigate risk factors or enhance protective factors and lead to lower stages of drug use. We found that strong ethnic identification acts to offset some risks, resulting in less drug use.

“For example, strong identification with Puerto Rican cultural factors offsets drug risks such as a father’s drug use, peer tolerance of drugs, and the availability of drugs. Identification with Puerto Rican friends offsets risks associated with family tolerance for drug use and drug availability,” Dr. Brook notes.

Ethnic identification also serves to amplify the effect of protective factors, Dr. Brook says. For example, among participants whose siblings were not drug users, those with a strong Puerto Rican affiliation were significantly more likely to be in a lower stage of drug use than those whose affiliation was weaker.

In a related study that focused on late-adolescent African Americans in New York City, Dr. Brook and her colleagues found a similar interaction between ethnic and cultural identification and drug use. The study involved 627 par-

ticipants—259 male and 368 female—aged 16 to 25 years.

The researchers found that components of ethnic identity—such as awareness of African-American history and tradition, identification with African-American friends, or participation in African-American cultural activities such as Kwanzaa—interacted with other factors to reduce risk or to enhance protection.

“In isolation, few specific components of ethnic identity play a role as main effects on drug use. Instead, they act in combination with family, personality, or peer influences to blunt the negative impact of risk factors and magnify the positive value of protective factors,” Dr. Brook says.

“Together, the research with Puerto Rican and African-American populations points out the importance of incorporating ethnic identity into drug programs,” Dr. Brook concludes. “It can be a valuable part of drug prevention programs in communities and can also be applied to individual treatment programs.”

Cultural Differences Lead to Different Patterns of Drug Use

In another NIDA-supported study, Dr. Tooru Nemoto and his colleagues at the University of California, San Francisco, have identified patterns of drug use among Asian drug users that are unique to ethnicity, gender, age group, and immigrant status.

“Adolescents who strongly identify with their communities and cultures are less vulnerable to risk factors for drug use.”

“Large multiracial studies have not distinguished between Asian ethnic groups,” Dr. Nemoto says. “The purpose of our study was to describe the patterns of drug use in Chinese, Filipino, and Vietnamese groups and to assess the relationship between cultural factors and drug use among the groups.”

The San Francisco study was based on qualitative interviews with 35 Chinese, 31 Filipino, and 26 Vietnamese drug users who were not enrolled in treatment programs. All participants were 18 years or older, with an average age of 32.5, and had used illicit drugs more than three times per week during the preceding 6 months. Overall, immigrants and women represented 66 percent and 36 percent, respectively. However, all Vietnamese were immigrants.

Overall, participants born in the U.S. began using drugs at an earlier age—15 years—than did immigrant Asians—19 years—and were more likely than immigrants to use more than one drug. In general, women started drug use at about the same age as men—about 17.5 years—but ethnic groups showed a varied pattern. Chinese women began earlier—at 15.2 years—than Chinese men—at 18.5 years. Filipino women began using drugs later—at 15.5 years—than Filipino men—at 13.1 years. Vietnamese women in the study started drug use much later—at 27.8 years—than did Vietnamese men—at 19.9 years.

Dr. Nemoto and his colleagues identified differences in drug use among the ethnic groups. Filipino drug users were most likely to have begun drug use with marijuana, while Vietnamese drug users in the study most often started

with crack or powder cocaine. Chinese and Vietnamese were twice as likely as Filipinos to be using crack as their current primary drug. Filipinos were four times more likely to be using heroin than were Chinese or Vietnamese. Filipino study participants were more likely than Chinese or Vietnamese to be injecting and less likely to be smoking drugs. There were also significant differences in the characteristics of drug user networks among the ethnic groups. For example, Filipinos were more than twice as likely as Chinese or Vietnamese participants to use drugs in groups that included members of other races or ethnic groups.

“These differences among ethnic groups have important implications for the way we design programs aimed at Asian drug users,” Dr. Nemoto says. “Prevention programs should address the common factors among Asian drug users, such as stigma associated with injection drug use, but we should also be careful to incorporate factors that are unique to each target group.”

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Drug Abuse Research Helps Curtail the Spread Of Deadly Infectious Diseases

NIDA Director Dr. Alan I. Leshner

Drug abuse plays a central role in the spread of infectious diseases that threaten our Nation's health. Injection drug use now accounts for about one-third of all new cases of AIDS reported in the U.S. each year, according to figures from the Centers for Disease Control and Prevention.

Other statistics show that drug abuse is strongly linked to the spread of hepatitis, tuberculosis (TB), and syphilis and other sexually transmitted diseases. To address this major public health challenge, NIDA has long supported a broad program of research on drug abuse and infectious diseases.

Over the last decade, NIDA-funded researchers have developed and evaluated a range of interventions to reduce the spread of HIV among drug abusers, their sexual partners, and their children. Drug abuse treatment and community-based outreach and education programs have consistently demonstrated that drug abusers will reduce the drug-use and sexual behaviors that put them at risk for HIV and other blood-borne infectious diseases and that these changes in behavior lead to declines in new HIV infections. For example, one study of heroin addicts conducted by NIDA-supported researchers at the University of Pennsylvania in Philadelphia found that injecting drug users (IDUs) in a methadone treatment program contracted HIV at one-sixth the rate of addicts who were not in treatment.

NIDA-supported researchers also have contributed to meeting the serious public health challenge posed by the re-emergence of TB in the last decade. HIV became prevalent among IDUs in the mid-1980s and transformed the latent TB infection that has always been widespread in this population into the contagious form of the disease. NIDA-supported epidemiologic, community, and treatment research among drug users at high risk for HIV and TB played an important role in a coordinated Federal and State initiative that led to the implementation of effective strategies to prevent and treat TB. As a result, from a peak of 26,673 cases in 1992, new TB cases fell to an all-time low of 19,851 in 1997.

NIDA's TB and HIV research has demonstrated that providing medical care to IDUs in conjunction with drug abuse treatment can curb the spread of infectious diseases. NIDA now is promoting further research to identify factors that support or hinder linkages between drug abuse treatment and primary medical care among a variety of populations, particularly women and racial and ethnic minorities.



Research has consistently demonstrated that drug abusers will reduce the drug-use and sexual behaviors that put them at risk for HIV and other blood-borne infectious diseases.

NIDA-supported research also has developed approaches that can check the spread of infectious diseases among the approximately 85 percent of IDUs who are not in treatment. For example, one long-term study in Baltimore providing directly observed preventive therapy and a variety of health care services in one convenient setting virtually eliminated new TB cases among out-of-treatment IDUs. We now are developing additional research initiatives to add drug abuse

treatment to vans that provide comprehensive medical services in neighborhoods with large populations of out-of-treatment heroin addicts. We believe these coordinated mobile clinics may lead to further reductions in drug abuse and infectious diseases in this population.

Noninjection drug use also fosters the spread of infectious diseases. For example, smokers

of crack cocaine, particularly women who exchange sex for drugs, are at high risk for infection with HIV, hepatitis, TB, and sexually transmitted diseases. In addition, it appears that many heroin users who begin by snorting that drug sooner or later progress to injection drug use with its attendant risks. Early data from a NIDA-supported study by scientists at National Development and Research Institutes, Inc., in New York City indicate that a substantial portion of heroin snorters become injectors, engage in a high level of risky drug-use and sexual behaviors, and begin to contract hepatitis C soon after they start injecting drugs. By also shedding light on the complex

individual and social factors that contribute to transition from noninjection to injection drug use, this study will help us develop new approaches to forestall the progression to injection drug use and infectious disease.

“Early data from a NIDA-supported study by scientists at National Development and Research Institutes, Inc., in New York City indicate that a substantial portion of heroin snorters become injectors, engage in a high level of risky drug-use and sexual behaviors, and begin to contract hepatitis C soon after they start injecting drugs.”

While we have made much progress in preventing and treating infectious diseases among drug abusers, the continued high prevalence of diseases such as HIV/AIDS and hepatitis in this population indicates that much remains to be done. Therefore, NIDA recently established the Center on AIDS and Other Medical Consequences of Drug Abuse. Headed by Dr. Henry Francis, the Center is coordinating a multidisciplinary program of research on the full spectrum of critical health issues associated with drug abuse. Components of the program include tracking

the extent and progression of infectious diseases among drug users, assessing the effect of illicit drugs on the immune system, linking drug abuse treatment and medical care, and developing new educational and behavioral strategies for drug abusers who are not in treatment. Ultimately, the program will generate new strategies for reducing the spread of infectious diseases.

Because drug abuse and infectious disease have implications for many areas of biomedical research, the Center also is fostering collaborative research efforts with other institutes of the National Institutes of Health (NIH), government agencies, and private sector groups. Currently, NIDA supports more than 10 interagency and interinstitute studies involving drug abuse and infectious disease. For example, the Women and Infants Transmission Study being conducted by NIDA, the National Institute of Allergy and Infectious Diseases, and the National Institute of Child Health and Human Development is investigating mother-to-infant transmission of HIV. NIDA also is participating in a new, congressionally mandated NIH research initiative that is responding to the health problems associated with hepatitis C. Approximately 4 million Americans are infected with this virus, which can cause chronic liver disease that results, in many cases, in death due to cirrhosis and liver cancer. NIDA-supported research will be critical to the success of the NIH initiative because of the major role injection drug use plays in the transmission of this insidious infection.

In the years ahead, drug abuse and infectious disease will continue to pose challenges to the Nation's health. NIDA's broad program of research on the medical consequences of drug abuse will continue to provide the scientific knowledge needed to overcome those challenges with multifaceted public health responses. **NN**

Infectious Diseases and Drug Abuse

Drug abuse involves health risks that often are as dangerous as the physiological effects of the drugs themselves. Injecting drug users (IDUs) are at high risk for direct exposure to a variety of blood-borne bacterial and viral infections. As a result, drug users are more likely than nonusers to contract a variety of infectious diseases and, when infected, to progress to serious illness and death.

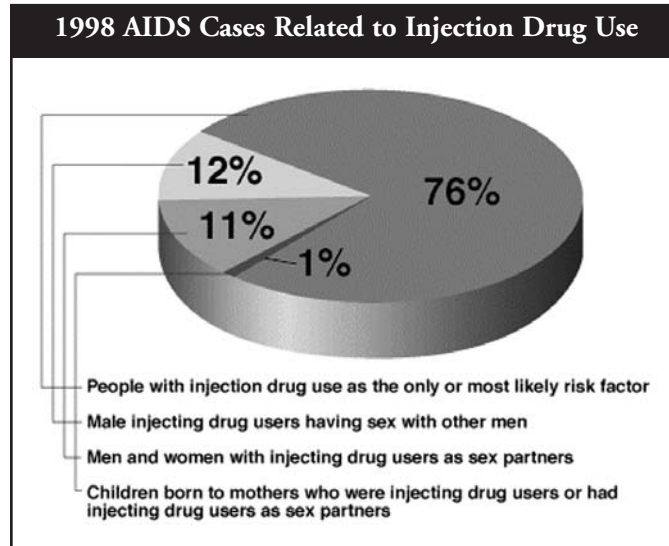
HIV/AIDS

Injection drug use has been responsible for more than one-third of all adult and adolescent AIDS cases reported in the U.S. since the beginning of the AIDS epidemic, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. More than one-half of all preadolescent AIDS cases in the U.S. have resulted from a transmission chain whereby a woman contracts HIV as a result of injection drug use and passes the disease to her child during pregnancy or birth. Of adult and adolescent AIDS cases, approximately 32 percent were among IDUs, and another 4 percent involved heterosexual sex with an IDU. During 1998, approximately one-third of all new AIDS cases in the U.S. were related directly or indirectly to injection drug use (See chart for a breakdown of the injection drug use-related cases).

Noninjection drug use can also contribute to HIV transmission. Studies have shown that inner-city youths who smoke crack cocaine are up to three times more likely to be infected with HIV than are inner-city youths who do not. Noninjecting drug users who trade sex for drugs or who engage in unprotected sex while under the influence of drugs increase their risk of infection.

Hepatitis

Hepatitis B (HBV) and hepatitis C (HCV) are viral diseases that destroy liver cells and can lead to cirrhosis and liver cancer. People can become infected with HBV through sexual intercourse with an infected person or through exposure to an infected person's blood, as may happen when IDUs share needles. Blood transfusion and needle sharing are the most common routes of infection



with HCV. NIDA-supported research has shown that the risk of infection by HBV and HCV is extremely high in the first year after beginning injection drug use. One study found overall HCV and HBV prevalences of 76.9 percent and 65.7 percent, respectively, in a group who had been injecting drugs for 6 years or less.

Tuberculosis

Tuberculosis (TB) is transmitted from person to person by airborne bacteria. This disease is most prevalent in

crowded low-income areas with substandard health conditions. Drug users are from two to six times more likely to contract TB than nonusers. CDC estimates that in 1996 at least 11 percent of new TB cases were in drug users with noninjecting drug users twice as likely as IDUs to contract the disease. Compared to others with TB, IDUs are more likely to develop the disease in multiple organs and sites, rather than only in the lungs.

Other Infectious Diseases

Drug users have a high incidence not only of HIV/AIDS but also of other sexually transmitted diseases including syphilis, chlamydia, trichomoniasis, gonorrhea, and genital herpes. The geographic distribution of syphilis and gonorrhea infections across the U.S. reflect the geographical distribution of the use of crack cocaine and its associated high-risk behaviors, such as unprotected sex and the exchange of sex for drugs.

Among IDUs, the most common cause for medical treatment is skin infection at the site of injection. Complications from these infections range from skin ulcers and localized abscesses to stroke, botulism, tetanus, destruction of lung tissue, and infection of the heart valves.

Bacterial and viral infections associated with injection drug use can progress to systemic infections and damage any body system. Directly observed medication therapy, in which the patient takes medications in the presence of a health care provider, is generally recommended for addicts, many of whom may have difficulty following treatment regimens. **NN**

Drug Use Among America's Teenagers Shows Slight Downward Trend

By Patrick Zickler, *NIDA NOTES* Staff Writer

The prevalence of illicit drug use among America's teenagers dropped slightly in 1998. The decrease follows a leveling off in 1997, and suggests that the increasing use of drugs by teenagers that marked most of the 1990s may have begun to turn around.

Data compiled by the NIDA-supported Monitoring the Future study show that, overall, teenagers were less likely to use marijuana, hallucinogens, or inhalants last year than they had been the year before. Heroin use leveled off in 1998, following several years of slight increases. Among all illicit drugs included in the survey, only crack and tranquilizers were used by a significantly higher percentage of teenagers in any grade in 1998 than in 1997, according to the study.

The Monitoring the Future study, funded by NIDA and conducted annually by the Institute for Social Research at the University of Michigan in Ann Arbor, surveyed nearly 50,000 students—including equal numbers of males and females—in 8th, 10th, and 12th grades at more than 420 public and private schools across the country. Data from the most recent survey, conducted in the spring of 1998, were released by Secretary of Health and Human Services Dr. Donna E. Shalala at a press conference in December 1998.

"These new findings are encouraging, since they represent a leveling off in teens' use of illicit drugs," Secretary Shalala said. "It's not easy to convince our young people that drug use is illegal, dangerous, and wrong, but it is absolutely critical to their future."

The survey also asked students about the risks associated with drug use. The percentage of students who said there is a "great risk" associated with drug use rose or remained unchanged for most illicit drugs.

"We seem to be in the middle of a turnaround in young people's use of most kinds of illicit drugs following an earlier period of sustained increases," Dr. Lloyd Johnston, principal investigator for the study, said. "These behaviors sometimes change very slowly, and often only after there has been some reassessment by young people of how dangerous these various drugs are. Such reassessment now appears to be occurring for many drugs, but very gradually."

Teenagers now are responding to increased knowledge of the facts about illicit drug use, NIDA Director Dr. Alan I.

Leshner said. "The more that scientific research helps us understand what addiction is and how illicit drugs change the brain and behavior, the better able students and others will be to make informed decisions. The findings from this year's report suggest that many of our educational efforts are beginning to pay off," Dr. Leshner said.

Highlights of the 1998 Monitoring the Future Study

- **Marijuana.** Use declined among all three grades, and this accounted for most of the overall decline in 1998 drug use. Eighth-grade use declined for the second successive year. Nonetheless, marijuana use is still prevalent: 22 percent of 8th-graders and nearly half of 12th-graders surveyed reported that they have tried marijuana. However, the perceived risk of marijuana use has increased among 8th-graders.
- **Heroin.** Although use did not decline, it remained unchanged among all students in 1998: 1.3 percent of 8th-graders, 1.4 percent of 10th-graders, and 1.0 percent of 12th-graders reported using heroin at least once during the previous 12 months. This leveling in heroin use follows a rise in perceived risk over the previous 2 years.
- **Stimulants.** Use decreased for the second consecutive year to 7.2 percent among 8th-graders, showed a 1-year drop to 10.7 percent among 10th-graders, and leveled off at 10.1 percent among 12th-graders.
- **Hallucinogens.** Overall use decreased slightly at all grade levels—to 3.4 percent among 8th-graders, 6.9 percent among 10th-graders, and 9.0 percent among 12th-graders. Decreases in use of MDMA, or ecstasy, were recorded for the second year in a row for 10th- and 12th-grade students.
- **Crack Cocaine.** Among 8th-graders, use of crack cocaine increased to its highest level, 2.1 percent, since 1991, when the drug was first included in the 8th grade survey. Slight increases—also to their highest levels in recent years—were reported for crack use by 10th-graders, to 2.5 percent, and 12th-graders, to 2.5 percent.
- **Inhalants.** Use declined among all students for the third consecutive year. In 1998, 11.1 percent of 8th-graders, 8.0 percent of 10th-graders, and 6.2 percent

of 12th-graders reported using inhalants at least once in the past year. This decrease follows an upward shift in 1996 in the proportion of students associating great risk with inhalant use.

- **Gender.** Overall, higher percentages of males than females reported using illicit drugs at least once during the previous year. As has been the case since 1991—the first year for which data are available—younger girls are more likely than boys to use illicit drugs other than marijuana, primarily due to their greater use of stimulants and tranquilizers; 12.1 percent of 8th-grade girls and 9.6 percent of boys reported using drugs other than marijuana. In 10th grade, 17.5 percent of girls and 15.6 percent of boys reported using drugs other than marijuana at

least once during the previous year. Among 12th-graders, 21.7 percent of boys and 18.0 percent of girls reported using drugs other than marijuana.

For More Information

- Additional information about the Monitoring the Future study can be obtained by calling NIDA Infofax at 1-888-NIH-NIDA (644-6432) or by accessing NIDA's home page on the World Wide Web at <http://www.nida.nih.gov/> and clicking on Information on Drugs of Abuse. Information is also available from the Monitoring the Future home page at the Institute for Social Research at the University of Michigan: <http://www.isr.umich.edu/src/mtf>. **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.

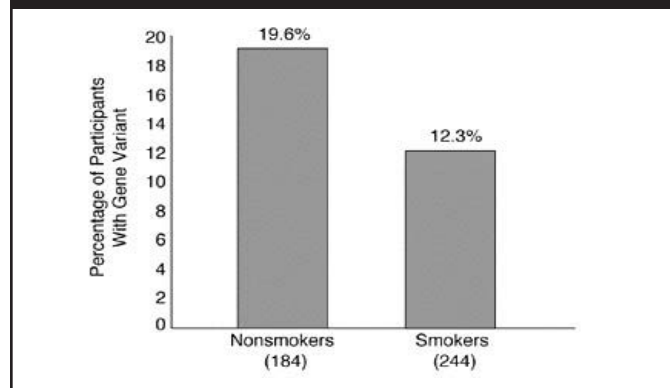
“This study shows the importance of looking at the role of genetics in drug addiction and treatment,” says Dr. Jonathan Pollock of NIDA’s Division of Basic Research. Ultimately, increased knowledge about underlying genetic vulnerability might lead to more effective treatments for nicotine addiction that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

- Pianezza, M.L.; Sellers, E.M.; and Tyndale, R.F. Nicotine metabolism defect reduces smoking. *Nature* 393(6687):750, 1998. **NN**

NIDA Research Provides Data To Document and Improve the Effectiveness of Drug Abuse Health Services

NIDA Director Dr. Alan I. Leshner

As part of its mission to treat and prevent drug abuse and addiction, NIDA has supported the development of numerous research-based drug abuse treatment protocols and drug abuse prevention models. In keeping with standard scientific methodology, these programs have been tested in tightly controlled practice settings with carefully selected populations.

Once these programs are tested the critical question becomes: Will the promising treatment outcomes produced in a controlled research environment hold in widely varying real-life treatment settings and for a wide range of patients? Likewise, will the prevention model that worked on a small scale continue to work in communities that may vary in any number of factors from size and ethnic composition to geography and the nature of their school systems?

To answer these questions, NIDA supports an extensive and growing portfolio of health services research. That portfolio is designed to give drug abuse treatment and prevention service providers the scientific data and research-based methodologies they need to gauge and enhance how well their programs will work for real-life patients in real-life settings. NIDA's health services research also encompasses economic analyses that provide answers to questions such as: Does this drug abuse program provide effective services that are accessible to patients at a reasonable cost? How does this program compare to similar programs in terms of its cost-effectiveness and accessibility? Does this program not only reduce drug abuse and addiction, but also reduce costs to society from drug-related crimes and health expenditures?

While much remains to be done, NIDA-funded scientists have built a solid foundation of science-based information that can be used to document and improve the effectiveness of drug abuse health services. Much of the Institute's research in this area is conducted at its health services research centers, which investigate the Nation's pressing drug abuse health services issues.

For example, investigators at the Center for Managed Care and Drug Abuse at Brandeis University in Waltham, Massachusetts, and Harvard University in Cambridge, Massachusetts, are assessing the impact of managed care on drug abuse treatment availability, content, duration, and utilization. They also are studying how managed care

affects the organization and financing of drug abuse treatment facilities. At the Community-Based Health Services Research Center on Chronic Drug Users at the University of Miami in Florida, researchers are using the Dade County, Florida, health services system as a case study to find ways to improve drug abuse patients' access to both primary medical care and drug abuse treatment. The investigators are exploring how the Dade County system identifies, assesses, and serves chronic drug users, and, in particular, whether health care access and effectiveness vary by ethnicity or gender.

The Institute has supported three nationwide studies to assess the effectiveness of drug abuse treatment using numerous measures of treatment outcomes. All three studies have shown that drug abuse treatment patients in the four most common types of treatment programs—out-patient methadone, outpatient nonmethadone, long-term residential, and short-term inpatient—dramatically reduce their drug use following treatment, reduce drug-related criminal activities, and improve their physical and mental health. (For results of the most recent study—the Drug Abuse Treatment Outcome Study—see *NIDA NOTES*, September/October 1997.)

These studies and other NIDA-funded research highlight the value of providing patients with services in addition to drug abuse treatment. A recent study at the Treatment Research Institute in Philadelphia has found that providing drug abuse patients with services based on their needs in three areas—employment, family relations, and psychiatric problems—can boost the effectiveness of treatment.

NIDA-funded studies on the economics of treatment and prevention services are comparing the costs of drug abuse services with measures that can be quantified in dollar amounts, such as reduced costs of crime and avoided costs for medical consequences of drug use. Other such studies compare the costs of drug abuse services with measures that cannot be quantified in dollar amounts, such as how long a patient remains abstinent or a patient's degree of social functioning. These studies consistently show that resources spent on drug abuse services result in substantial savings to society. For example, results from the Midwestern Prevention Project—a comprehensive, NIDA-funded prevention study that was conducted in Kansas City, Kansas; Kansas City, Missouri; and Indianapolis, Indiana—indicated that every dollar spent on prevention

***An economic analysis of the
Midwestern Prevention Project
indicated that every dollar spent
on prevention programs saved \$68
per affected family in health
and social costs.***

programs saved \$68 per affected family in health and social costs.

To help treatment providers improve treatment outcomes and reduce costs, NIDA is developing a manual to guide them in conducting economic analyses on their own programs. The new manual—titled *Measuring and Improving Cost, Cost-Effectiveness, and Cost-Benefit for Substance Abuse Treatment Programs*—will provide managers with step-by-step procedures for analyzing the costs of their services and for producing economic analyses. These analyses will provide valuable insights into how providers can serve their patients more efficiently. In the future, the economic data generated by treatment providers throughout the country may be pooled by researchers to produce further large-scale economic studies of drug abuse treatment, which, in turn, will give policymakers and insur-

ance companies more science-based information to help them make decisions related to financing drug abuse treatment. In the coming months, the manual will be available both in print and on NIDA's home page on the World Wide Web. The Web site will also enable treatment providers to communicate with each other about the manual and their findings.

To keep pace with rapid advances in health services research, NIDA regularly evaluates its health services research agenda by drawing on resources both in the drug abuse field and in the health services research field at large. In December 1997 the Institute began hosting a series of meetings intended to help define an agenda for health services research. These meetings culminated in a research symposium at the annual conference of the Association for Health Services Research in June. We will use the information and ideas gleaned from these meetings in the coming months as we develop plans for advancing our research to improve health services for drug abusers.

We must press forward in our search to find ways to provide quality treatment to all drug abuse patients at reasonable costs. Likewise, we must continue to work to insure that promising drug abuse prevention research findings translate to real reductions in drug use among our Nation's children. **NN**

New Publications Disseminate Research Findings on Nicotine

Two new publications that provide research-based information on nicotine addiction were released at NIDA's Addicted to Nicotine Conference in July.

"Nicotine Addiction," an eight-page report, provides the latest information about nicotine and its addictive properties, including:

- how nicotine in tobacco smoke and chewing tobacco affects the body;
- how nicotine tolerance develops over time;
- the medical consequences of nicotine use;
- gender differences in nicotine sensitivity; and
- the risks of smoking during pregnancy.



Current treatments for nicotine addiction, including nicotine replacements, behavioral therapies, and a new non-nicotine prescription drug, also are discussed. A glossary and list of resources for further information are included. "Nicotine Addiction" is part of the NIDA *Research Report* series.

"The Brain's Response to Nicotine" is a new addition to NIDA's award-winning *Mind Over Matter* magazine series. The series is designed to teach students in grades 5 through 9 how



NIDA Director Dr. Alan I. Leshner presents the new NIDA publication, "Nicotine Addiction," to conference participants.

specific drugs affect the brain. The full-color mini-magazine on nicotine describes how tobacco smoke delivers nicotine to the brain, how nicotine disrupts brain function, and why it is so difficult for people to stop smoking. The magazine unfolds into an 11-by-23-inch poster displaying an image of the nerve cells involved in pain and touch.

Both publications can be downloaded from NIDA's home page on the World Wide Web at www.nida.nih.gov. Copies are available from the National Clearinghouse on Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686 or (301) 468-2600, TDD number: (800) 487-4889, fax: (301) 468-6433, e-mail: info@health.org. **NN**

New NIDA Center Will Address Health Issues Associated With Drug Abuse

By Barbara Cire, NIDA NOTES Associate Editor

NIDA has established a new center to coordinate research, collaborate with other of the National Institutes of Health (NIH) institutes and related organizations, and provide leadership to NIDA offices and divisions on issues about HIV/AIDS and other medical consequences of drug abuse. The Center for AIDS and Other Medical Consequences of Drug Abuse, headed by Dr. Henry Francis (right), was established through a merger of NIDA's Office on AIDS and Clinical Medical Branch, but its mission and responsibilities go beyond those of these two components.

"The new Center represents an important initiative to increase NIDA's multidisciplinary drug abuse research," says NIDA Director Dr. Alan I. Leshner. "The Center will allow us to address the full spectrum of health issues associated with drug abuse, including HIV/AIDS."



Dr. Henry L. Francis

The Center will develop multidisciplinary national and international programs on HIV/AIDS; the medical, health, and developmental consequences of drug abuse; and the effects of drug use on other diseases. Program areas include the origins, treatment, and prevention of hepatitis C; HIV disease progression; the links between drug abuse treatment and medical care; tuberculosis in drug users; clinical research on human development and drug abuse; and prescription drug abuse.

"The connection between HIV/AIDS and injection drug use is well-known," says Dr. Francis. "Now is the time to step up our examination of that connection as well as the connections between drug abuse and other diseases related to drug abuse, including hepatitis, tuberculosis, hypertension, and sexually transmitted diseases in addition to AIDS. A number of mental health conditions also are associated with drug abuse, including severe depression, schizophrenia, personality disorders, and manic-depressive

disorder. Sometimes mental health problems precede drug abuse, but in other cases they co-occur with drug abuse. It is important to address the impact of these disorders on drug abuse and the impact of drug abuse on these disorders."

The Center is currently supporting several collaborative studies with other NIH Institutes and government agencies, as well as nongovernment groups. For example, NIDA is participating in the Women's Interagency HIV Study/HIV Epidemiology Research Study with the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute, the National Institute of Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research, and the Centers for Disease Control and Prevention. This study is examining the medical and psychosocial impact of HIV on women. NIDA is also collaborating with NIAID and NICHD on the Women and Infants Transmission Study, which is investigating mother-to-infant transmission of HIV.

"Drug addiction is a cross-over disease that permeates virtually all of the research areas addressed by NIH," says Dr. Francis. "Thus, a multidisciplinary approach is best suited to exploring the health aspects of drug abuse."

Prior to this appointment, Dr. Francis served for 2 years as chief of the Clinical Medicine Branch in the Division of Clinical and Services Research at NIDA. He was the director of the U.S. Public Health Service and Belgium Projet SIDA (Project AIDS) Research Laboratories in Kinshasa, Zaire, from 1984 to 1988. Dr. Francis received his medical degree from Howard University College of Medicine and performed his clinical training in internal medicine at the Long Beach Veterans' Administration Department of Medicine at the University of California at Irvine. He was a fellow, and later assistant professor, in the Division of Infectious Diseases at The Johns Hopkins Medical School. He is widely published and has written articles on HIV/AIDS that have appeared in the *Journal of the American Medical Association*, *Lancet*, the *New England Journal of Medicine*, the *Journal of Immunology*, and the *Journal of Infectious Diseases*, among others. **NN**

Prenatal Cocaine Exposure Costs at Least \$352 Million Per Year

Prevention of cocaine or crack use during pregnancy could save \$352 million per year, according to a study by researchers at Brown University in Providence, Rhode Island. The research, which analyzed data from eight longitudinal studies of school-age children prenatally exposed to cocaine, was reported in the October 23 issue of *Science*.

The study, funded by the Robert Wood Johnson Foundation, found that up to 80,550 children will have subtle deficits in IQ and language development as a result of prenatal exposure to cocaine. Special education to keep them from failing in school will cost at least \$352 million per year nationwide, researchers estimate.

“These figures are underestimates,” notes Dr. Barry Lester, NIDA grantee and lead member of the research team.

“These are costs attributable only to new cases each year, and do not include the accumulating costs and burdens associated with annual additions.”

“Every dollar of prevention saves five times that amount in treatment and other costs to society,” says NIDA Director Dr. Alan I. Leshner. “This study emphasizes the need for more drug abuse prevention efforts, particularly those directed at women of child-bearing age. The findings also argue for early identification and intervention for children most at risk for developing these problems.”

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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

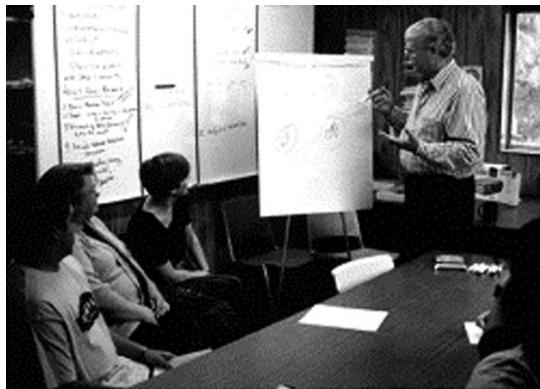
Men who abuse drugs are more likely to reduce their sexual risks of HIV infection if they are given risk-reduction information on the street, while women drug abusers respond better if they are given this information in an office with counseling. This is one of the findings of a NIDA-funded study on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

Source

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Gender Matters in Drug Abuse Research

NIDA Director Dr. Alan I. Leshner

Accumulating evidence indicates that drug abuse may begin and progress differently, have different consequences, and require different prevention and treatment approaches for women and men. Therefore, NIDA has strongly supported research to identify gender differences and gender-specific aspects of drug abuse and addiction and to apply these findings toward more effective drug abuse prevention, treatment, and services for both women and men.

Historically, NIDA has supported a broad program of research on the effect of women's drug use on pregnancy, maternal health, and childhood development. A little more than 5 years ago, NIDA broadened the scope of its gender-related research by issuing program announcements calling for research to examine the causes and consequences of drug abuse among women of all ages, regardless of their parental status. In the fall of 1994, NIDA sponsored a landmark national conference on addiction and women's health. This meeting launched our expansion of research on the role of gender in all aspects of drug abuse and addiction. Since then, our Women and Gender Research Group, which is made up of representatives from every NIDA Division and Office, has been working to further develop NIDA's research on women's health and gender differences and to disseminate the findings to professionals in the field and the general public.

Today, gender-related research is integrated throughout NIDA's entire portfolio. This research extends from basic molecular and cellular studies to clinical and epidemiologic studies and is grouped into four major areas: etiology, consequences, prevention, and treatment and services. Through this research, we are learning more and more about differences between women and men in the origins of drug abuse, the consequences of drug abuse and addiction, and the factors that influence drug abuse relapse and recovery.

Our research on the origins of drug abuse has found gender differences in factors affecting initiation, progression, and maintenance of drug use. For example, basic

behavioral and neurochemical research has suggested that women may be more sensitive than men to the rewarding effects of drugs, perhaps due to differences in brain chemistry. Animal studies also have shown that females respond more than males to the stimulating and reinforcing properties of abused drugs. Other studies indicate that the intensity of a drug's effects on women varies during different phases of the menstrual cycle. These physiological differences may help account for data indicating that women may proceed to drug abuse and addiction more rapidly than men do after initial drug use.

Evidence also indicates that psychosocial factors, such as childhood physical and sexual abuse, depression and posttraumatic stress disorder, relationships with a significant other, and partner violence play a more important role for women than for men in beginning and continuing drug use. For example, one research study suggests that women's tobacco use is

controlled more by social and sensory factors and less by dependence on nicotine itself, compared to men's tobacco use.

NIDA-supported research also is finding gender differences in the consequences of drug abuse. For example, both animal and human studies indicate that men may be at greater risk than women for strokes and for mental deficits from chronic cocaine

abuse. Other research suggests that the female hormone estrogen may play a role in reducing cocaine toxicity in women.

One of the most devastating health consequences of illicit drug use for both women and men is AIDS, with half of all new HIV infections now linked to injection drug use. Approximately two-thirds of AIDS cases in women and more than half of pediatric AIDS cases in the United States are related to injection drug use by women or their sexual contact with an injecting drug user.



"In the last 5 years, NIDA has greatly increased scientific knowledge about gender-related differences in almost every aspect of drug abuse and addiction."

NIDA's comprehensive AIDS initiative is uncovering significant gender-related differences in factors that contribute to and protect from HIV risk. For example, one study of female injecting drug users has found that the family plays a more important role for women than for men in resistance to needle-sharing behaviors.

Other studies in our AIDS research portfolio are identifying gender-specific strategies to decrease injection drug use and high-risk sexual behaviors among women and men. For example, researchers at Northern Arizona University in Flagstaff have found that male drug abusers are more likely to reduce their high-risk sexual behaviors if given HIV risk-reduction information on the street, while female drug abusers respond better if this information is given along with counseling in the more protective environment of an office.

The ultimate goal of our research is to apply our increased understanding of gender-specific drug abuse factors to the development of prevention and treatment interventions that better meet the unique needs of both women and men. For example, a recent NIDA-supported study indicates that treatment interventions need to address differences in psychosocial factors that influence women's and men's relapse to drug use following treatment. In the study, researchers at the University of Pennsylvania found that negative emotions and interpersonal relations are linked to relapse among cocaine-dependent women while men are more likely to experience positive emotions prior to relapse.

In the last 5 years, NIDA has greatly increased scientific knowledge about gender-related differences in almost every aspect of drug abuse and addiction. However, we still have tremendous gaps to fill in that knowledge. We need to learn more about how gender relates to the impact

of violence and victimization, devise better gender-specific treatment for comorbid mental disorders, and learn how to adequately address gender-related cultural factors in prevention and treatment, to name just a few.

“Through this research, we are learning more and more about differences between women and men in the origins of drug abuse, the consequences of drug abuse and addiction, and the factors that influence drug abuse relapse and recovery.”

To fill those gaps and build on our current knowledge, we are encouraging research that addresses gender-specific issues and gender differences in such diverse drug abuse areas as origins and pathways, biomedical factors, comorbid mental disorders, epidemiology, medical and health consequences, health services, special populations, HIV/AIDS, prevention, and treatment.

Evidence from NIDA's gender-related research indicates that prevention and treatment strategies that address gender differences can be more effective than one-size-fits-all approaches in preventing drug abuse and relapse following treatment. Through our continued strong emphasis on the role of gender throughout our research portfolio, NIDA is working to speed the day when gender differences are successfully addressed in all areas of drug abuse prevention and treatment.

For More Information

- An overview of NIDA's research program on women's health and gender differences, details of research advances and opportunities, program announcements, publications, and research reports can be found under “Women's Health and Gender Differences,” on NIDA's home page on the World Wide Web at www.nida.nih.gov. Information about women and drug abuse also is available from Infobox, NIDA's automated information retrieval system, at 1-888-644-6432. In addition, the “Bulletin Board” includes a description and ordering information for a recently released NIDA publication, *Drug Addiction Research and the Health of Women*. **NN**

Publications Focus On Women's Health

NIDA has released two companion publications on research related to drug addiction and women's health. *Drug Addiction Research and the Health of Women* grew out of presentations at a national conference of the same name held by NIDA in 1994. In the 581-page volume, indepth reviews of current research provide extensive data on the differences between men and women in the causes and effects of drug abuse and addiction.

The companion volume, the 142-page *Drug Addiction Research and the Health of Women: Executive Summary*, contains condensed versions of conference presentations and discussions.

Both publications can be obtained through the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, at 1-800-729-6686. Request NCADI publication #BKB258 for the research volume and #BKB259 for the executive summary. The publications also can be downloaded from NIDA's home page on the World Wide Web by accessing the list of NIDA publications on women's health and gender differences located at <http://www.nida.nih.gov/WHGD/WHGDPub.html>. **NN**

Facts About Nicotine and Tobacco Products

About 62 million people in the United States ages 12 and older, or 29 percent of the population, are current cigarette smokers, according to the 1996 National Household Survey on Drug Abuse. This makes nicotine, the addictive component of tobacco, one of the most heavily used addictive drugs in the United States.

Effects of Nicotine

When a person inhales cigarette smoke, the nicotine in the smoke is rapidly absorbed into the blood and starts affecting the brain within 7 seconds. In the brain, nicotine activates the same reward system as do other drugs of abuse such as cocaine or amphetamine, although to a lesser degree. Nicotine's action on this reward system is believed to be responsible for drug-induced feelings of pleasure and, over time, addiction. Nicotine also has the effect of increasing alertness and enhancing mental performance. In the cardiovascular system, nicotine increases heart rate and blood pressure and restricts blood flow to the heart muscle. The drug stimulates the release of the hormone epinephrine, which further stimulates the nervous system and is responsible for part of the "kick" from nicotine. It also promotes the release of the hormone beta-endorphin, which inhibits pain.

People addicted to nicotine experience withdrawal when they stop smoking. This withdrawal involves symptoms such as anger, anxiety, depressed mood, difficulty concentrating, increased appetite, and craving for nicotine. Most of these symptoms subside within 3 to 4 weeks, except for the craving and hunger, which may persist for months.

Health Effects of Tobacco Products

Besides nicotine, cigarette smoke contains more than 4,000 substances, many of which may cause cancer or damage the lungs. Cigarette smoking is associated with coronary heart disease, stroke, ulcers, and an increased incidence of respiratory infections. Smoking is the major cause of lung cancer and is also associated with cancers of the larynx, esophagus, bladder, kidney, pancreas, stomach, and uterine cervix. Smoking is also the major cause of chronic bronchitis and emphysema.

Women who smoke cigarettes have earlier menopause. Pregnant women who smoke run an increased risk of having stillborn or premature infants or infants with low birthweight. Children of women who smoked while pregnant have an increased risk for developing conduct disorders.

Cigar and pipe smokers and users of chewing tobacco and snuff can also become addicted to nicotine. Although cigar and pipe smokers have lower death rates than cigarette smokers do, they are still susceptible to cancers of the oral cavity, larynx, and esophagus. Users of chewing tobacco and snuff have an elevated risk for oral cancer.

Treatment

Like addiction to heroin or cocaine, addiction to nicotine is a chronic, relapsing disorder. A cigarette smoker may require several attempts over many years before that person is able to permanently give up smoking. Less than 10 percent of unaided quit attempts lead to successful long-term abstinence. However, studies have shown significantly greater cessation rates for smokers receiving interventions compared to control groups who do not receive the interventions. Interventions that involve both medications and behavioral treatments appear to show the most promise.

The primary medication therapy currently used to treat nicotine addiction is nicotine replacement therapy, which supplies enough nicotine to the body to prevent withdrawal symptoms but not enough to provide the quick jolt caused by inhaling a cigarette. Four types of nicotine replacement products are currently available. Nicotine gum and nicotine skin patches are available over the counter. Nicotine nasal spray and nicotine inhalers are available by prescription. On average, all types of nicotine replacement products are about equally effective, roughly doubling the chances of successfully quitting.

Another medication recently approved by the Food and Drug Administration as an aid for quitting smoking is the antidepressant bupropion, or Zyban®. The association between nicotine addiction and depression is not yet understood, but nicotine appears to have an antidepressant effect in some smokers. Paradoxically, though, bupropion is more effective for treating nicotine addiction in nondepressed smokers than in smokers who are depressed.

For More Information

- More information about nicotine addiction and tobacco can be found at the NIDA Web site at <http://www.nida.nih.gov>, or by calling Infotax, NIDA's automated information retrieval system, at 1-888-NIH-NIDA. Information is also available from the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686. The NCADI Web site is <http://www.health.org>. **NN**

Exploring the Role of Child Abuse in Later Drug Abuse: Researchers Face Broad Gaps in Information

By Neil Swan, NIDA NOTES Staff Writer

As many as two-thirds of all people in treatment for drug abuse report that they were physically, sexually, or emotionally abused during childhood, research shows. However, the role of child abuse—physical trauma, rape and sexual abuse, neglect, emotional abuse, and witnessing or being threatened with violence or other abuse—in the pathway to drug abuse needs closer examination. Although studies probing the effects of child abuse have increased in recent years, researchers still are confronted with broad gaps in information.

“The sheer weight of the many reports over the years certainly implicates child abuse as a possible factor in drug abuse for many people,” says Dr. Cora Lee Wetherington, NIDA’s Women’s Health Coordinator. “But we lack hard data that clearly establish and describe the role of child abuse in the subsequent development of drug abuse. Is child abuse indeed a cause of drug abuse, or is child abuse a marker for other unidentified factors?”

Many critical questions remain unanswered, NIDA researchers agree. How can child abuse victims be identified and studied to track the variables that may contribute to subsequent drug abuse? What factors lessen or strengthen the risk that child abuse will progress to drug abuse? What, in fact, constitutes child abuse?

Answers to questions such as these will help develop creative new drug abuse therapies and prevention strategies. With new knowledge, special interventions could target victims of child abuse to prevent progression to drug abuse. A better understanding of the consequences of child abuse would enable researchers to develop ways to tailor drug abuse treatment to adults who are victims of child abuse. Awareness of this potential has prompted interest among NIDA researchers in further studies into the relationship between child abuse and progression to drug abuse.

However, important obstacles hamper these investigations, which involve not only the researchers and the victims and their families, but also doctors, hospitals, psychologists,

child welfare agents, police, and the justice system. The involvement of so many professional disciplines and divergent interests makes identifying victims of child abuse and gathering information from them and their families extremely difficult. Some critical information is not publicly available due to both the need for confidentiality laws designed to protect minors and the secrecy spawned by feelings of guilt or shame by victims, abusers, and family members.

The involvement of so many professional disciplines and divergent interests makes identifying victims of child abuse and gathering information from them and their families extremely difficult.

These barriers severely limit data gathering during the period when child abuse is occurring. Most data are gathered years later, in what are called retrospective assessments, from victims’ memories and self-reports. Thus, much assessment occurs only after victims have grown up or at least reached adolescence, entered treatment programs for drug abuse, and often are also experiencing other psychological disorders.

Nevertheless, researchers are making inroads. Most information about the role of child abuse has come indirectly—from studies of drug abuse that bring to light information about childhood trauma. Some of these studies trace stress-related disorders in adult drug abusers back to childhood traumas. One example is a NIDA-funded review by Dr. Lisa M. Najavits and her colleagues at Harvard Medical School in Boston that examined 49 studies involving drug-abusing women with post-traumatic stress disorder (PTSD). Victims of PTSD re-experience trauma and terror through unexpected flashbacks or nightmares. Child abuse is one trauma that is frequently reported by PTSD patients who are drug abusers.

While drug abusers overall show high rates of coexisting PTSD diagnoses, female drug abusers show much higher rates of this dual diagnosis than do males who abuse drugs. Various studies reviewed by Dr. Najavits report that from 30 percent to 59 percent of women in drug abuse treatment also have PTSD—two to three times higher than the rate among men in treatment, according to Dr. Najavits’ review.

A better understanding of the consequences of child abuse would enable researchers to develop ways to tailor drug abuse treatment to the needs of drug abusers who say that they are victims of child abuse.

A history of trauma independent of PTSD is even more common among women in drug abuse treatment. The reviewed studies show that from 55 percent to 99 percent of these women reported a history of physical or sexual trauma. Most of the trauma occurred before age 18 and was commonly related to repetitive childhood physical or sexual assault. When the women are victims of both types of abuse, they are twice as likely to abuse drugs as are those who experienced only one type of abuse.

In another study, Dr. Najavits and her colleagues reviewed data from NIDA's Collaborative Cocaine Treatment Study, which collected treatment and outcome data from patients at five drug abuse treatment sites in eastern cities. Dr. Najavits examined lifetime traumatic events and current PTSD symptoms of 122 adult cocaine-dependent men and women outpatients. She found a high rate of lifetime exposure to traumatic events—an average of 5.7—and a 20.5 percent rate of currently diagnosed PTSD. The patients with PTSD showed significantly more impairments and different circumstances related to their trauma. For example, they reported that their first trauma occurred at an average age of 8.4 years, significantly younger than patients without a current PTSD diagnosis, whose first reported trauma was at the average age of 13.1.

Another NIDA-funded study, which documents that women rape victims are dramatically more likely to abuse drugs than are women who are not victims, also directly implicates child abuse. Dr. Dean G. Kilpatrick at the Medical University of South Carolina found that more than 61 percent of rapes of the 4,008 women in his study occurred by age 17. About half of those occurred by age 11; these obviously were cases of child abuse. The rape victims, compared to others who were not raped, were:

- more than three times as likely to have used marijuana;
- six times more likely to have used cocaine; and
- more than 10 times as likely to have used drugs other than cocaine, including heroin and amphetamines.

One recent study illustrates both progress in studying the relationship of child abuse to subsequent drug abuse and

the difficulty in gathering data that specifically address that relationship. The 1997 NIDA-funded study examined data from previous ethnographic studies of drug-abusing adults in New York City. The study found a significant statistical association between inhalant abuse and the abusers' reports that they were abused as children. However, the data do not demonstrate a causal relationship between the two, says Dr. Michael Fendrich of the University of Illinois at Chicago, the study's principal author. Evidence of a causal role for child abuse would require more data to substantiate that the onset of child abuse occurred before the onset of inhalant abuse, he points out.

The fact that most data marking a trail from child abuse to drug abuse are collected retrospectively poses a variety of problems for researchers. Investigators recognize that memory is subjective. Also, drug abusers may choose consciously to emphasize the role of parents or others in their retrospective accounts of events leading to their drug abuse. Thus, researchers, may seek additional data from other sources, such as juvenile court records of child abuse cases.

But NIDA-funded researchers are seeking innovative approaches to address these information-gathering problems to understand the connections between child abuse and later drug abuse. Dr. Cathy Spatz Widom of the State University of New York at Albany is comparing rates of drug abuse between a group of adults who had court-substantiated cases of child abuse and neglect and a control group of their childhood peers who did not have such records. Her initial findings show little difference in rates of drug abuse between the two groups. She recognizes that other factors are, of course, involved. For example, since many cases of child abuse never wind up in court, some in the control group with no court records may have been abused as well. Also, court-ordered interventions and therapies may have reduced the prevalence of drug abuse among court-documented child abuse victims. Even so, the preliminary results cause Dr. Widom to express concerns. "Child abuse is a factor in subsequent drug abuse, but it may be much less a factor than we now believe," she says. "Child abuse may be an important factor primarily for certain subgroups—some groups of women, for example—more than for the population in general." Other factors, such as poverty or family substance abuse problems, play a role, too, she says.

Difficulties such as these have hindered development of drug abuse treatment and prevention approaches that specifically address the needs of child abuse victims. However, some progress has been made in enhancing treatment for specific groups, such as drug-abusing women with PTSD, that include high percentages of child abuse victims.

Recognizing the need for broad new research agendas, NIDA continues to encourage studies into child abuse and its relationship to drug abuse during adolescence and young adulthood. Examining the role of child abuse is a major goal of the Interagency Consortium on Violence Against Women and Violence Within the Family that NIDA has joined with a number of other Federal agencies. Also under discussion is a NIDA-sponsored scientific meeting in 1998 on drug abuse and the childhood environment.

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Innovative Treatment Helps Traumatized Drug-Abusing Women

By Neil Swan, NIDA NOTES Staff Writer

A NIDA-funded researcher has developed an innovative treatment program to meet the special needs of drug-abusing women who also are diagnosed with posttraumatic stress disorder (PTSD), a disorder often associated with physical, sexual, or other abuse during childhood. PTSD victims re-experience their trauma, sometimes years later, through unexpected and recurring flashbacks or nightmares. The trauma that sparks PTSD may range from battlefield shock or childhood sexual molestation to violence related to drug dealing.



Dr. Lisa Najavits of Harvard Medical School has developed an innovative treatment program for drug-abusing women with post-traumatic stress disorder resulting from traumas such as child abuse.

PTSD symptoms include “avoidance” behavior, which may be marked by loss of interest in favorite activities, avoidance or suppression of thoughts or emotions, feelings of detachment, or difficulty thinking about the distant future. PTSD victims may suffer increased arousal or anxiety, as shown in extra vigilance against perceived dangers, trouble concentrating, exaggerated responses to being startled, and outbursts of anger.

PTSD combined with drug abuse can be devastating for women struggling to survive in the street drug culture. One study, which evaluated women crack cocaine abusers with PTSD in New York City’s Harlem, found that they are forced into vicious cycles in which they use crack to counteract the distress of trauma, suffer more drug-related trauma, and then turn to crack again.

Development of new treatment strategies for drug abusers with coexisting PTSD, especially women, should be a high priority, says Dr. Lisa M. Najavits of Harvard Medical School, who conducted a NIDA-funded review of research focusing on women with these problems. Treatments developed either for PTSD or substance abuse alone may not be sufficient, she says. Further, existing

treatments for men with PTSD and drug abuse may not be directly applicable to women, she adds.

Dr. Najavits developed an innovative treatment program called “Seeking Safety” that consists of 24 sessions that teach women new coping skills to manage both disorders at once. Patients learn how to ask for help, set boundaries in relationships, nurture themselves, and fight cues and urges to relapse to drug use.

The safety theme is emphasized as the key to recovery from both PTSD and drug abuse.

“Safety” in this situation means abstaining from drugs and alcohol, reducing self-destructive behavior, establishing a network of supportive people, and guarding against the dangers associated with both disorders, such as HIV and domestic violence.

Of 27 women enrolled in the “Seeking Safety” program, 17 completed treatment. After treatment, these women showed significant reductions in drug use, trauma-related symptoms, suicide risk, and suicidal thoughts. They showed improvements in social adjustment, family functioning, problem solving, depression, and thoughts about substance abuse, according to Dr. Najavits. “While this is a small sample, an uncontrolled pilot study, the data indicate that, when provided with treatment tailored to their needs, these difficult-to-treat women appear highly responsive and show improvements in both of their diagnoses,” she says.

Her treatment design is now undergoing further evaluation in three demonstrations where it is being compared to usual treatment regimens.

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NIDA Probes the Elusive Link Between Child Abuse and Later Drug Abuse

NIDA Director Dr. Alan I. Leshner

Substantial evidence points to childhood victimization as a major risk factor for later drug abuse. At least two-thirds of patients in drug abuse treatment centers say they were physically or sexually abused as children. However, we know relatively little about the details of that apparent link between child abuse and later drug use. NIDA-supported researchers are working intensively on this critically important public health question.

Determining the exact relationship between child abuse and drug abuse is exceedingly difficult given the role that variables such as poverty, family dysfunction, the level of social support for victims, or the child's gender and age play. Further, not all child abuse victims later become drug abusers.

What factors protect a child abuse victim from becoming a drug abuser? What factors make an abused child more vulnerable to drug abuse? In addition, child abuse victims may suffer severe emotional damage—even years later as adults. How can investigators conduct research without risk of exacerbating that damage?

NIDA has built a solid foundation of information and methodologies that researchers can use in seeking answers to these questions. For example, an expert panel convened by the Institute in 1996 reviewed the research on the role of childhood trauma in later drug abuse. Among the panel's conclusions was that the characteristics of the trauma, the child, and the child's environment interact to either buffer or aggravate the impact, which subsequently can produce a wide range of dysfunctional behaviors that can include drug abuse. NIDA researchers have extensively examined and evaluated risk and protective factors for drug abuse. Researchers have developed drug abuse prevention protocols that



Research to better treat the emotional scars of drug abusers who are child abuse victims can draw on NIDA research on treating drug abusers with coexisting mental and emotional problems.

maximize protective factors and target risk factors. These findings can serve as a starting point for developing prevention approaches that specifically target abused children. In addition, research to better treat the emotional scars of drug abusers who are child abuse victims can draw on NIDA research on treating drug abusers with coexisting mental and emotional problems.

However, many challenges for research in this area are unique to child abuse. Because society must act decisively to deter child abuse and at the same time protect its victims, legal questions relating to privacy, confidentiality, and informed consent—and the legal rights of accused abusers—limit researchers' access to information about child abuse.

These challenges pose a different set of questions for researchers. How can abused children be appropriately identified and their experiences accurately classified? How can reports and statements about abusive incidents be gathered and evaluated? Researchers usually have approached their investigations retrospectively, looking back over time and examining the psychological histories of adult patients being treated for drug abuse. That is where studies have found the strong correlations between childhood abuse and the subsequent development of drug abuse in adolescence and adulthood.

However, these studies rely primarily on memories of adult drug abusers. Scientists have long wrestled with the subjectivity of memory. With this in mind, NIDA-funded scientists are evaluating and refining methods for gathering, assessing, and verifying retrospective recall and looking for other sources of information, including court records.

NIDA is well situated to help these researchers and others bridge bureaucratic and disciplinary gaps among the many governmental and social service entities—health and child welfare agencies, drug abuse treatment and prevention

service providers, doctors and hospitals, and the justice system—that are seeking to expand their knowledge of, and response to, child abuse and drug abuse. NIDA can also bring past experience to bear to enhance integration of diverse scientific disciplines, pooling of resources, and rapid dissemination of research findings and viable prevention and treatment strategies. NIDA's current leadership role in the Interagency Consortium for Research on Violence Against Women and Violence Within the Family, which has child abuse as an important focus, is a prime example of how the Institute can respond to this need for coordination and cooperation.

In addition, NIDA continues to recruit, encourage, and support researchers who will seek further answers to questions surrounding the links between child abuse and drug abuse. For example, could early identification of child abuse victims coupled with intervention prevent

subsequent drug abuse? Do child abuse victims respond differently to different drug abuse treatment approaches? Does a history of child abuse affect treatment, retention, and relapse outcomes? The Institute also is planning a major scientific conference on drug abuse and the childhood environment that will address these and other issues related to children and drug abuse.

On the broad scale, NIDA's public health mission and experience will be of great value here, combining the expertise of its grantees and staff in many disciplines to shed more light on the elusive link between child abuse and drug abuse. And as our stockpile of science-based knowledge in this area grows, we can speed our pursuit of two goals: preventing abused children from becoming drug abusers and designing better treatments for that majority of drug abusers who report that they are also the victims of child abuse. **NN**

NIDA's "Report Card"

NIDA constituent groups have a lot to say about NIDA's activities, and the Institute is taking note.

Each year at NIDA's constituent conference, members of national groups in the field of drug abuse take on the role of advisors, providing invaluable advice and feedback to the Institute, noted NIDA Director Dr. Alan I. Leshner at this year's gathering. In what has become an important part of the 2-day meeting, constituents split up into work groups to focus on specific drug abuse issues. Out of their discussions come recommendations to NIDA program staff about research and other activities they think the Institute should undertake or strengthen to advance its public health mission.

After the conference, NIDA carefully sifts through these recommendations, folding them into the many research and program initiatives it implements every year. At the next constituent conference, NIDA reports on the actions it has taken in direct response to the input it received at previous conferences. NIDA calls this detailed list of activities its "Report Card."

This year's Report Card lists 109 NIDA activities that address constituents' recommendations. Below is a sampling of these activities.

- Established a Memorandum of Understanding with the Substance Abuse and Mental Health Services Administration to collaborate in information exchange and dissemination, planning NIDA's health services research program, collaborative research and services projects, and facilitating linkages between researchers and service providers.
- Teamed with Howard University Research Center in Washington, DC, to sponsor a meeting with faculty and staff from historically black colleges and universities who are forming a consortium to research substance abuse and other health issues among women on black college campuses.
- Is expanding its home page on the World Wide Web, at <http://www.nida.nih.gov>, and its links to constituency group Web sites and will continue to add more education materials to its Web site.
- Launched a new Children and Adolescents Initiative with two major components: preventing drug use and preventing individuals, their offspring, and society from suffering the health consequences of drug abuse.
- Launched a major Treatment Initiative to increase dramatically the quality and extent of drug treatment and to foster the interchange of useful information on drug addiction treatment.
- Published the first ever science-based guide to drug abuse prevention, *Preventing Drug Use among Children and Adolescents*.
- Is funding a Resource Center that will enhance NIDA's resources and strengthen its ability to identify and answer key research questions about the financing, organization, costs, and outcomes of drug abuse treatment and prevention services.
- Coordinated the development of abstracts on key research related to drug abuse and HIV/AIDS for the 1998 World AIDS Conference in Geneva to highlight and present U.S. research findings in this area. **NN**

Interagency Pacts and NIH Collaborations Extend NIDA's Research Reach

By Neil Swan, *NIDA NOTES* Staff Writer

Teamwork with sister Institutes of the National Institutes of Health (NIH) and other Federal agencies is increasing the cost-effectiveness and extending the reach of NIDA's research.

In one current research collaboration, NIDA is a key participant in a broad new effort extending across several Federal agencies to examine the links among violence, crime, and drug abuse. Research focuses on a host of criminal, medical, and social problems that are often related to drug abuse. These problems include sexual and physical abuse of children, violence against women, teenage crime and violence, trends in public attitudes toward violence, and violence-related demands on the Nation's courts, prisons, and delivery of health services.

Called the Violence Initiative, the cooperative research enterprise involves more than 20 Federal agencies collaborating under an Interagency Agreement. Two departments spearhead the Initiative: the Department of Health and Human Services (HHS), with NIDA taking a lead role; and the Department of Justice, represented by its research agency, the National Institute of Justice (NIJ). NIJ conducts research to fight crime, improve criminal justice, and evaluate criminal justice programs.

The 3-year Interagency Agreement for violence-related research also involves the Department of Housing and Urban Development, which has an interest in crime and social issues in public-supported housing. Also participating are the Department of Education, the Centers for Disease Control and Prevention (CDC), and other NIH Institutes in addition to NIDA—agencies with diverse objectives but a common interest in violence, its causes, and its consequences.

The Initiative is formally named the Interagency Consortium for Research on Violence Against Women and Violence Within the Family. It allows NIDA and the other agencies to bridge the gap between two bodies of research—studies relating to drug abuse, drug addiction, and mental health and studies relating to social and criminal justice questions. The Initiative spans academic disciplines to make the benefits of NIDA's biological and behavioral drug abuse research—ranging from basic neuroscience studies to investigations of the cost-effectiveness of drug abuse treatment innovations—applicable to those agencies interested in the many drug-related aspects of violence.

The research interests of NIDA and NIJ frequently overlap. For example, NIJ is vitally interested in causes of recidivism—the return to jail of inmates who have committed new crimes since their release—says Dr. Donald Vereen, NIDA's representative to the founding interdepartmental group. Recidivism and other disruptive or criminal behaviors may relate to what research has shown are drug-induced changes in the brains of drug abusers, which may be associated with drug craving, explains Dr. Vereen, who is NIDA's special assistant to the Director for medical affairs. Thus, drug abuse research can help in designing inmate drug abuse education and treatment programs, he says. NIDA-funded research already has provided much of the impetus toward innovative “drug courts” that seek to address both criminal justice and addiction problems by striving to keep offenders enrolled in drug abuse treatment programs, he says.

The initial research findings under the Initiative have not yet been reported, but previous cooperation between NIJ and NIDA has already proved productive, says Sally Hillsman, NIJ deputy director. “For example, we have benefited greatly from the work of NIDA's Community Epidemiology Work Group [which monitors trends in drug use patterns in selected U.S. cities].”

After the agreement was signed in late 1995, the participating agencies called for research proposals relating to various aspects of violence. Ten projects have now been funded, all of them studying drug or alcohol abuse-related violence issues, according to Dr. Coryl Jones of NIDA's Epidemiology Research Branch, who is monitoring the projects. Sometimes the substance abuse factor in the violence studies becomes much more apparent as the project continues, she says. For example, one Initiative project is studying violence toward female care providers—wives and daughters—over age 55. As the project continues, researchers are finding strong evidence that drug and alcohol abuse by the women's mates or parents is an important factor in their victimization by violence, she says.

Planning for the \$1.8 million Violence Initiative evolved from policymakers' interest in the Violence Against Women Amendment to the Violent Crime Control and Law Enforcement Act of 1994. “Early on, NIDA Director Dr. Alan Leshner got involved. He pushed us to get people from agencies outside of NIDA to participate,” says Dr. Vereen.

The agencies are able to collaborate thanks to the Interagency Agreement, a formal contract that spells out terms and financial commitments for participant agencies. “The Interagency Agreement is tailor-made for broad cooperative efforts like the Violence Initiative,” says Dr. Vereen. “It’s good for research as an enterprise, and it’s good for science. It takes advantage of an existing infrastructure. All the participating agencies get something out of it.”

The Interagency Agreement is a good tool for funding in situations when there is no handy grant mechanism,” says Carol Cornwell, a budget analyst in NIDA’s Program and Financial Management Branch, who manages the Initiative’s funds since NIDA was designated “banker” for the collaborative operation. “Several of the Violence Initiative’s participating agencies do not have a grant-issuing mechanism. But they can participate in the Interagency Agreement, making funding contributions, and have a say in the type of research that is funded.”

NIDA is also involved in other Interagency Agreements, including collaborating with the State Department to improve drug abuse research in South America (see “NIDA Advances Drug Abuse Research in Andean Countries,” *NIDA NOTES*, September/October 1997). The Institute is also working with other NIH Institutes, the Department of Energy, and the Department of Veterans Affairs to develop improved “informed consent” policies to ensure that people participating in research are adequately informed of related ethical issues and risks to their health.

Interagency Agreements are only one way that NIDA teams up with fellow Federal agencies. There are also collaborations in which NIDA joins with other NIH Institutes to conduct mutually beneficial research. These collaborations have proven to be productive and beneficial, says Dr. Vincent Smeriglio of NIDA’s Clinical Medicine Branch.

NIDA currently is involved in four major collaborations with other NIH Institutes and public health agencies. In the Maternal Lifestyles Study, NIDA collaborates with the National Institute of Child Health and Human Development (NICHD), the HHS Administration on Children, Youth, and Families, and the Center for Substance Abuse Treatment. The agencies are studying the health and development of infants and children who are exposed to illicit drugs during their mothers’ pregnancies. More than 11,000 mothers were interviewed about their pregnancies and drug use, and some 1,400 infants are enrolled in followup studies. The continuing project is building valuable information for developing enhanced

interventions to better address prenatal drug exposure and its possible consequences.

The Women and Infants Transmission Study (WITS) is a six-site collaborative project studying mother-to-infant transmission of HIV. NIDA is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH Institute involved in HIV and AIDS research, and NICHD. More than 1,200 HIV-infected women and 800 of their children have been enrolled. Approximately half of the WITS participants

are current or former drug abusers. NIDA joined the collaboration to support and promote focused research regarding the impact of drug use on the transmission and course of HIV disease.

Reaching for Excellence in Adolescent Care and Health (REACH) is an NICHD-initiated project with NIDA as a key collaborator. REACH seeks to learn more about HIV disease progression and its relationship to other

health factors, such as drug use among adolescents aged 12 to 19. NIDA support emphasizes research on both the impact of drug use on the course of HIV disease as well as the impact of HIV on drug use. Also participating in the REACH collaboration are NIAID and the Health Resources and Services Administration.

The Women’s Interagency HIV Study (WIHS) and the companion HIV Epidemiology Research Study (HERS) investigate the medical and psychosocial impact of HIV on women. Most of the women being studied have a history of current or past drug use. The studies have enrolled 2,500 HIV-positive women and 775 HIV-free women. NIDA collaborates in these studies with NIAID, NICHD, the National Cancer Institute, the National Institute of Dental Research, and the CDC. NIDA funding supports research on how drug use and addiction may influence women’s vulnerability or resistance to HIV infection, the consequences of coinfection with HIV and other diseases associated with drug abuse, the effectiveness of HIV medical treatment, and biomedical factors related to the development of HIV disease.

“Each of these collaborations ensures that NIDA’s knowledge and expertise in drug abuse and related conditions are pooled with the knowledge of our colleagues in other Institutes and agencies conducting vital HIV research,” says Dr. Smeriglio. “It’s a highly cost-effective way to bolster NIDA’s clinical research and to expand interest in drug abuse issues among a larger pool of investigators.” Together with the Interagency Agreements, these collaborations broaden the consequences of NIDA research and extend NIDA’s science-based findings into new realms. **NN**

“The Interagency Agreement is tailor-made for broad cooperative efforts like the Violence Initiative. It’s good for research as an enterprise, and it’s good for science.”

MERIT Awardee Examines Long-Term Effects Of Prenatal Cocaine Exposure in Rats

By Steven Stocker, *NIDA NOTES* Contributing Writer

NIDA MERIT (Method to Extend Research In Time) Award winner Dr. Sheldon Sparber, at the University of Minnesota Medical School in Minneapolis, studies the effects of prenatal drug exposure on the fetus and newborn and the effects that may continue into adulthood. His animal studies on opiates and opiate withdrawal have greatly influenced the treatment of opiate-addicted pregnant women in methadone maintenance programs and their newborns, and his current research on cocaine could prove to be just as important.

In the 1980s, Dr. Sparber's animal studies provided a new perspective on whether opiate-addicted women should be treated with methadone. Earlier research findings had suggested that methadone is dangerous to the fetus and probably should not be given to pregnant heroin addicts. However, Dr. Sparber's group showed that the toxic effects on the offspring demonstrated in the earlier studies were due to excessively high doses of methadone and the stress of sudden withdrawal from methadone. "Unlike with adults, severe sudden withdrawal can be deadly for fetuses and infants," explains Dr. Sparber. "This is true for both animals and humans. But if you maintain human pregnant mothers on low but adequate doses of methadone and provide the newborns with medications, if necessary, to allow them to go through slow, mild withdrawal, their prognosis can be quite good."

In his current research, Dr. Sparber is investigating the effects of prenatal cocaine exposure in chickens and rats. He has found that cocaine injected into chicken eggs interferes with the hatching of the chicks, probably by restricting blood flow to the embryos. He also has discovered that this effect could be blocked with a medication called ritanserin, which, according to Dr. Sparber, opens up the possibility of a treatment to prevent the adverse effects of prenatal cocaine exposure.

In his studies with rats, Dr. Sparber is finding that prenatal cocaine exposure causes only minimal effects on brain chemistry and behavior—until the rats reach middle age. When tested at age 10 months to a year, rats that were exposed to cocaine during the last trimester of pregnancy start to show serious learning and memory deficits. "If the data from our animal studies are real and can be generalized to humans exposed to cocaine in utero, it would

mean that those people might start showing learning and memory deficits at about age 30 to 40 or perhaps later," says Dr. Sparber.



Dr. Sheldon Sparber

As part of the research funded by the MERIT Award, Dr. Sparber will be investigating whether cocaine's long-term effects can be prevented by altering the rearing environment of the infant rats or by treating the pregnant mothers with medications such as ritanserin. According to Dr. Sparber, the MERIT Award with its longer period of funding will allow him to take risks in his research that he might not be willing to take with a conventional grant. "The MERIT Award gives you the opportunity to do innovative work that you wouldn't normally do if you had a 3-year grant," says Dr. Sparber. He adds that many important discoveries in biomedicine are made

through serendipity. "If you have your eyes open and don't have any preconceived notions about what you're going to see, you might come up with some very exciting observations."

Dr. Sparber has been funded continuously by NIDA since 1972. Dr. Jerry Frankenheim of NIDA's Division of Basic Research describes Dr. Sparber as being "at the cutting edge of his field." He salutes Dr. Sparber's "willingness to tackle the truly relevant questions in psychopharmacology, no matter how tough."

Dr. Sparber is a professor of pharmacology, psychiatry, and psychology at the university. He has published more than 150 scientific papers and has edited two books.

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Contributions of Behavioral Research To AIDS Studies Recognized

By Neil Swan, NIDA NOTES Staff Writer

Behavioral and social sciences research is playing an increasingly critical role in the Nation's public health response to the spread of AIDS, according to experts at a National Institutes of Health (NIH) symposium last summer.

Dr. James Curran, an AIDS epidemiologist and professor at Emory University in Atlanta, said that science has made significant advances in recognizing the "previously marginal" role for behavioral studies related to AIDS. He spoke at the half-day symposium, Substance Abuse and AIDS: Research from the Behavioral and Social Sciences. The meeting at the NIH campus in Bethesda, Maryland, was cosponsored by NIDA.

AIDS is still a young epidemic, said Dr. Curran, formerly head of the Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention (CDC) in Atlanta. Early public responses tended to "ghettoize" those with AIDS, downplaying its spread into the general population through heterosexual contacts, he said. As a result, the public mistakenly has failed to recognize the importance of heterosexual contacts in the spread of HIV. Among women, particularly among poor and minority women, heterosexual sex is key to the currently increasing rate of HIV infections, he said. Statistics from the CDC support this view. In September, the CDC reported that the number of AIDS cases is increasing faster among women than among men and that sex with infected men has overtaken drug abuse as the leading cause of HIV infection among women. From 1991 through 1995, the number of men diagnosed with AIDS increased by 12.8 percent, versus an increase of 63 percent for women. However, many of the sex partners of these HIV-infected women are men whose own infections are drug abuse related.

Behavioral factors play an important part in these gender differences, say experts. Studies show that homosexual men, who now account for approximately 48 percent of all AIDS patients, are often well educated, aggressive about their treatment options, and responsive to prevention efforts. But many women with HIV are poor, are not well educated, and may have limited access to health care. As a result, these women may not respond as well as some men do to prevention or treatment efforts.

Behavioral studies are vital to learning more about the spread of the HIV infection, agreed Dr. William Paul,

former director of NIH's Office on AIDS Research. After reviewing NIH-supported AIDS research, outside experts recommended strengthening the social sciences and behavioral components of the research portfolio, advice now being heeded in NIH's AIDS research agenda, said Dr. Paul. NIDA ranks third among NIH Institutes in the level of funding it receives for AIDS studies, and much of the NIDA-supported research is already devoted to behavioral and social sciences investigations into the link between drug abuse and AIDS.

"AIDS and drug abuse are two epidemics that are totally intertwined," NIDA Director Dr. Alan I. Leshner reminded those attending the session. "It's impossible to speak about one and not the other. Behavioral and social science research is critical to gaining insights into the epidemiology of AIDS, and it helps the broader scientific community get a handle on this intersection of drug abuse and AIDS."

Studies of social and personal networks are vital to understanding HIV transmission and prevention, said Dr. Carl Latkin, a NIDA-supported researcher at Johns Hopkins University in Baltimore. "We need to look not so much at individual behavior but more at social-network aspects of behavior," he said. "We need to learn more about support networks that provide protection against HIV transmission and risk networks that actually promote high-risk behaviors."

Numerous studies have documented that significantly lower rates of HIV risk behaviors are practiced by drug abusers who are enrolled in treatment programs, said Dr. David Metzger, another NIDA-funded researcher at the University of Pennsylvania. "The consistency of these findings suggests that increasing the access to drug abuse treatment is a legitimate and absolutely necessary HIV prevention activity," he said. "Although the data [supporting the effectiveness of drug abuse treatment in preventing HIV transmission] are strongest for methadone treatment of opiate dependence, there also is growing awareness of the important role that noninjection drug use has played in the sexual transmission of HIV."

He noted that the protective effects of drug abuse treatment are not immediate and not universal. This underscores the need to investigate all modalities of treatment to document the effectiveness of each in changing behaviors to prevent HIV transmission. **NN**

"Increasing access to drug abuse treatment is a legitimate and absolutely necessary HIV prevention activity."

Study Sheds New Light on the State of Drug Abuse Treatment Nationwide

By Michael D. Mueller and June R. Wyman, *NIDA NOTES* Staff Writers

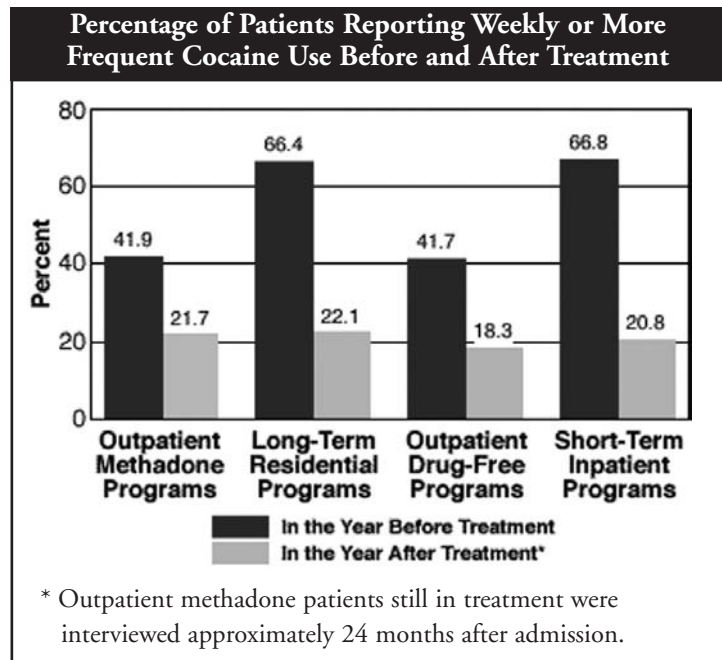
The four most common forms of drug abuse treatment are all effective in reducing drug use. That is the major finding from a NIDA-sponsored nationwide study of drug abuse treatment outcomes. The Drug Abuse Treatment Outcome Study (DATOS) tracked 10,010 drug abusers in nearly 100 treatment programs in 11 cities who entered treatment between 1991 and 1993.

“DATOS is the largest study of drug abuse treatment outcomes since the early 1980s and the most important in the last 10 years in terms of telling us how treatment programs are doing,” says Dr. Bennett Fletcher, chief of NIDA’s Services Research Branch.

DATOS investigators measured treatment outcomes using a random sample of approximately 3,000 patients. The researchers compared patients weekly and daily drug use for the 12 months before they entered treatment with their weekly and daily drug use 12 months after they stopped treatment. Patients in outpatient methadone treatment who were still in treatment were interviewed approximately 24 months after admission. Other outcomes that the researchers measured included:

- whether patients reported fewer illegal acts, including assault, robbery, burglary, larceny, forgery, and fencing stolen property;
- whether patients were working full time, defined as at least 35 hours per week; and
- whether patients reported fewer attempts or thoughts of suicide, which was used as a marker for depression. The researchers chose that marker because several previous studies had established its validity as an indicator of depression.

The four types of programs with the number of programs that DATOS studied in parentheses were outpatient methadone (29), outpatient drug-free (32), long-term residential (21), and short-term inpatient (14). Three of the four types were also studied in DATOS’s two predecessors: the Drug Abuse Reporting Program (DARP), which included admissions to treatment from 1969 to 1973, and the Treatment Outcome Prospective Study (TOPS), which covered admissions from 1979 to 1981. The short-term



In all four types of treatment programs that the Drug Abuse Treatment Outcome Study examined, the percentage of patients reporting frequent use of cocaine dropped dramatically after treatment.

“The Drug Abuse Treatment Outcome Study found reductions in the use of all drugs—including cocaine, heroin, and marijuana—after treatment.”

inpatient treatment programs, originally developed to treat alcohol abuse but admitting increasing numbers of cocaine abusers during the 1990s, were studied in DATOS but not in the two earlier projects.

Highlights From the Study

For the four treatment types, DATOS investigators found reductions almost without exception in the use of all drugs including cocaine, heroin, and marijuana after treatment. Likewise, after treatment a smaller percentage of patients reported committing illegal acts, working less than full time, and thinking about or attempting suicide. The data also revealed that:

- Except in outpatient methadone programs, cocaine was the primary drug of abuse, with alcohol running a close second. Cocaine abuse was common even in

outpatient methadone treatment programs for heroin addicts. About 42 percent of patients who entered methadone treatment programs also abused cocaine.

- Heroin use had decreased since the 1979-to-1981 period that TOPS studied. Large declines in the abuse of depressants such as barbiturates and tranquilizers had also occurred since TOPS.
- Short-term inpatient treatment programs yielded significant declines in drug use, even though patients stayed in these programs no more than 30 days. “This is one of our most surprising findings,” Dr. Fletcher says. “This treatment mode had a high percentage of patients reporting daily or weekly use of cocaine in the year before treatment and a sharp decline in weekly and daily use after treatment.” The percentage of patients reporting illegal acts and thoughts of suicide also declined significantly after treatment in these programs. The researchers are exploring whether continuing involvement in outpatient services and mutual help groups may have contributed to these positive outcomes.
- In every city studied in DATOS, support services such as medical, legal, financial, psychological, employment, and family services had declined dramatically since TOPS, while the need for those services had increased.
- Patients surveyed by DATOS reported that it took them about 7 years after they first used their primary drug to enter treatment.

New Demographics

Demographic characteristics of patients studied in DATOS had changed since the earlier study. For example, DATOS patients were older and had more years of schooling than TOPS patients, and a greater percentage of them were women.

In DATOS, 39 percent of patients admitted to outpatient methadone programs were women compared to approximately 31 percent in TOPS. Women made up approximately 33 percent of the patients admitted to long-term residential programs, as opposed to 22 percent for TOPS. Outpatient drug-free programs saw little change from TOPS to DATOS, with women accounting for approximately 33 percent of patients in these programs in both studies. In DATOS, about 37 percent of patients admitted to short-term inpatient

programs, which were not included in TOPS, were women. The researchers are conducting additional analyses to further explore the characteristics and outcomes for women in DATOS.

Substance Abuse and Psychological Disorders

DATOS researchers looked at co-occurring psychological disorders and dependencies in 7,402 patients in the DATOS programs who were diagnosed as substance dependent. They found that 32.1 percent of those patients were dependent on cocaine alone. Of that 32.1 percent, 59.1 percent were male. Another 26.3 percent of the patients were dependent on both cocaine and alcohol, and, of those, 69.8 percent were male. In addition, 10.6 percent of the patients were dependent on heroin alone, and 64.2 percent of those were male.

The prevalence of co-occurring psychological disorders among the group was high, especially for antisocial personality disorder (APD) and major depression. APD was characterized as a pattern of disregard for the rights of others, irresponsibility, and lack of remorse. Major depression was characterized as either a depressed mood or a loss of interest or pleasure for 2 weeks or more.

The prevalence of those two disorders differed widely among men and women. Approximately 40 percent of the group was diagnosed with APD, and males were twice as

Four Common Types of Drug Abuse Treatment

Investigators with the Drug Abuse Treatment Outcome Study (DATOS) studied patients in the four most common kinds of treatment programs:

- **Outpatient methadone programs** administer the medication methadone to reduce cravings for heroin and block its effects. Counseling, vocational skills development, and case management to help patients access support services are used to gradually stabilize the patients functioning. Some patients stay on methadone for long periods, while others move from methadone to abstinence.
- **Long-term residential programs** offer around-the-clock, drug-free treatment in a residential community of counselors and fellow recovering addicts. Patients generally stay in these programs several months or up to a year or more. Some of these programs are referred to as therapeutic communities.
- **Outpatient drug-free programs** use a wide range of approaches including problem-solving groups, specialized therapies such as insight-oriented psychotherapy, cognitive-behavioral therapy, and 12-step programs. As with long-term residential treatment programs, patients may stay in these programs for months or longer.
- **Short-term inpatient programs** keep patients up to 30 days. Most of these programs focus on medical stabilization, abstinence, and lifestyle changes. Staff members are primarily medical professionals and trained counselors. Once primarily for alcohol abuse treatment, these programs expanded into drug abuse treatment in the 1980s.

likely as females to be diagnosed with the disorder. While 12 percent of the group had experienced a major depression, female patients were twice as likely as male patients to have done so.

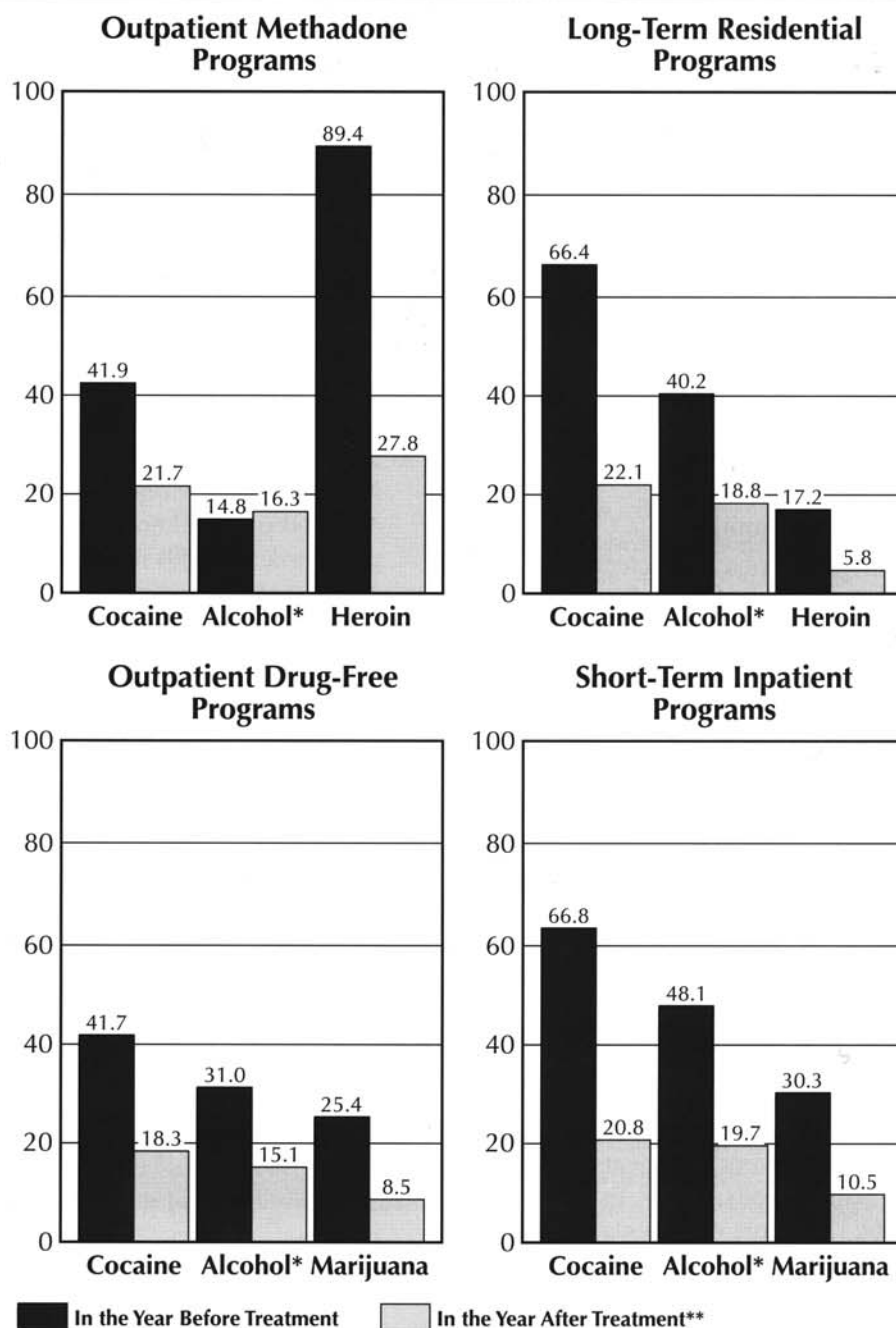
When the researchers looked at retention rates, they found big differences within each of the four treatment types and among individual programs.

Keeping Patients in Treatment

When the researchers looked at retention rates, they found big differences within each of the four treatment types and among individual programs. “We found a lot of diversity in how well they’re doing at keeping patients in treatment, and we wanted to know why,” says Dr. Dwayne Simpson of Texas Christian University in Fort Worth.

The investigators found that programs with low retention rates tended to have patients with the most problems, particularly antisocial personality disorder, cocaine addiction, or alcohol dependence. In addition, heroin abusers who also abused crack cocaine but not powder cocaine had significantly lower retention rates than other heroin abusers did. “These programs are dealing with some tough people. Programs with the highest concentration of these problem patients naturally tend to have low retention,” Dr. Simpson says.

Percentage of Patients Reporting Weekly or More Frequent Substance Use Before and After Treatment



* Weekly or more frequent use with 5 or more drinks at a sitting.
 ** Outpatient methadone patients still in treatment were interviewed approximately 24 months after admission.

Patients in programs surveyed for DATOS showed a marked reduction in drug use after treatment regardless of the type of treatment program in which they participated. DATOS analyses focused on marijuana use instead of heroin use among patients in short-term inpatient programs and outpatient drug-free programs because the number of patients using heroin in those programs was too small to allow statistical comparisons.

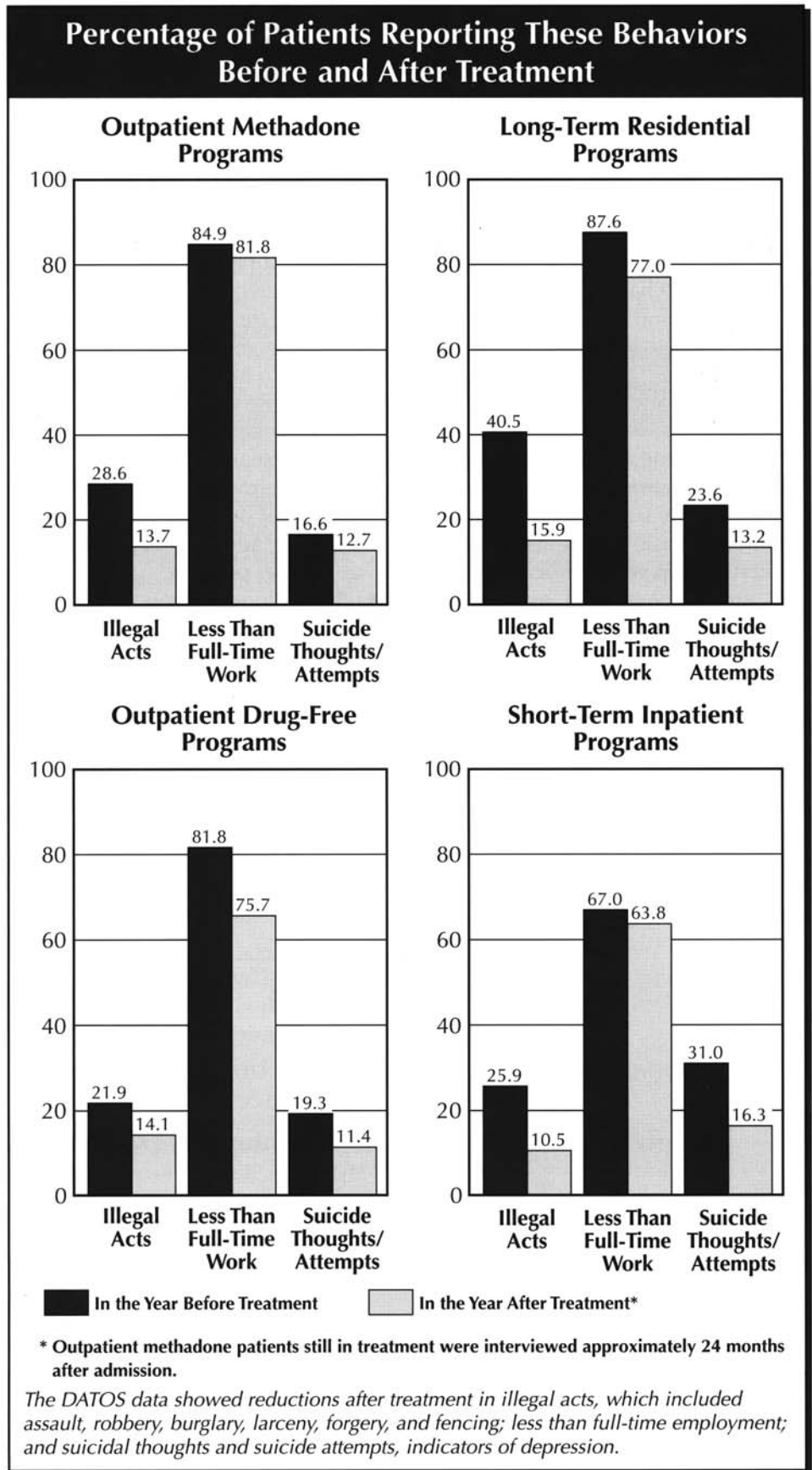
What makes patients stay in treatment? The researchers found that the major predictors were:

- high motivation;
- legal pressure to stay in treatment;
- no prior trouble with the law;
- getting psychological counseling while in treatment; and
- lack of other psychological problems, especially antisocial personality disorder.

Lessons From DATOS

What were the overall conclusions? “Clearly there were significant changes from before to after treatment in each of the four modalities,” says Dr. Fletcher. That finding raises some interesting questions, he adds. “For example, retention has been our most powerful and consistent predictor of treatment outcomes—yet even people in short-term inpatient treatment for 30 days or less improved significantly.” Although DATOS replicated the finding from DARP and TOPS that time in treatment is important, the relationship to retention of other factors such as motivation, psychiatric comorbidity, and treatment process needs to be studied more, he says.

One would also expect worse outcomes from DATOS compared to TOPS because of the steady decline in availability of support services, says Dr. Fletcher. A possible explanation for the better DATOS outcomes is that although support services have decreased, core treatment services have improved. “Core services—basic treatment techniques such as drug abuse counseling, mutual-help groups, and patient participation in devising treatment plans—may have improved over the past 10 years. What we’re seeing may be a result of this improvement, even though availability and use of noncore support services have declined,” Dr. Fletcher says.



The study's encouraging results verify the effectiveness of drug abuse treatment no matter what its form, says NIDA Director Dr. Alan I. Leshner. "The service system has changed dramatically over the last two decades. This study gives us a unique opportunity to understand the effect of those changes and to have an impact on the way treatment is delivered," Dr. Leshner says.

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National Study Offers Strong Evidence of the Effectiveness of Drug Abuse Treatment

NIDA Director Dr. Alan I. Leshner

A newly released nationwide study shows impressive reductions in drug use for patients in the four common types of drug abuse treatment. This good news comes from the NIDA-supported Drug Abuse Treatment Outcome Study (DATOS)—a major research effort that tracked more than 10,000 patients in almost 100 programs in 11 cities around the Nation over 3 years. Building on two earlier nationwide studies of treatment outcomes, DATOS investigators have amassed a wealth of information on drug abuse treatment outcomes, psychological disorders, retention rates, and treatment histories of drug abusers. The study also provides new information on changes in availability of drug abuse treatment services—ranging from basic drug abuse counseling to medical, legal, employment, and financial help—over the last two decades.

DATOS overwhelmingly confirms the effectiveness of drug abuse treatment. Although the two earlier studies and many smaller-scale studies have documented this effectiveness, DATOS proves it with nationwide findings for the 1990s. Among the patients that DATOS studied, drug use dropped significantly from the 12 months before treatment to 12 months after treatment began. This was true for all four types of treatment studied: outpatient methadone, outpatient drug-free, long-term residential, and short-term inpatient. Treatment also led to significant improvements in other aspects of patients' lives such as reduced involvement in illegal acts.

DATOS is one of the few national longitudinal studies to collect data on psychological disorders among drug abusers in treatment. The study also provides invaluable insight into critical differences between men and women entering drug abuse treatment. Knowing the gender-

specific problems of addicts entering treatment can help providers tailor treatment to patients' specific needs.



The Drug Abuse Treatment Outcome Study overwhelmingly confirms the effectiveness of drug abuse treatment with new nationwide findings.

DATOS also provides a wealth of information on the demographic characteristics and treatment histories of addicts in treatment. As more data are analyzed, researchers will be able to link patients' treatment outcomes to their backgrounds, gender, treatment histories, psychological disorders, and the specific services they have or have not received. This knowledge will enable us to refine and strengthen treatment by helping service providers determine what treatments work best for what kinds of patients.

Although much of the news from DATOS is good, there is also cause for concern. The study identified an alarming drop over time in the provision of services such as medical, legal, employment, and financial help. This decline is of special concern, since drug abusers often need help in one or more of these areas to get into and stay in treatment. Since NIDA's last national study of treatment outcomes, conducted from 1979 to 1981, the provision of these services has declined strikingly while the need for them has increased. From 1991 to 1993, during

the time DATOS researchers were collecting data, the typical length of stay in short-term inpatient treatment dropped from 28 days to 14 or fewer days as insurers reduced coverage for addiction treatment. These changes did not go unnoticed by patients. More than half of DATOS participants in the four kinds of treatment programs surveyed did not report receiving support services that they said they needed. And, nearly 75 percent of patients in short-term inpatient programs reported not getting the psychological help they needed.

The reality is that we now have a treatment system that faces major resource constraints. As drug abuse treatment comes increasingly under managed care and resources are more tightly controlled, we must stay focused on the scientific facts about addiction and how to treat it adequately. Managed care providers must make tough

decisions in allocating their resources, and DATOS can provide the hard scientific data they need to guide those decisions.

Given the wealth of findings coming from this study, our challenge is to communicate this information to health care organizations, managed care companies, and public policymakers. We have a new mechanism in place to do that. Disseminating research findings is a primary goal of NIDA's new Treatment Initiative, as described in the last

issue of *NIDA NOTES*. (See "NIDA Initiative Will Stimulate Improvements in Drug Abuse Treatment," and "NIDA Launches Drug Abuse Treatment Initiative," in *NIDA NOTES*, July/August 1997.) The DATOS results together with the Treatment Initiative can help us bridge the gap between public perceptions of drug addiction and what science has again shown—that drug abuse and addiction can be treated successfully with science-based methods, adequate treatment, and vigilant followup. **NN**

Gender, Ethnicity, and Age Make a Difference In Drug Dependence

A new analysis of data from the National Household Survey on Drug Abuse offers information about gender differences in drug dependence.

NIDA grantee Dr. Denise Kandel at Columbia University in New York City and her colleagues looked at survey data from the years 1991, 1992, and 1993 and found, for example, that:

- Among adolescents, rates of dependence on alcohol and marijuana are higher in females than in males, but only rates of cocaine dependence are significantly higher in females.



- Adolescent females are significantly more at risk for becoming dependent on alcohol and marijuana than are women in any other age group.
- Among adults, rates of dependence on alcohol and marijuana are higher among males than among females, but rates of dependence on nicotine are lower among males.



- Among people who used drugs in the last year, whites are more likely than other ethnic groups to be dependent on nicotine. African Americans are more likely to be dependent on cocaine.

The findings were reported in the June 10, 1997 issue of *Drug and Alcohol Dependence*.**NN**

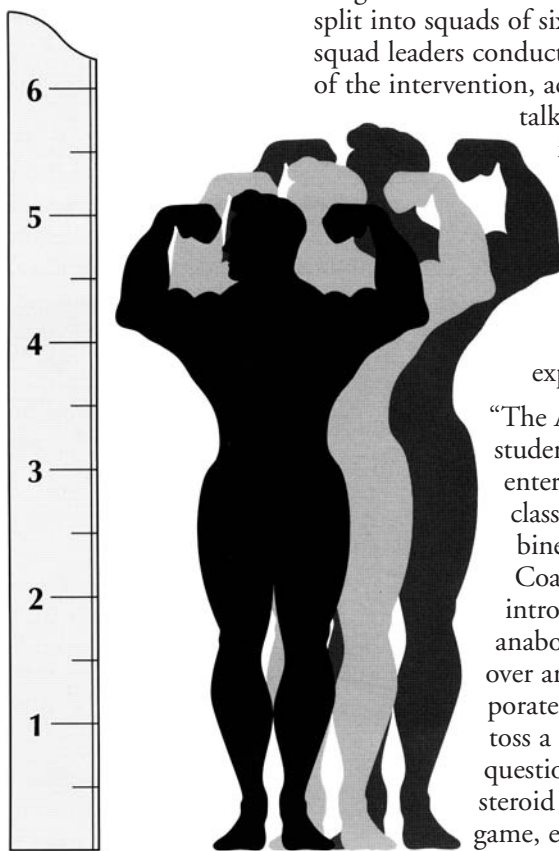
Steroid Prevention Program Scores With High School Athletes

By Robert Mathias, NIDA NOTES Staff Writer

A NIDA-funded drug abuse prevention program is showing high school football players that they do not need to take anabolic steroids to build powerful muscles and improve athletic performance. By educating student athletes about the harmful effects of anabolic steroids and providing nutrition and weight-training alternatives to steroid use, the program has increased football players' healthy behaviors and reduced their intentions to use steroids.

Until now, anabolic steroids, drugs derived from the male hormone testosterone, have rarely been the focus of drug abuse prevention studies, says Dr. Ro Nemeth-Coslett of NIDA's Division of Epidemiology and Prevention Research. This may be because steroids are not widely abused. Only about 2 percent of 8th, 10th, and 12th grade students have ever used steroids, according to the NIDA-supported Monitoring the Future study for 1996. However, steroid abuse occurs more often among young people who are involved in physical training because anabolic steroids can increase muscle mass, strength, and stamina, Dr. Nemeth-Coslett points out.

Although adolescent boys, particularly those involved in athletics such as football or body building, make up the majority of high school steroid users, national surveys show that adolescent girls also are vulnerable to the lure of steroid use. However, that lure contains a hook—anabolic steroid use can have severe physical and emotional consequences for both males and females. Physical effects can include stunted growth, high blood pressure, and liver tumors. Psychological effects can include wide mood swings that range from episodes of uncontrolled anger and aggressiveness to clinical depression when steroid use is stopped.



Students in the ATLAS program learn that stunted growth and many other harmful effects can result from steroid use.

“The Adolescents Training and Learning to Avoid Steroids (ATLAS) program uses a team-oriented educational approach that motivates and empowers student athletes to make the right choices about steroid use,” says Dr. Linn Goldberg of Oregon Health Sciences University in Portland, who led the research team that developed and tested the program. The program consists of classroom, weight-training, and parent information components. Together, they give student athletes the knowledge and skills to resist steroid use and achieve their athletic goals in more effective, healthier ways, he says.

In ATLAS's classroom component, football coaches and student leaders conduct seven highly interactive sessions that explore the effects of steroids, the elements of sports nutrition, and strength-training alternatives to steroid use. These classes also hone the athletes' decisionmaking and drug-refusal skills. In a typical session, the football team is split into squads of six or seven students, with student squad leaders conducting the sessions and teaching most of the intervention, according to Dr. Goldberg. “It's kids

talking to kids; that's an important ingredient in our program,” he says. Coaches, who have a substantial influence on these student athletes, also play an important role on the steroid prevention team, Dr. Goldberg says. Coaches introduce topics and wrap up each session, he explains.

“The ATLAS program is voluntary, and students get no credit for it, so it better be entertaining,” he says. As a result, ATLAS classroom sessions are designed to combine fun and games and learning. Coaches move from squad to squad and introduce a topic, such as the effects of anabolic steroids. Then squad leaders take over and initiate an action game that incorporates the topic. For example, players may toss a football to each other as they answer questions about problems that stem from steroid use. “Although they are playing a game, each one is paying attention and listening because someone is flipping the ball to them,” says Dr. Goldberg. “No one is

saying to them, ‘Watch out, steroids cause liver disease, acne, and so forth,’” he notes. “But while they are laughing and having a good time, they are actually watching and learning at every step of the way.”

“Football players are athletes; they like to compete,” Dr. Goldberg notes. Therefore, several games pit squads against each other to try and earn the most points for correct answers about weight training, nutrition, and steroids. In addition to games, “students do mock public service announcements, they do ‘rap,’ they do songs, and they do newspaper articles in the classroom sessions,” he says.

In ATLAS's weight-training component, research staff members conduct seven hands-on sessions that teach the students proper weight training techniques. These sessions are designed to help student athletes build the muscular strength and agility needed to achieve their athletic goals without using steroids.

In the parent information component, parents participate in an information and discussion session about the program with the ATLAS staff. The staff gives the parents a family sports nutrition guide and encourages them to support and reinforce the antisteroid and nutritional goals of the program at home. Students in the program say their parents are more opposed to steroid use after the intervention and often provide healthier meals at home, according to Dr. Goldberg.

Late last year, Dr. Goldberg reported results of an ongoing study of ATLAS's effectiveness in preventing steroid use among more than 1,500 football players from 31 high schools in the Portland area. Some 702 football players at randomly selected schools received the 7-week program during football season. Another 804 football players at matched schools served as a control group and received only a standard informational brochure on the dangers of steroid use.

Assessments conducted immediately after the intervention and 1 year later show that, compared with control students, student athletes who participated in the ATLAS program knew more about exercise, nutrition, and the harmful effects of anabolic steroids. ATLAS participants also had an increased sense of personal vulnerability to negative effects of steroids, more unfavorable attitudes toward their own and others' use of steroids, and reduced intent to use steroids. ATLAS students also showed greater improvement in their nutritional habits than did control students. For example, they were more likely to eat high-protein low-fat meals at school, home, and fast-food restaurants. In addition, ATLAS students were more likely than students who did not participate in the program to use established weight-lifting and strength-conditioning techniques.

“The program's positive effects flow from changing the student athletes' attitudes and perceptions about steroids and then changing their nutrition and exercise behaviors,” Dr. Goldberg says. These changes in behavior are reinforced by conducting periodic tests of the athletes' body composition, strength, and power. “If they are training properly, they are a heck of a lot stronger. So, it's real positive reinforcement to them,” he says.

“Student athletes who participate in the ATLAS program achieve,” Dr. Goldberg says. The year before they entered the program, the football teams that were randomly assigned to receive the intervention had much worse won-lost records in football than the teams in the control group had, he says. At the end of the first year, the two groups' records were about the same, but teams in the ATLAS program did slightly better. At the end of the

Adolescent Girls Abuse Steroids, Too

What do anabolic steroids have in common with amphetamines, tobacco, diet pills, laxatives, and anorectics? They all are drugs used by adolescent girls seeking to stay thin, says Dr. Linn Goldberg of Oregon Health Sciences University. The use of these drugs, which often goes hand in hand with eating disorders, is particularly prominent among adolescent girls engaged in athletic activities ranging from track and field, soccer, basketball, and volleyball to school dance and drill teams, Dr. Goldberg says.

Dr. Goldberg and his colleague Dr. Dianne Elliot have been conducting preliminary research, funded by NIDA, to identify risk factors that influence adolescent girls' use of harmful drugs. Among other things, the researchers have found that many adolescent girls use drugs to maintain thinness, Dr. Goldberg says. National surveys indicate that girls account for about one-third of the high school students who abuse steroids, Dr. Goldberg says. “The primary reason that these girls use steroids is to lose fat and gain lean muscle,” he says.

Dr. Elliot and Dr. Goldberg have already developed an effective steroid prevention program for male high school athletes described beginning on the previous page. Now, they are developing a similar drug abuse prevention program for adolescent girls. In their future research, the researchers hope to test the effectiveness of the intervention in reducing drug use and eating disorders among female athletes in Oregon's public middle and high schools.

The prevention program gives student athletes the knowledge and skills to resist steroid use and achieve their athletic goals in more effective, healthier ways.

second year, the won-lost records of the ATLAS teams were substantially better than those of the control teams, with some of the ATLAS teams making the playoffs at the end of the season. "I don't know whether these teams' improved performance is due to the ATLAS program," Dr. Goldberg says. "I do know some of those schools hadn't been to the playoffs in 25 years. The data showing improvements in program participants' body composition and muscle mass are consistent with these teams' success," he says.

For More Information

- ATLAS, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Rd., CB 615, Portland, OR 97201-3098, (503) 494-7900.

Source

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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

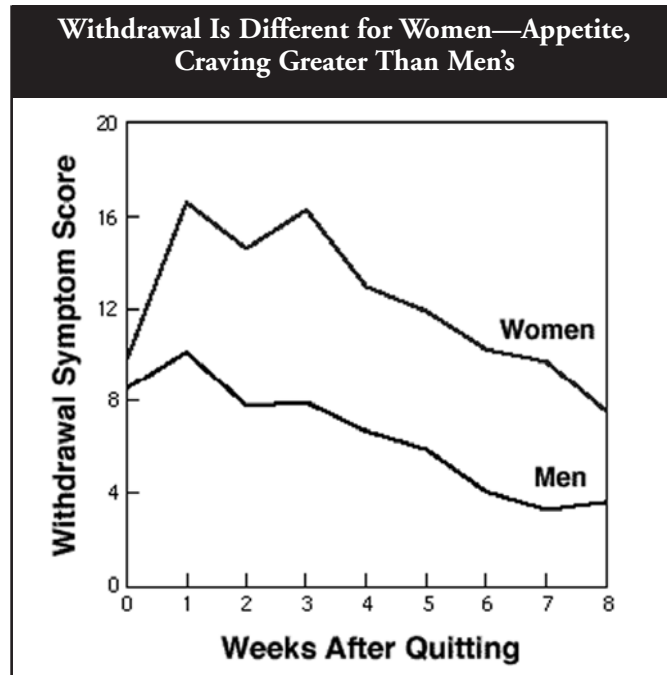
By Neil Swan, NIDA NOTES Staff Writer

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 support and rely less on nicotine replacement.



*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.*

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.

NIDA Responds to the Changing Dynamics of the AIDS Epidemic

NIDA Director Dr. Alan I. Leshner

Drug abuse and the spread of HIV/AIDS, as well as other infectious diseases such as hepatitis and tuberculosis, are inextricably linked public health problems that require many and multifaceted solutions.

A majority of new HIV infections in this Nation are related to drug abuse—through sharing of contaminated drug injection paraphernalia, through sexual contact with an injection drug user, or through the transmission of HIV perinatally. NIDA has expanded its research efforts in this area to meet this challenge. The Institute has also set policies to ensure that all participants in NIDA-supported AIDS research are offered HIV testing and counseling.

NIDA-funded research has found that, through drug abuse treatment, prevention, and community-based outreach programs, drug abusers can change their behaviors.

They can reduce or eliminate drug use, drug-related HIV risk behaviors such as needle sharing, unsafe sex practices, and, in turn, the risk of HIV/AIDS. NIDA research also is working to reduce HIV and other AIDS-related illnesses and improve overall survival rates for HIV-infected drug abusers by increasing their access and adherence to medical treatment. With a comprehensive research portfolio that is responsive

to the changing dynamics of the AIDS epidemic, NIDA is improving the quality of life for many, as well as saving both lives and enormous costs to society.

NIDA-funded research has clearly shown that drug abuse treatment is highly effective in preventing the spread of HIV. Numerous studies have shown that individuals who enter drug abuse treatment programs reduce their drug use, which, in turn, leads to fewer instances of HIV high-risk behaviors.

NIDA's research into this field began early in the AIDS epidemic. One of the Institute's first investigations of drug use patterns among injection drug users (IDUs)—conducted in methadone treatment programs in New York City, Philadelphia, and Baltimore—found that not only did participants report reduced sharing of needles, but also, 70 percent reported that they no longer injected drugs daily.

In addition to reducing injection drug use, individuals in drug abuse treatment programs have been found to have significantly lower HIV infection rates than drug abusers not in treatment. Researchers in Philadelphia compared HIV infection rates among drug abusers enrolled in methadone treatment programs to rates among those not in treatment. During the first 18 months of the study, those who remained out of treatment were nearly seven times more likely to have become infected with the AIDS virus than those in treatment. The investigators also found that the longer drug abusers remained in treatment, the less likely they were to become infected.

In aggregate, studies that look at abuse of drugs other than heroin and other injection drugs also are showing that drug abuse treatment lowers rates of HIV risk behaviors and infection. The bottom line is that providing access

to effective drug abuse treatment programs is a proven way to prevent the spread of HIV/AIDS.

This is encouraging news. The discouraging news, of course, is that only a small percentage of those who need drug abuse treatment receive it. In fact, about 85 percent of chronic drug abusers are not in drug abuse treatment at any given time.

To reach that 85 percent, NIDA launched research to develop community-based outreach interventions to reduce the spread of HIV. The National AIDS Demonstration Research (NADR) Program was the first multisite research program to deliver and evaluate HIV risk reduction outreach programs to drug abusers not in treatment. As part of the interventions, outreach staff indigenous to the selected communities met with IDUs in their natural settings to distribute HIV risk reduction information and offer additional counseling and HIV testing. The outreach workers acted as credible messengers, provided risk reduction materials and education, and arranged for IDUs to receive free, private HIV testing and counseling. The ongoing Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program uses similar behavioral interventions to reduce HIV risk taking and increase protective behaviors.

“Drug abuse treatment, prevention, and community-based outreach programs can change behaviors to decrease the risk of HIV/AIDS.”

These programs and other NIDA-funded research have helped identify intervention models that enable IDUs to reduce their drug use, needle-sharing practices, unsafe sex behaviors, and, importantly, their HIV infection rates.

For example, a 4-year study at one of the first NADR projects in Chicago used ex-addicts to deliver HIV prevention services such as HIV testing and counseling. IDUs who were exposed to the intervention showed a significant decrease in the rate of new HIV infections. This is just one illustration of how outreach can help IDUs not in treatment change their HIV risk behaviors.

While we continue to fund research on interventions that change behaviors and prevent HIV transmission, we are also studying how to link HIV-infected drug abusers to the medical care they need for their HIV and related illnesses. Other NIDA-funded research is examining ways to increase drug abusers' compliance with medical treatment. Long-term studies are examining the influence of drug use on the progression of HIV and on the effectiveness of medical treatment.

We are also funding research that is examining the special needs of HIV-infected women who are drug abusers. Unfortunately, with AIDS now being the fourth leading cause of death among women 15 to 44, the need is greater than ever to address the multitude of issues concerning this population. Among other things, NIDA-funded

research is investigating the impact of drug use on maternal-infant HIV transmission, the course of the disease in drug-abusing women and their infants, and treatment with HIV medications to reduce transmission.

Given the public health implications of HIV/AIDS and drug abuse, NIDA must work to disseminate its research findings to the public health community at large. NIDA is teaming with the Centers for Disease Control and Prevention to reach their network of public health professionals in order to inform them what NIDA's research is showing about the inextricable link between these two diseases.

Despite substantial progress in HIV/AIDS prevention with drug abusers, unacceptably high numbers of new HIV infections are occurring in drug abusers, their sex partners, and their children. Many drug abusers still are engaging in high risk practices. To curtail or reverse this trend, NIDA will continue to build a comprehensive research portfolio that will respond to the changing dynamics of the AIDS epidemic. Equipped with the knowledge that drug abuse treatment, prevention, and community-based outreach programs can change behaviors to decrease the risk of HIV/AIDS, NIDA is in a position to develop the most innovative and effective programs possible through its research. **NN**

CDC Report Highlights Link Between Drug Abuse and Spread of HIV

By Neil Swan, *NIDA NOTES* Staff Writer

An extensive review of existing research data confirms that behavior associated with drug abuse is the single largest factor in the spread of HIV/AIDS in this country. Half of all new infections with HIV, the virus that causes AIDS, now occur among injecting drug users (IDUs), according to the data review, which was conducted at the Centers for Disease Control and Prevention (CDC) in Atlanta.

The study focused on three groups recognized as being at highest risk for transmission of HIV: IDUs, men who have sex with men, and heterosexual men and women who are at risk because they have sex with IDUs and/or bisexual or gay men. The review used data gathered from America's 96 largest cities, where HIV infection rates are the highest in the Nation. The trends in HIV infection rates found in these cities also apply to the Nation's population in general, says the CDC reviewer Dr. Scott D. Holmberg.

Most newly HIV-infected IDUs live in northeastern cities from Boston to Washington, DC, as well as in Miami and San Juan, Puerto Rico, reports the CDC reviewer. In these cities, where injection drug use rates are also the highest among the 96 cities surveyed, an average of 27 percent of all IDUs are HIV-infected.

"These data confirm and underscore the connection between injection drug use and the continuing spread of HIV and AIDS," says NIDA Director Dr. Alan I. Leshner. "Drug abuse and HIV are truly interlinked epidemics."

"The information further demonstrates that NIDA has a critical role indeed in addressing the drug abuse-HIV connection and in focusing scientific research to understand and deal with the further spread of this devastating disease," he says.

The data confirm earlier figures from periodic CDC reports on the number of newly diagnosed cases of AIDS and HIV infection, which suggested that the proportion of new HIV cases linked to drug abuse was close to one-half. (See "NIDA Plays Key Role in Studying Links Between AIDS and Drug Abuse," *NIDA NOTES*, May/June 1995, p. 1.)

Dr. Holmberg set out to estimate the size and direction of the HIV epidemic in major U.S. cities with populations greater than 500,000. He compiled a large computer model for tracking disease trends by reviewing more than 350 documents, several large research data sets, and information from 220 public health authorities. Some of the reports date back 10 or more years.

The 96 metropolitan areas Dr. Holmberg looked at have an estimated 1.5 million IDUs, 1.7 million gay and bisexual men, and 2.1 million at-risk heterosexuals. Among these three risk groups there are currently an estimated 565,000 HIV infections, with 38,000 new infections occurring each year. Using these data to make nationwide projections, the review concludes that there are about 700,000 current HIV infections, with 41,000 new HIV infections occurring each year in the U.S. population.

HIV Infections Among At-Risk Populations In America's 96 Largest Cities

Risk Group	Estimated Number in Risk Group	Estimated Percent HIV Positive	Estimated New HIV Infections Each Year Per 100 Group Members
Injecting Drug Users	1.5 million	14.0%	1.5
Men Who Have Sex With Men	1.7 million	18.3%	0.7
At-Risk Heterosexuals*	2.1 million	2.3%	0.5

* Men and women who are at risk because they have sex with injecting drug users and/or bisexual or gay men.

Chart shows percentages of at-risk groups in major cities who tested positive for HIV. Estimates were compiled in 1996.

An estimated 19,000 IDUs are infected each year in these 96 metropolitan areas, indicating an HIV incidence rate of about 1.5 infections per 100 IDUs per year, Dr. Holmberg reports. Infection rates are lower for the other two high-risk groups. Although gay and bisexual men still represent the group with the greatest number of current HIV infections, the rate of infection—except in young and ethnic/minority gay men—is much lower now than it was a decade ago, Dr. Holmberg reports. For gay and bisexual men, the HIV infection rate per 100 persons per year is 0.7; for at-risk heterosexuals—those who have sex with IDUs or gay and bisexual men—the rate is 0.5 infections per 100 persons per year. At-risk heterosexual women outnumber at-risk heterosexual men about 4 to 1.

In the research review, HIV incidence rates for metropolitan areas were broken down by estimated numbers of HIV-infected people in each of the three at-risk groups. An estimated HIV infection rate for each group in each city was also provided. “This is highly valuable epidemiological information for better targeting prevention strategies,” says Dr. Leshner.

“The HIV epidemic is now clearly driven by infections occurring among injecting drug users, their sex partners, and their offspring,” concludes Dr. Holmberg in his review. However, NIDA-funded efforts to educate IDUs to modify their risky drug use behaviors have proven effective, he says. Evidence shows that HIV infection rates

in injecting drug users have declined over the past several years in the largest drug-using communities, he reports.

In cities in New York and northern New Jersey, the epicenter of the AIDS epidemic among injecting drug users, many IDUs are switching to practices that may lessen their risk of contracting HIV, such as using sterile, never-used needles and syringes; cleaning needles and paraphernalia; sniffing rather than injecting heroin and cocaine; or abstaining from drug use altogether. This shows that drug abuse and AIDS prevention programs targeting IDUs are working, Dr. Holmberg says.

His review further illuminates the link between the AIDS epidemic and drug abuse as primarily a public health issue. Within this public health perspective, the CDC scientist’s review also provides important insights for policymakers, clinicians, and administrators who are planning and implementing drug abuse and HIV prevention and treatment programs. Targeting HIV treatment and prevention programs to IDUs also holds potential for reducing the spread of other blood-borne infections, including hepatitis B and C viruses.

Source

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Mental Health Problems of Addicted Mothers Linked to Infant Care and Development

By Robert Mathias, *NIDA NOTES* Staff Writer

Women who abuse cocaine while they are pregnant often share many characteristics, such as addiction, poverty, and low literacy levels. However, they differ in the quality of care they give their children, a NIDA-funded study says. In fact, how well cocaine-addicted mothers care for their infants appears to be strongly influenced by the type and severity of psychological problems these women suffer from, according to the study. The quality of care these mothers provide is important because it affects the cognitive development of their cocaine-exposed infants, the study notes.

“Self-reported symptoms of psychological problems among addicted women really did affect maternal caregiving,” says Dr. Judy Howard of the University of California at Los Angeles (UCLA), who directed the study. This finding indicates that drug abuse treatment programs should work on other issues, such as mental health problems, in addition to helping addicted mothers become abstinent, Dr. Howard says.

The UCLA study of cocaine-addicted women and their infants was one of NIDA’s Perinatal-20 treatment research demonstration projects. The 5-year program, which ended last year, evaluated the effectiveness of providing comprehensive therapeutic programs that include drug abuse treatment plus a range of additional social and health services for drug-abusing women of child-bearing age and their children. The projects in the program have yielded new information about the characteristics and treatment needs of pregnant and parenting women who abuse drugs. (See “NIDA’s Perinatal-20 Projects,” *NIDA NOTES*, November/December 1994, p. 6.)

The cocaine-abusing women in the study, which was conducted by Dr. Howard and Dr. Leila Beckwith, also of UCLA, were similar demographically to the women in many of the other Perinatal-20 projects. On average, they were about 29 years old, had less than a high school education, were single, had a history of being physically or sexually abused, and belonged to minority groups. The women had a long history of cocaine and other drug abuse.


Despite their similarities, including heavy drug use, “these women are not a homogeneous group,” stresses Dr. Howard. The women in this study exhibited a wide range of psychological symptoms and maternal caregiving abilities that affected the development of their infants, she says. Specifically, mothers who reported more symptoms of a narcissistic, paranoid, histrionic, or borderline personality disorder were the least sensitive caregivers. In turn, many of these mothers’ babies showed signs of delayed cognitive development at 6 months of age, Dr. Howard notes.

Recently, Dr. Howard and her colleagues conducted a further analysis of the data collected about the women’s drug use and parenting behaviors 6 months after they gave birth. That analysis indicates that although the women who exhibited the most severe psychological symptoms reduced their drug use, they were still the least sensitive caregivers.

“These findings suggest a clinically significant relationship between a mother’s psychopathology and her ability to care for her newborn, which, in turn, might negatively affect her child’s development,” says Dr. Elizabeth Rahdert, a research psychologist with NIDA’s Division of Clinical and Services Research, who has been involved with the Perinatal-20 program since its inception. In addition, the finding that many of these women have severe mental health problems suggests that treatment programs should include a psychiatric component to assess and address women’s mental health problems on an individual basis, Dr. Rahdert says. Social service programs that do not have mental health professionals on their staff can make sure women receive the therapy they need by establishing strong links to the mental health care system within their communities, says Dr. Rahdert.

Mental health professionals should play a key role in drug treatment for drug-abusing mothers, agrees Dr. Howard, but they need to be trained in addiction-related problems, she says. In the final analysis, the study’s findings argue for comprehensive treatment programs and coordination of addiction treatment, mental health, and pediatric services to adequately meet the needs of these women and their children, concludes Dr. Howard.

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National Survey of Drug Use During Pregnancy Available

Copies of NIDA's *National Pregnancy and Health Survey*—a national assessment of the extent of drug use by women during pregnancy—are available free from the National Clearinghouse for Alcohol and Drug Information (NCADI).

The survey findings show that an estimated 5.5 percent of the 4 million women who gave birth in the United States in 1992 used illegal drugs while they were pregnant. The survey results provide vital information for physicians and other health practitioners, public health policymakers, lawmakers, and drug abuse prevention and treatment practitioners.

The survey, which was published in 1996, notes that the data may actually underestimate true rates of drug use but adds that the findings clearly indicate that “a substantial number of newborns were exposed to harmful substances in utero.” (The survey results are summarized in “NIDA Survey Provides First National Data on Drug Use During Pregnancy,” *NIDA NOTES*, January/February 1995, p. 6.)

The 460-page publication contains estimates on the number of women who used drugs during pregnancy, their demographic characteristics, and their patterns of drug use. For example, the survey report provides drug use estimates by race and ethnicity, age, marital status, employment condition, and method of hospital payment.

The survey gathered information from self-report questionnaires filled out by a national sample of 2,613 women who delivered live babies in 52 urban and rural hospitals during 1992. The data indicate that an estimated 221,000 women who gave birth that year had used illicit drugs while they were pregnant. The two illicit drugs most frequently used during pregnancy were marijuana, by 2.9 percent of all women who gave birth, and cocaine, by 1.1 percent.

The survey found that 20.4 percent of women delivering live babies smoked cigarettes and 18.8 percent drank alcohol during pregnancy. Significantly, the survey also revealed a strong link between the use of cigarettes and alcohol and the use of illicit drugs. This finding emphasizes the need for doctors and other practitioners to closely monitor the use of both licit drugs—cigarettes and alcohol—and illicit drugs during pregnancy, say public health authorities.

The survey report provides detailed information on the results of urine testing and on the design and execution of the survey. It also makes recommendations for improving the design of similar surveys.

The publication, *National Pregnancy and Health Survey—Drug Use Among Women Delivering Livebirths: 1992*, is available from NCADI, P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686, TDD: (800) 487-4889. Ask for NCADI publication No. BKD192. **NN**

Type A or B? Classification May Help in Treating Cocaine Abuse

By Neil Swan, NIDA NOTES Staff Writer

For a number of years, researchers have been testing the concept of classifying, or subtyping, alcoholics as Type A or Type B. Now they are finding the concept useful in studying cocaine abusers, too.

Subtyping is a system for classifying and studying individuals who share one or more common characteristics. Subtyping alcoholics provides a greater understanding of the complex interactions between genetic, personality, and environmental risk factors in the development of alcoholism, as well as resiliency against succumbing to these risk factors.

This typing process for alcoholics assesses multiple characteristics of each client, such as factors leading to abuse, severity of symptoms, and consequences of heavy drinking. By typing alcoholics as A or B using defining characteristics, researchers can better sort out the factors associated with their abuse problems and devise appropriate treatment strategies.

Alcohol abuse is more severe among Type B alcoholics than among those who are Type A. Type B alcoholism appears to be more related to hereditary factors than Type A and to be more likely to occur among men than women. Type Bs are more impulsive and tend to have a stronger family history of alcohol abuse; they have more childhood conduct problems and more severe alcohol dependence, polydrug abuse, and psychiatric disorders, especially antisocial personality.

Inspired by advances in subtyping alcoholics, Dr. Samuel A. Ball of Yale University School of Medicine and his colleagues conducted a NIDA-funded study examining whether subtyping is valid for cocaine abusers as well. They found strong evidence that it is.

“Our research may prove useful in explaining different causes of abuse in different types of cocaine abusers,” says Dr. Ball. “We found that certain vulnerability factors, such as family history, sensation-seeking behavior, and childhood conduct problems, seem to predispose cocaine users to a more virulent form of cocaine dependence—Type B,” he explains. “Other cocaine abusers who don’t have these characteristics [Type As] may develop their cocaine dependence more from social or environmental influences relative to inherited, temperamental, or psychiatric influences.”

Classifying Cocaine Abusers

	TYPE A	TYPE B
Cause of Abuse Problem	More Environmental	More Genetic
Gender	Equal Male/Female	More Male
Personality	Low Impulsivity and Sensation Seeking, High Harm Avoidance	High Impulsivity, Sensation Seeking
Childhood Factors	Few Early Risk Factors	Conduct Disorder
Age of Onset	Later	Earlier
Substance Abuse Severity	Less Severe, More Episodic	More Chronic and Severe; Polydrug
Psychopathology	Lower Severity, More Affective	Higher Severity, More Antisocial

After years of studies, researchers are able to identify factors that classify alcoholics as Type A or Type B. Recent NIDA-funded studies show that, in general, the same multiple criteria are valid in classifying cocaine abusers. Results may prove useful in explaining different causes of abuse and in designing specific prevention and treatment interventions.

The researchers studied abuse characteristics in 399 cocaine abusers, 69 percent of whom were male. Of these, 298 had sought treatment, 149 in an outpatient treatment program and another 149 in an inpatient, hospital-based program. The remaining 101 were cocaine abusers not in treatment. The study participants had a median age of 28 and were, generally, single, high school graduates, and had a low socioeconomic status. Fifty percent were white, 48 percent were African American, and 2 percent were Hispanic.

As part of a larger diagnostic study of cocaine abusers, for which Yale University’s Dr. Bruce J. Rounsaville was principal investigator, participants were given a battery of standard assessment tests that included the Sensation Seeking Scale, the Addiction Severity Index, the Schedule for Affective Disorders and Schizophrenia, and Family History Research Diagnostic Criteria tests. Subsequently, Dr. Ball and his colleagues sorted these measures into three variables, similar to the factors generally used to categorize alcoholics:

- predisease risk factors, such as family history of substance abuse, childhood conduct disorder and attention-deficit disorder, sensation-seeking traits, and age when drug abuse began;

- substance abuse variables, including frequency of cocaine use, years of heavy cocaine use, cocaine dependence symptoms, alcohol dependence symptoms, polydrug use, and medical and social consequences; and
- psychiatric problems, such as symptoms of depression and antisocial personality disorder, and the severity of these psychiatric problems.

Based on placement within the variables identified by the assessment tests, the researchers classified the cocaine-abusing study participants as either Type A or Type B and then examined differences in behavioral and other characteristics between the two groups.

Researchers found that cocaine abusers classified as Type B scored higher than Type As in assessments of sensation seeking, aggression, criminality, violence, and impairment of social adjustment. Type Bs also used greater amounts of cocaine more frequently and for longer durations than Type A cocaine abusers. Type Bs also suffered more adverse effects from their drug use, such as unconsciousness, chest pain, and violence, and they reported a greater degree of additional drug abuse to relieve withdrawal distress. Type B abusers became involved with cocaine at younger ages for: first use, first binge, first regular use, first daily use, and first symptoms of addiction.

No differences were found between the two subtypes in regard to the length of time between first use of cocaine and first symptoms of dependence; route of use, such as snorting, smoking, or injection; number of strategies used in attempting to control use; and previous periods of abstinence from illicit drugs or alcohol.

Overall, more than half of the participants were classified as Type As, but among those in inpatient treatment, there were nearly equal numbers of Type As and Bs. Among the outpatient and not-in-treatment participants, 75 percent were Type A. This suggests that studies assessing only cocaine abusers who are enrolled in inpatient treatment may not provide valid estimates of the relative proportion of Type A and B abusers who are in outpatient treatment or not in treatment, Dr. Ball warns.

With few exceptions, the classification model assessment results seemed consistent across gender and race. Although women and African Americans were Type As more often than men and whites were, a significant number of women and African Americans showed the kind of Type B abuse risk factors, severity, impairment, and antisocial behavior that some researchers had previously thought were related to alcoholism among men and among whites.

Percentages of Type A and Type B Cocaine Abusers

	TYPE A	TYPE B
Males	61%	39%
Females	79%	21%
African American Males	68%	32%
African American Females	86%	14%
White Males	57%	43%
White Females	78%	22%

A classification of cocaine abusers by Dr. Samuel A. Ball shows results similar to these found in many studies of alcoholics. Although women and African Americans are more often Type As compared to men and whites, a significant number of women and African Americans nevertheless show the kind of Type B abuse risk factors, severity, impairment, and antisocial behavior thought by some earlier researchers to be related to alcoholism among men and among whites.

“If Type A substance abuse is in fact more influenced by social relationships and environment, relative to genetic and personality factors, then we might speculate that women and African Americans might be more susceptible to developing alcohol or cocaine addictions for more socially, environmentally, or culturally determined reasons,” says Dr. Ball. But future research is needed on this topic to determine if this typology holds in other ethnic groups such as Latinos/Hispanics, Asians, and Native Americans, as well as in other cultures and countries, he adds.

Dr. Rounsaville, who coauthored the study, notes that while there has been some experimental work using typology-based treatment and prognostic findings, the practice of assessing and classifying substance abusers as Type A or B is not now widely practiced in drug abuse treatment programs. For one thing, classification procedures must be validated and made suitable for simple, routine use in treatment programs. But typology research continues with hope that advances can lead to new insights for evaluating causes of substance abuse and for preventing and treating it in the treatment program setting, he adds.

Sources

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Drug Use During Pregnancy Associated With Increased Risk of Transmitting HIV to Infants

By Robert Mathias, *NIDA NOTES* Staff Writer

A national, multicenter study has found that HIV-infected women who used illicit drugs during pregnancy had a higher risk of transmitting HIV to their infants than did HIV-infected women who did not use drugs while pregnant.

The study, known as the Women and Infants Transmission Study (WITS), was launched in 1989 by the National Institute of Allergy and Infectious Diseases (NIAID) to track the natural history of HIV in infected women and their infants. The study currently is funded by NIAID, NIDA, and the National Institute of Child Health and Human Development.

In the study, researchers analyzed data on 530 HIV-infected pregnant women and their infants who were treated in obstetric and pediatric clinics in five cities across the United States. The analysis showed that the HIV perinatal transmission rate for women who used drugs during pregnancy was 27 percent compared with a 16 percent transmission rate among HIV-infected women who did not use drugs. Forty-two percent of the women in the study used illicit drugs during pregnancy; 44 percent of those women used multiple drugs. The most commonly used drug was cocaine, used either alone or in combination with other drugs.

The study's findings emphasize the critical role of drug abuse treatment in prenatal health care for HIV-infected

pregnant women who use drugs, according to Dr. Evelyn M. Rodriguez of the Health Resources Services Administration and her colleagues in the WITS. The WITS findings also underscore the importance of ensuring that all HIV-infected women receive information on how AZT (zidovudine) treatment during pregnancy can significantly reduce perinatal transmission of HIV, the researchers conclude.

Large multisite studies such as the WITS enable researchers to investigate both the behavioral and basic biological factors that may contribute to maternal-infant transmission of HIV, according to Dr. Vincent Smeriglio and Katherine Davenny of NIDA's Division of Clinical and Services Research, who are members of the WITS research staff. Further research is planned to verify the association between maternal drug use and infant HIV infection and to clarify the possible mechanisms of this association, they indicate.

Source

- Rodriguez, E.M.; Mofenson, L.M.; Chang, B.H.; Rich, K.C.; Fowler, M.G.; Smeriglio, V.; Landesman, S.; Fox, H.E.; Diaz, C.; Green, K.; and Hanson, I.C. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS* 10(3):273-282, 1996. **NN**

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

- Lukas, S.E.; Sholar, M.B.; Lundahl, L.H.; et al. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. *Psychopharmacology* 125(4):346–354, 1996. **NN**

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 marijuana

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."

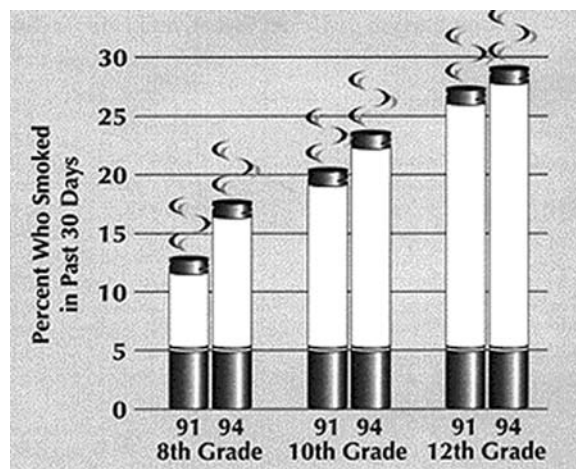
In previous research, Dr. Kandel had examined the intergenerational effects of drug use by following a cohort of New York State adolescents who were periodically reinterviewed over the course of 19 years. That research indicated that a mother's cigarette smoking had a greater effect than a father's on 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 followup 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.

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 confirmed the findings from the New York State survey, says

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.

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

- Kandel, D.B.; Wu, P.; and Davies, M. Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health* 84(9):1407–1413, 1994. **NN**

31% of New York Murder Victims Had Cocaine in Their Bodies

By Neil Swan, *NIDA NOTES* Contributing Writer

Nearly 3 out of every 10 homicide victims in New York City in the early 1990s had evidence of cocaine in their bodies when they died. Overall, murder victims in the city are 10 to 50 times more likely than members of the general population to be cocaine users, depending on age, race, and gender, according to NIDA-funded research using data from the New York City medical examiner.

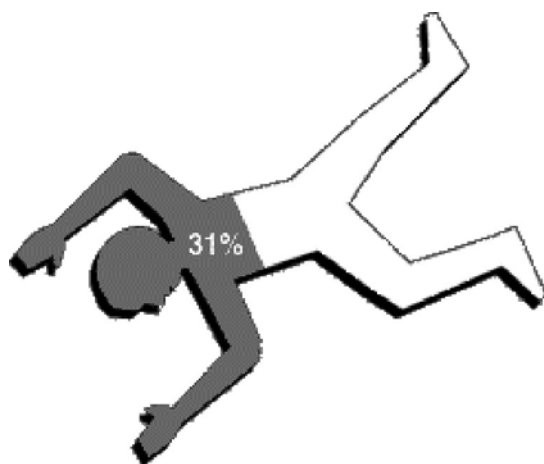
Dr. Kenneth Tardiff of Cornell University Medical College in New York City headed a team of researchers that studied the 4,298 homicides that occurred in New York City during 1990 and 1991. Cocaine was found in the bodies of 31 percent of the victims. About three-fourths of all the murders involved firearms.

“Homicide victims may have provoked violence through irritability, paranoid thinking, or verbal or physical aggression, which are known

to be pharmacologic effects of cocaine,” the researchers hypothesized. Drug dealers’ efforts to protect their sales territories from invading competitors also promote violence and homicide, they suggested.

Young African-American and Latino men were more likely to be victims of homicide than were members of all other demographic groups, the study found. Two-thirds of the victims were between the ages of 15 and 34, 86 percent were male, and 87 percent were African American or Latino. The rate of homicide was highest for African-American males ages 15 to 24, followed by African-American males ages 25 to 34. The next highest homicide rates were among young Latino men ages 25 to 34 and 15 to 24, respectively.

African-American women and Latino women had much lower rates of death by homicide than their male counterparts.



Cocaine was found in 31 percent of the 4,298 people murdered in New York City in 1990 and 1991.

Percentage of New York City Homicide Victims in 1990 and 1991 Positive for Cocaine Metabolites in Each Age Group by Gender and Race*

Age in Years	White		African American		Latino		Asian/Other		Total (n=3,890)
	Male (n=272)	Female (n=74)	Male (n=1,583)	Female (n=276)	Male (n=1,344)	Female (n=184)	Male (n=138)	Female (n=19)	
14 or under	0	25.0	2.4	0	3.7	0	0	0	4.1
15-24	18.4	16.7	18.9	35.6	23.7	28.1	8.6	0	21.5
25-34	37.5	59.1	44.4	71.8	43.4	36.1	4.9	0	43.9
35-44	34.0	26.7	49.3	40.8	42.0	31.0	12.1	0	40.9
45-54	12.2	0	27.8	20.0	26.4	14.3	0	0	20.7
55 or over	2.3	0	14.0	0	16.3	0	0	0	7.2
Total	22.4	25.7	31.6	39.5	39.9	27.7	6.5	0	31.0

* Denominators include only cases in which there were toxicologic analyses for benzoylecgonine, a cocaine metabolite, and in which the interval between injury and death was 48 hours or less.

This table was adapted from an article that appeared in *The Journal of the American Medical Association*, Vol. 272, No. 1, July 6, 1994, pp. 43-46. Copyright 1994, American Medical Association.

Characteristics of Homicide Victims Killed in 1990 and 1991 in New York City (Residents Only)

Characteristics	# of Cases	% of All Homicides
AGE IN YEARS		
Less than 1	46	1.1
1-14	93	2.2
15-24	1,442	33.7
25-34	1,457	34.0
35-44	693	16.2
45-54	289	6.8
55-64	126	2.9
65 and older	132	3.1
Total	4,278*	100.0
GENDER		
Male	3,682	85.7
Female	614	14.3
Total	4,296*	100.0
RACE		
White	402	9.4
African American	2,069	48.2
Latino	1,648	38.4
Asian/other	171	4.0
Total	4,290*	100.0
CAUSE OF DEATH		
Firearms	3,131	72.8
All other methods	1,167	27.2
Total	4,298	100.0

* Numbers are less than 4,298 because of unknowns for age, gender, and race.

This table was adapted from an article that appeared in *The Journal of the American Medical Association*, Vol. 272, No. 1, July 6, 1994, pp. 43-46. Copyright 1994, American Medical Association.

However, their rates were slightly higher than those of white males, particularly in the 15- to 34-year-old age group. White females had the lowest homicide rates of any demographic group.

Among some of the young demographic groups of victims, cocaine use surprisingly was higher among females than among males. For example, 59 percent of white women and 72 percent of African-American women ages 25 to 34 had been using cocaine before they died compared with 38 percent of white men and 44 percent of African-American men in that age group. This “high proportion” of cocaine users among white and African-American female homicide victims is contrary to surveys showing that women in general are less likely to be drug users and shows that drug use is a key risk factor for homicide victimization among women, the study authors said. “It is possible that female users of cocaine are more likely than nonusers to be victims of violence from spouses, boyfriends, or, in the case of prostitutes, their clients,” said the researchers.

The investigators attributed the high homicide rate they found among African Americans and Latinos to the increased availability and abuse of crack cocaine and the increased availability and lethal firepower of guns.

“There is no clear answer as to how we can decrease the heavy use of cocaine, particularly in our cities,” the researchers said. “There is a major need for public treatment programs, but these will be very expensive, and treatment for cocaine addiction has no methadone analog yet. Prevention programs aimed at schools require adequate evaluation.”

Source

- Tardiff, K.; Marzuk, P.M.; Leon, A.C.; Hirsch, C.S.; Stajic, M.; Portera, L.; and Hartwell, N. Homicide in New York City: Cocaine use and firearms. *JAMA* 272:43-46, 1994. **NN**

NIDA Expands Its Research on Addiction and Women's Health

By Robert Mathias, NIDA NOTES Staff Writer

Women's health, long neglected in medical research, stepped into the spotlight at a NIDA-sponsored conference held last September to assess the current state of scientific knowledge about addiction and women's health. In addition to showcasing what is known about women and drug abuse, NIDA hosted the conference to identify the many gender-related issues that the field of drug abuse research needs to address to meet the health needs of women.



NIDA is expanding its research on women to gain a better understanding of drug abuse and addiction and their impact on women's health.

Some photos taken from NIDA videotape "Door to Recovery."

Health of Women. "We want to know what we have missed. We want to know what we can do to improve our research priorities with regard to women. And, most of all, we want to improve the situation for those women who are suffering from drug addiction," said Dr. Finnegan, who now directs the Women's Health Initiative at the National Institutes of Health.

NIDA Director Dr. Alan I. Leshner told conference participants that NIDA is placing a high priority on research on drug addiction among women, noting that "historically, drug abuse research has focused primarily on men, as has most health research. Drug abuse may present significantly different challenges to women's health, may progress

"NIDA wants to hear from you," Dr. Loretta P. Finnegan, NIDA's former senior advisor on women's issues, told the nearly 200 scientists, health care professionals, treatment practitioners, representatives of women's groups, and policy and program staff from NIDA and other Federal agencies who attended the landmark conference on Drug Addiction Research and the

"Drug abuse may present significantly different challenges to women's health, may progress differently in women than in men, and may require different treatment approaches."

differently in women than in men, and may require different treatment approaches. And that, of course, is why we're here," Dr. Leshner said.

"Not only does this conference mark the demise of male-only research, it also signals a new era in NIDA's approach to research on women," said Richard A. Millstein, NIDA's deputy director. "While we can say with some accuracy that NIDA has had a long history of studying women and gender differences, the fact is that most of those studies have been among pregnant women and their offspring," Millstein said. "We need to expand beyond that to look at women independently, not just in relation to their status as mothers of children," he said.

Conference participants from a wide range of disciplines heeded the call from NIDA policymakers to raise the critical questions that the Institute needs to address as it expands its research agenda on women, drug abuse, and addiction. For 2 1/2 days, scientists and practitioners presented gender-related findings from epidemiologic, basic, clinical, and health services research studies and discussed the implications of these findings for the prevention and treatment of drug abuse, addiction, and related diseases such as HIV/AIDS among women. The fact that nearly 70 percent of AIDS cases among women are drug related coupled with the rapid rise of AIDS among women makes it imperative that we address drug abuse problems in women, said Dr. Mary Jeanne Kreek, a NIDA-funded researcher at Rockefeller University, in her keynote address to the conference.

Conference presentations covered such topics as:

- the nature and extent of drug abuse among women. Speakers pointed to a lack of reliable epidemiological data on drug abuse among different groups of minority women and among women of different sexual orientation;

- the many factors thought to be involved in the etiology of drug use among women, including childhood and adolescent sexual victimization, partner violence, and anxiety disorders and depression, which are much more prevalent among women than men;
- a history of inadequate and inappropriate treatment of women's anxiety and affective disorders, resulting in overprescription and abuse of psychotherapeutic medications;
- biological and behavioral mechanisms that may underlie women's patterns of drug use and differences in how drugs affect men and women. For example, animal and human studies indicate a possible link between the menstrual cycle of women addicts and drug seeking;
- the medical and health consequences of drug abuse, which include disruption of women's menstrual cycles, reproductive function, and immune function and a high risk of contracting HIV/AIDS;
- the psychiatric consequences of drug abuse, which include phobic, depressive, and antisocial personality disorders;
- the social and behavioral consequences of drug abuse, such as homelessness and high-risk sexual behaviors;
- the legal consequences of drug abuse, such as the criminalization and prosecution of drug-abusing mothers, particularly those from minority groups;
- the impact of negative social, economic, and legal circumstances on drug abuse and addiction among African-American, Native-American, Hispanic, Asian/Pacific Islander, and lesbian women.

Taken together, conference presentations underscored that the causes, correlates, pharmacokinetics, mechanisms, and consequences of drug abuse and addiction vary considerably in men and women. Yet, as a number of speakers pointed out, most drug abuse prevention and treatment interventions have been shaped by men's characteristics and needs.

Drug abuse prevention and treatment interventions for girls and women need to respond to specific gender-based risk factors, such as childhood sexual abuse, partner violence, and the prevalence of anxiety and depressive disorders, a number of researchers said. For example, the high incidence of anxiety and depression among women suggests that psychosocial and behavioral treatments might be particularly effective for women, said Dr. Karla Moras of the University of Pennsylvania.

Researchers and practitioners alike also need to acknowledge that women who abuse drugs are not a homogeneous group, noted several conference participants. Adolescents, pregnant women, housewives, older women, women from different ethnic groups, and lesbians may all experience significant variations in the factors that lead to drug abuse and addiction. For example, the effects of racism and community violence may contribute to making African-American women more vulnerable to depression and substance abuse. In like manner, a disproportionately large percentage of lesbians appear to suffer from drug and alcohol disorders that may be related to their having to deal with negative societal responses to their sexual orientation, said Marj Plumb of the National Center for Lesbian Rights.

Overall, NIDA's conference on addiction and women's health indicated that "despite some promising findings, the basic take-home message is that there are more gaps in knowledge about women in all areas of drug abuse research than there are findings," said Millstein. NIDA plans to start filling those gaps by incorporating into its agenda recommendations from conference participants that the Institute support more research on the impact of women's biology, environment, relationships, and experiences on health behaviors, Millstein said.

"As we all strive to move the concerns of women to a higher level in our overall priorities, we can be proud that we've done so much. But, we have a great deal more to accomplish," summed up Dr. Finnegan, who headed the NIDA Women's Advisory Committee, which organized the conference. **NN**

NIDA Survey Provides First National Data on Drug Use During Pregnancy

By Robert Mathias, NIDA NOTES Staff Writer

More than 5 percent of the 4 million women who gave birth in the United States in 1992 used illegal drugs while they were pregnant, according to the first nationally representative survey of drug use among pregnant women. The NIDA-sponsored survey, which was released last fall, provides the best estimates to date of the number of women who use drugs during pregnancy, their demographic characteristics, and their patterns of drug use.

“Information from NIDA’s National Pregnancy and Health Survey can help to guide public health policymakers who have to make decisions about prevention and treatment programs aimed at reducing the problem of drug abuse during pregnancy,” said NIDA Director Dr. Alan I. Leshner. Dr. Leshner reported the survey’s findings at a press briefing held during NIDA’s conference on Drug Addiction Research and the Health of Women last September.

The survey gathered self-report data from a national sample of 2,613 women who delivered babies in 52 urban and rural hospitals during 1992. Based on these data, an estimated 221,000 women who gave birth in 1992 used illicit drugs while they were pregnant. Marijuana and cocaine were the most frequently used illicit drugs—2.9 percent, or 119,000 women, used marijuana and another 1.1 percent, or 45,000 women, used cocaine at some time during their pregnancy.

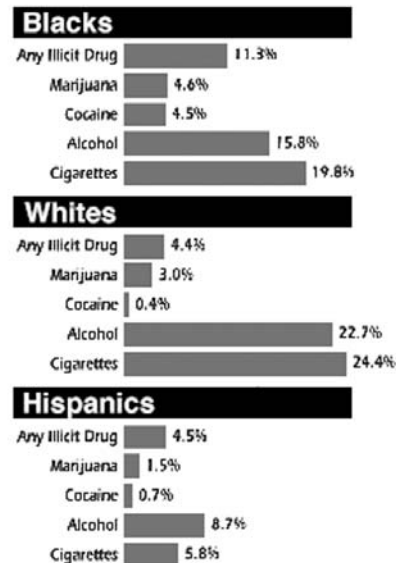
The survey found a high incidence of cigarette and alcohol use among pregnant women. At some point during their pregnancy, 20.4 percent, or 820,000, pregnant women smoked cigarettes and 18.8 percent, or 757,000, drank alcohol.

“We know for certain that these [legal] substances affect the health of the fetus and a woman during and after pregnancy,” said Dr. Loretta D. Finnegan, NIDA’s former senior advisor on women’s issues. Health care practitioners should ask women about their use of cigarettes and alcohol during prenatal checkups and educate them about the health risks of licit drugs, said Dr. Finnegan, who now directs the Women’s Health Initiative at the National Institutes of Health.

The survey found that an estimated 113,000 white women, 75,000 African-American women, and 28,000 Hispanic women used illicit drugs during pregnancy.

The survey also uncovered a strong link between cigarette smoking and alcohol use and the use of illicit drugs in this population. Among those women who used both cigarettes and alcohol, 20.4 percent also used marijuana and 9.5 percent took cocaine. Conversely, of those women who said they had not used cigarettes or alcohol, only 0.2 percent smoked marijuana and 0.1 percent used cocaine. “This finding reinforces the need for health practitioners to monitor the status of both licit and illicit drug use during pregnancy,” said Dr. Leshner.

Drug Use During Pregnancy* Among Racial and Ethnic Groups



*Percent of American women who gave birth in 1992 and used drugs during pregnancy



Besides providing the first national estimates of drug use during pregnancy, the survey also examined differences in the amount and types of drugs used by several racial and ethnic groups of women. Overall, 11.3 percent of African-American women, 4.4 percent of white women, and 4.5 percent of Hispanic women used illicit drugs while pregnant. While African Americans had higher rates of drug use, in terms of actual numbers of users, most women who took drugs while they were pregnant were white. The survey found that an estimated 113,000 white women, 75,000 African-American women, and 28,000 Hispanic women used illicit drugs during pregnancy.

The survey also described different patterns of licit and illicit drug use among white women and ethnic minorities. African-American women had the highest rates of cocaine use, mainly “crack,” during pregnancy. About 4.5 percent of African-American women used cocaine compared with 0.4 percent of white women and 0.7 percent of Hispanic women who did so.

White women had the highest rates of alcohol and cigarette use. Nearly 23 percent of white women drank alcohol and 24.4 percent smoked cigarettes. By comparison,

15.8 percent of African-American women and 8.7 percent of Hispanic women drank alcohol and 19.8 percent of African-American women and 5.8 percent of Hispanic women smoked cigarettes. “These findings point to the importance of attending to cultural issues in drug abuse prevention and treatment efforts,” said Dr. Finnegan.

Although women who used drugs during pregnancy generally decreased their rates of drug use throughout their pregnancy, they did not discontinue drug use, Dr. Leshner noted. “This finding indicates how gripping an illness drug addiction can be, even in the face of what may seem to be the ultimate incentive to stay drug free,” Dr. Leshner said. Nevertheless, “it is a disease that can be treated and managed with appropriate interventions,” he stressed.

“With the information the survey provides about the patterns of drug use by women during pregnancy, we will be better able to identify priorities we must address,” said Dr. Finnegan. This will enable researchers to develop and test more effective approaches to the differential drug abuse treatment and prevention needs of women of childbearing age, she concluded. **NN**

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 teach-

ers' 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.



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.

Dr. Brook and 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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Filling the Gender Gap in Drug Abuse Research

By Dr. Alan I. Leshner, NIDA Director

Drug abuse and addiction among women are major public health problems. More than 4.4 million women currently use illicit drugs, and women make up more than 37 percent of the illicit-drug-using population. Yet, as with the other major diseases of our time, most research on addiction has been conducted with men.

In recent years, the National Institutes of Health has implemented a new initiative to promote research on women's health. To ensure that the field of drug abuse is in the vanguard of this exciting new era of women's health research, NIDA is expanding its agenda to increase our understanding of drug abuse and addiction and their impact on women's health. Our expanded research on addiction and women's health will look at differences between men and women who abuse drugs. Across our entire research portfolio, from basic science to clinical applications, we will be supporting studies that examine gender differences in vulnerability and resilience to drug dependence; in metabolism and the effects of drugs; in the medical, behavioral, and social consequences of drug abuse; and in the prevention and treatment of drug abuse.

Most of what we already know about women and addiction has come from years of NIDA-supported research on drug abuse during pregnancy and the impact of a woman's drug use on her offspring. This research has been both needed and appropriate because drug abuse during pregnancy affects the health of more than 5 percent of all pregnant women and their children, according to NIDA's recently released National Pregnancy and Health Survey.

While continuing NIDA's research on prenatal drug abuse, we have been working to broaden the scope of this research to reflect the fact that drug abuse affects women regardless of their maternal role. In 1993, NIDA issued program announcements to stimulate research on the causes and consequences of drug abuse among women of all ages, to assess gender differences in the behavioral effects of abused drugs, and to promote studies of drug abuse treatment for women of childbearing age. NIDA's AIDS program announcements have addressed partner notification of HIV-infected drug users and strategies to reduce sexual practices that put women at risk of

contracting HIV. We have held technical reviews at which researchers discussed methodological issues in the study of drug abuse among women and the impact of drug abuse and HIV infection on women and children. And NIDA's Medications Development Division has worked to ensure that the percentages of women in our clinical trial of

potential drug abuse treatment medications reflect the gender makeup of the drug-abusing population.

Last September, NIDA's Women's Advisory Committee organized a landmark conference on drug addiction and women's health. At the conference, researchers and practitioners discussed what we know, what we don't know, and what we should be

doing to fill the gaps in our knowledge about women and drug abuse.

In response to recommendations from participants at our women's conference, we will be working to conduct more research on biological and behavioral mechanisms of drug abuse among women. And we will be considering the effects of race, ethnicity, sexual orientation, and psychological and socioeconomic circumstances on the use and abuse of drugs by women.

We also will be expanding our research on how addiction affects women's health, including how addiction affects the progression of AIDS in women. Nearly 70 percent of AIDS cases among women are related to their use of injecting drugs or to their having sex with an injecting drug user. NIDA's national AIDS community outreach programs have educated drug-dependent women about AIDS risk factors and strategies to change their high-risk behaviors. We are now emphasizing the need to explore the links between drug abuse and AIDS among women in all areas of our research agenda.

We already know that there are differences between men's and women's vulnerability to HIV infection and risk behaviors. Furthermore, AIDS appears to progress differently in men and women. We need to know why these differences exist to design more targeted interventions.

From the time they are diagnosed with HIV infection, women die of AIDS much more rapidly than men do. Research findings presented at NIDA's women's conference suggest this apparent accelerated course of

We will be expanding our research on how addiction affects the progression of AIDS in women.

HIV infection may occur because HIV-positive women enter treatment at much later stages of infection than men do. We need more research to find out why women infected with HIV wait so long before presenting themselves for treatment. Among the possible avenues for gender-based exploration are the role of social and cultural stigmas and the availability, accessibility, and appropriateness of AIDS treatment for drug-dependent HIV-positive women.

The expanded women's research program that we have launched reflects NIDA's commitment to filling the gender gap that exists in drug abuse research, prevention, and

treatment. To carry out that commitment, we have established a women's health issues group at NIDA to coordinate and monitor our women's research efforts. With the assistance and guidance of scientists, public health and drug abuse prevention and treatment practitioners, and the members of NIDA's national advisory bodies, we will be working to ensure that research on addiction and women's health ultimately reveals the biological and behavioral factors we need to address to improve drug abuse prevention and treatment for women. **NN**

About Women, Drug Abuse, and AIDS

- Almost half of all women in their childbearing years, ages 15 to 44, have used illicit drugs at least once in their lives.
- 10.3 million women age 12 and older have used at least one illegal drug in the past year.
- More than 4.4 million women age 12 and older currently use illegal drugs.
- 4 million women have taken prescription drugs non-medically during the past year.
- An estimated 221,000 women who gave birth in the United States in 1992 used illicit drugs while they were pregnant.

- AIDS is now the fourth leading cause of death among women ages 25 to 44 in the United States.
- More than 34,000—about 67 percent—of the AIDS cases among women are drug related.

Sources

- 1993 National Household Survey on Drug Abuse
- NIDA National Pregnancy and Health Survey
- Centers for Disease Control and Prevention
HIV/AIDS Surveillance Report, June 1994. **NN**

Drug Use During Pregnancy

NIDA's National Pregnancy and Health Survey, conducted during 1992, is the first national survey of drug use among pregnant women in the United States. The survey collected data from a representative sample of the 4 million women

who delivered babies during 1992. Data from the survey, presented in the chart below, provide the best estimates to date of the number of American women who use drugs during pregnancy and their patterns of drug use. **NN**

Substance Used	Percentage of Pregnant Women	Number of Pregnant Women
Any illicit drug ¹	5.5	220,900
Marijuana	2.9	118,700
Cocaine	1.1	45,100
Crack	0.9	34,800
Other cocaine	0.3	12,700
Methamphetamine	0.1	4,500
Heroin	0.1	3,600
Methadone	0.1	3,400
Inhalants	0.3	12,100
Hallucinogens	0.2	8,700
Nonmedical use of any psychotherapeutics ²	1.5	61,200
Amphetamines	0.0	1,200
Sedatives	0.3	10,300
Tranquilizers	0.0	1,900
Analgesics	1.2	48,700
Alcohol	18.8	756,900
Cigarettes	20.4	819,700
Medical use of any psychotherapeutics ³	10.2	412,300
Amphetamines	0.3	13,400
Sedatives	3.6	144,100
Tranquilizers	1.4	55,400
Analgesics	7.6	305,200

¹ Use of marijuana, cocaine (all forms), methamphetamine, heroin, methadone, inhalants, hallucinogens, or nonmedical use of psychotherapeutics during pregnancy.

² Nonmedical use of any prescription amphetamines, sedatives, tranquilizers, or analgesics during pregnancy.

³ Medical use of any prescription amphetamines, sedatives, tranquilizers, or analgesics during pregnancy.

