

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

By Robert Mathias
NIDA NOTES Staff Writer

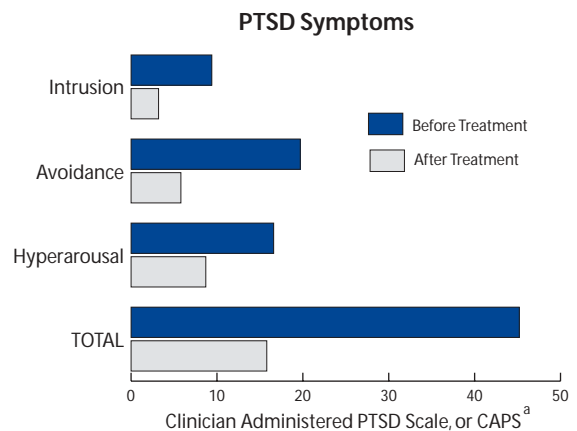
Many individuals who abuse cocaine, alcohol, and other substances also suffer from posttraumatic stress disorder (PTSD) related to life-threatening or other traumatic events they have experienced or witnessed. Individuals with PTSD suffer recurring flashbacks, anxiety, and other symptoms that can impede 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.” *continued on page 6*

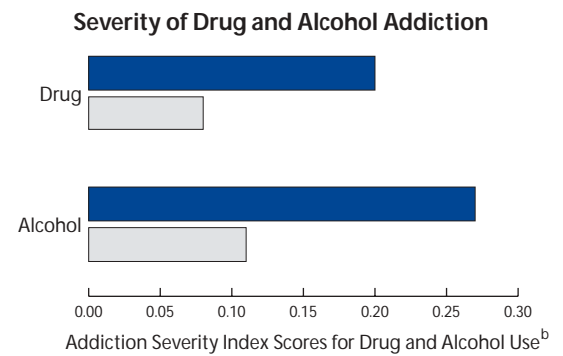
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Combination Psychotherapy Reduces Posttraumatic Stress Disorder (PTSD) Symptoms and Cocaine Use

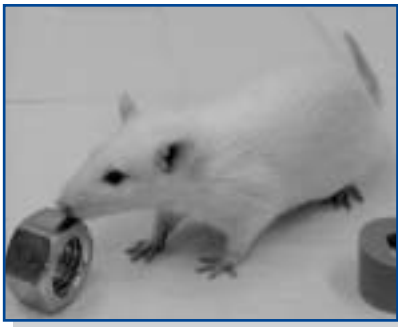


^aHigher scores indicate more frequent and intense PTSD symptoms



^bHigher scores indicate more severe drug and alcohol 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.



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A Double Dose of Research for Patients Addicted to Both Drugs And Alcohol

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

Addiction researchers and treatment professionals have long known that drug addiction and alcoholism are strongly linked. In the last decade, research has broadened our understanding of many shared neurobiological and behavioral mechanisms that underpin the two disorders. Yet, while two in five substance abuse treatment patients abuse both drugs and alcohol, the treatment they are likely to receive will target only one disorder. A lack of science-based information on concurrent treatment of drug and alcohol abuse limits the ability of treatment professionals to provide the comprehensive treatment these patients need.

Recent research suggests that some medications developed to treat drug or alcohol abuse may be useful for treating both problems. This information, along with our increased understanding of the underlying factors that drive drug and alcohol abuse, provides a strong rationale for a coordinated research effort to meet the critical need for treatments for people suffering from both disorders. Toward that end, NIDA and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) have issued a joint program announcement (PAS-03-029) to spur both drug and alcohol abuse researchers to investigate all aspects of pharmacological treatment for dually addicted patients.

Coordinated research on dually addicted patients will address the needs of the overwhelming number

of Americans who abuse both alcohol and illicit drugs. More than 2.4 million of the 5.6 million people who abused illicit drugs in 2001 also abused alcohol, according to the National Household Survey on Drug Abuse. In fact, the more heavily someone abused alcohol, the more likely he or she was to use illicit drugs, the survey found. In 2001, nearly two of every three American teenagers, ages 12 to 17, who engaged in frequent drinking binges also abused drugs. In comparison, only 1 in 20 young people who didn't drink at all used drugs.

The substantial portion of drug- and alcohol-abusing patients in community treatment programs provides additional evidence of the need for science-based information on treating dual addiction. Patients who abuse both drugs and alcohol accounted for more than 42 percent of admissions to substance abuse treatment facilities reported by State agencies in 2000, the last year for which these data are published. Alcohol abuse is even more likely among patients who abuse certain drugs, such as cocaine, methamphetamine, and marijuana. For example, more than half of cocaine-abusing patients who entered treatment in 2000 also abused alcohol.

To develop effective treatments for patients who abuse both drugs and alcohol, we need to understand why so many people do so. Part of the answer probably has to do with genes—underlying genetic variations that may play a role in common brain mechanisms that fuel both disorders.

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Recent research suggests that some medications developed to treat either drug or alcohol abuse may be useful in treating co-occurring substance abuse.

A Double Dose of Research for Patients Addicted to Both Drugs and Alcohol

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NIDA-supported brain imaging studies conducted at Brookhaven National Laboratory in Upton, New York, have documented similarities in the structure and function of the brains of alcoholics and chronic cocaine abusers that appear to be implicated in the abuse of both substances. Individuals with either disorder have low levels of dopamine D₂ receptors in the brain's reward pathways that may impair their capacity to derive

We aim to generate a broad spectrum of useful clinical information about appropriate sequencing or combining of medications and behavioral therapies, possible drug interactions that could affect optimal dosages, and unique requirements of specific groups of dually addicted patients...

pleasure from normally rewarding activities. This deficit may make them more vulnerable to the rewarding effects of alcohol and cocaine.

Dually addicted individuals also may combine alcohol and illicit drugs because of interactions between abused substances in the body. Because both drugs and alcohol activate brain areas involved in reward, combining substances may increase these effects. Other alcohol-drug interactions may counter unpleasant effects that often accompany or follow substance abuse. Clinical reports suggest that cocaethylene, a combined cocaine-alcohol metabolite that is formed in the body following concurrent alcohol and cocaine use, appears to reduce the anxiety that can accompany cocaine use. Recent research in rats confirms that cocaethylene plasma levels remain high as cocaine levels fall, producing a delayed, relatively long-lasting rewarding effect that may counter the aversive effect induced when cocaine plasma levels recede.

While the perceived benefits of combining alcohol and drugs may play a big part in the high percentages of people who do so, the addictive effects and harmful consequences of both substances increase when they are used together. Dually addicted patients are more likely to drop out of treatment and have poorer results than patients who abuse only one substance. However, since most studies on treating drug and alcohol abuse have examined these disorders separately, drug and alcohol treatment counselors now have little science-based information on which to base their treatment of these patients.

The joint NIDA-NIAAA program announcement addresses this critical need for effective approaches to treating dually addicted patients.

The joint NIDA-NIAAA program announcement addresses the critical need for effective approaches to treating dually addicted patients.

Our research partnership seeks studies that will evaluate the efficacy of established drug and alcohol treatment medications and novel pharmacological agents in patients with concurrent addictions. We aim to generate a broad spectrum of useful clinical information about appropriate sequencing or combining of medications and behavioral therapies in dually addicted patients, possible drug interactions that could affect optimal dosages, and unique requirements of specific groups of patients, such as minorities, the elderly, and adolescents.

Drug and alcohol abuse wreak incalculable damage on individuals, families, and communities. When they occur together, these disorders double the challenge to researchers and treatment providers. Now, NIDA and NIAAA have launched a concerted scientific response to address these challenges. Ultimately, this expanded research will fuel the development of new treatments that will enable substance abuse treatment programs to more effectively meet the needs of the many patients who abuse both alcohol and illicit drugs.

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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.

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.

Two-Object Recognition Test Mimics Test Used with Infants



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

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

“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

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

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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 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

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Manipulating Dopamine Levels Changes Smoking Behavior

By Patrick Zickler
NIDA NOTES Staff Writer

NIDA-supported researchers have demonstrated that lowering and raising the concentration of dopamine in the brain changes smoking behavior and nicotine intake in smokers. After taking a chemical compound that blocks release of dopamine to the brain's pleasure center, smokers lit up sooner and smoked more cigarettes than they did after taking a compound that stimulates dopamine release.

Nicotine triggers the release of dopamine in the brain, and the pleasurable sensations that result are thought to be a driving force in establishing addiction. Animal studies, in which brain cells can be carefully analyzed after nicotine administration, confirm the link between dopamine and addictive behavior. This study demonstrates that in humans, an individual's smoking behavior can be manipulated by stimulating or blocking dopamine release.

Dr. Nicholas Caskey and his colleagues at the University of California at Los Angeles (UCLA) and the Veterans Affairs West Los Angeles Healthcare Center monitored the smoking behavior of heavy smokers who received oral doses of either haloperidol or bromocriptine.

"Our study was designed to use these compounds to decrease or increase availability of dopamine in a single group of otherwise healthy smokers and evaluate the effect on smoking behavior," explains Dr. Caskey.

Haloperidol is used to treat some psychiatric disorders, and earlier studies found that patients with

	Haloperidol (inhibits dopamine)	Bromocriptine (enhances dopamine)
Total number of cigarettes smoked	3.0	2.3
Total puffing time (seconds)	77.6	52.0
Number of puffs taken	44.8	31.1
Time between cigarettes (minutes)	32.1	41.2

Smokers who received haloperidol, a dopamine antagonist, smoked more cigarettes during a 5-hour period and took more puffs per cigarette than did smokers who received bromocriptine, which enhances dopamine's effects.

schizophrenia smoked more during treatment with haloperidol than when they were not taking the anti-psychotic medication. Other studies have shown decreased smoking and craving for nicotine among smokers who received bromocriptine (used to treat Parkinson's disease and disorders of the pituitary gland).

Participants in the study (14 men, 6 women, average age 30 years) smoked 15 or more cigarettes per day for at least 2 years. On average, they had been smoking more than 12 years and smoked 20 cigarettes per day at the time of the study. All participants received both haloperidol and bromocriptine over the course of the study, which consisted of two 5-hour sessions spaced roughly a week apart. In their first session, the participants received an oral dose of either 2.0 mg haloperidol or 2.5 mg bromocriptine; in their second session, the participants received the other drug. Over the next 5 hours, the

participants were allowed to smoke their preferred brand of cigarettes at will, using a cigarette holder linked to a device that measured characteristics of each puff. They also answered questions about craving and discomfort.

With haloperidol, participants smoked more cigarettes (in total, three cigarettes) per session and smoked them faster (44.8 total puffs, or roughly 15 puffs per cigarette) than they did with bromocriptine (2.3 cigarettes, with 13.5 puffs per cigarette). Participants also reported greater craving with haloperidol (4.5 on a 1–7 scale) than with bromocriptine (3.8). "These results show that smoking behavior can be manipulated within the same subjects by alternately blocking and stimulating dopamine and indicates the importance of dopamine in smoking," Dr. Caskey says.

There currently are no human trials investigating the effectiveness of bromocriptine treatment as part of

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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.

Ethnic Differences

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

Typical Behaviors in Adolescent Psychiatric Disorders

Externalizing Behaviors

- 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

Internalizing Behaviors

- 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

“Studies have consistently documented high rates of psychiatric disorders among adolescent substance abusers. They also have found that certain co-occurring disorders are associated with certain treatment outcomes. For example, depression or attention-deficit/hyperactivity disorder (ADHD) may contribute to early dropout and poor treatment outcomes,” says Dr. Robbins. “Therefore, treating substance abuse alone may not be enough. Treatment providers need to address the constellation of emotional and behavioral problems presented by each individual.”

The researchers recruited 167 Hispanic and African-American 12- to

17-year-olds referred for outpatient treatment for substance abuse between October 1997 and March 2000. Participants' substance use was assessed before treatment with the Adolescent Drug Abuse Diagnosis, a standard assessment tool that provides information on the frequency of use of alcohol, marijuana, cocaine, and other drugs during the preceding month. The youths also completed the Diagnostic Interview Schedule for Children—Predictive Scales, a questionnaire that screens for nine psychiatric disorders, including social phobias, panic, anxiety, major depression, ADHD, oppositional defiant disorder (ODD), and conduct disorders (CD).

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

Co-Occurring Psychiatric Disorders Vary by Ethnicity And Gender in Adolescent Substance Abusers

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.

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.

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

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However, clinicians should not rule out the possibility of a disorder based on the patient's gender," says Dr. Latimer. "For example, although co-occurring disruptive disorders are more common among males than females, this shouldn't obscure the equally important finding that high rates of these disorders are also present among substance-abusing females."

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

About 68 percent of the girls and 75 percent of the boys were diagnosed with alcohol abuse or dependence, while about 85 percent of the girls and 93 percent of the boys were diagnosed with marijuana use disorders. More than 17 percent of the girls and 21 percent of the boys were diagnosed with abuse or dependence on some other drug

or drugs. The patterns of single-substance versus polysubstance use also varied with gender. Girls were more likely to be diagnosed with abuse or dependence on only one drug, while boys were more likely to be diagnosed with simultaneous abuse or dependence on more than one drug.

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**

Researchers Probe for Clues to ADHD Medications' Protective Effects

By Jill Schlabig Williams, NIDA NOTES Contributing Writer, and Patrick Zickler, NIDA NOTES Staff Writer

More than 2 million American children—an estimated 5 to 10 percent of preteens—have been diagnosed with attention-deficit/hyperactivity disorder (ADHD). For many of these children, treatment with psychostimulant medications such as Ritalin (methylphenidate, or MPH) suppresses the impulsivity, fidgeting, and inability to concentrate that characterize the disorder. Appropriate use of psychostimulants in children with ADHD also has been shown to reduce the likelihood that these children will develop drug or alcohol use disorders when they reach adolescence and adulthood (see “Studies Link Stimulant Treatment of ADHD in Childhood to Lower Risk of Later Substance Abuse,” page 13).

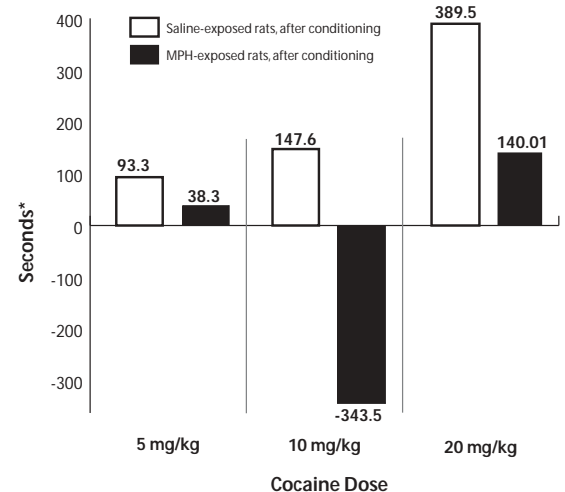
While the benefits of psychostimulant treatment for ADHD are clear, scientists are only beginning to explore how these medications help protect children with ADHD against later drug abuse. Two possible explanations have been proposed—one neurobiological and the other psychosocial. Stimulant medications might make drugs less desirable through direct neurobiological effects in the brain that reduce the pleasurable effect that drugs elicit. A second explanation is that the medications may reduce children's vulnerability by helping them act less impulsively, perform better in school, and relate better to others, thereby reducing negative feelings and the likelihood of joining socially deviant peer groups—

psychosocial characteristics known to be risks for drug-taking. Possibly, both mechanisms contribute to reduced risk.

Two recent NIDA-supported studies have begun to investigate the neurobiological effect of stimulant medications by studying rats exposed to MPH. Researchers at the McLean Hospital in Belmont, Massachusetts, and the Chicago Medical School exposed rats to MPH during periods when the animal brain is in developmental stages that correspond to human childhood and adolescence.

Scientists stipulate that while responses observed in laboratory animals are suggestive, they do not necessarily indicate that humans will be affected in the same way. Moreover, because researchers have yet to identify the specific brain features that give rise to ADHD, it is even less possible to say whether the current results with MPH have relevance for young people who receive MPH for that disorder. With those caveats, however, the results of these preliminary studies suggest that MPH does have a neurobiological effect that lasts into adulthood.

Adults Rats Exposed to MPH (Ritalin) During “Childhood” Spent Less Time In Cocaine-Associated Environment



*Bars represent seconds spent in cocaine-associated room minus seconds in saline-associated environment.

Source: Andersen et al., Nature Neuroscience, 2002.

Before place conditioning, rats spent equal time in the saline- and cocaine-associated rooms. After place conditioning, rats exposed to saline in childhood showed a dose-related preference for the cocaine-associated room. However, MPH-exposed rats actively avoided the room they had been conditioned to associate with cocaine at a 10 mg/kg dose. Although these rats spent slightly more time in the room they associated with cocaine at a 20 mg/kg dose, this difference did not reach the level of statistical significance and thus did not show that they were attracted to this room more than the saline-associated room.

Exposure During Childhood

At McLean Hospital, Dr. Susan Andersen and her colleagues injected groups of eight male rats with either MPH (2 mg/kg) or saline twice daily. The animals were exposed to the medication during a period when the rat brain is in a developmental stage equivalent to human childhood—on days 20 through 35 following birth.

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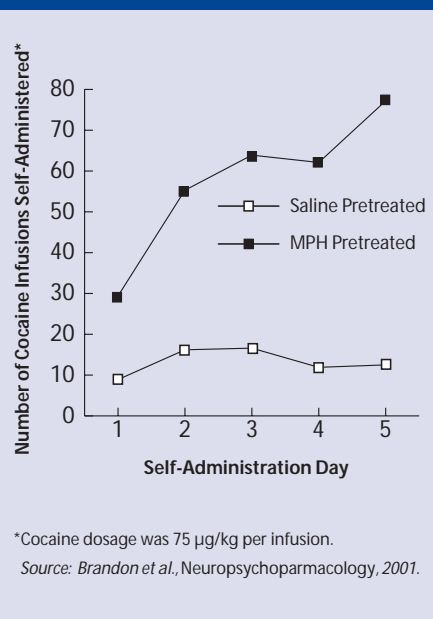
Researchers Probe for Clues To ADHD Medications' Protective Effects

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At adulthood (day 60), the rats were tested with a method called place conditioning, in which they learn to associate drug effects with a particular environment. On two consecutive days, the rats received two conditioning trials in which both saline-exposed and MPH-exposed rats were given saline and confined for 1 hour to a side room of a three-room cage before being returned to the central room. Three hours later, the rats received cocaine in a 5, 10, or 20 mg/kg dose and were confined to the other side room for 1 hour before being returned to the central room. On the third day of the study, the rats were allowed to freely explore the entire cage for 30 minutes, while researchers measured the time they spent in the room associated with saline and in the room associated with cocaine.

Adult rats that initially received placebo in childhood showed a dose-related preference for the room associated with cocaine. The higher the dose of cocaine they received, the more time they spent in the room they had learned to associate with cocaine. However, the MPH-exposed rats did not follow this pattern. After receiving either moderate or high cocaine doses, they did not establish place preference for the cocaine-associated room. MPH-exposed rats that received a moderate cocaine dose tended to avoid the cocaine-associated room, spending less time there than in the saline-associated room. MPH rats that received a high dose of cocaine spent slightly more time in the cocaine-associated room, but only about one-third as much time as the unexposed rats. "Their

Adult Rats Exposed to MPH (Ritalin) During "Adolescence" Self-Administered More Cocaine



Adult rats exposed to MPH during the period corresponding to human adolescence self-administered significantly more cocaine than did rats exposed to placebo in adolescence. Rats self-administered 75 µg/kg of cocaine by poking their noses into a hole in their treatment chamber. This action switched on an infusion pump for 3 seconds, delivering cocaine via a jugular catheter.

response was definitely blunted," Dr. Andersen says.

The findings reported by Dr. Andersen's research group suggest that, in rats, MPH exposure has a neurobiological effect that is protective later in life. "Rats exposed to MPH during the period equivalent to human childhood experience behavioral changes that endure into adulthood and are more sensitive to cocaine's unpleasant effects," Dr. Andersen observes.

Despite these findings, Dr. Andersen cautions, it is still too early to make assumptions about any neurobiological effect of MPH on vulnerability to cocaine abuse.

"There is still a great deal of research to be done in this area. We need to investigate the role of dose, gender, age of exposure, and treatment duration and to examine how MPH affects other reward systems, such as responses to sex or food," concludes Dr. Andersen.

Exposure During Adolescence

At the Chicago Medical School, Dr. Cindy Brandon, Dr. Frank White, and colleagues exposed male rats to daily doses of MPH (2 mg/kg) or saline from days 35 to 42 after birth, when the rats are going through a period of brain development corresponding to human adolescence. When the rats reached adulthood (56 days of age), they were put into boxes with two holes into which they could poke their noses. Poking through one hole triggered an infusion of cocaine (75 µg/kg). Poking through the other hole triggered an infusion of saline solution. The scientists recorded the number of pokes in both holes over 5 days.

Rats that had not been exposed to MPH during adolescence triggered few infusions, and the rate did not increase over the course of the experiment. Rats that had been exposed to MPH in adolescence, however, began self-administering cocaine on the first day and triggered increasingly more infusions on each successive day. By day 5, they were self-administering cocaine at a rate more than seven times that of the rats not exposed to MPH. "Adult animals exposed to MPH during adolescence were considerably more vulnerable to the reinforcing effects of cocaine," Dr. White explains. "From these results, it is reasonable to suspect that in humans, adolescent exposure to MPH may increase future vulnerability to low doses of cocaine."

Studies Link Stimulant Treatment of ADHD in Childhood to Lower Risk of Later Substance Abuse

Children treated for attention-deficit/hyperactivity disorder (ADHD) with stimulant medications are less likely to develop substance abuse disorders later in life than are children with ADHD who are not given stimulants, according to NIDA-supported researchers. Dr. Timothy Wilens and his colleagues at the Massachusetts General Hospital and Harvard Medical School in Boston reviewed long-term studies in which stimulant-treated and untreated children with ADHD were evaluated later in life and concluded that stimulant therapy cuts in half the likelihood of subsequent substance abuse disorders.

The researchers examined six studies with a combined total of 647 children with ADHD who had been treated with stimulants and 360 who had not. On average, the studies followed up on the participants for 6 years (range 4 to 15 years) after treatment ended and they were more than 20 years old (range 15 to 22 years of age). Four of the six studies included treated and untreated participants with similar severity in their initial diagnoses. The studies found less incidence of any substance abuse disorder in participants treated with stimulants. One study in which the severity of initial diagnosis was not similar for treated and untreated groups found that participants who received stimulants were more likely to smoke and to abuse cocaine, but not more likely to abuse alcohol or marijuana. The other study in which diagnostic severity was not matched found that stimulant-treated participants were more likely to abuse alcohol or marijuana.

“Considering all six studies, there was an almost twofold decrease in the likelihood of substance abuse disorders risk for youths treated previously with stimulant medication,” Dr. Wilens says.

The Harvard group’s findings counter concerns voiced by some practitioners that exposure to stimulants might increase children’s disposition to subsequently abuse drugs. “These findings should reassure clinicians and families by providing compelling evidence that pharmacotherapy with stimulants for ADHD does not lead to substance abuse disorders, but instead seems to have protective effects,” says Dr. Wilens.

Source

- Wilens, T.E., et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics* 111(1):179-185, 2003. **NN**

Implications for Future Research

This study, like the work done by Dr. Andersen’s group, suggests that exposure to MPH has a neurobiological effect that persists into adult life. However, in this study, the effect is to increase risk rather than to confer protection. “It’s important to keep in mind that my study and Dr. Andersen’s study measured two different behaviors. Place preference studies can be seen as a model of the animals ‘wanting’ the drug, while self-administration studies involve actually taking the drug. These methods are not measuring the same processes in the brain,” Dr. Brandon says.

“What these animal studies suggest is that, on a neurobiological level, early exposure to MPH has effects that persist into later life,” says Dr. Susan Volman of NIDA’s Division of Neuroscience and Behavioral Research. “They also indicate that the timing of exposure—whether the animals are exposed during childhood or adolescence—plays a role in later behavior in the animals.”

Only continued investigation will clarify the extent to which the neurobiological results seen in rats, which do not have ADHD, might also be relevant to humans with or without ADHD. “There’s still a great

deal we need to learn about exposing a developing brain to MPH,” Dr. Volman says. “We just don’t know enough yet about the enduring changes that may result.”

Sources

- Andersen, S.L., et al. Altered responsiveness to cocaine in rats exposed to methylphenidate during development. *Nature Neuroscience* (5):13-14, 2002.
- Brandon, C.L.; Marinelli, M.; Baker, L.; and White, F.J. Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. *Neuropsychopharmacology* 25(5):651-661, 2001. **NN**

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

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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

continued from page 5

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

Manipulating Dopamine Levels Changes Smoking Behavior

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smoking cessation therapy, but NIDA-supported investigations of selegiline, another medication that acts on the dopamine system, are under way. “There are very few studies

that look at the effect of dopamine on smoking in subjects who don’t also suffer psychiatric disorders,” observes Dr. Allison Chausmer of NIDA’s Division of Neuroscience and Behavioral Research. “The findings in this study, particularly the results seen for bromocriptine, offer additional support for investigating potential

medications that help control smoking by acting on the dopamine system.”

Source

• Caskey, N.H., et al. Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine & Tobacco Research* 4(3):259-266, 2002. **NN**

Treating Adolescent Substance Abuse by Addressing Family Interactions

Brief Strategic Family Therapy (BSFT) is described in the latest addition to the *Therapy Manuals for Drug Addiction* series. The short-term intervention is used to treat adolescent drug use that occurs along with other problem behaviors. This therapy focuses on an adolescent's drug use within the context of family dynamics

The BSFT manual introduces counselors to concepts they need to understand the family as a vital context within which adolescent drug abuse occurs. It also describes strategies for creating a therapeutic relationship with families, assessing and diagnosing maladaptive patterns of family interactions, and changing family interaction patterns from maladaptive to adaptive.

BSFT can be adapted to a range of family situations and used in a variety of service settings—such as mental health clinics, drug abuse treatment programs, and other social service settings. It also can be delivered

in various ways, such as on an outpatient basis or in combination with residential or day treatment. Treatment lasts 8 to 24 sessions, depending on the severity of the problem.

In addition to targeting an adolescent's conduct problems at home and at school, BSFT addresses oppositional, aggressive, violent, or risky sexual behavior; association with antisocial peers; and delinquency. Family dynamics are a key focus of this therapy.

Over 25 years of extensive evaluation has found BSFT to be effective in treating adolescent drug abuse, conduct problems, association with antisocial peers, and impaired family functioning. It has been shown to be particularly successful with cultural groups that emphasize family and interpersonal relationships. BSFT has not been tested with adult addicts and is not considered a treatment for adult addiction.



The upcoming manual and the series of which it is a part exemplify NIDA's commitment to applying basic research findings to treatment needs. In addition to describing scientifically based therapies for addiction, the five manuals provide guidance on content for counseling sessions and effective counseling techniques. Audiences include drug abuse treatment practitioners, mental health professionals, and others involved in treating drug abuse and addiction. **NN**

Therapy Manuals Offer a Range of Treatment Strategies

The four earlier therapy manuals can be downloaded from NIDA's Web site, www.drugabuse.gov, or ordered through the National Clearinghouse for Alcohol and Drug Information, www.health.org or 800-729-6686 (TDD, 800-487-4889). The *Brief Strategic Family Therapy* manual also will soon be available from these sources.

- *A Cognitive-Behavioral Approach: Treating Cocaine Addiction* (Manual 1) describes cognitive-behavioral coping skills treatment, a short-term, focused approach to helping cocaine-dependent individuals abstain from cocaine and other drugs.
- *A Community Reinforcement Plus Vouchers Approach: Treating Cocaine Addiction* (Manual 2) integrates a community reinforcement approach with an incentive program that uses vouchers. Patients earn points to redeem for retail items by remaining in treatment and abstaining from cocaine.
- *An Individual Counseling Approach to Treat Cocaine Addiction: The Collaborative Cocaine Treatment Study Model* (Manual 3) presents a guide for the individual treatment of cocaine addiction that emphasizes an individual's physical, emotional, spiritual, and interpersonal needs in supporting recovery.
- *Drug Counseling for Cocaine Addiction: The Collaborative Cocaine Treatment Study Model* (Manual 4) describes the Group Drug Counseling (GDC) model developed for the Collaborative Cocaine Treatment Study (CCTS), a multisite clinical trial. The study found the combination of GDC and individual drug counseling to be more effective than GDC alone or the combination of GDC and psychotherapy.

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National Institute on Drug Abuse
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