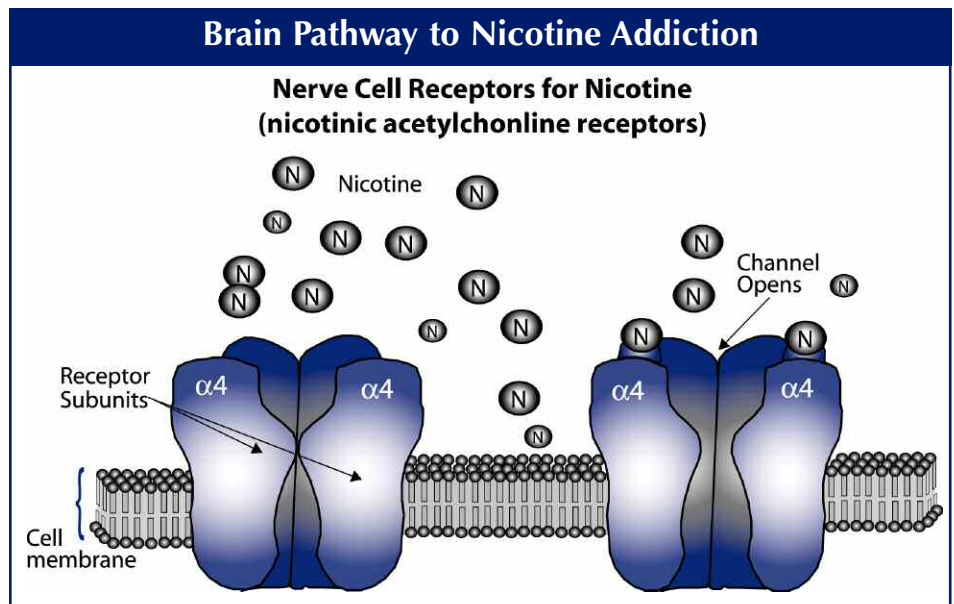


Site on Brain Cells Appears Crucial To Nicotine Addiction

By Patrick Zickler, NIDA NOTES Staff Writer

Using genetic engineering, NIDA-supported scientists have produced a strain of mice with special characteristics that can help researchers identify and study key steps in the development of nicotine addiction. By altering a single amino acid in just one of a mouse's 30,000 genes, the scientists produced mice that are exceptionally sensitive to the effects of nicotine. The modified mice show behaviors associated with addiction when exposed to nicotine doses far too small to cause similar effects in other mice. Their dramatically increased sensitivity suggests that the brain cell site affected by the modified gene is crucial to development of nicotine addiction.

Dr. Andrew Tapper and colleagues at the California Institute of Technology in Pasadena and at the University of Colorado in Boulder built on work by other scientists which indicated that a site on some brain cells—the $\alpha 4$ subunit of nicotine receptors—plays a key role in the brain's response to nicotine.



Nicotine attaches to nerve cells in the brain at receptors on the cell membrane. The receptors comprise five subunits that fit together like sections of an orange. When a nicotine molecule binds to one of these subunits, the segments pull away from each other, creating an open channel through the cell membrane. This initiates a series of electrical and chemical signals that trigger release of dopamine by other brain cells. One type of subunit, designated $\alpha 4$, appears to play a central role in development of nicotine addiction; mice engineered to have especially sensitive $\alpha 4$ subunits exhibit behaviors characteristic of nicotine addiction when exposed to a dose of nicotine just one-fiftieth of that normally needed to elicit these behaviors.

What's Inside

NIDA RESPONDS TO NEW ABUSE PATTERNS in Director's Column	3
DISULFIRAM reduces cocaine abuse	4
TWIN STUDY LINKS MARIJUANA ABUSE to suicide and depression	12

The previous work involved “knock-out” mice, in which scientists had disabled a gene that directs development of the $\alpha 4$ site. When exposed to nicotine, the $\alpha 4$ knock-out mice did not respond with increased release of the pleasure-causing brain chemical dopamine, a reaction thought to be a key factor in the development of nicotine addiction.

The results with knock-out mice suggested that $\alpha 4$ sites on brain cells are necessary for development of nicotine addiction, but didn't address the question of whether the sites are sufficient by themselves to initiate the

continued on page 6



Cognitive-behavioral therapies help women suffering from posttraumatic stress disorder, p. 7



Substance abuse persists longer than mental health symptoms after World Trade Center attacks, p. 14

Research Findings

Site on Brain Cells Appears Crucial to Nicotine Addiction 1
 Genetic Engineering Reveals Proteins' Key Role in Sensitivity to Cocaine 6
 Disulfiram Reduces Cocaine Abuse 4
 Disulfiram May Work for Men, but Not Women 5
 Cognitive-Behavioral Therapies Curb Substance Abuse and Symptoms of PTSD 7
 NIDA Research Illuminates Associations Between Psychiatric Disorders and Smoking 8
 Network Therapy Enhances Office-Based Buprenorphine Treatment Outcomes 10
 Twin Study Links Marijuana Abuse, Suicide, and Depression 12

Director's Column

NIDA Responds to Changing Drug Abuse Patterns. 3

Bulletin Board

Trauma-Related Substance Abuse Persists After Mental Health Symptoms Abate 14
 NIDA Support Brings First fMRI to South Africa 14

Tearoff

NIDA Web Site Addresses Consequences of Steroid Abuse 15

NIDA News and Information at Your Fingertips

Information about NIDA research, programs, and events is quickly and easily accessible through NIDA's home page at www.drugabuse.gov.

NIDA's home page includes:

- Information on Drugs of Abuse
- Publications (including *NIDA NOTES*)
- Calendar of Events
- Links to NIDA Organizational Units
- Funding Information
- International Activities
- Links to Related Web Sites

The screenshot shows the NIDA website interface with a top navigation bar containing 'HOME', 'ABOUT NIDA', 'NEWS & EVENTS', 'FUNDING', and 'PUBLICATIONS'. Below this are tabs for 'RESEARCHERS & HEALTH PROFESSIONALS', 'PARENTS & TEACHERS', 'STUDENTS & YOUNG ADULTS', and 'EN ESPAÑOL'. The main content area is divided into several sections: 'NEW! COMMUNITY DRUG ABUSE PREVENTION INHALANTS', 'News & Events' with a link to 'Inhalant Abuse: Research Report', 'Students & Young Adults' with educational resources, 'Parents & Teachers' with drug information, 'Researchers & Health Professionals' with grants and funding, 'En Español' with resources in Spanish, 'Publications Catalog', 'NIDA Sites' with various specialized web pages, and 'Drugs of Abuse' with a list including Alcohol, Cocaine, Ecstasy/MDMA, Heroin, Inhalants, Marijuana, Methamphetamine, PCP/Phencyclidine, Prescription Medications, Smoking/Nicotine, and Steroids. A 'Related Topics' section includes Drug Testing, Prevention Research, Stress & Drug Abuse, Treatment Research, and Trends & Statistics.



NIDA Responds to Changing Drug Abuse Patterns

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

Two new NIDA initiatives address the accelerating increase in abuse of opioid pain medications and bring a powerful new transdisciplinary conceptual framework called social neuroscience to bear on the broad questions of abuse and addiction. Together, the initiatives exemplify the depth of NIDA-supported research capabilities and the flexibility that makes it possible to respond quickly to new patterns in drug abuse and to incorporate innovative research approaches.

Abuse of Opioid Pain Medications

Opioid analgesics, medicine's most effective tools for relieving severe and chronic pain, are being diverted and abused on an alarming scale. In 2003, an estimated 31.2 million Americans aged 12 or older abused a prescription pain medication (took the drug for the feeling it produced, not the condition for which it was prescribed) at least once, an increase of more than 1.5 million over the year before. The prevalence of opioid analgesic abuse is alarming among adolescents; in 2003, high school seniors abused opioids more than any other illicit drug except marijuana.

The abuse of opioids by adolescents is a major focus of NIDA's research. Most of our understanding of opioid abuse and addiction is derived from research in 20- to 40-year-olds; however, exposure to opioids during adolescence—a critical time for brain development—may result in neurobiological changes and behavioral consequences that differ from those in adulthood. NIDA's initiative will help determine how short-term and chronic opioid administration affect the developing brain. Among the important questions are: Does exposure to these medications in one's teens and early 20s increase the likelihood of abuse later in life? Will adolescents who have been treated with opioids or abused them require higher therapeutic doses as adults to achieve adequate pain management?

In addition to intensifying our investigations of opioids' effects in adolescents, the initiative will stimulate research into questions that apply to the elderly, who might be at increased risk for developing addiction because of age-related changes in metabolism or because they are taking other medications. We also need research that tells us whether pain patients are more vulnerable or less vulnerable to the addictive effects of these drugs, and how best to treat co-occurring pain and addiction. Can we

develop medications that act at the site of pain rather than deep within the central nervous system, as opioids do? NIDA's intensified investigation will help assure that pain patients have the treatment they need, with medications carrying the smallest possible risks for abuse and addiction.

Social Neuroscience

Researchers have described in detail many of the biological variables in drug abuse and addiction, and they have identified a wide array of social circumstances that foster or protect against the problems that NIDA is dedicated to reducing and eventually eliminating. Our newest initiative will merge these historically separate investigatory realms to examine how neurobiology and the social environment interact in the processes of initiation, maintenance, relapse to, and treatment of abuse and addiction.

Our social neuroscience initiative will help us better understand how neurobiological mechanisms and responses—genetic, hormonal, and physiological—underlie, motivate, and guide social behaviors related to abuse and addiction. In one example of such a relationship, NIDA-funded scientists recently found that when they transferred monkeys from isolation to group living, the animals that became dominant in the new social structure underwent biological changes that resulted in stronger limbic dopamine signaling and less interest in cocaine compared with the animals that became submissive (see "Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction," *NIDA NOTES* Volume 17, No. 5, p. 7). A social neuroscience perspective might also investigate the neurobiological mechanisms underlying the heightened sensitivity to social influences and decreased sensitivity to negative consequences that—together with other special characteristics of their age—make adolescents particularly vulnerable to drug abuse. In adults, too, the confluence of the brain's neurobiological response to drugs and influences from the social environment can have a profound impact on whether an individual begins, continues, or quits abusing drugs. In addition to new insights into the initiation and consequences of drug abuse, social neuroscience might help explain how group, 12-step, or faith-based interventions might bring about positive change. **NN**

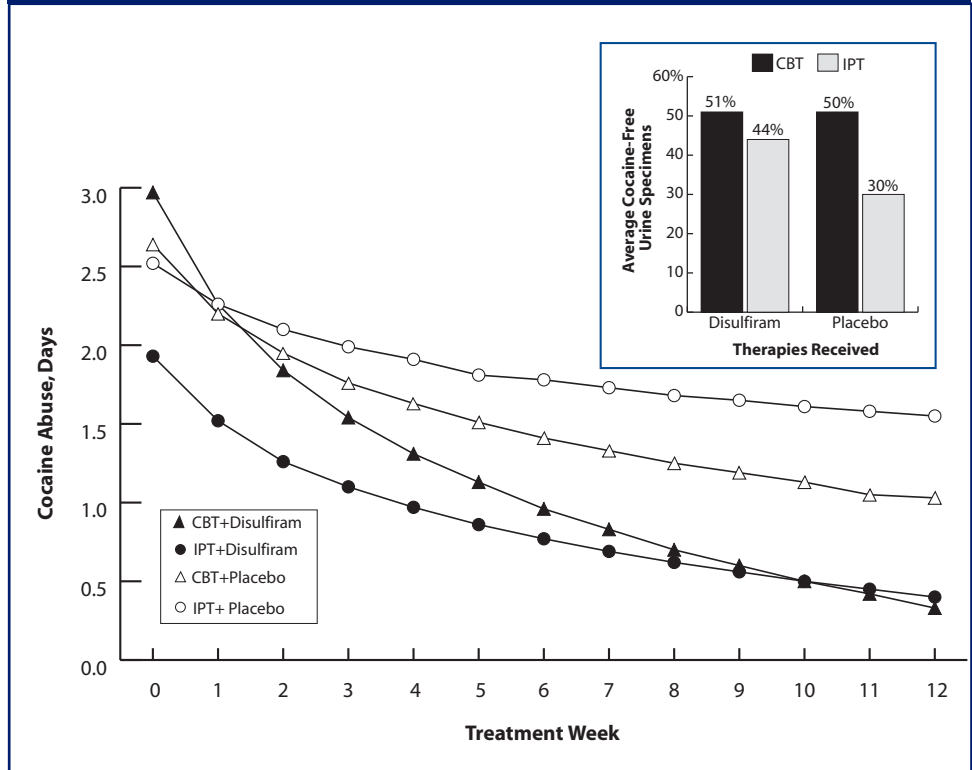
Disulfiram Reduces Cocaine Abuse

By Lori Whitten, *NIDA NOTES* Staff Writer

Disulfiram, a well-established medication for the treatment of alcoholism, has helped people addicted to cocaine reduce abuse of the drug from 2.5 days a week to 0.5 days a week on average. The finding builds on previous studies in which NIDA-funded researchers demonstrated the medication's promise in two subgroups of cocaine abusers—alcoholics and those with co-occurring opioid addiction. Their current results suggest that disulfiram is effective in treating the general population of cocaine-addicted patients, including those who are nonalcoholic. The medication's effectiveness in nonalcoholic patients adds to evidence that disulfiram works directly to reduce cocaine abuse rather than indirectly by reducing concurrent alcohol abuse. The investigators also found that, like disulfiram, cognitive-behavioral therapy (CBT) reduced cocaine abuse by 2 days.

Dr. Kathleen Carroll and her colleagues at Yale University School of Medicine in New Haven, Connecticut, treated 121 outpatients for 12 weeks. The 32 women and 89 men met the criteria for cocaine dependence specified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) and reported abusing cocaine 13 days on average during the month and 2.5 days during the week before treatment. During the study, each patient received either 250 mg/day of disulfiram or placebo and participated in weekly individual sessions of behavioral therapy, either CBT or IPT (interpersonal psychotherapy). CBT coaches patients to recognize and cope with situations that tend to induce drug craving and abuse. In IPT, patients clarify and address key personal problems related to the substance abuse. On average, patients attended eight behavioral therapy sessions. The type of therapy did not affect rates of treatment completion.

Both Disulfiram and CBT Reduce Cocaine Abuse in Patients



Over the 12-week study, patients taking disulfiram or participating in cognitive-behavioral therapy (CBT) demonstrated greater reductions in cocaine abuse than those taking placebo or receiving interpersonal psychotherapy (IPT).

All patients abused cocaine on fewer days during treatment than they had in the weeks before. The extent of recovery depended on the therapy. By the end of treatment, patients taking disulfiram reduced weekly cocaine abuse by 2 days on average, compared with 1 day for those taking the placebo, no matter which psychotherapy group they participated in. Similarly, patients who participated in CBT reduced weekly cocaine abuse by 2 days on average, compared with 1 day for IPT participants regardless of which medication they received. The data were based on self-reported cocaine abuse, but weekly urine tests generally corroborated (84 percent) patient information. More urine samples from participants receiving

disulfiram and CBT (51 percent), placebo and CBT (50 percent), and disulfiram and IPT (44 percent) were cocaine negative during the study than those from participants taking the placebo and IPT combination (30 percent); the latter demonstrated the least favorable treatment outcomes.

Dr. Carroll and her colleagues verified compliance with the daily medication regimen by testing urine samples for tracers that were added to the medication and the placebo. Taking the capsules every day was associated with better outcomes among patients who received either disulfiram or placebo, although disulfiram's effectiveness remained superior to placebo's when the researchers took medication compliance into account. Dr. Carroll

emphasizes that “not taking medication can undercut the benefits of all pharmacotherapies, and an important goal of behavioral therapy is improvement of medication compliance.”

Dr. Dorynne Czechowicz of NIDA’s Division of Clinical Neuroscience, Development and Behavioral Treatment says the findings highlight the importance of integrating addiction medication and behavioral treatment. “All patients in the study participated in some form of behavioral therapy, which facilitated recovery from substance abuse and helped patients stick to the medication regimen,” she says.

Disulfiram had a more pronounced benefit for patients who were not alcohol-dependent at the outset of the study and for those who abstained from alcohol during the study. Patients who drank while taking disulfiram tended to take less of the medication than those who did not drink. Instead of deterring drinking and thereby reducing cocaine abuse, the unpleasant physical consequences of mixing

alcohol with the medication led patients to stop taking disulfiram when they wanted to drink or abuse cocaine. “These findings seem to validate the clinical observation that patients have to stop drinking before they can kick cocaine abuse,” says Dr. Carroll.

Patients participating in CBT showed better outcomes than those in IPT, regardless of concurrent drinking. CBT, a well-established behavioral treatment, might be the best option for some patients, including those facing co-occurring alcohol and cocaine addiction, she says. Patients without concurrent alcoholism may be candidates for disulfiram, CBT, or a combination.

Disulfiram interacts with cocaine to produce an unpleasant sense of hyperstimulation. In laboratory studies, people experiencing a disulfiram-cocaine interaction demonstrated increased heart rate and blood pressure and reported anxiety, paranoia, and restlessness. Animal studies suggest that disulfiram, like cocaine, enhances the

activity of the neurotransmitter dopamine. Possibly, when someone has taken disulfiram, subsequent administration of cocaine elevates dopamine to excessive levels that produce discomfort and aversion.

Animal research suggests that disulfiram increases levels of dopamine by blocking an enzyme that breaks dopamine down. People with low levels of the enzyme, dopamine- β -hydroxylase (DBH), have increased dopamine activity. Hormones, as well as genes, may influence DBH levels. Researchers suspect that estrogen hormones increase DBH, attenuating the effect of disulfiram, which could explain why women seem to benefit less than men.

Source

•Carroll, K.M., et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: A randomized placebo-controlled trial. *Archives of General Psychiatry* 61(3):264-272, 2004. **NN**

Disulfiram May Work for Men, but Not Women

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

Dr. Kathleen Carroll of Yale University School of Medicine and her colleagues have conducted several studies on the medication’s effects on cocaine abuse and have moved on to the next step—determining which types of patients benefit from the treatment. There were not enough women in their recent study (see “Disulfiram Reduces Cocaine Abuse”) to analyze sex differences, so the investigators combined data from two of their other treatment studies to compare men’s and women’s responses to disulfiram. “We know that men and women react to cocaine differently. For example, women progress more quickly to cocaine addiction than men. Sex differences in treatment response seemed likely,” says Ms. Charla Nich, lead investigator of the study.

In one study, the investigators treated alcohol- and cocaine-addicted patients with disulfiram and various behavioral therapies; in the second, they tested disulfiram in opioid- and cocaine-addicted patients under treatment with methadone. Altogether, 191

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

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

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

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

Nicotine Addiction

continued from page 1

behaviors associated with addiction. To answer that question, says Dr. Henry Lester of the California Institute of Technology, “We decided to create animals with hypersensitive $\alpha 4$ receptors. That way, instead of eliminating the response to nicotine, we could emphasize it and study the processes that lead to nicotine addiction. So we developed the $\alpha 4$ ‘knock-in’ mouse.”

The scientists compared the behavioral effects that are in part characteristic of nicotine addiction—reward, tolerance, and sensitization—in their knock-in mice and unmodified mice. According to Dr. Lester, the results indicate that activation of the $\alpha 4$ site by nicotine is sufficient to initiate the effects.

Reward: The researchers measured nicotine reward in their mice with a technique called “conditioned place preference,” which is based on the assumption that if animals like an experience, such as receiving nicotine, they will gravitate to the place where they have had that experience rather than another where they haven’t. In the experiment, mice with unmodified $\alpha 4$

receptors exhibited a preference for a compartment associated with a nicotine dose of 0.5 mg/kg of body weight—a typical dose ingested by a human smoker. The investigators then tested the rewarding effect of one-fiftieth of that amount, 10 μ g/kg, on the unmodified and the $\alpha 4$ knock-in mice. When allowed to move freely between the chambers for 20 minutes following nicotine administration, the unmodified mice showed no preference for the nicotine-associated compartment; they spent slightly less time in that chamber than they had before. In contrast, modified mice showed a marked preference for the compartment associated with nicotine, spending an average of 2 minutes more in that chamber following nicotine administration.

Tolerance and sensitization: To test tolerance to nicotine, the investigators subjected the unmodified and knock-in mice to repeated doses of nicotine, 15 μ g/kg daily over 9 days, and then compared the changes in nicotine-induced hypothermia. The unmodified mice showed no change in body temperature, but the knock-in mice exhibited a decrease of 3°C on the first and second days, and smaller decreases each

successive day, suggesting they had developed tolerance to the nicotine-induced hypothermia. In tests for sensitization, only the genetically engineered mice increased activity levels (measured by counting the number of times the animals cross a beam of light in the 60 minutes following injection) in response to daily injections of 15 μ g/kg over 9 days.

“This work represents a significant step forward in understanding how nicotine hijacks the brain’s normal signaling process,” says Dr. Joni Rutter of NIDA’s Division of Basic Neurosciences and Behavior Research. “And the research approach—moving from manipulation of a single protein to an animal’s behavioral response to nicotine—also holds great promise. If the $\alpha 4$ site is also found to play a large role in human nicotine addiction,” Dr. Rutter adds, “it is a promising focus for research into medications that might block nicotine’s effects.”

Source

•Tapper, A.R., et al. Nicotine activation of $\alpha 4$ receptors: Sufficient for reward, tolerance, and sensitization. *Science* 306(5698):1029-1032, 2004. **NN**

Genetic Engineering Reveals Proteins’ Key Role in Sensitivity to Cocaine

Genetic engineering strategies like those used at the California Institute of Technology to study nicotine addiction have helped other investigators identify a pair of proteins that seem to influence cocaine addiction.

Dr. Peter Kalivas and his colleagues at the Medical University of South Carolina in Charleston developed a strain of mice lacking two genes, called *Homer1* and *Homer2*, that direct production of proteins linked to cocaine’s effects in the brain. The researchers found that the *Homer* “knock-out” mice were more sensitive than unmodified mice to the behavioral effects of cocaine.

Compared with unmodified mice, animals missing either *Homer1* or *Homer2* developed stronger place conditioning—when allowed to move freely, they would spend more time in a compartment where they had received cocaine than in a compartment with no drug association. The knock-out mice also were more sensitive to cocaine’s stimulatory effect; when placed in a chamber equipped with photoelectric beams that could measure activity, the knock-outs were approximately 50 percent more active than unmodified mice following cocaine injections. To verify the role of the *Homer* genes in increased sensitivity to cocaine, the researchers restored *Homer* genes in the brains of the knock-outs, eliminating the previously seen differences in stimulation and place conditioning.

“The fact that *Homer* deletions result in these augmented responses to cocaine suggests that disruption of Homer protein-regulated signaling in the brain is a central step in development of cocaine addiction,” Dr. Kalivas says. Additional evidence of this role is seen in changes that *Homer* deletion causes in levels of the brain messenger chemical glutamate, he adds. *Homer* knock-out mice that had never been exposed to cocaine had nucleus accumbens (NAc) glutamate concentrations about 50 percent lower than mice with the genes—an effect similar to that seen in mice after cocaine withdrawal. This effect, too, was reversed when the scientists injected *Homer* genes into the NAc.

The association between *Homer* activity and the conditions of cocaine withdrawal is particularly intriguing, according to Dr. Kalivas, because other researchers have shown that Homer protein levels rise and fall in response to environmental cues and changing levels of stress. “*Homer* may be a window to study the molecular basis of the important link between environmental stress and cocaine addiction.”

Source: Szumlinski, K.K., et al. Homer proteins regulate sensitivity to cocaine. *Neuron* 43(3):401-413, 2004. **NN**

Cognitive-Behavioral Therapies Curb Substance Abuse and Symptoms of PTSD

By Lori Whitten, NIDA NOTES Staff Writer

Two types of cognitive-behavioral therapy (CBT) for drug abuse, “relapse prevention” and “seeking safety,” have shown promise in the treatment of women who abuse drugs and also have post-traumatic stress disorder (PTSD). Women participating in either therapy for 3 months showed decreases not only in substance abuse, but also in PTSD symptoms.

The result surprised NIDA-funded investigators, who expected seeking safety, but not relapse prevention therapy, to improve PTSD symptoms. “The patients seemed to apply the skills developed during CBT therapy—identifying and coping with emotional triggers without abusing drugs—to dealing with trauma-related problems,” says Dr. Denise Hien, the study’s lead investigator and director of the Women’s Health Project at St. Luke’s/Roosevelt Hospital Center in New York City.

The study participants—107 urban women, aged 18 to 55, with low incomes—faced many barriers to recovery, including difficulties with

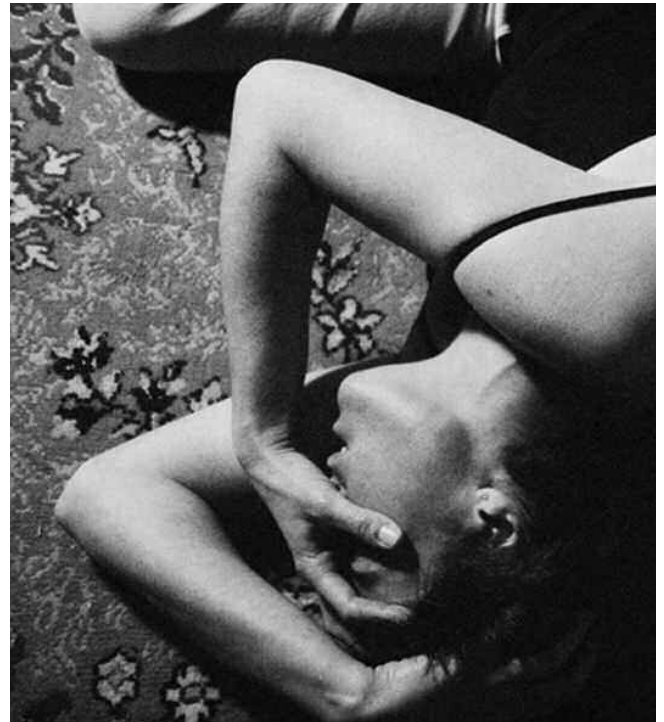
employment and parenting, and medical conditions. Most abused alcohol, marijuana, or cocaine, and experienced moderate depression-related problems at the beginning of treatment. All had PTSD symptoms, most with the full spectrum and a minority with fewer signs of the condition.

Although some had developed PTSD as the result of experiencing or witnessing a single traumatic episode (e.g., an accident or natural disaster), 82 percent had experienced chronic recurring sexual or physical abuse.

PTSD severity was not related to substance abuse levels. One in three patients in substance abuse treatment also experience PTSD.

During the study, 75 of the women participated in twice-weekly, 1-hour individual sessions of either seeking safety or relapse prevention CBT for 12 weeks. Compared with the other 32 study participants, who received a variety of standard treatments within the community, patients receiving CBT reduced their substance abuse and experienced fewer and less severe PTSD symptoms after 3 months of treatment. CBT patients maintained these gains 6 months after therapy, whereas those receiving community care experienced worse substance abuse and PTSD symptoms over time.

About half of the 75 women received a form of CBT called relapse



prevention, which focuses on managing cravings, strengthening motivation to stop abuse, and enhancing personal relationships and networks to support recovery. They identified situations that might provoke them to relapse and developed specific strategies for avoiding and coping with these. Through role-playing and other activities, the women practiced drug refusal and general decision-making and problemsolving skills. The remaining CBT patients, the seeking safety group, addressed PTSD and substance abuse as interrelated problems. Rather than delving into the trauma, these participants identified its effects on their current lives, including substance abuse. They practiced techniques to ease emotional pain, stop blaming themselves for the trauma, and cope with difficult interpersonal and potential relapse situations.

continued on page 13

Patients receiving CBT reduced their substance abuse and experienced fewer and less severe PTSD symptoms after 3 months of treatment.

NIDA Research Illuminates Associations Between Psychiatric Disorders and Smoking

By Patrick Zickler, NIDA NOTES Staff Writer

Nearly half of all cigarettes sold in the United States are sold to people with mental illness, and men and women with mental disorders are twice as likely as the general population to smoke. A recent NIDA-supported epidemiological analysis reveals relationships between psychiatric disorders and smoking that have important implications for public health. The findings suggest that treating psychiatric illness can contribute to reductions in smoking intensity and nicotine addiction, and that addressing smoking during substance abuse treatment is vital to counter an increased risk for nicotine addiction that may accompany recovery.

Dr. Naomi Breslau, at Michigan State University in East Lansing, used data from the Tobacco Supplement to the National Comorbidity Survey (NCS) to study the relationships between the temporal onset of psychiatric disorders, psychiatric symptoms, and smoking. The NCS, mandated by Congress to assess the prevalence of psychiatric disorders in the United States, surveyed a representative sample of the national population between 1990 and 1992, eliciting information about the onset of psychiatric disorders—as defined by the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised* (DSM-III-R)—and the time course of their symptoms. Disorders included in the NCS are major depression, dysthymia (similar to clinical depression, but with longer-lasting and milder symptoms), agoraphobia, generalized anxiety disorder, simple and social phobias, panic disorder, posttraumatic stress disorder, and alcohol or drug abuse or addiction. The NCS Tobacco Supplement asked respondents whether they smoked, when they

Active Psychiatric Disorders Increase Likelihood of Daily Smoking, Nicotine Addiction				
	Relative Risk of Transition to Daily Smoking		Relative Risk of Developing Nicotine Addiction	
	When Symptomatic	When Remitted	When Symptomatic	When Remitted
Depressive Disorders				
Major Depression	1.6	0.6	2.2	NE
Dysthymia	1.6	1.5	1.2	NE
Anxiety Disorders				
Agoraphobia	1.4	0.1	1.8	NE
GAD	2.1	NE	1.8	NE
Simple Phobia	1.5	0.9	1.8	13.6
Social Phobia	1.3	2.8	1.8	1.6
Panic Disorder	0.9	1.7	1.4	5.8
PTSD	2.0	2.5	2.1	0.7
Substance Use Disorders				
Alcohol A/D	1.5	0.5	1.7	5.2
Drug A/D	1.8	0.9	1.5	4.1

GAD indicates general anxiety disorder; NE, not evaluated; PTSD, posttraumatic stress disorder; and A/D, addiction/dependence.

Researchers found that active psychiatric disorders, with the exception of agoraphobia and panic disorder, were associated with increased risk of transition to daily smoking. In contrast, past disorders (those that had been inactive for a year or more) generally did not predict transition to daily smoking. Researchers also found an increased risk of transition to nicotine addiction associated with a wide range of active disorders, but only four past disorders. Risks are presented as odds ratios; a relative risk of 2.0 indicates twice the likelihood.

began smoking daily, at what age they experienced symptoms matching DSM criteria for nicotine dependence, and whether they had stopped smoking regularly a year or more before they took part in the survey.

Analyzing the responses from 4,414 survey participants, Dr. Breslau found that:

- Men and women with histories of substance abuse, major depression, and most anxiety disorders reported increased rates of transition to daily smoking, but only during periods when they were experiencing symptoms. When their illnesses had been asympto-

matic for a year or more, they became daily smokers at rates no higher than respondents who never experienced psychiatric illness;

- Substance abuse and major depression predicted transitions from voluntary smoking to nicotine addiction when actively symptomatic (the association was borderline for drug, as opposed to alcohol, abuse). In the case of substance abuse, this relationship became markedly stronger when the problems had remitted for at least a year;

■ Most anxiety disorders increased risk for nicotine addiction when symptomatic. For individuals with simple phobia or panic disorder, these risks multiplied during periods of remission. For those with posttraumatic stress disorder, the risk reverted to baseline when symptoms had been absent for a year; and

■ None of the psychiatric disorders studied affected respondents' chances of successfully quitting smoking, either when active or when remitted.

"We found that the majority of the psychiatric disorders, when active, predicted the onset of daily smoking," Dr. Breslau says. "Respondents with one active disorder were 1.3 times as likely, and those with four or more active disorders were 2.2 times as likely to begin daily smoking as those with no active disorders. This suggests that early treatment may be able to prevent patients who are not currently daily smokers from progressing to that status."

"Similarly," Dr. Breslau says, "most disorders—when active—pre-

dicted that smokers would progress from daily smoking to nicotine addiction. In this transition from one stage of smoking to another, daily smokers with one active disorder were on average 1.8 times as likely as those with no active disorder to develop addiction, and the odds of developing nicotine addiction increased with the number of active disorders. This suggests that successful control of psychiatric symptoms before smokers become addicted can prevent them from making that transition."

Substance abuse, however, is an important exception to this general observation. Respondents with past but not active alcohol and drug abuse disorders had risk ratios two to three times as high as respondents with current active disorders involving these substances. "This association suggests that cessation of substance abuse may induce greater smoking intensity. In treatment for substance use disorders it is important to be conscious of smoking behavior, to guard against the possibility that a person in treatment for one damaging condition might increase the danger posed by

another. Treatment should assist patients who are abusing alcohol or drugs and who smoke to quit both," Dr. Breslau says.

When Dr. Breslau looked for a relationship between mental disorders and quitting smoking, she found that neither active nor remitted disorders made respondents more or less likely to quit smoking successfully during the year preceding the survey.

"The relationship between tobacco use and comorbid psychiatric disorders is complex," says Dr. Kevin Conway of NIDA's Division of Epidemiology, Services and Prevention Research. "While we see variations across the range of disorders included in the comorbidity survey, the consistent pattern in this study emphasizes the importance of active expression of psychiatric disorders—not simply a history of the disorder—in relation to smoking stages."

Source

•Breslau, N.; Novak, S.P.; and Kessler, R.C. Psychiatric disorders and stages of smoking. *Biological Psychiatry* 55(1):69-76, 2004. **NN**

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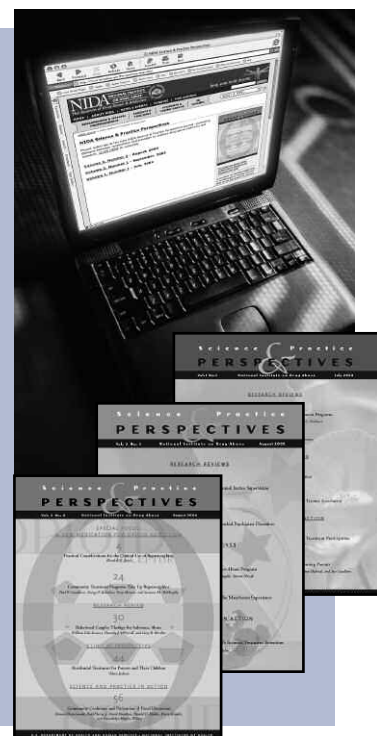
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Network Therapy Enhances Office-Based Buprenorphine Treatment Outcomes

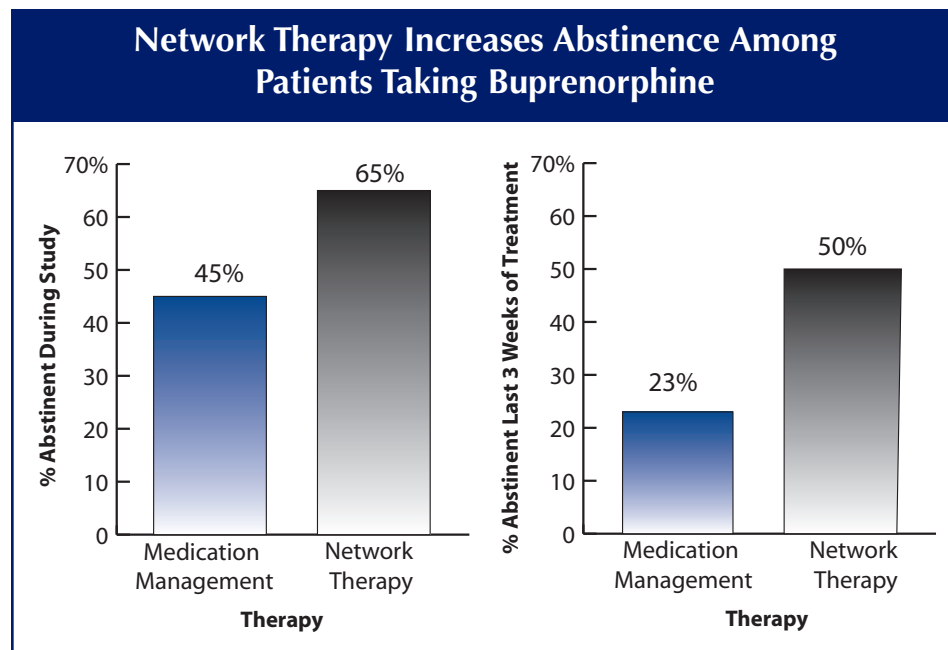
By Lori Whitten, NIDA NOTES Staff Writer

Network therapy—an office-based behavioral treatment that engages family and close friends in the recovery process—enhances abstinence among outpatients being treated with buprenorphine for opioid addiction. By the end of an 18-week NIDA-funded study, abstinence rates of patients who participated in network therapy (NT) were twice as high as those of a comparison group receiving standard medication management (MM) along with buprenorphine.

“NT transforms a few close relations from well-wishers to a team with skills to help patients achieve and maintain abstinence,” says Dr. Marc Galanter, lead investigator of the study. In previous research, Dr. Galanter and his colleagues showed NT’s promise as a therapy for cocaine addiction in both office- and community-based treatment settings; the new results in patients with opioid addiction add to the hopes that NT may offer a psychosocial adjunct to office-based buprenorphine treatment.

Dr. Galanter and colleagues at New York University Medical Center treated 66 heroin-addicted outpatients, aged 21 to 65, who reported abusing the drug for 12 years on average. Most (73 percent) had previous experience with addiction treatment, and about a third (30 percent) had tried methadone maintenance. Most lived with family or friends (77 percent) and were employed (67 percent). The investigators selected patients who could form a network—a few drug-free relatives or friends willing to help the patient achieve and maintain abstinence—and randomly assigned them to either MM or NT.

All patients received a standard course of combined buprenorphine/



Among patients taking buprenorphine for heroin addiction, more of those who participated in network therapy attained abstinence during the 18-week study and throughout the last 3 weeks of treatment, compared with those who participated in medication management.

naloxone tablets (16 mg/4 mg a day) taken under the tongue. Each patient also participated in two half-hour sessions per week of psychosocial treatment—either NT or MM—with a resident training in psychiatry. In MM, the therapist monitors the patient’s response to the medication and encourages him or her to abstain from opioid abuse. The number of MM sessions and time investment are equivalent to those of NT, but the patient does not learn specific behavioral strategies for maintaining abstinence.

At the beginning of the study, patients chose people with whom they had an enduring relationship. Two people, on average, participated in each NT session with the patient. From the first NT session, therapists emphasized the primary guideline for this treatment approach: to focus on

helping the patient achieve abstinence and to avoid discussions of relationship history, blaming, and emotional conflict. During sessions once a week, patients and their helpers communicated openly about events and people related to the patient’s drug abuse and learned cognitive-behavioral techniques used widely in relapse prevention. As the supporters developed an understanding of relapse prevention, they helped the patient anticipate problem situations and develop recovery plans. They concentrated on creating an environment that helped the patient establish a drug-free residence, avoid substance-abusing peers, and stick to a medication regimen.

Although network members offer active support, patients in NT take full responsibility for their recovery. In

weekly one-on-one sessions with a therapist, patients in the study strengthened the cognitive-behavioral skills they learned in network sessions, including monitoring of drug-abuse triggers, coping with craving, managing stress, and problemsolving. Patients made and carried tools to assist them in recovery, such as cards to help them weigh drugs' attractions against the costs of abuse, written plans to deal with emergencies, and contact information for network members. The therapist encouraged patients to participate in 12-step programs, which can offer role models for abstinence and friendships with nonabusers. Throughout treatment, the researchers verified abstinence from illicit opioids with weekly urine tests.

Patients participating in MM and NT spent the same amount of time in therapy, 70 days on average, but more NT participants achieved abstinence by the end of treatment. Half receiving NT attained this goal, confirmed by opioid-free urine tests, during the last 3 weeks of treatment, compared with 23 percent of MM patients. More NT than MM patients produced opioid-free urine samples

during the study (65 percent versus 45 percent). NT patients participated in 10 network sessions on average; those who attended more sessions sustained abstinence longer during the study. Whether the network comprised family or friends did not affect treatment outcomes.

An Office-Based Approach

"My colleagues and I designed NT principally for addiction treatment providers who do not have a large support team," Dr. Galanter says. "We find that those with psychotherapy experience learn the NT approach in about 10 training sessions with subsequent supervision." (See "Network Therapy Expands Treatment Capabilities of Small Practice Providers," *NIDA NOTES*, Vol. 18, No. 2, p. 5.)

"In this approach, a patient and therapist collaborate with a small group to achieve stable abstinence, weaving the contributions of each member and different treatment techniques into a supportive tapestry for a drug-free lifestyle. The network counteracts the environmental and social factors—for example, substance-abusing peers—that often compromise recovery," says Dr. Galanter. Although NT can help patients who have a few close associates willing to support their recovery, the therapy is probably not appropriate for homeless or mentally ill people or those who cannot achieve abstinence on their own for even 1 day.

Studies show that many heroin-addicted patients in treatment continue to abuse some form of opioids, with only about 20 percent of those on buprenorphine medication demonstrating opioid-negative urine tests at the end of 1 month of treatment. Extending the therapy to 2 to 6 months increases the percentage of opioid-negative urine tests to 50 to 60 percent. Dr. Dorynne Czechowicz of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment says, "It's

"The network counteracts the environmental and social factors—for example, substance-abusing peers—that often compromise recovery."

impressive that NT therapy enhanced the results typically seen with short-term buprenorphine medication." She emphasizes that the researchers should examine whether NT reduces abuse of other drugs among opioid-addicted patients, particularly cocaine, which puts people who are in recovery at high risk for opioid abuse relapse. She adds that investigators should also conduct longer-term studies to determine whether patients maintain these treatment gains and demonstrate NT's effectiveness in general medical practice.

Dr. Galanter and his colleagues have posted a brief introduction to NT on the Internet (<http://www.med.nyu.edu/substanceabuse/manuals/nt/>). The American Psychiatric Association sells a training video on NT as an office-based addiction treatment; the video is appropriate for any mental health professional (<http://www.appi.org/book.cfm?id=62142>).

Source

•Galanter, M., et al. Network therapy: Decreased secondary opioid use during buprenorphine maintenance. *Journal of Substance Abuse Treatment* 26(4):313-318, 2004. **NN**

As the supporters developed an understanding of relapse prevention, they helped the patient anticipate problem situations and develop recovery plans.


Twin Study Links Marijuana Abuse, Suicide, And Depression

By Patrick Zickler, NIDA NOTES Staff Writer

Men and women who smoked marijuana before age 17 are 3.5 times as likely to attempt suicide as those who started later. Individuals who are dependent on marijuana have a higher risk than nondependent individuals of experiencing major depressive disorder and suicidal thoughts and behaviors. The researchers who discovered these relationships, in a recent NIDA-funded large-scale epidemiological study, say that although the causes are not clear, their findings demonstrate the importance of considering associated mental health issues in the treatment and prevention of marijuana abuse.

Dr. Michael Lynskey and colleagues at the Washington University School of Medicine in St. Louis, Missouri, gathered data from four groups of same-sex twin pairs (508 identical, 493 fraternal; 518 female, 483 male) enrolled in the Australian Twin Registry. The groups and findings were:

- Among the 277 pairs who were discordant for marijuana dependence (that is, one twin but not the other met the criteria for a diagnosis of marijuana dependence), the dependent twins were 2.9 times as likely as their nondependent co-twins to think about suicide without attempting it, and 2.5 times as likely to make a suicide attempt;
- Among the 311 pairs discordant for early marijuana initiation (just one twin in each pair smoked marijuana before age 17), the early initiators were 3.5 times as likely as their twins to attempt suicide, but no more likely to suffer a major depressive disorder (MDD);
- Among the 156 pairs discordant for diagnosis of MDD before age 17, fraternal but not identical twins with early diagnosis of MDD were 9.5 times as likely to develop marijuana dependence; and

Marijuana Abuse and Depressive Disorders In Twin Pairs					
		Major Depressive Disorder		Suicidal Thoughts	Attempted Suicide
		Identical Twins	Fraternal Twins		
Pairs in which one twin	Developed dependence on marijuana	1.16	3.40	2.89	2.53
	First smoked marijuana before age 17	0.86	1.14	1.10	3.49
Marijuana Dependence					
Pairs in which one twin		Identical Twins		Fraternal Twins	
	Had suicidal thoughts before age 17	1.78		5.50	

The study identified relationships between twins' histories of marijuana abuse and mental health problems.

- Among the 257 pairs discordant for having suicidal thoughts before age 17, fraternal but not identical twins with early suicidal thoughts were 5.5 times as likely as their twins to become dependent on marijuana.

“Overall, the associations between marijuana abuse and depressive disorders suggest a relationship that is contributory but not necessarily causal. Depressive disorders in and of themselves do not cause people to abuse marijuana, and marijuana abuse and dependence do not of themselves cause depression or suicidal behavior,” Dr. Lynskey says. “Nevertheless, clinicians treating patients for one disorder should take the other into account at initial assessment and throughout treatment. In the context of treatment, both need to be addressed, because it is not necessarily the case that eliminating one disorder will get rid of the other.” The fact that two of the relationships were observed in fraternal but not identical twins suggests that the experiences related in each—marijuana dependence and MDD, and marijuana dependence and suicidal thoughts—may share a common underlying genetic basis, notes Dr. Lynskey.

The associations identified in this study are complex, but point to a

simple policy implication, observes Dr. Lynskey. “It is important to see that prevention efforts aimed at one disorder may well have the additional benefit of preventing or reducing the other,” he says.

“Drug abuse and depression co-occur at rates much greater than chance and constitute a serious public health concern,” says Dr. Naimah Weinberg of NIDA’s Division of Epidemiology, Services and Prevention Research. “Understanding how each disorder may contribute to the development and course of the other, and what factors may underlie their co-occurrence, has important implications for prevention and treatment of these disabling conditions. Genetic epidemiologic approaches, such as those applied by Dr. Lynskey and his colleagues, are very powerful tools to help parse out the etiologic relationships between co-occurring disorders.”

Source

•Lynskey, M.T., et al. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Archives of General Psychiatry* 61(10):1026-1032, 2004. [NN](#)

Cognitive-Behavioral Therapies Curb Substance Abuse and Symptoms of PTSD

continued from page 7

During the final 4 weeks of treatment, the CBT patients on average abused substances less frequently, consumed smaller amounts, spent less money on alcohol and drugs, and experienced fewer alcohol- and drug-related problems than patients in standard care. Before treatment, the CBT and community care patients showed the same Addiction Severity Index (ASI) alcohol scores, which averaged 0.4. The average score fell to 0.31 for the CBT patients after treatment, but did not change for those receiving community care. ASI drug scores also tended to decline for the CBT patients, but not for the comparison group.

The CBT patients, but not those in standard care, reported that their initial strong desires to use drugs eased over the course of the study, becoming mild-to-moderate urges that were easier to resist. The CBT patients also experienced less frequent and intense PTSD symptoms and reported fewer intrusive thoughts and avoidance symptoms compared with those receiving standard care. On the Clinician Administered PTSD Scale (CAPS), patients with a score above 65 are usually diagnosed as having PTSD. Before treatment, both the CBT and community care patients were above this clinical threshold, with average scores of 71.4 and 73.9, respectively. After therapy, only CBT patients showed significant improvement, with the average score falling to 54.5, whereas community care participants still showed signs of PTSD and an average CAPS score of 68. These gains had a significant impact on their lives; for example, they reduced the level of interference with occupational functioning, whereas those in standard care reported more interference problems. Only women who participated in

CBT demonstrated improvement in depression-related problems, which changed from moderate to mild on average, according to clinician ratings.

People who have survived trauma often feel that life is meaningless and out of control. In CBT, whether relapse prevention or trauma-focused, the therapist helps the patient break the link between negative feelings, thoughts, and unhealthy behaviors and prepare to react differently in the future. “Cognitive-behavioral therapies offer patients a set of problemsolving skills and strategies that help bring life back under their control,” says Dr. Cecilia McNamara of NIDA’s Division of Clinical Neuroscience, Development and Behavioral Treatment. With practice, their skills improve, which probably explains why the benefits of CBT endure and, according to one study, even increase at later followup points.

Relapse prevention is a well-established treatment for substance abuse, but Dr. Hien’s study suggests that the therapy conveys general coping skills that patients can apply to PTSD. Several small studies have suggested seeking safety’s promise in improving both PTSD symptoms and drug abuse, but clinicians remain concerned that addressing trauma in therapy might trigger relapse and impede addiction treatment. “Our findings suggest that seeking safety—rather than ‘opening Pandora’s box,’ as some clinicians have thought—did not seem to worsen patients’ problems and actually improved substance abuse and PTSD symptoms,” says Dr. Hien. Women who participated in seeking safety attended, on average, as many therapy sessions and stayed in treatment as long as those in relapse prevention, suggesting that the seeking safety treatment does not reopen the trauma, and adding to the evidence that the therapy is not harmful. Although this preliminary study doesn’t provide a conclusive answer for trauma- and addiction-treatment practitioners, it suggests that both seeking safety and relapse prevention

may help people who experience both problems. Dr. Hien says it is a good first step toward evidence-based guidance on managing these commonly co-occurring conditions. Other researchers are studying seeking safety therapy in diverse patient populations, including men and adolescents.

Additional studies are needed to find out whether seeking safety therapy is feasible for community providers. Dr. Hien’s study offered patients 24 individualized sessions with clinical psychologists trained in seeking safety and relapse prevention

“Cognitive-behavioral therapies offer patients a set of problemsolving skills and strategies that help bring life back under their control.”

CBT, a level of therapy that may not be available to most people. Dr. Hien is working with NIDA’s Clinical Trials Network to conduct a study in which community drug abuse counselors will offer a modified form of seeking safety in typical patient populations and treatment settings. Patients are currently signing up to participate in this nationwide study: For information, see http://www.nida.nih.gov/CTN/brochures/pat_info_ctn_015.html.

Source

•Hien, D.A., et al. Promising treatments for women with comorbid PTSD and substance use disorders. *American Journal of Psychiatry* 161(8):1426-1432, 2004. **NN**

Trauma-Related Substance Abuse Persists After Mental Health Symptoms Abate

Mental health symptoms that New York City residents developed following the September 11, 2001, terrorist attacks resolved significantly within 9 months, but residents continued to report elevated levels of tobacco, marijuana, and alcohol use. Rates of depression and posttraumatic stress disorder (PTSD), which were high 1 to 2 months after the attacks, dropped in 6 to 9 months, NIDA-funded researchers found in a followup survey. Substance abuse rates, however, which also were elevated 1 to 2 months after the attacks compared with preattack levels, did not decline substantially.

Dr. David Vlahov and his colleagues at the New York Academy of Medicine conducted telephone interviews of 1,570 randomly selected adults between 6 and 9 months after September 11. Nearly 10 percent of participants reported smoking more cigarettes in the month before the survey than they remembered smoking in the month before the attacks, while 17.5 percent said they drank more alcohol and 2.7 percent said they smoked more marijuana—elevations similar to those reported by a different group of New York City residents

1 to 2 months after the event (see “Depression, PTSD, Substance Abuse Increase in Wake of September 11 Attacks,” *NIDA NOTES*, Vol. 17, No. 4, p. 1).

In the study conducted 1 to 2 months after the event, Dr. Vlahov and colleagues had interviewed people who lived close to the World Trade Center. To compare the results of that study with the current findings, the researchers analyzed the responses of 854 people from the same area of the city. Participants reported a dramatic drop in PTSD symptoms, from 7.5 percent to 0.6 percent, and in symptoms of depression, from 9.7 percent to 5.3 percent, compared with the earlier study group.

For the entire group of participants, key findings on the relationship between mental health symptoms and substance abuse 6 to 9 months after the disaster are:

- More individuals who increased their smoking reported current PTSD symptoms (4.3 percent) compared with those who did not (1.2 percent).
- Symptoms of depression were more common among those who increased substance use compared



with those who did not: 14.6 versus 5.2 percent for smoking, 11.8 versus 5.2 percent for drinking, and 34.1 versus 5.3 percent for marijuana abuse.

- Fifteen percent of those directly affected by the attacks smoked more cigarettes, compared with 8 percent of those not directly affected.

Source

• Vlahov, D., et al. Consumption of cigarettes, alcohol, and marijuana among New York City residents six months after the September 11 terrorist attacks. *American Journal of Drug and Alcohol Abuse* 30(2):385-407, 2004. **NN**

NIDA Support Brings First fMRI to South Africa

South Africa's Tygerberg Academic Hospital now has the continent's first functional magnetic resonance imaging (fMRI) system. The machine was installed in November 2004 as part of an ongoing NIDA-funded collaboration between McLean Hospital, Harvard Medical School, and the South African Medical Research Council (MRC) Unit on Anxiety and Stress Disorders at the University of Stellenbosch, Tygerberg, South Africa.

With the new fMRI system, MRC researchers have a state-of-the-art tool they can use to observe people's brain

activity under a variety of conditions. Dr. Deborah A. Yurgelin-Todd of Harvard and Dr. Paul Carey of the MRC plan to use the system to compare marijuana abusers' and control subjects' brains as they make decisions and perform tasks involving behavior inhibition and memory. Dr. Yurgelin-Todd and her colleagues have trained their MRC colleagues in use of the fMRI and the project's protocol. To facilitate collaboration and the analysis and interpretation of their results, investigators in both countries will deposit their data in a shared database. **NN**



Dr. David Olson, left, of the Brain Imaging Center, McLean Hospital, Harvard Medical School, and Dr. Paul Carey, MRC Unit on Anxiety and Stress Disorders, prepare to test Africa's first fMRI system, installed with NIDA funding.

NIDA Web Site Addresses Consequences of Steroid Abuse

Despite its dangers, anabolic steroid abuse continues as athletes and others attempt to gain competitive advantage and to enhance their musculature, NIDA Director Nora D. Volkow said in recent testimony before the Government Reform Committee in the U.S. House of Representatives. “We are now facing a very damaging message that is becoming pervasive in our society—that bigger is better, and being the best is more important than how you get there.”

Dr. Volkow’s statement is one example of what visitors can find on NIDA’s Web site, <http://www.steroidabuse.gov>, which is devoted to educating the public about the dangers of anabolic steroids. The site provides resources, publications, and links to public service announcements about the consequences of steroid abuse. In the full text of Dr. Volkow’s March 17, 2005, testimony before the Government Reform Committee, she discusses the Institute’s many efforts to find treatments to mitigate the adverse effects of anabolic steroid abuse and to better understand how these substances affect the body and brain.

Anabolic-androgenic steroids are synthetic substances related to male sex hormones. “Anabolic” refers to muscle-building, and “androgenic” refers to these substances’ effect of promoting masculine characteristics such as hair growth or a deepened voice. Steroid drugs are available legally only by prescription to treat conditions that occur when the body produces abnormally low amounts of testosterone, such as delayed puberty and some types of impotence. They are also prescribed to treat body-wasting in patients with AIDS and other diseases that result in loss of lean muscle mass. Abuse of anabolic steroids

**ANABOLIC
STEROID
ABUSE**

STERIODS?
Not in my game plan.
How about you?



can lead to serious health problems, some irreversible.

Anabolic steroids differ from other drugs of abuse in that many of their “reinforcing effects” (i.e., those effects that keep a person using a drug) are not experienced immediately or rapidly. The main reasons people abuse steroids are to improve their performance in sports by increasing muscle size and to enhance their appearance by reducing body fat. Although these effects can take months to develop, once they do, they may comprise a strong incentive to continue abuse.

The most recent NIDA-University of Michigan Monitoring the Future survey found that in 2003 and 2004, about 2.5 percent of 12th-graders reported abusing steroids during the past year. This is a peak level among this group, and translates into an estimated 79,000 high school seniors involved with these substances. Meanwhile, the percentage of 12th-graders concerned that steroids might do them harm had fallen to 56 percent from a high of 71 percent in 1992. When students view drugs as less harmful, their levels of abuse often increase. On the positive side, among 8th-graders, steroid abuse in the past year declined from 1.4 percent in 2003 to 1.1 percent in 2004.

Anabolic steroids are taken orally or injected, typically in “cycles” of weeks or months. Cycling involves taking multiple doses of steroids over a specific period of time, stopping for a period, and starting again. In addition, users often combine (or “stack”) several types of steroids to maximize the substances’ effects while—or so abusers believe—minimizing their negative effects.

“Some percentage of steroid abusers become addicted to the drugs, as evidenced by their continuing to take steroids in spite of seriously adverse medical and behavioral problems,” Dr. Volkow said. “One of the most dangerous consequences is the severe depression that can occur during withdrawal, which, if not recognized and treated properly, can result in suicide weeks after drug discontinuation. Indeed, untreated, depressive symptoms have been known to persist for a year or more after the abuser stops taking the drugs.”

Other consequences of anabolic steroid abuse can include liver and heart disease, stroke, and increased aggression. People who inject anabolic steroids run the added risk of contracting and/or transmitting HIV/AIDS or hepatitis through sharing contaminated needles. In addition, there are some sex-specific side effects:

- For men—shrinking of the testicles, reduced sperm count, infertility, baldness, enlarged breasts, increased risk for prostate cancer.
- For women—growth of facial hair, male-pattern baldness, changes in or cessation of the menstrual cycle, enlargement of the clitoris, deepened voice.
- For adolescents—permanent short stature due to premature cessation of skeletal growth.

NIDA’s Web site also features links to the Institute’s “Game Plan” public service announcements, which encourage young men and women to work with what nature has provided and not to “cheat” by using steroids and thereby expose themselves to the negative side effects associated with these drugs. NIDA released its most recent Game Plan in June 2005. **NN**

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Staff Writers: Lori Whitten, Ph.D., and Patrick Zickler, *MasiMax Resources, Inc.*

Design/Layout: Maggie Bray, *MasiMax Resources, Inc.*

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