

Standard Treatments Help Depressed Smokers Quit

As smoking rates fall in the United States, mentally ill individuals comprise a larger percentage of people who continue to light up.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Smoking cessation interventions that are effective in the general population also help for depressed smokers, suggests a study of outpatients at four mental health clinics. Dr. Sharon Hall and colleagues at the University of California, San Francisco; the University of Rhode Island; and Kaiser Permanente Northern California found that depressed smokers who were treated with a combination of motivational counseling, nicotine patches, and behavioral therapy were more likely than their

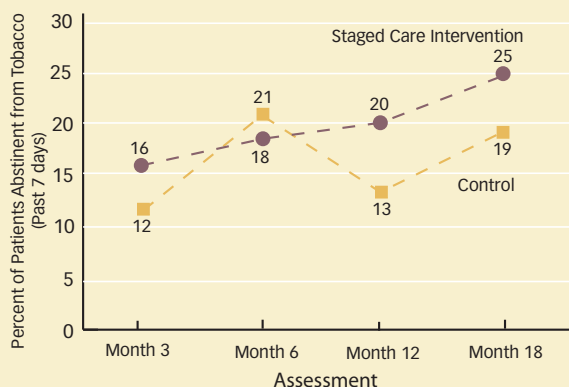
counterparts who did not receive the interventions to be smoke-free at 12- and 18-month assessments.

“Patients in our study mirrored the general population of smokers in their readiness to quit, acceptance of treatment, and cessation outcomes—findings that surprised me and my colleagues,” says Dr. Hall, lead investigator of the study. Further, patients with severe symptoms of depression both accepted the interventions and benefited from them. “Our findings suggest that clinicians should offer depressed outpatients nicotine addiction treatment and should start with available smoking cessation interventions. They need not be overly concerned about patients’ levels of depression,” says Dr. Hall.

The investigators recruited 322 men and women from a university-based clinic and three sites of a health maintenance organization who were being treated for depression and smoked daily. Most of the volunteers (79 percent) were taking psychiatric medication for moderate depression. On average, they had smoked for 24 years, smoked 15 cigarettes a day, and had tried to quit six times.

At the start of the study, the participants provided information on their depression severity and treatment, smoking behavior (confirmed by expired air carbon monoxide measurements), nicotine dependence level,

MORE DEPRESSED SMOKERS QUIT WITH STAGED CARE INTERVENTION Among smokers in outpatient treatment for depression, more who participated in the Staged Care Intervention achieved abstinence at the 12- and 18-month followups compared with participants in the control group.



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Genes and Smoking

Most of the 44.5 million American adults who smoke cigarettes would prefer not to. Why do so many would-be quitters fail, even with the help of stop-smoking interventions like nicotine replacement? Why, for that matter, do people become addicted to smoking in the first place? The answers lie partly in our genes.

NIDA researchers in collaboration with Perlegen Sciences, Inc., a private company, recently completed a search of the entire human genome for differences between individuals who are nicotine-dependent and those who smoked but never became dependent. Their target: single nucleotide polymorphisms (SNPs), locations on the genome where individuals differ by just one chemical unit in the makeup of their DNA. From 2.2 million known SNPs, researchers have identified roughly 40 to 80 that are highly correlated with nicotine addiction.

Once researchers link an SNP statistically to drug abuse, the question becomes: Does the gene do anything that might explain why people with one of its forms are more vulnerable to drugs than people with another? Some of the genes researchers have implicated in addiction affect the dopamine reward circuit. Others involve neurotransmitter systems and neural pathways not previously known to figure in smoking's effects. Researchers will use techniques such as brain imaging to correlate genetic differences with differences in brain structure or function and psychological tests to match them to behavior. Findings from the genome exploration may ultimately yield novel, more effective interventions.

Genetic variations can only partly explain why people become addicted to nicotine: A person's genetic makeup, experiences, and surroundings all combine to determine whether he or she will smoke and, if so, how difficult quitting will be. NIDA-funded epidemiologists and behavioral scientists are conducting a large longitudinal study to elucidate these interactions. They have been following pairs of twins, now 17 years old, collecting information about participants' smoking and environmental factors like stressors and peer relationships that can increase the risk of substance abuse or protect against it. The next step will be to analyze these data, together with information on the twins' genetic and biological traits.

NIDA-supported researchers are also working to discover why interventions like nicotine replacement therapy (NRT) work for some people and not others. By comparing smokers who have successfully used pharmacotherapy with those whose efforts to quit have failed, the researchers hope to identify groups of genes that predict who will do well with NRT, with bupropion, or with varenicline, the newest smoking cessation drug. The ultimate goal is to tailor the treatment to the smoker. Ultimately, we hope genetic studies will lead to strategies that protect vulnerable young people from addiction. ■

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Incentives Reduce Stimulant Abuse During Methadone Maintenance

Methadone maintenance patients who earned chances to win prizes by providing stimulant-negative urine samples were twice as likely as those who received usual care to attain abstinence from these drugs in a study conducted at six outpatient programs. Dr. Maxine Stitzer and colleagues in the NIDA Clinical Trials Network found that adding an abstinence-based incentive to usual care—daily methadone and individual and group counseling at least once a month—tripled the likelihood of continuous stimulant abstinence for 4 or more weeks during the 12-week study. Prizes for the incentive program cost about \$120 for each of the 388 participants, on average, or \$1.42 a day. Prize-based incentives have proven successful in helping stimulant abusers attain abstinence during community-based treatment (see “Low-Cost Incentives Improve Outcomes in Stimulant Abuse Treatment,” *NIDA Notes*, Vol. 21, No. 1), and the new findings demonstrate the intervention’s efficacy for a diverse population of opioid-addicted patients receiving usual care in typical treatment settings.

> [Archives of General Psychiatry](#) 63(2):201-208, 2006.



Naltrexone–Nicotine Patch Combination Shows Promise

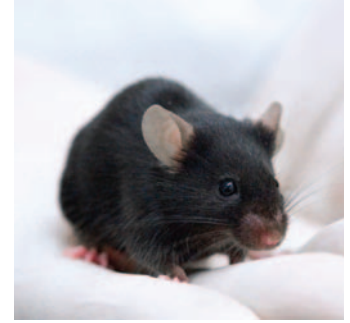
Supplementing nicotine replacement therapy with naltrexone yielded improvements in outcomes in a double-blind 6-week trial. Among the 295 enrollees who completed the trial, quit rates were 72 percent with 100 mg of naltrexone, 51 percent with 25 mg, 48 percent with 50 mg, and 48 percent with a naltrexone placebo. Patients who took the 100 mg dose reported the greatest reductions in nicotine cravings and withdrawal symptoms. The investigators observed that patients receiving the 25 mg and 50 mg doses gained the least weight, and suggested that combination therapy with low-dose naltrexone and the patch be considered for smokers concerned about weight gain. The researchers cautioned that naltrexone augmentation for smoking cessation requires further study, as abstinence differences evened out by a 3-month followup, and did not recur at 6- and 12-month followups.

> [Archives of Internal Medicine](#) 166(6):667-674, 2006.

Scientists Pinpoint Brain’s Sweet Tooth

Drs. Susana Peciña and Kent Berridge of the University of Michigan have traced rats’ liking for sweets to a 1-cubic millimeter site in the medial shell of the nucleus accumbens. Using fine-grained brain mapping, the researchers correlated μ -opioid activation of this area [by D-Ala²-N-Me-Phe⁴-Glycol⁵-enkephalin (DAMGO)] with the facial reactions rats exhibit upon receiving infusions of sweet tastes into the mouth. Enhancing μ -opioid activity in this hedonic “hot spot” produced two to four times the number of positive reactions (e.g., licking) to sucrose relative to other regions of the medial shell. Stimulating the hot spot with DAMGO also reduced the rats’ negative reactions to a bitter taste by 25 percent. The findings suggest that opioid circuits in the medial shell involved in liking (e.g., positive facial expressions in reaction to a taste) and wanting (e.g., pressing a lever for a substance) are related but not identical, as activating μ -opioid circuits in widely distributed areas of the medial shell increased food intake.

> [The Journal of Neuroscience](#) 25(50):11777-11786, 2005.



Antipsychotic Drug Prevents Morphine Tolerance in Mice

Dr. Zaijie Jim Wang and colleagues at the University of Illinois suppressed morphine tolerance and dependence in mice by blocking calcium/calmodulin-dependent protein kinase II (CaMKII), which may contribute to chronic pain in the central nervous system. In a followup study, the investigators found elevated levels of CaMKII activity in the brain and spinal cord (an 81 percent and 222 percent increase, respectively) of mice displaying morphine tolerance compared with mice that did not. Trifluoperazine, an antipsychotic drug and a CaMKII inhibitor newly identified by these researchers, prevented both the increase in CaMKII activity and the development of opioid tolerance and disrupted established opioid tolerance in the animals. The findings suggest that CaMKII-suppressing drugs may reduce morphine tolerance and ultimately be of value in treating pain and fighting opioid addiction.

> [Neuroscience Letters](#) 397(1-2):1-4, 2006; [Journal of Pharmacology and Experimental Therapeutics](#) 317(2): 901-909, 2006.

Vaccine May Reduce Fetal Exposure to Nicotine

Antibodies that block nicotine's path across the blood brain barrier may also inhibit placental absorption.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

Vaccine-induced antibodies that facilitate smoking cessation by blocking nicotine penetration into the brain also markedly reduce the drug's passage across the *ex vivo* human placenta, a NIDA-funded study has demonstrated. The finding suggests that maternal immunization during pregnancy may be safe and may to some extent protect the fetus from exposure to nicotine.

The adverse effects of maternal smoking during pregnancy include increased rates of miscarriage, premature delivery, low birth weight, neonatal mortality, and sudden infant death syndrome (SIDS). Increasingly, research has linked prenatal smoking exposure to children's neurobehavioral problems, such as attention deficit-hyperactivity disorder. The role of nicotine in causing this damage is not entirely clear, but animal studies suggest the drug may compromise fetal development directly or through its effects on the placenta. "We desperately need medications that can help women quit smoking during pregnancy, medications that are both effective and do not themselves harm the fetus. This study supports the potential use of immunization," says Dr. Paul Pentel of the University of Minnesota Medical School, one of the investigators.

THE EXPERIMENTAL PROCEDURE

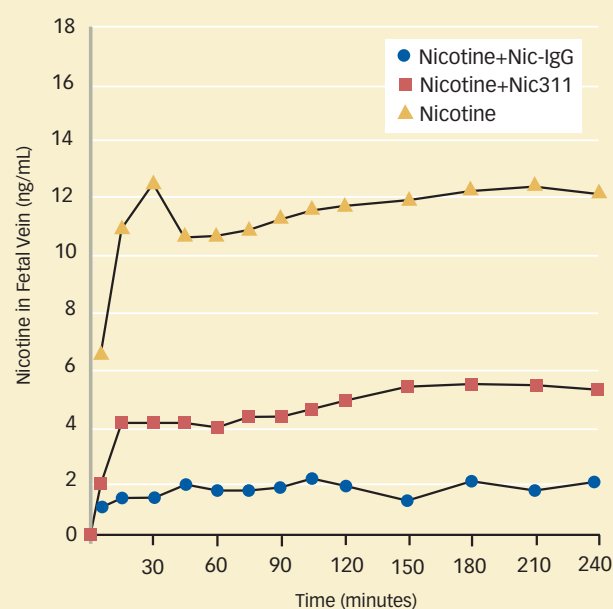
NicVAX, a vaccine being developed by Florida-based Nabi Biopharmaceuticals with NIDA support, joins the nicotine mol-

ecule to a protein. The resulting molecule provokes the production of antibodies that combine with circulating nicotine to create a complex molecule that is too large to cross the blood-brain barrier. When the amount of nicotine reaching the brain drops far enough, the concept goes, "the smoker will no longer get a rewarding effect and will quit," says Dr. Scott Winston, a Nabi researcher. A recent small-scale clinical study found dose-related improvements

in 30-day quit rates among 68 immunized smokers ("Nicotine and Cocaine Vaccines Move Forward," *NIDA Notes*, Vol. 20, No. 5).

The two antibodies used in the placenta transfer study, nicotine immune globulin (Nic-IgG) and a monoclonal antibody (Nic311) were taken, respectively, from rabbits and mice that produced them in response to immunization with NicVAX. The research team, headed by Dr. Mahmoud Ahmed of the University of Texas Medical Branch, Galveston, tested the antibodies' effects on placental tissue and cross-placental nicotine transfer using a method developed in the mid-1980s: An intact lobule was dissected from placentas

RESULTS OF MEASURING THE CONCENTRATION OF NICOTINE IN THE FETAL VEIN The addition of a nicotine-specific antibody significantly reduces the appearance of nicotine in the fetal vein. Of two antibodies tested, Nic-IgG was more effective than NIC311.



taken immediately after delivery and placed in phosphate-buffered saline. The researchers inserted catheters into blood vessels on the maternal and fetal side of the placental lobule and perfused each with tissue culture medium from a separate reservoir, creating distinct maternal and fetal circuits. They monitored placental function and viability for 2 hours, and then added nicotine to the fluid in the maternal reservoir. "We used a concentration (40 ng/mL) that has been reported in the circulation of mothers who smoke," Dr. Ahmed says. Either Nic311 or Nic-IgG along with nicotine was added to the maternal reservoir. Following these infusions, the

researchers continued to monitor placental tissue health and tracked nicotine and antibody concentrations in both maternal and fetal circuits for 4 more hours.

SAFETY REASSURANCE

“Our primary interest in these studies was vaccine safety: Would it be safe to vaccinate women who may become pregnant, or during pregnancy? Antibodies might protect the fetus, but we also worried that they might escort nicotine across the placenta or sequester it in the fetus, increasing exposure,” says Dr. Pentel. “The studies look reassuring.”

When nicotine alone was added to the maternal circuit, it readily crossed the placenta; its concentration in the fetal circuit increased rapidly over the first 30 minutes. It did not change in the next 210 minutes. The addition of either antibody markedly reduced the rate at which nicotine crossed the placenta. With Nic₃₁₁, nicotine reached a concentration of 1.8 ± 0.8 ng/mL in the fetal circuit in the first 5 minutes—about one-fourth of the transfer in the absence of the antibody. There was no significant increase in fetal circuit nicotine after the first 30 minutes. Nic-IgG had an even more pronounced effect: The concentration of nicotine in the fetal circuit was about one-half what it had been with

Nic₃₁₁ after the first 5 minutes (1.0 ± 0.04 ng/mL); it, too, rose little after that. Both antibodies also reduced the amount of nicotine retained in placental tissue.

“There was no effect of nicotine or either antibody on placental function or viability,” Dr. Ahmed says. No appreciable amount (less than 1 percent) of either antibody appeared in the fetal circuits at any point in the experiment, suggesting that placental transfer was negligible.

Whether vaccination would protect the fetus from nicotine if a mother continued smoking is not yet clear. “I’m not sure that the effect would be large enough,” Dr. Pentel says. Previous animal studies in which he was involved found that while antibodies sharply slow the rate at which a single dose of nicotine reaches the brain, they do not stop the process altogether. “When nicotine is administered chronically in a way that approximates daily smoking, its long-term accumulation in the fetal brain looks the same in vaccinated and unvaccinated animals.” Vaccination of pregnant rats reduced nicotine transfer to the fetal circulation and brain for 25 minutes after a single dose, but did not change accumulation in the fetal brain when nicotine was administered chronically. In another study, maternal vaccination did not prevent nicotine-induced upregulation of nicotinic

cholinergic receptors or changes in gene expression (*c-fos*) in the fetal rat brain, Dr. Pentel observes. The *ex vivo* system used in the current study is not intended to model the effects of continual daily smoking, he says, but rather provides insight into the shorter term effects of antibodies on nicotine transfer across the placenta, as well as placental viability.

Dr. Amrat Patel, of NIDA’s Chemistry and Pharmaceuticals Branch, says the current study represents an important advance beyond animal research in suggesting that nicotine-specific antibodies can reduce placental transfer of nicotine in humans as well, but more work is needed to know whether the effect will be sufficient to prevent neurotoxicity. “We need to determine how much nicotine is necessary to cause fetal damage, and how to make sure nicotine does not approach that level.” Antibodies with higher affinity for nicotine may make a difference, he says; as vaccine research continues, “we’ll probably progress to develop antibodies that are even better able to sponge up nicotine.” ■

SOURCE

Nekhayeva, I.A., et al. Effects of nicotine-specific antibodies, Nic₃₁₁ and Nic-IgG, on the transfer of nicotine across the human placenta. *Biochemical Pharmacology* 70(11):1664-1672, 2005.

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■ STANDARD TREATMENTS

[Continued from page 1]

readiness to quit smoking, previous quit attempts, and commitment to abstinence. They repeated these self-reports 3, 6, 12, and 18 months later.

The active intervention in the study was Staged Care Intervention (SCI). At the outset and months 3, 6, and 12, participants assigned to SCI answered a computerized questionnaire about smoking, its advantages and disadvantages, triggers for smoking-related thoughts and behaviors, and ways to change these thoughts and behaviors. The computer provided an individualized feedback report that the patients and counselors reviewed together in a 15-minute session. The report classified each patient's readiness to quit based on the Stages of Change model, compared his or her responses with those of others in the program, showed changes from earlier reports, and identified triggers for smoking and strategies to move to the next stage. If the patient expressed a desire to quit, he or she began an 8-week cessation treatment. Each participant in the control group received a self-help guide to smoking cessation and a list of programs in the area, but no therapeutic contact or advice about smoking cessation.

OPPORTUNITY TO ENGAGE

About one-third (34 percent) of SCI participants entered cessation treatment. They received nicotine patches (7, 14, or 21 mg, depending on level of smoking and week of study) and six 30-minute counseling sessions. The focus of counseling was immediate and complete cessation at an agreed-upon date. During sessions, patients developed a commitment to abstinence, established a quit plan, identified reasons for smoking, reviewed the benefits of quitting, and received information on nutrition and exercise. Patients who did not attain abstinence with nicotine patches were prescribed bupropion if their mental health care provider deemed it medically appropriate.

The researchers included all SCI partici-

Computer Feedback Nurtures Change

Excerpts from two feedback reports illustrate individualized care:

Feedback for a person who has no immediate intention to stop smoking: Your answers on the last survey show that you need to begin to change the way you look at yourself as a smoker. You can do this by thinking more about your attitudes and beliefs about your smoking.

For example:

- If you think smoking could be bad for your health, be specific about how smoking is affecting you. (For example: Cigarettes give me a sore throat—or cause my cough—or make me feel tired all the time.)
- How would your life change if you quit? (For example: I would set a better example for others—or I'd have more money to spend on things I enjoy.)
- What might be difficult if you quit? Can you plan in advance how you will handle those difficulties? (For example: I could get more exercise so I won't gain weight.)

Feedback for a person who intends to quit in the next 6 months: You seem to be well aware of the risks of smoking ... you're doing as well as others who have used this program to help themselves quit smoking! To make more progress:

- Weigh the "pros" and "cons" of smoking;
- Learn more about quitting; and
- Keep thinking of how you're doing.

pants, including those who did not enter cessation treatment, in their data analysis. At the 12-month assessment, 20 percent of participants in the SCI group and 13 percent in the control group had verified 7-day tobacco abstinence. The SCI group's advantage persisted at the 18-month assessment (25 percent versus 19 percent). More SCI (44 percent) than control group participants (34 percent) endorsed permanent abstinence—an attitude the researchers say predicts success in changing behavior. The intervention was particularly effective for heavy smokers: Among participants who smoked more than a pack of cigarettes a day, those assigned to SCI were about twice as likely as controls to report a quit attempt during the study.

"The findings of Dr. Hall and her colleagues suggest that, even among severely depressed smokers who are not motivated to quit, the SCI increases abstinence rates compared with a standard control," says Ms. Debra Grossman of NIDA's Division of Clinical Neuroscience and Behavioral Research. The finding adds to the justification for American Psychiatric Association and Agency for Health Care Research and

Quality recommendations to offer smoking cessation therapy to people with mental disorders.

"The high prevalence of smoking in mental health clinics presents an opportunity to engage people with depression in smoking cessation," says Dr. Hall. She adds that one advantage to doing so is the supportive environment of such settings: if cessation worsens depression, then patients can obtain additional help. Dr. Hall notes that the treatment benefits seen among the study population of mostly employed patients enrolled in a health maintenance organization might not apply to depressed people who are disadvantaged or in treatment at publicly funded hospitals. Dr. Hall's team plans to conduct a cost-effectiveness analysis of the intervention to help clinic directors decide on resource allocation. ■

SOURCE

Hall, S.M., et al. Treatment for cigarette smoking among depressed mental health outpatients: a randomized clinical trial. *American Journal of Public Health* 96(10):1808-1814, 2006.

Depot Naltrexone Appears Safe and Effective for Heroin Addiction

A long-lasting, injectable formula of naltrexone performed well in a pilot clinical trial.

BY SARAH TEAGLE,
NIDA Notes Contributing Writer

In a NIDA-supported pilot study, a new formulation of naltrexone that patients receive by injection once every 30 days appeared safe and helped heroin-addicted outpatients persevere in treatment. Investigators observed a dose-dependent relationship between the medication, called depot naltrexone, and patient retention rates.

Naltrexone helps patients overcome urges to abuse opiates by blocking the drugs' euphoric effects. Some patients do well with it, but the oral formulation, the only one available to date, has a drawback: It must be taken daily, and a patient whose craving becomes overwhelming can obtain opiate euphoria simply by skipping a dose before resuming abuse.

"What's exciting about this slow-release formula is that it provides continuous protection for a month at a time, freeing patients from having to decide to take or not take the medication every day," says Dr. Sandra Comer, lead investigator of the study. "By increasing treatment retention, depot naltrexone may allow patients greater contact with appropriate supportive counseling and ease their transition to a life without heroin."

Dr. Comer and her collaborators recruited 60 heroin-addicted, predominantly male (77 percent) adults, aged 18 to 59 years, through advertising in local newspapers and word of mouth in New York City and Philadelphia. To be eligible, patients could not be addicted to any drugs other than heroin, caffeine, or nicotine. After initial heroin detoxification, the investigators randomly assigned participants to receive low-dose depot naltrexone, high-dose depot naltrexone, or placebo at the

beginning of weeks 1 and 5. All participants received twice-weekly relapse prevention behavioral therapy.

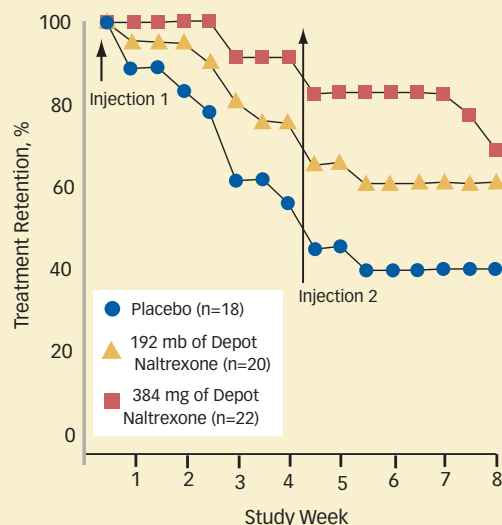
After 8 weeks, 68 percent of the patients receiving 384 mg of naltrexone remained in treatment, compared to 60 percent of those receiving 192 mg, and 39 percent of those on placebo. The percentage of urine samples negative for opioids was highest for the group receiving 384 mg of naltrexone (62 percent) and lowest for the placebo group (25 percent). After receiving the medication, patients in the naltrexone groups reported "needing heroin" significantly less than those taking placebo.

The study participants experienced no apparent serious side effects. Despite previous reports associating high doses of naltrexone with hepatotoxicity, only one patient developed elevated liver enzymes, which the researchers attributed to a new-onset hepatitis C infection rather than the medication. Heroin overdose, another potential concern for patients on naltrexone, was not observed in the study; several patients did abuse heroin while on naltrexone, but reported no pleasure from it.

Encouraged by their results, Dr. Comer and her colleagues are beginning a 6-month trial with a larger number of participants. "We want to make sure the depot formula helps over a longer period of time," she explains. "Having more tools is really helpful for providers. Some people do better on methadone, others on naltrexone. We'll have more success if we can offer both."

NALTREXONE HELPS PATIENTS STAY IN TREATMENT

More patients receiving 384 mg of depot naltrexone attended each weekly treatment session, compared with those receiving a smaller dosage of depot naltrexone or those who received placebo.



Dr. Richard Hawks of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse, says pharmaceutical companies are developing even longer-acting versions of naltrexone—a 6-month sustained-release formula. "But a drug alone never works," he says. "To be effective, the medication must be combined with behavioral therapy. Many years of behavioral therapy research shows that the longer someone is in treatment, the longer the time to relapse. Longer-acting, sustained-release medications help maximize this effect."

SOURCE

Comer, Sandra D., et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence. *Archives of General Psychiatry* 63(2):210-218, 2006.

Uneven Regional Brain Development Contributes to Adolescent Risk-Taking

Along with immature impulse regulation, heightened motivational drive appears to predispose adolescents to risky behavior.

BY LORI WHITTEN,
NIDA Notes Staff Writer

From drag racing to abusing drugs, teenagers sometimes act with scant apparent regard for consequences. Scientists have linked this impulsiveness and risk-taking to immaturity of the brain region called the orbitofrontal cortex (OFC), which helps us control impulses to seek gratification when they are out of line with our overall goals. New NIDA-funded research suggests that, in addition to having an underdeveloped restraint system, the teenage brain generates more intense impulses than a child's or an adult's.

Drs. B.J. Casey and Adriana Galvan and colleagues at Cornell and Stanford Universities undertook the research because they doubted that the protracted development of the OFC fully explained age-related patterns of risk-taking. "Children and adolescents both have an immature prefrontal area, but only adolescents make risky decisions," says Dr. Galvan. "We speculated that the adolescent brain must be unique in some way that promotes risk-taking."

The researchers hypothesized that the nucleus accumbens (NAc) might play a complementary role to the OFC's in adolescent risk-taking. The NAc—whose functions include alerting and motivating us when we have an opportunity to obtain something desirable—generates the very impulses to act that the OFC moderates in the interests of safety and longer-term goals. As a result, if the NAc activity were highly sensitized at the same time the OFC response was weak, the drive to act could more markedly overbalance the inclination to caution—and youths

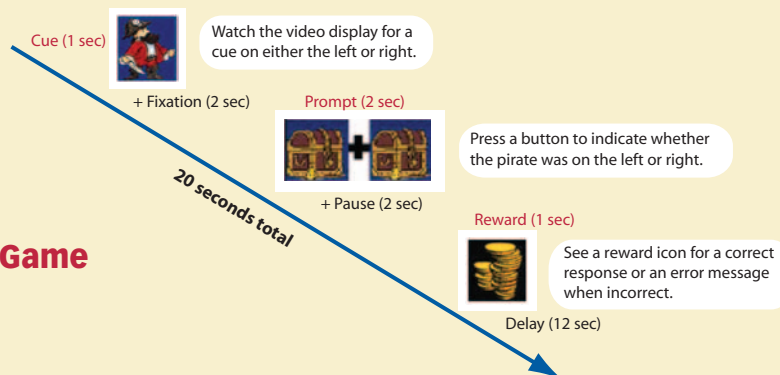
Pirates and Payoffs Game Reveals Differences in Brains of Adults, Teens, and Kids

Researchers continuously measured changes from baseline neural activity during the cue, prompt, and reward experiences. They also measured response speed to the prompt, which indicated whether participants had learned the cue-reward association. Before the imaging session, each participant was told that he or she could earn up to \$25 for quick and accurate responses on the task, which was to:

Cues and Rewards



The Game



would take more chances. Drs. Casey and Galvan's experiment confirmed their hypothesis, and also produced insights into the interplay between the NAc and OFC during reward learning.

PIRATES AND PAYOFFS

The investigators gave 13 children, 12 adolescents, and 12 adults an opportunity to win up to \$25 playing a video game. First, a picture of a pirate would flash on the video screen, followed by a brief pause, then a picture of treasure chests. The goal was to remember which side the pirate appeared on and indicate it by pressing a button as quickly as possible after the chests appeared. After each correct response, the screen showed a picture of coins, signaling either a small, medium, or large payoff.

The researchers did not tell the participants about one element of the game: The pirate picture had three variants, each linked to one of the payoff levels. A correct response after a picture of the pirate holding a cup produced a picture of a single coin; the pirate with his sword brought two piles of coins; and the pirate with a telescope yielded four piles.

The participants played 90 rounds each and responded accurately on at least 96 percent of tries. The researchers registered the participants' reaction times and recorded brain activity in the NAc and OFC with functional magnetic resonance imaging.

RESPONDING TO LARGE TREASURE

The neural responses during the large payoff confirmed previous findings that the OFC is underdeveloped in childhood and

adolescence, relative to adulthood. Specifically, OFC activity was more diffuse—spread through a larger volume of tissue—among the two younger groups in the study, relative to the adults. Greater activity diffusion generally is a sign that a brain region is less mature and lacking tight organization. Children’s OFC activity remained the same no matter which coin picture appeared and was the most intense of all the groups, suggesting that the process of evaluating the consequences of responding required greater effort.

Consistent with the researchers’ hypothesis, the adolescent study participants exhibited twice as much NAc activity when they saw the large payoff, compared to the adults and children. “Our findings suggest that a normally developing adolescent’s NAc and associated subcortical brain circuits dopamine-rich areas that generate emotion, motivation, and reward—mature earlier than the prefrontal brain region,” Dr. Galvan explains. As a result, until OFC

development catches up in a person’s early twenties, NAc-generated motivational drive overbalances OFC-instituted caution and forethought.

LEARNING AND MOTIVATION

The data on brain activity, together with observations of the study participants’ reaction times, illuminated the dynamics of learning at each of the three developmental stages. Overall, the adults’ performance and brain scans pointed to an integrated and—by the end of the trial—complete process of learning and responding. The adolescents demonstrated learning powers and processes intermediate between adults and children, and the chil-

dren exhibited no obvious signs of learning.

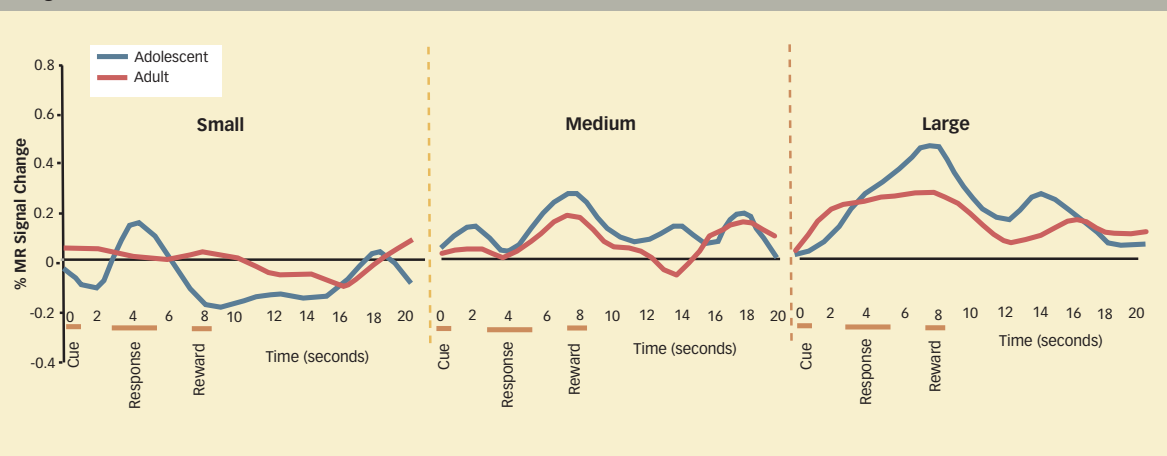
- **Adults:** Although only one adult could articulate the connections between the three pirate pictures and their associated payoff levels, every adult’s reaction times indicated that his or her brain registered these relationships. At the start of the game, the adults responded equally quickly to all three pictures; by the end, they were responding fastest to the pirate linked to the big payoff, slowest to the small-payoff pirate, and with intermediate speed to the moderate-payoff pirate.

Like their reaction times, the adults’ NAc activity levels quickly settled into a pattern of high, moderate, and low

responded quickest to the pirate that predicted the maximum payoff, and with similar slower speeds to the medium and small payoff pirates. It is likely that the adolescents felt highly motivated to obtain the highest reward, but failing that, desired the medium reward no more than the low one.

Like the adults, the teens ultimately evolved a trilevel pattern of NAc responsiveness, one for each of the three rewards. The teens’ NAc activity levels also suggested that they experienced an all-or-nothing response to the rewards: by the later trials, they were higher than adults’ responses to the large treasure, but

REWARD RESPONSE IS MAGNIFIED IN ADOLESCENTS Teens exhibited exaggerated activity—a bigger dip during the small and a spike during the large payoffs—in the nucleus accumbens compared with adults, as seen in a composite of trials late in the game.



responses corresponding to the sizes of the rewards in play in each round. Their OFC activity levels declined from the early to the later rounds. The researchers suggest that the high initial OFC levels reflected the region’s involvement in early learning, as it received information on the sizes of the payoffs and fed it back to the NAc. Once the NAc attuned its responses appropriately to the significance of each pirate, the need for OFC participation lessened, and OFC activity accordingly declined.

- **Adolescents:** Instead of reacting with rapidity proportional to the reward size associated with each pirate, the teens

lower in response to the low payoff at the end of the trials (see chart).

- **Children:** Children reacted to all the pirate pictures with similar speed from the first to the last rounds of the game. Consistent with their lack of learning, their NAc intensity remained constant throughout the game, no matter the size of the reward on offer.

“The children’s lack of learning may reflect the immaturity of the OFC in this early developmental stage or that the task was too complex for them to learn in the few trials given,” says Dr. Galvan. It is also possible, she says, that children perceived the reward values differently than adoles-

UNEVEN BRAIN DEVELOPMENT

[Continued from page 9]

cents or adults. “The kids were happy to play the game and have an opportunity to win money, regardless of the amount,” she observes.

BRAIN-BASED PREVENTION

“Our behavioral and imaging results suggest that the adolescent dopamine system is ‘turned up’ relative to adults’, exaggerating rewards for teens,” says Dr. Casey. Although people who care for teens may worry about risk-taking, the researchers say the power imbalance between impulse and behavior control during adolescence relative to adulthood makes sense. “Adolescence is when people strike out on their own, explore new opportunities, and seek social status—all risks worth taking in healthy contexts,” says Dr. Casey.

“The results are impressive and consistent with previous findings of refinement and specialization of the brain’s cerebral cortex as people mature,” says Dr. Laurence Stanford of NIDA’s Division of Clinical Neuroscience and Behavioral Research. “With age and maturation of the frontal cortex, the ability to control impulses generally improves,” he says. Extrinsic influences, including drug abuse, however, may alter the normal course of maturation.

“To understand how drugs might change the motivational system and goal-oriented behavior, we first must understand how young people process rewards and the normal development of the brain circuits involved. Such information may help prevention specialists develop targeted interventions that are more meaningful to young people,” says Dr. Stanford. ■

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Interim Methadone Raises Odds of Enrolling in Comprehensive Treatment

Patients reduced heroin abuse and criminal activity while awaiting admission to a treatment program.

BY SARAH TEAGLE,
NIDA Notes Contributing Writer

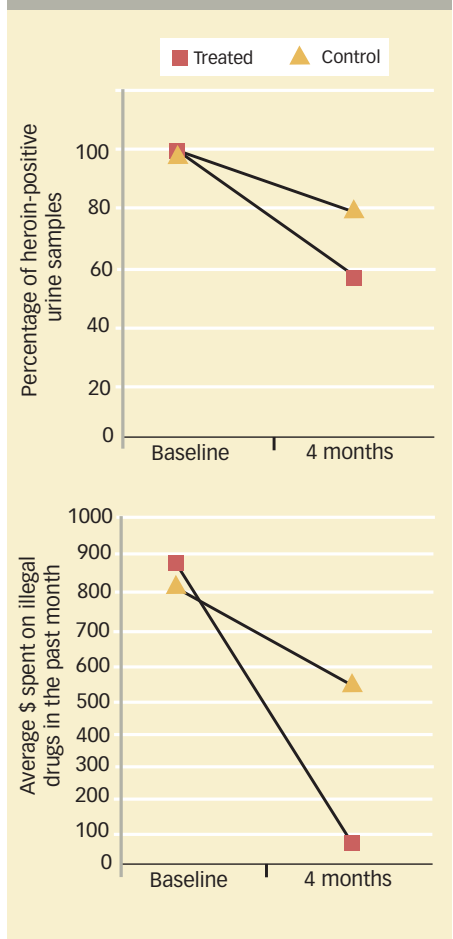
Providing methadone maintenance to heroin addicts while they are wait-listed for a treatment program can increase the likelihood they will enroll when spaces open up, say NIDA-funded researchers. The finding corroborates several previous studies in Europe and the United States. In the new study, participants who received methadone maintenance reported reduced use and criminal activity.

Across the Nation, full-to-capacity opioid treatment programs commonly put heroin-addicted men and women who present for treatment on waiting lists. By the time a treatment slot becomes available, the deferred applicants often have lost touch with the program or no longer desire treatment. The underlying idea of interim methadone maintenance is to capitalize on individuals’ possibly transient motivation by providing help when help is requested, explains Dr. Robert Schwartz, who conducted the study with colleagues from the Friends Research Institute, the University of Maryland, and The Johns Hopkins University.

BENEFITS EARLY AND LATE

The researchers recruited 319 heroin-addicted men and women who placed themselves on the wait list of a single community-based program for methadone

HEROIN USE AND MONEY SPENT ON ILLEGAL DRUGS AMONG PATIENTS RECEIVING INTERIM METHADONE TREATMENT COMPARED TO CONTROLS



maintenance. The men and women typified people on methadone wait lists in the Baltimore area, in that most were African-American and reported abusing heroin daily as well as cocaine during the past month. The

investigators randomly assigned each individual to receive free interim methadone maintenance for up to 120 days—the maximum time programs can legally provide methadone to an unenrolled individual—or to remain on a wait list. Both groups received information on how to access the waiting lists of the 11 other public methadone programs in the area.

The investigators interviewed each participant at the start of the study; upon his entry into comprehensive methadone treatment or, if he or she did not go into treatment, after 120 days; and 6 months after the second interview. Participants reported their alcohol, heroin, and cocaine abuse and provided urine samples at all three time points; those in the interim treatment group also provided samples at weeks 6 and 7 post-entry.

The results showed that 76 percent of study participants receiving interim methadone entered comprehensive care within 4 months, compared with only 21 percent in the control group. At the time of the last interview, 78 percent of interim methadone patients had entered a full-service program, compared with 33 percent of controls. Of the study participants who entered comprehensive treatment programs, 80 percent of those who had received interim methadone and 64 percent of controls were still attending at their last interviews.

The men and women who received interim treatment reported abusing heroin on a mean of 4 of the last 30 days prior to the 4-month followup interview, compared with 26 days for wait-listed patients. At the end of 4 months, the interim methadone group had a 57 percent rate of heroin-positive urine samples, while the control group had a 79 percent positive rate (see chart, page 10). The substantial difference in opiate-positive drug tests remained at the last interview, with a 48 percent positive rate among interim-treated patients, compared to a 72 percent positive rate among con-

trols. Participants who received interim methadone reported spending less money on drugs and receiving less illegal income in the past month compared with controls. On average, study participants reported spending \$872 monthly on illegal drugs at the beginning of the study. By the end, the methadone-maintained participants had reduced these expenditures dramatically, to an average of \$76, compared with \$560 among the controls—a difference that was also maintained at the 6-month followup. “If we can corroborate this self-report data from other sources, the money saved from not spending on drugs would more than pay for the interim medication,” Dr. Schwartz notes. “It costs about \$20 to \$30 per week per person. That is cheap, especially when you consider the cost of criminal activity foregone, and the hospitalizations and incarcerations avoided.”

While more of the participants who received methadone entered full-service treatment, they took longer to do so (a mean of 117 days) compared to those in the control group (59 days). However, Dr. Schwartz says, “People in the interim group knew they were going to get full service at the clinic where they were receiving their interim medication at the end of the study. Those in the control group who accessed treatment probably represent a higher-motivated subgroup—they actively sought it out using the local program information we gave them.”

Dr. Thomas Hilton of NIDA’s Division of Epidemiology, Services and Prevention Research says, “Dr. Schwartz and his team have demonstrated that interim medication is a significant recruitment tool. This might even be an appropriate way to start treatment for everyone needing methadone maintenance. It exposes patients to some degree of structure, helps them ease into a more intensive, full-service program and accommodate their lifestyle to the structure required in the full service program.” Interim methadone also

Study Specifics

Participants assigned to interim methadone began receiving the medication on their second day in the study, after completing an initial one-on-one orientation and physical exam. Nursing staff administered a dose of 20 mg, which increased by 5 mg per day with a target of 80 mg. Participants could slow or stop the dose schedule by seeing a nurse; they could exceed the 80 mg target by meeting with the program’s emergency counselor. The only other service provided was emergency counseling, and three interim participants requested and received emergency counseling during the 4 months of treatment. Patients who failed to show up for three consecutive doses were discharged from the interim methadone—a program-wide rule that did not change for study participants. The clinic staff did not contact individuals who missed doses.

may be an important tool for retention, says Dr. Hilton, because patients may be ready for the medication before they’re ready for counseling. After a few months on methadone alone, patients may be better able to engage with a counselor, making the relationship more productive. Six methadone programs in the Baltimore area have taken their cue from the study’s findings and now offer interim maintenance. “What the interim treatment approach does is add patients to existing programs,” Dr. Schwartz explains. “It is not hard for the staff to do, it’s less expensive, and it’s effective. We hope it becomes more widespread.” ■

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Serotonin System May Have Potential as a Target for Cocaine Medications

By targeting specific receptors of the neurochemical serotonin, investigators hope to advance the development of potential relapse prevention agents.

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA-supported researchers have weakened rats' behavioral responses to environmental cocaine cues by manipulating the neurotransmitter serotonin. Moreover, such manipulation can make the drug seem less stimulant-like to the rats. The findings suggest that medications that act on the serotonin system might help recovering cocaine abusers sustain abstinence, say Dr. Kathryn Cunningham and colleagues at the Center for Addiction Research at the University of Texas Medical Branch in Galveston and the Polish Academy of Sciences in Krakow.

While cocaine makes its primary pharmacological impact on the neurotransmitter dopamine, it also increases levels of other chemical messengers, including serotonin (5-HT). Previous research with animals has shown that 5-HT_{2C} and 5-HT_{2A} receptors—two proteins on brain cell surfaces that mediate serotonin's effects on cellular activity—regulate behavioral responsiveness to cocaine. For example, activating the 5-HT_{2C} receptor reduces the animals' typical behavioral responses to cocaine—including hyperactivity, self-administration, and return to drug-seeking following abstinence. Dr. Cunningham's studies showed that the 5-HT_{2C} receptor affected responsiveness to cocaine-associated environments, and that both receptors affected the animals' experience of the drug.

HYPERACTIVITY AND DISCRIMINATION

Dr. Cunningham and colleagues first examined the effect of manipulating 5-HT_{2C}

receptors on a behavior called conditioned hyperactivity: When researchers repeatedly move an animal from its home cage and give cocaine in a test cage, the drug-paired environment comes to evoke the same behavioral effect as the stimulant itself when saline is administered, so that the animal starts moving about restlessly as soon as it finds itself in the cage. Experience has shown that compounds that inhibit conditioned hyperactivity usually also reduce behaviors that are laboratory stand-ins for human relapse.

Dr. Cunningham and colleagues administered cocaine (15 mg/kg) to rats daily for 7 days in a test cage. Two days later, they gave some of the rats a compound that activates the 5-HT_{2C} receptor (MK 212), some a compound that blocks it (SB 242084), and others saline, and returned the animals to the test cage. Compared with the saline-treated animals, who showed the usual conditioned

hyperactivity, rats given the 5-HT_{2C}-receptor-stimulating compound moved around less (by about 40 percent), while those that received the blocker showed an exaggerated hyperactive response (by 25 percent) to the test cage. A separate group of animals was given cocaine only in their home cage and saline in the test cage. These animals showed normal activity when tested 2 days later, which was unaffected by the 5-HT_{2C} receptor compounds. These data strengthen the conclusion that the 5-HT_{2C} receptor is important in the cocaine-environment link.

In another study, Dr. Cunningham's team used an experimental protocol called drug discrimination to determine whether drug compounds that act at the 5-HT_{2C} and 5-HT_{2A} receptors would alter the way cocaine made the rats feel (see textbox, below). Prior research had indicated that

The Drug Discrimination Protocol

In their second experiment, Dr. Cunningham and colleagues used a drug discrimination procedure to determine whether the test compounds changed how cocaine felt to the animals. To each rat, they first gave randomly alternating infusions of cocaine and saline. After each infusion, the rat could obtain a water reward by pressing Lever A if it had received cocaine or Lever B if it had received saline. After numerous repetitions, the rat regularly pressed the correct lever—demonstrating that it had learned the challenge, wanted the reward, and could discriminate between the experiences produced by cocaine and saline. Next, the researchers observed the rat's performance when it was given a receptor blocker prior to cocaine:

- Rats given a 5-HT_{2A} receptor blocker no longer went as reliably to Lever A, indicating that they were less able to distinguish cocaine from the placebo;
- Rats given a 5-HT_{2C} receptor blocker pressed more on Lever A, indicating enhanced cocaine-like effects.

the two receptors oppose each others' effects on the cocaine response, and the researchers hypothesized that blocking the 5-HT_{2A} receptors would make cocaine feel less stimulant-like to the rats, whereas inhibiting 5-HT_{2C} receptors would enhance the drug's effects. Rats given a compound that blocks 5-HT_{2A} receptors (SR 46349B) prior to cocaine reduced their pressing on the lever associated with cocaine's effects compared with one linked with saline. Animals pretreated with a compound that blocks 5-HT_{2C} receptors (SDZ SER-082) increased their pressing on the cocaine lever over the saline lever. The results bore out the hypothesis.

"Taken together, the findings of these studies support the idea that the serotonin 5-HT_{2C} receptor plays a role in linking environmental cues and the experience of cocaine, as well as the subjective effects of the drug. The 5-HT_{2A} receptor also influences these behaviors, but in the opposite direction," says Dr. Cunningham. "From the medication development perspective, a drug with dual action at both receptors—that is, one that simultaneously stimulates the 5-HT_{2C} receptor and blocks the 5-HT_{2A} receptor—might be effective in reducing cue-induced craving. We know of no such compound, and our team is working to develop one." She adds that agents that stimulate 5-HT_{2C} or inhibit 5-HT_{2A} receptors do not fully mimic cocaine or affect other behaviors, suggesting limited side effects.

"It is not really surprising that serotonin is implicated in addiction given its importance to essential behaviors—including sleep, eating, mood, cognitive processes, and self-regulation—and its influence on dopamine," says Dr. Minda Lynch of NIDA's Division of Basic Neuroscience and Behavioral Research. "Serotonin influences dopamine in the brain's reward pathway and cortex, so examining the behavioral effects of serotonin-influencing compounds in animals is a reasonable approach in the investigation of potential pharmacotherapies," says Dr. Lynch. She agrees that a dual-action

compound that operates on the serotonin 5-HT_{2C} and 5-HT_{2A} receptors might eventually help prevent relapse. "However, a great deal of further testing in animals is needed. A good next step would be to confirm the findings in animal protocols that mimic cue-induced relapse," says Dr. Lynch. ■

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Filip, M.; Bubar, M.J.; and Cunningham, K.A. Contribution of serotonin (5-HT) 5-HT₂ receptorsubtypes to the discriminative stimulus effects of cocaine in rats. *Psychopharmacology* 183(4):482-489, 2006.

More Data Point to Serotonin

Dr. Janet Neisewander and colleagues at Arizona State University confirmed the therapeutic potential of compounds that act on the two serotonin receptors (5-HT_{2A} and 5-HT_{2C}) that Dr. Cunningham's team examined. Using a self-administration-extinction-trigger-exposure model of testing for relapse (see "Animal Experiments in Addiction Science," *NIDA Notes* Vol. 20, No. 5), the researchers found that:

- Ketanserin—a compound that blocks the 5-HT_{2A} and 5-HT_{2C} receptors—attenuated cue-induced relapse to cocaine, but not drug-triggered relapse. Because ketanserin blocks both receptors, the investigators did not know which might have been responsible for preventing cue-induced relapse. By combining data from this experiment and the one described below, the researchers were able to zero in on the 5-HT_{2A} receptor.
- SB 242084, a selective blocker of 5-HT_{2C} receptors, did not affect cue-induced or cocaine-triggered drug-seeking. The findings suggested that the results seen with ketanserin most likely were due to its ability to block the 5-HT_{2A} receptor. The researchers concluded that blocking the 5-HT_{2A} receptor might help prevent relapse triggered by environmental cues associated with taking cocaine, the same inference as Dr. Cunningham's team.

In another experiment, Dr. Neisewander's team found that SB 242084 interfered with the ability of a drug that augments serotonin, *d*-fenfluramine, to prevent cue-induced cocaine seeking. Because blocking the 5-HT_{2C} receptor made *d*-fenfluramine ineffective, the investigators concluded that stimulating the receptor may help prevent cue-induced relapse.

The compounds tested by Dr. Neisewander's team will not necessarily be developed as medications to prevent cocaine relapse, but the results of the study do suggest that drugs that act on serotonin may be potential pharmacotherapy candidates. The findings add to a growing number of studies that suggest the promise of a dual-action pharmacotherapeutic approach for relapse prevention—that is, a drug that simultaneously blocks 5-HT_{2A} receptors and stimulates 5-HT_{2C} receptors.

"Recent evidence suggests that serotonin is involved in motivation for various pleasurable experiences, including food. Researchers developing medications for obesity also are studying the effect of stimulating the 2C receptor, which may be a point of intersection for several addictions," says Dr. Cunningham.

Source: Burmeister, J.J., et al. Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology* 29(4):660-668, 2004.

Meeting Reviews Progress On Prescription Opioid Misuse

More than 400 researchers and clinicians gathered in Bethesda, Maryland March 5-6 to discuss a growing public health challenge: balancing appropriate pain treatment with efforts to minimize prescription opioid misuse. NIDA co-sponsored the conference, “Pain, Opioids, and Addiction: An Urgent Problem for Doctors and Patients,” with the American Medical Association and in conjunction with the National Institutes of Health Pain Consortium.



Dr. Pamela Palmer presents “New Opioid Formulations: Hope on the Horizon” at the March conference.

About 50 million people suffer from chronic pain in the United States, and opioids are the most powerful medications available for most types of pain. However, opioids can lead to negative health consequences, including abuse and addiction. The number of prescriptions written for opioid pain relievers has increased dramatically in recent years, thereby increasing opportunities for abuse.

Treatment advances may improve pain relief for patients while reducing the risk of abuse. Dr. Pamela P. Palmer of the University of California, San Francisco, an anesthesiologist and pain medicine physician and researcher, discussed ways that opioid medications can be formulated to minimize the risk of abuse. Extended-release or crush-resistant formulations tend to offer a better safety profile and reduce the potential for abuse. For example, putting opiates into a gel matrix from which they cannot be extracted for the purposes of abuse may prove to be a successful strategy. Similarly, new devices that dispense opioids more safely also may improve pain relief for outpatients and inpatients.

A new class of opioids—designed and synthesized by NIDA-funded researchers—that targets functionally paired receptors in the brain may provide pain treatment with fewer side effects to patients and less potential for abuse. The team is testing the compounds in animals, says Dr. David J. Daniels of the University of Minnesota, with promising results: with chronic administration, the pain relieving effects of the compounds do not diminish nor does physical dependence develop. Behavioral assays in animals also suggest that the compounds would have low potential for abuse.

With training, people may be able to harness the power of the brain to fight pain. Dr. R. Christopher deCharms of Omneuron, Inc. in Menlo Park, California, leads research in this new approach to pain management. The strategy involves training participants to control the activity of neural regions linked with pain by viewing real-time functional magnetic resonance imaging (rtfMRI) scans of their brains. Volunteers and people with chronic pain who receive

such training can alter the activity of a key brain region with concomitant pain modification—a result not seen among participants who trained without the rtfMRI. Dr. deCharms and colleagues continue to test this approach to chronic pain management and have expanded studies to substance abuse treatment.

Meeting participants agreed that research is urgently needed to support the development of pain treatments with little or no risk of abuse and the identification of patients who may be vulnerable to opioid abuse and addiction. Filling such research gaps will ultimately provide evidence-based guidance on pain management that minimizes the risks of opioid abuse and addiction.

NIDA Investigator Receives 2006 Waletzky Memorial Award

Dr. Yavin Shaham, an investigator in NIDA’s Intramural Research Program (IRP), is the recipient of the 2006 Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism. He accepted the award at NIDA’s “Frontiers in Addiction Research” miniconference in Atlanta October 13.

“Yavin Shaham’s work has had far greater impact in the field of addiction than that of any other investigator in his generation,” said Dr. Roy Wise of the IRP’s Behavioral Neuroscience Research Branch in nominating Dr. Shaham for the award.

Stress-induced relapse has been a central focus of Dr. Shaham’s research since 1992. Using animal models, he and his colleagues have demonstrated that stress can trigger a resumption in drug-seeking after a prolonged abstinence; they have also made great strides in identifying the neural systems involved in this process. Dr. Shaham’s work has “shifted the paradigm in the addiction field from compulsive drug-taking to compulsive drug-seeking,” Dr. Wise observed.

More recently, Dr. Shaham and his team established that exposure to drug-related cues can induce cravings for heroin and cocaine long after withdrawal, and that those cravings grow stronger over time—in the case of cocaine, remaining markedly elevated even after 6 months. They continue to explore the cellular basis for this so-called “incubation” of craving as well as for stress-induced relapse.

The \$25,000 award is presented each year to a young scientist within 15 years of obtaining a doctoral degree and is intended to reward and encourage innovative research into the neurobiology of drug addiction and alcoholism. The Waletzky family established the award in 2003 in memory of Jacob P. Waletzky, who died at age 29 of cocaine-induced cardiac arrhythmia.



2006 Jacob P. Waletzky Memorial Award winner Dr. Yavin Shaham.

Latest Information on MDMA/Ecstasy, Steroids, and HIV/AIDS Is Available on NIDA's Web Site

NIDA has updated its *Research Reports* on MDMA/ecstasy and steroids and published a new report on HIV/AIDS. The Institute's *Research Report* series provides educators, parents, clinicians, and others the latest available information on drugs and drug-related topics. They are available on NIDA's Web site, www.drugabuse.gov.

HIV/AIDS

Approximately four of every 10 AIDS deaths in the United States are related to drug abuse. This somber message is depicted on the cover of the Report on HIV/AIDS. The Report's contents focus on the roles that intravenous drug use and drug-influenced high-risk sex play in spreading the epidemic.

Along with the latest data on AIDS cases and deaths, the Report describes changes in the epidemic over the past 25 years; the disparate impact of the disease on different subpopulations; effective approaches for prevention; and NIDA's ongoing support of research to develop strategies to prevent and treat the disease.

MDMA/ECSTASY

This Report brings welcome news from recent surveys, which indicate that abuse of this club drug may be on the decline. The 2004 National Survey on Drug Use and Health estimates that the number of current adolescent and adult methylenedioxymethamphetamine (MDMA/ecstasy) abusers in the United States declined from 676,000 in 2002 to 450,000 in 2004. Similarly, the 2005 Monitoring the Future (MTF) survey found that past-year abuse fell 59 percent among middle and high school students between 2001 and 2005.

Nevertheless, more than 11 million reported trying the stimulant-hallucinogen at least once in their lives. The report describes the characteristics and history of ecstasy, the scope of its abuse in the United States, and its harmful effects.

STEROIDS

This updated Report provides new data on anabolic androgenic steroid abuse among teenagers. Based on the 2005 MTF Survey,



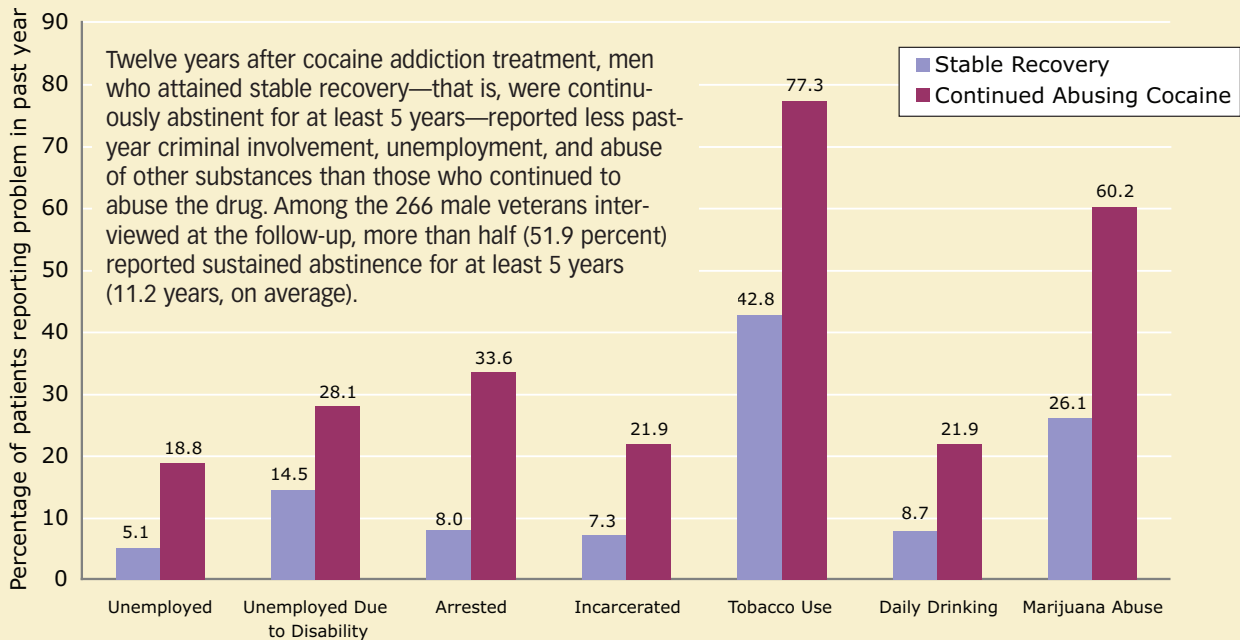
steroid abuse by teens in 8th and 10th grade has declined since 2000. The trend among 12th graders was different: abuse increased from 2000 to 2004, and then dropped in 2005 from 2.5 percent to 1.5 percent.

NIDA Director Dr. Nora D. Volkow points out that steroids differ from other drugs of abuse in that their appeal lies in their ability to change one's appearance and performance. As such, they may be a more insidious source of danger. "The effects of steroids can boost confidence and strength, leading the abuser to overlook the potential serious and long-term damage that these substances can cause," she notes.

The Report describes what steroids are, how they are abused, and the harmful side effects that can result. It also lists sources of additional information and resources.

- www.drugabuse.gov/ResearchReports/hiv/hiv.html
- www.drugabuse.gov/ResearchReports/MDMA/default.html
- www.drugabuse.gov/ResearchReports/Steroids/AnabolicSteroids.html

Abstinent Patients Continue to Show Benefits of Treatment



Twelve years after cocaine addiction treatment, men who attained stable recovery—that is, were continuously abstinent for at least 5 years—reported less past-year criminal involvement, unemployment, and abuse of other substances than those who continued to abuse the drug. Among the 266 male veterans interviewed at the follow-up, more than half (51.9 percent) reported sustained abstinence for at least 5 years (11.2 years, on average).

SOURCE: Hser, Y.I. et al. A 12-year follow-up of a treated cocaine-dependent sample. *Journal of Substance Abuse Treatment* 30(3): 219-226, 2006.

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