

Low-Cost Incentives Improve Outcomes in Stimulant Abuse Treatment

In community-based treatment programs, the intervention added \$2.42 per patient per day to counseling costs.

BY LORI WHITTEN,
NIDA Notes Staff Writer

The opportunity to win rewards worth as little as \$1 for abstinence can help motivate outpatients to stay in behavioral therapy and remain drug-free, according to a NIDA Clinical Trials Network (CTN) study. At eight community-based addiction treatment programs across the United States, stimulant abusers who could earn a chance to win a prize by providing drug-free urine samples were four times as likely as peers who were not offered this incentive to attain 12 weeks of continuous abstinence. Prizes for the incentive intervention cost the programs about \$200, or \$2.42 a day per participant.

“Many addiction treatment clinics face the challenge of high patient dropout rates. Reinforcing abstinence helps keep patients interested in attending treatment for longer periods, which can facilitate behavioral changes to keep them off drugs for the long haul,” says Dr. Nancy Petry of the University of Connecticut School of Medicine, coleader of the study. Prior research has found that, no matter how it is achieved, duration of abstinence during treatment is one of the best predictors of abstinence 1 year later. “More patients achieve this therapeutic milestone with a boost from incentive programs,” says the

study’s other coleader, Dr. Maxine Stitzer of The Johns Hopkins University School of Medicine.

The CTN investigators randomly assigned 415 treatment-seeking stimulant abusers (see chart) to one of two conditions: usual care or usual care plus abstinence-based incentives for 12 weeks. Usual care typically consisted of group counseling, although some patients received individual and family therapy. Patients gave urine and breath samples twice weekly. Research assistants tested the urine samples for stimulants, opiates, and marijuana, and tested the breath samples for alcohol.

[Continued on page 6]

CHARACTERISTICS OF STUDY PARTICIPANTS

Patients at eight community-based clinics across the country were ethnically diverse and generally reflected the national population of treatment-seeking stimulant abusers.

| Characteristic | % |
|-----------------------------|----|
| Ethnicity | |
| White | 42 |
| African-American | 35 |
| Hispanic | 12 |
| Other | 9 |
| Male | 44 |
| Unemployed | 65 |
| On parole or probation | 35 |
| Abuse of other drugs | |
| Alcohol | 42 |
| Marijuana | 20 |
| Opioids | 9 |

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Steroid Abuse Is a High-Risk Route to the Finish Line

Starting last fall, capitalizing on the interest raised by the Winter Olympics in Turin, Italy, NIDA intensified its campaign to warn young people that steroid abuse is a dangerous way to become faster, stronger, and bigger.

Boys and girls who abuse these drugs before reaching their full natural height may prematurely halt bone growth, resulting in permanently shorter stature. Boys and men who abuse steroids risk shrinkage of the testicles, reduced sperm count, infertility, baldness, development of breasts, and an increased risk for prostate cancer. Girls and women are subject to menstrual abnormalities, voice deepening, breast shrinkage, male-pattern baldness, and an increase in sex drive, acne, body hair, and clitoris size. Some of these adverse effects—including breast enlargement in men, menstrual abnormalities in women, and reduced height in both sexes—may be permanent. For both sexes, steroid abuse increases the risk of liver and heart disease, stroke, aggression, and depression. Users of injectable steroids may acquire hepatitis, HIV, and other infections if they use contaminated needles.

In recent animal studies, NIDA-supported researchers tested the effects of chronic exposure to anabolic (muscle-building) and androgenic (masculinizing) steroids on brain circuits that underlie aggression and reproductive behaviors. They found that in mice, a regimen corresponding to chronic human abuse of these drugs reduced levels of the receptor for the neurochemical GABA. Adolescent female mice were particularly sensitive to the effects of the steroid on GABA, which is critical to the display of female sexual behaviors and is involved in the regulation of hormone release and ovarian maturation.

The need to educate young people about the serious health risks associated with steroids remains urgent. Among American teens, such abuse declined over the past decade, but that encouraging trend shows signs of weakening, especially among younger boys and girls. In 2005, according to the annual NIDA-funded Monitoring the Future (MTF) Survey, the number of high school seniors reporting steroid abuse dropped significantly, to 1.5 percent, from peak levels of about 2.5 percent just a year before. The rates were unchanged, however, among 10th graders (1.3 percent) and 8th graders (1.1 percent).

NIDA has responded by updating our *Research Report on Steroids* to provide the public with the newest information about steroids and their abuse. The *Research Report* is available on NIDA's Web site at www.drugabuse.gov/ResearchReports/Steroids. A Spanish version is available at www.drugabuse.gov/ResearchReports/Esteroides/Esteroides.html. "Game Plan," a public service announcement that has aired more than 8,000 times in 75 television markets across the United States, reminds young athletes that "quick fixes" can be dangerously deceptive and that cheating is damaging in the long run. NIDA will continue to conduct and publicize research on steroids, and to drive home the point that, ultimately, steroid abuse is a losing strategy. ■

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First-time Patients Opt for Office-Based Buprenorphine

Patients starting buprenorphine treatment in a New Haven, Connecticut primary care clinic (PCC) are more likely to be new to treatment than those beginning methadone at an opioid treatment program (OTP), report Dr. Lynn Sullivan and colleagues at Yale University School of Medicine. The findings suggest that compared with methadone, office-based buprenorphine treatment attracts individuals who have less extensive addiction histories, are relatively healthier, and have more socioeconomic resources.

The investigators compared 96 patients entering a clinical trial of buprenorphine/naloxone in a PCC with 94 participants entering a local OTP. Fifty-four percent of PCC patients were new to treatment, compared with 39 percent of those in the OTP. Among PCC patients, treatment novices were younger and more likely to be White than peers with prior methadone treatment. PCC patients reported fewer years of opioid addiction (10 versus 15, on average), lower rates of injection drug use (44

versus 60 percent), and less hepatitis C (25 versus 61 percent).

Three-fourths of PCC patients versus half of OTP participants were male, and more PCC patients were employed full-time (46 versus 15 percent). Consistent with prior research, methadone history did not affect treatment retention or abstinence rates attained with buprenorphine.

> *Drug and Alcohol Dependence* 79(1):113-116, 2005.

Ethnicity Influences Early Smoking and Progression to Drug Abuse

African-Americans are less likely than European-Americans and Latinos to begin smoking in early adolescence or report dependence on illicit drugs during young adulthood. In a 10-year study, Dr. William Vega at the University of Medicine and Dentistry of New Jersey and Dr. Andres Gil at Florida International University monitored smoking and progression to other drug abuse in 1,208 students, starting at age 11 and ending at age 20. Among participants who began smoking in early adolescence, African-Americans were least likely to report that they still smoked or that they abused or were dependent on illicit drugs as young adults. European-Americans were most likely to still be smoking as 20-year-olds, and U.S.-born Latinos most likely to report abuse or dependence on drugs other

than marijuana. These relationships held when the researchers factored in the influences of gender, socioeconomic status, education, parental smoking, and early alcohol use.

> *Addiction* 100(9):1358-1369, 2005.



Stress Response May Underlie African-Americans' Reduced Pain Tolerance

Recent NIDA-funded research suggests a physiological difference as the explanation for African-Americans' reported low tolerance for pain. Dr. Susan Girdler and colleagues at the University of North Carolina at Chapel Hill monitored the stress responses of 51 African-American and 55 other participants, mostly Caucasians, while subjecting them to three different types of painful stimuli—ischemic, heat, and cold. The results suggest that blood pressure rises and physiological stress responses helped to offset pain sensations among the non-African-Americans, but not the African-Americans. For example, among the non-African-Americans, greater stress-induced increases in blood pressure and release of norepinephrine correlated with more tolerance to

subsequent pain. No such relationship was seen among African-Americans, who exhibited less marked blood pressure rises and relatively low levels of the stress hormones.

> *Psychosomatic Medicine* 67(6):948-956, 2005.

Methylphenidate for Comorbid Cocaine Abuse, ADHD

In an inpatient study with 14 non-treatment-seeking volunteers, Columbia University researcher Dr. Stephanie Collins and colleagues reported that a regimen of 40-60 mg/day of sustained-release methylphenidate (SR-MPH) reduced ratings on scales of "feel high," "good drug effect," and other measures of cocaine's reinforcing effects among seven abusers affected by attention deficit hyperactivity disorder (ADHD). The medication increased the cardiovascular effects seen with cocaine alone, but not to dangerous levels. Although preliminary, the findings suggest that a therapeutic approach of using slow-acting stimulants to reduce craving for cocaine—parallel to the use of methadone or buprenorphine in opiate addiction—may be possible for cocaine-addicted patients with ADHD. Although the researchers did not formally assess SR-MPH's effects on participants' ADHD symptoms, they did not note any obvious benefits.

> *Drug and Alcohol Dependence* 82(2):158-167, 2006.

Study Finds Withdrawal No Easier With Ultrarapid Opiate Detox

Three serious adverse events among 35 ultrarapid procedures were all related to unreported preexisting medical conditions.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Heroin-addicted patients who undergo so-called ultrarapid, anesthesia-assisted detoxification suffer withdrawal symptoms as severe as those endured by patients in detoxification by traditional methods, according to a NIDA-funded clinical trial. Researchers Dr. Eric Collins and colleagues at the College of Physicians and Surgeons of Columbia University concluded that there is no compelling reason to use general anesthesia in the treatment of opiate dependence, especially as it presents particular safety concerns. The new findings corroborate those of three international studies.

The ultrarapid detox technique, developed about 15 years ago by clinicians who hoped to mitigate the discomfort of withdrawal and speed the initiation of relapse prevention therapy, relies on a

general anesthetic to sedate the patient for several hours while an opiate blocker precipitates withdrawal. The method is not covered by insurance, which makes it difficult to determine how many patients have received anesthesia-assisted detox.

To compare anesthesia-assisted detox with other approaches, Dr. Collins and colleagues enrolled 106 people seeking heroin detox at Columbia University Medical Center's Clinical Research Center. The patients, aged 21 through 50, had abused heroin every day during the past month. All spent 3 days as Center inpatients during detox, then were

scheduled for twice-weekly outpatient relapse prevention psychotherapy and naltrexone maintenance (50 mg/day) for 12 weeks.

The investigators randomly assigned the participants to one of three detox methods (see chart). The goal of each method was to minimize patients' discomfort during withdrawal. In the ultrarapid approach, physicians put patients under anesthesia for 4 to 6 hours while administering naltrexone, a medication that precipitates withdrawal by blocking opioid molecules from their receptors in the brain. In the second method, patients

RESEARCHERS COMPARE THREE OPIATE DETOX METHODS Investigators studied the safety profile and withdrawal symptom control of three detoxification methods used in 106 patients at Columbia University Medical Center.

| | Inpatient treatment | | | | Outpatient treatment |
|------------------------|----------------------|---|--|--|---|
| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 through week 12 |
| Anesthesia-Assisted | | Anesthesia 4-6 h → 2 h monitoring in post-anesthesia unit → naltrexone induction (50 mg) Clonidine and nonopioid medications as needed for withdrawal symptoms | Begin naltrexone maintenance (50 mg/day) (continue through end of study) Ancillary withdrawal medications continued | Discharge from inpatient treatment Ancillary withdrawal medications continued | Twice-weekly psychotherapy Naltrexone maintenance medication (50 mg/day) |
| Buprenorphine-Assisted | Buprenorphine (8 mg) | Clonidine and nonopioid medications as needed for withdrawal symptoms | Naltrexone induction (12.5 mg) Ancillary withdrawal medications continued | Discharge from inpatient treatment Naltrexone induction continues (25 mg) Ancillary withdrawal medications continued | Twice-weekly psychotherapy Naltrexone maintenance medication (50 mg/day) |
| Clonidine-Assisted | | Clonidine and nonopioid medications as needed for withdrawal symptoms | Ancillary withdrawal medications continued | Ancillary withdrawal medications continued Discharge from inpatient treatment | Twice-weekly psychotherapy Begin 2-day naltrexone induction on day 7 (12.5 mg, then 25 mg), followed by naltrexone maintenance starting on day 9 (50 mg/day) |

remained awake and took a single dose of buprenorphine, a medication that eases withdrawal symptoms by moderating and smoothing the rate of opioid clearance from the brain. In the third approach, patients also remained awake and received clonidine and other nonopioid medications as needed to counter symptoms for all 3 inpatient days. These medications were available to all groups as needed for the duration of the inpatient phase. Throughout detox, the researchers closely monitored patients for complications, assessed physical indications of withdrawal, and asked the participants to rate their subjective experiences.

Once awakened from anesthesia, patients in the ultrarapid detox group demonstrated and reported symptoms of discomfort comparable to those experienced by participants receiving the buprenorphine- and clonidine-assisted methods (see chart). Three patients receiving the anesthesia-assisted method experienced serious adverse events—pulmonary and psychiatric complications as well as a metabolic complication of diabetes, all of which required hospitalization. The complications were related to preexisting medical conditions that the patients had failed to reveal when they were screened for admission into the study. No adverse events occurred with the other detox methods.

Treatment outcomes among the three groups were similar. Following detox, the researchers offered all the patients relapse prevention therapy consisting of outpatient counseling and naltrexone, which counteracts the pleasurable effects of subsequently administered opioids. More than 90 percent of the patients who received the anesthesia- and buprenorphine-assisted detox completed naltrexone induction; only 21 percent of those receiving clonidine completed induction. By the third week, more than half the patients in all three groups had dropped out of the study; only 18 percent remained in treatment the full 12 weeks. The percentages of patients submitting opiate-positive urine samples during outpatient

treatment also were comparable, roughly 63 percent, across the three detox methods.

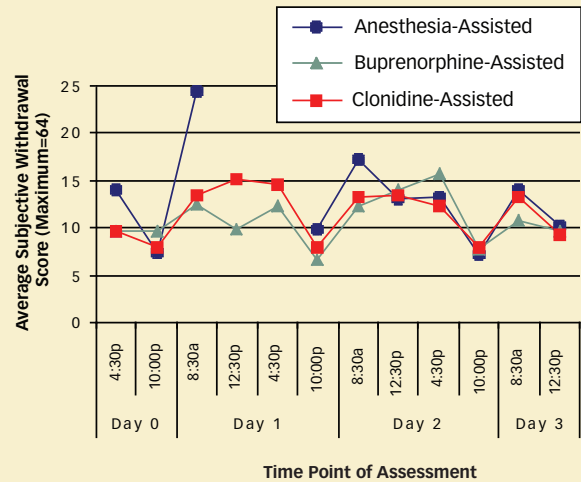
“NO ADVANTAGE”

“Although providers advertise anesthesia-assisted detox as a fast and painless method to kick opiate addiction, the evidence does not support those statements,” says Dr. Collins. “Patients should consider the many risks associated with this approach, including fluid accumulation in the lungs, metabolic complications of diabetes, and a worsening of underlying bipolar illness, as well as other potentially serious adverse events,” he says. Those with preexisting medical conditions—including some psychiatric disorders, elevated blood sugar, insulin-dependent diabetes, prior pneumonias, hepatitis, heart disease, and AIDS—are particularly at risk for anesthesia-related adverse events. “Careful screening is essential with the anesthesia-assisted method, because the thought of sleeping through withdrawal is so compelling that some patients may conceal their medical histories,” says Dr. Collins.

“We now have several rigorous studies indicating that anesthesia-assisted detox—a costly and risky approach—offers no advantage over other methods,” says Dr. Ivan Montoya of NIDA’s Division of Pharmacotherapies and Medical Consequences of Drug Abuse. Dr. Montoya notes, “The low retention of patients in subsequent outpatient treatment in the present study, which is not unusual for the opiate-addicted population, highlights the need to engage people in long-term recovery after detoxification.” Naltrexone can help motivated patients stay off opiates, but many do not stick to the

IN THREE DETOX METHODS, WITHDRAWAL SYMPTOM SEVERITY WAS SIMILAR

During a 72-hour inpatient detoxification stay, patients rated each of 16 withdrawal symptoms—for example, “I feel like vomiting,” “I have cramps in my stomach,” “I feel anxious,” and “My eyes are tearing”—on a scale from 0 (not at all) to 4 (extremely). Symptom severity generally did not differ between heroin-addicted patients receiving anesthesia-, buprenorphine-, or clonidine-assisted methods. Researchers did not assess withdrawal symptoms for the anesthesia-assisted group during general anesthesia and the immediate recovery period.



regimen of daily tablets because of the medication’s side effects of anxiety and restlessness. Long-acting monthly injections of naltrexone, which are now available for alcoholism treatment, may work better for patients and show promise in NIDA-supported clinical trials.

Dr. Montoya also points out that with the current epidemic of prescription painkiller abuse, clinicians need more research on cost-effective detox methods for these opiates (see “2003 Survey Reveals Increase in Prescription Drug Abuse, Sharp Drop in Abuse of Hallucinogens” *NIDA Notes*, Vol. 19, No. 4). Some clinics are using buprenorphine for this purpose, and NIDA-funded investigators are studying various methods to improve prescription opiate detox and help patients engage in longer term treatment. ■

SOURCE

Collins, E.D., et al. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: A randomized trial. *Journal of the American Medical Association* 294(8):903-913, 2005.

■ LOW-COST INCENTIVES

[Continued from page 1]

Each participant in the incentive condition received immediate feedback on his or her samples. After submitting stimulant- and alcohol-negative samples, the patient could draw from an opaque container with 500 chips, each with words of encouragement or an assigned value: Half of the chips simply said, “good job;” 209 could be traded for \$1 prizes, 40 for \$20 prizes, and 1 for a \$100 prize. Prizes were conferred immediately and included many options, ranging from toiletries, snacks, and bus tokens to kitchen items, telephones, and retail store certificates for televisions, music players, and DVD players. The number of draws earned increased by one each week in which all the patient’s samples were stimulant- and alcohol-negative, but fell back to one following a positive sample or an unexcused absence. When a participant first achieved two consecutive weeks of abstinence, he or she received a \$20 prize. Participants who submitted stimulant- and alcohol-negative samples could earn two bonus draws a week if their urine samples were also opioid- and marijuana-negative.

More patients in the incentive program (49 percent) than in usual care (35 percent) completed 12 weeks of counseling. Patients in the incentive group achieved an average duration of sustained abstinence of 4.4 consecutive weeks, compared with only 2.6 weeks among counseling-only patients. Nineteen percent of patients receiving the incentive intervention attained 12 weeks of continuous abstinence compared with 5 percent of those in usual care. Intervention patients also attended more counseling sessions (19 versus 16) and submitted more stimulant-negative urine samples during treatment than patients in usual care (48 versus 36 percent).

Blending Initiative Disseminates Information on Low-Cost Incentives

Clinicians and administrators who wish to learn more about using low-cost incentives to motivate patients to stay off drugs can get information through the Blending Initiative, a program established by NIDA and the Substance Abuse and Mental Health Services Administration to speed the adoption of scientific findings into drug abuse treatment. The Blending Initiative has developed an awareness program that disseminates practical information on low-cost incentive programs and a summary of research evidence that supports their use as an adjunct to addiction treatment.

A DVD/CD-ROM describes the principles underlying incentive programs, the range of behaviors that clinics can target, and findings from studies of the intervention with a variety of patient populations. In the video component, clinicians, patients, and managers describe their experiences with the use of low-cost incentives in Manhattan and Connecticut outpatient methadone treatment programs. Viewers observe a group of Connecticut clients participating in a prize draw and a panel of directors and clinical managers discussing implementation challenges, ways to overcome problems, and the reasons they think the low-cost incentive program is effective. The CD-ROM component includes a flexible PowerPoint presentation suited for executive briefings or a 3-hour workshop. The Blending Initiative expects to release the information package in fall 2006, and it will be posted on NIDA’s Web site, www.drugabuse.gov and on the Addiction Technology Transfer Center (ATTC) Web site, www.nattc.org.

“We anticipate that the awareness campaign will leave the addiction treatment community wanting more, for example, Web-based training and workshops on how to implement low-cost incentive programs,” says Ms. Lonneta Albright, director of the Great Lakes ATTC and leader of the Promoting Awareness of Motivational Incentives Blending Team.

The 2006 Blending Initiative program, “Bridges to the Future,” was held October 16 and 17, 2006 in Seattle, Washington (see www.sei2003.com/blendingseattle/topics.htm).

INCENTIVES ACCENTUATE

THE POSITIVE

“Incentive programs, including low-cost ones, add excitement and additional reasons to attend substance abuse treatment. Many substance abusers are ambivalent about treatment, and rewards may help them stay involved in counseling,” says Dr. Petry. Extending retention in treatment may prolong abstinence, in part, because it gives counselors more time to help patients re-engage in a drug-free lifestyle, says Dr. Stitzer. Helping patients sustain abstinence once they leave therapy is a challenge for all

treatments, including incentive programs.

Some previous clinical trials of voucher-based incentive programs showed benefits of the treatment persisting for 1 to 2 years, but others found no added value over the long term compared with usual care. Further research will focus on followup with patients to determine the conditions under which incentive interventions, particularly as applied by community-based treatment programs, support extended abstinence.

Other relatively small, often single-site NIDA-funded clinical trials over the past 15 years have demonstrated that motivational

incentives are an effective adjunct to standard therapy for opiate-, marijuana-, alcohol-, and cocaine-addicted patients. Patients in most of those early studies always received vouchers exchangeable for goods or services, rather than chances to win prizes, for positive behaviors; costs typically ran to about \$1,000 per patient over 3 months, with the result that few community programs adopted the motivational incentive approach. Dr. Petry developed her prize-drawing system to make incentives affordable for community programs. She has tested it successfully in several Connecticut treatment programs, and now its effectiveness is confirmed by the CTN trial. NIDA is collaborating with the Substance Abuse and Mental Health Services Administration's Addiction Technology Transfer Center to promote awareness of the low-cost motivational incentive technique (see textbox, page 6).

The CTN researchers note that some community-based treatment providers resist the idea of motivational incentives based on a belief that clinicians should not reward patients for behaviors “that they are supposed to do anyway.” In response, the researchers point out that groups and individuals often use external incentives to motivate others—from employees’ bonuses to children’s allowances for household chores. Dr. Stitzer advocates a shift in perspective from punishing lapses to celebrating successes. She observes that counselors have often changed their views when they have seen incentives help revolving-door patients stay in therapy. “Incentive programs—the idea of catching people being good and rewarding the behavior—can infuse addiction treatment with a positive outlook and reinvigorate patients and counselors,” says Dr. Stitzer. ■

SOURCE

Petry, N.M., et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: A National Drug Abuse Treatment Clinical Trials Network Study. *Archives of General Psychiatry* 62(10):1148-1156, 2005.

Buprenorphine Plus Behavioral Therapy Is Effective For Adolescents With Opioid Addiction

A new study looks at extending the role of buprenorphine for treatment of adolescents.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

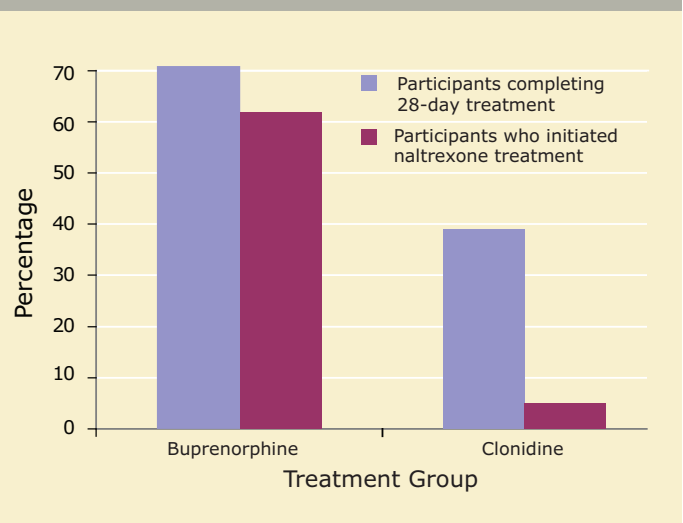
Adolescents addicted to opioids responded better to buprenorphine than clonidine in a clinical trial in which all patients also received behavioral therapy. In the NIDA-supported comparison trial at the University of Vermont, adolescents who received buprenorphine attended more scheduled counseling sessions than peers who received clonidine and had higher rates of successful induction to a relapse prevention regimen of naltrexone. The study, led by Dr. Lisa Marsch, is the first published randomized controlled study of treatments for adolescents addicted to opioids.

“Heroin abuse among American teens has doubled over the past decade, and abuse of prescription opioids such as OxyContin and Vicodin has increased even more,” says Dr. Marsch. “In light of

those figures, it’s important to have a scientific basis for selecting treatments for opioid-dependent teens. We know from previous research and clinical experience that buprenorphine and, to a lesser extent, clonidine are among the medications that have been shown to be effective for treating opioid-addicted adults, but we haven’t known how helpful they can be for adolescents.”

Dr. Marsch and colleagues enrolled 36 opioid-addicted adolescents, aged 13 to 18, in a 28-day outpatient treatment program. Half the participants (9 male, 9 female) received buprenorphine in tablet form, the

BUPRENORPHINE DETOXIFICATION SETS STAGE FOR RECOVERY Opioid-addicted adolescents who entered a detoxification program with buprenorphine were more likely than others receiving clonidine to maintain abstinence throughout a 28-day detoxification program and more likely to begin treatment with naltrexone after detoxification.



rest (5 male, 13 female) clonidine via transdermal patch; each patient also was given a placebo resembling the other treatment. Medication dosages varied depending on each participant's weight and the amount of drug he or she reported abusing before beginning treatment; dosages of buprenorphine were in the low to moderate range of those typically given to opioid-addicted adults.

All participants also received behavioral therapy based on the Community Reinforcement Approach: three 1-hour sessions each week of counseling on methods to minimize involvement in situations that might lead to drug-taking, training to help recognize and control urges to abuse opioids, and encouragement to recruit family members as allies for abstinence. Participants earned vouchers worth \$2.50 for the first opioid-negative urine sample, plus an additional \$1.25 for each subsequent one, and a \$10 bonus for each set of three consecutive negative samples. Continuous abstinence could earn participants \$152.50

in vouchers redeemable for rewards such as ski passes, CDs, gym passes, and clothing.

Buprenorphine and clonidine both supported high rates of abstinence. Among participants who completed treatment, rates were 78 percent and 81 percent, respectively, confirmed by urine samples provided at the thrice-weekly sessions. However, nearly twice as many buprenorphine as clonidine recipients completed the 4-week treatment (72 percent compared with 39 percent). "The high rate of retention in the buprenorphine group is particularly noteworthy," Dr. Marsch says, "because long-term success in recovery is directly related to the amount of time patients spend in treatment." And, she adds, the willingness of most patients who received buprenorphine to continue treatment with naltrexone following completion of the 28-day program is similarly encouraging. Sixty-one percent of the buprenorphine group, but only 5 percent of those who received clonidine accepted naltrexone.

"Dr. Marsch's research is an important first step in systematically studying adolescents who are addicted to opioids," says Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. "We know that there are differences in the patterns of opiate abuse and addiction in young people compared with adults. We need dedicated studies like this one to understand how teens are affected by opiate drugs and how best to treat them."

The next step in Dr. Marsch's research will involve a larger sample of young opioid abusers. "We want to evaluate buprenorphine's effectiveness if treatment is extended to 2 months rather than 28 days," she says. "We will also examine the most effective doses and dosing regimens for various subgroups of young patients." ■

SOURCE

Marsch, L.A., et al. Comparison of pharmacological treatments for opioid-dependent adolescents: A randomized controlled trial. *Archives of General Psychiatry* 62(10):1157-1164, 2005.

Science & Practice PERSPECTIVES

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Brain Mechanism Turns Off Cocaine-Related Memory in Rats

An exploration of memory’s molecular basis suggests potential novel therapeutic approaches to cue-induced craving.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer


Scientists at the University of California, Irvine, have added to evidence that a brain enzyme controls key memory processes that link drug experiences, the surroundings in which they take place, and the urge to repeat them. In a series of experiments, inhibiting the enzyme attenuated a rat behavior that is a laboratory stand-in for human cue-induced drug-seeking. The findings suggest that in the future, therapeutically manipulating levels of the enzyme might cut addicted individuals’ vulnerability to environmental triggers for drug craving and abuse.

The NIDA-funded scientists, Drs. Courtney Miller and John Marshall, focused on the enzyme in an attempt to elucidate the ways cellular activities promote cue-induced drug-seeking.

“Although studies have established that nerve cells in the core of the nucleus accumbens are critically involved,” Dr. Miller says, “we haven’t had much information about the molecular mechanisms that transform environmental cues into an urge to repeat drug-associated behavior.” One likely candidate for a role in the process, however, was extracellular signal-regulated kinase (ERK). This enzyme is known both to foster the new cellular connections that register emotional and object recognition memories in the brain and to be affected by cocaine.

The researchers explored ERK’s role in a behavior called conditioned place preference (CPP). By exhibiting CPP—lingering in a part of a cage where it has had a drug experience—an animal indicates that it remembers the experience, associates it with the preferred cage area, and is seeking to have it again (for more on CPP, see “Animal Experiments in Addiction Science,” *NIDA Notes*, Vol. 20, No. 5). In previous research, blocking ERK activity in the nucleus accumbens (NAc) prior to exposing rats to drugs prevented them

ENZYME BLOCKAGE DISRUPTS DRUG-SEEKING In experiments with rats, researchers used a compound called U0126 to block ERK, an enzyme that facilitates memory formation and consolidation.

| Days 1-9 | Day 10 | Day 11 | Day 26 | Conclusions |
|---|--|--|---|--|
|  <p>Researchers trained rats to associate cocaine with a specific setting. The animals signaled their successful conditioning by exhibiting conditioned place preference—spending more time in a chamber where they had received cocaine injections over 9 days.</p> | Group 1 Rats received infusions of U0126 or a control vehicle. After 30 minutes, they were tested for CPP. Rats given U0126 showed no preference for a cocaine-associated chamber. Control rats did show preference for the cocaine-associated chamber. | Rats given U0126 still exhibited no CPP. Control rats retained CPP. | | Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours. |
| | Group 2 Rats were tested for CPP and immediately infused with either U0126 or the control vehicle. | Rats given U0126 showed no CPP. Control rats showed CPP. | | Inhibiting ERK activity immediately after cocaine-associated memories are retrieved can make the memories unavailable for subsequent retrieval at 24 hours and for at least 2 weeks. |
| | Group 3 Rats were tested for CPP and immediately infused with either U0126 or the control vehicle. | | Rats given U0126 showed no CPP. Control rats showed CPP. | |
| | Group 4 Rats received an infusion of U0126 and remained in their home cage with no testing and therefore no opportunity for memory retrieval. | Rats showed a strong CPP for the cocaine-associated environment. | | ERK inhibition is effective only when induced at the time of memory formation or memory retrieval. |

from developing CPP. Drs. Miller and Marshall reasoned that if blocking ERK forestalls initial formation of the memory links underlying CPP, it might also weaken links that had already been formed. The potential therapeutic implications would be significant if this were so; they would suggest that manipulating ERK might be a means to disrupt drug-environment associations that are already established by the time patients begin therapy.

To test their hypothesis, the researchers administered cocaine to rats daily for 9 days, after which the rats exhibited CPP whenever they were placed back in their test cage. The researchers then conducted a series of trials and assays that showed:

- *CPP involves activation of ERK:* Rats that lingered in the cocaine-associated area of the test cage had higher ERK levels in the core area of the NAc than a group of rats that had not been exposed to cocaine or a third group exposed to cocaine but not trained to exhibit CPP.
- *Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours:* The investigators infused a compound called U0126, which reduces ERK activity, directly into the NAc cores of some of the CPP-trained rats. When placed in the test cage 30 minutes later, these rats gravitated to the cocaine-associated area much less consistently than did a group of CPP-trained rats that were injected with saline rather than U0126. Tested again 24 hours later, they still exhibited little or no preference for the area.
- *Inhibiting ERK activity at the time cocaine-associated memories are retrieved can make them unavailable for subsequent retrieval for at least 2 weeks:* Rats were placed in the test cage and given U0126 immediately after exhibiting CPP. When retested the following day, they showed no partiality to the drug-associated cage area, nor did a similarly treated group of animals

New Findings on Memory Have Implications For Treatment

Groundbreaking research on the molecular basis of long-term memory could open a new path to the treatment of drug addiction, post-traumatic stress disorder (PTSD), and other conditions in which memories exert a powerful influence on behavior, according to neuroscientists who presented research at a NIDA conference, "Frontiers in Addiction Research." Their findings suggest that when long-term memories are recalled, they return to a state in which they can be altered or erased before undergoing "reconsolidation" for future potential use. This discovery could lead to the development of medications that disrupt the reconsolidation process and thereby prevent memories associated with drug abuse or trauma from being reestablished.

Dr. Karim Nader of McGill University in Montreal, Canada, explained the process of reconsolidation and how interventions based on that process might work. The goal, he said, is not to simply erase memory, but rather to modulate the memory so that its effects are more manageable in conditions such as PTSD or addiction. "Our research shows that when a consolidated long-term memory is reactivated, it returns to a labile state similar to short-term memory. Neurons must synthesize new proteins in order for the memory to persist. If protein synthesis is inhibited after reactivation, reconsolidation can't occur," he said.

Although he cautioned that there is an enormous amount of work to be done before testing the effect in human patients, Dr. Nader said his animal studies have significant clinical implications. "In the case of drug addiction, if drug-related memories could be reactivated and prevented from being restored, drug-seeking behavior could in principle be greatly reduced in one session," he said. "It sounds like science fiction, but it is not."

Dr. Susan Volman of NIDA's Division of Basic Neuroscience and Behavioral Research and Dr. Barbara Sorg from Washington State University cochaired the session on "Reconsolidation of Memory: A New Approach to Treat Drug Addiction?" at the conference, which was held in Washington, D.C., November 11, 2005, in conjunction with the annual meeting of the Society for Neuroscience.

tested 2 weeks later. "These animals had effectively recollected their cocaine experience on day 1, but on day 2 and even 14 days later, there was no evidence that the memory was active," Dr. Miller notes.

"This last observation provides powerful evidence that disruption of ERK activity blocks memory reconsolidation," Dr. Miller says. "Memories are unstable during the interval between being recalled and being refiled, and, if the reconsolidation process

is disrupted, the memory can be lost. The animals behave as though it had never been formed to begin with. The fact that powerful memories associated with drugs may become pliant and susceptible to disruption by ERK inhibition during reconsolidation suggests opportunities for new therapies.” For example, pending much further research, it is conceivable that an approach combining exposure to a cue with administration of an ERK inhibitor might prevent a patient from reconsolidating—and thus erase—the memory chain linking the cue to craving.

“This research provides important new understanding of the processes that take place when the brain is manipulating memories, and it identifies specific molecules that help shape those processes,” comments Dr. Jerry Frankenheim of NIDA’s Division of Basic Neuroscience and Behavioral Research. “The fact that the intervention with U0126 came after the animals had already learned the cocaine-place association may be important for translating this research to possible clinical application. There are many ways to block the initial consolidation of memory, but the approach used in this research—interrupting reconsolidation—is much more relevant to intervening in cocaine abuse,” he adds. ■

SOURCE

Miller, C.A., and Marshall, J.F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* 47(6):873-884, 2005.

Blocking Protein Also Stops Drug-Linked Memory

NIDA-sponsored researchers at Mount Sinai School of Medicine, New York, have found another way to break the chain of molecular events that binds drug-taking to a familiar environment: inhibiting protein synthesis. Earlier research established that gene-directed protein manufacture is necessary to stabilize a new memory and that blocking this molecular process can keep lasting memories from being formed and even disrupt an established memory.

The Mount Sinai researchers, led by Dr. Cristina Alberini, performed experiments similar to those done by Drs. Miller and Marshall, but exposed the rats to morphine rather than cocaine and used chemicals that blocked protein synthesis rather than ERK. Like ERK inhibition, the protein blocker weakened conditioned place preference, but it did so only when given in close conjunction with an actual morphine administration.

Unlike the ERK inhibition technique used by the UC researchers, “blocking protein synthesis only worked after a repeat of the full experience,” says Dr. Susan Volman of NIDA’s Division of Basic Neuroscience and Behavioral Research. But the take-home message is the same: “It is possible to disrupt the strong association between a drug and place cues.”

The chemicals used in this experiment inhibit protein synthesis in general, and it will take a lot more research to develop pharmacotherapy that goes after specific proteins and molecular pathways involved in CPP, Dr. Volman says. But potential applications, she suggests, might go beyond the addiction-environment link: “If we can use protein synthesis inhibition to uncouple place from relapse, perhaps we’ll ultimately be able to uncouple cues like paraphernalia, or even the memory of the drug experience.”

SOURCE

Milekic, M.H., et al. Persistent disruption of an established morphine conditioned place preference. *Journal of Neuroscience* 26(11):3010-3020, 2006.

NIDA at Your Fingertips

News and information about NIDA research, programs, and events is quickly and easily accessible through NIDA’s home page:



www.drugabuse.gov

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

Marijuana Smoking Is Associated With a Spectrum of Respiratory Disorders

Two NIDA-funded studies identify health risks that underscore the importance of curbing marijuana abuse.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

A large new epidemiological study suggests that marijuana smoke can cause the same types of respiratory damage as tobacco smoke. Significant associations between marijuana smoking and a variety of respiratory diseases also have been confirmed by an extensive review of clinical literature.

MONITORING THE EFFECTS OF TOBACCO AND MARIJUANA

Dr. Brent Moore and colleagues at Yale University, the National Cancer Institute, and the University of Vermont evaluated data from a nationally representative sample of 6,728 adults. Their analysis indicated that a history of more than 100 lifetime episodes of smoking marijuana, with at least one episode in the past month, increased an individual's risk of chronic bronchitis, coughing on most days, wheezing, chest sounds without a cold, and increased phlegm.

“The most significant difference between tobacco smoke and marijuana smoke is their principal active ingredients—nicotine in tobacco and delta-9-tetrahydrocannabinol (THC) in marijuana. Beyond that, marijuana contains at least as much tar and half again as many carcinogens as smoke from conventional tobacco,” says Dr. Moore. “Quitting marijuana smoking may benefit respiratory health as much

as quitting cigarettes, in addition to the clear and considerable health, psychological, and social benefits of no longer abusing an illicit drug.”

The information Dr. Moore and his colleagues analyzed was gathered through the third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994. Participants included 4,789 nonsmokers of either tobacco or marijuana; 1,525 smokers of tobacco but not marijuana; 320 smokers of both marijuana and tobacco; and 94 who smoked marijuana only. On average, marijuana abusers had smoked the drug on 10 of the preceding 30 days, with 16 percent reporting daily or almost daily smoking. Tobacco smokers consumed roughly the same number of cigarettes—averaging 19.2 per day—whether or not they also smoked marijuana. Survey participants answered questions about their experiences of a range of respiratory symptoms and were examined for signs of respiratory abnormalities.

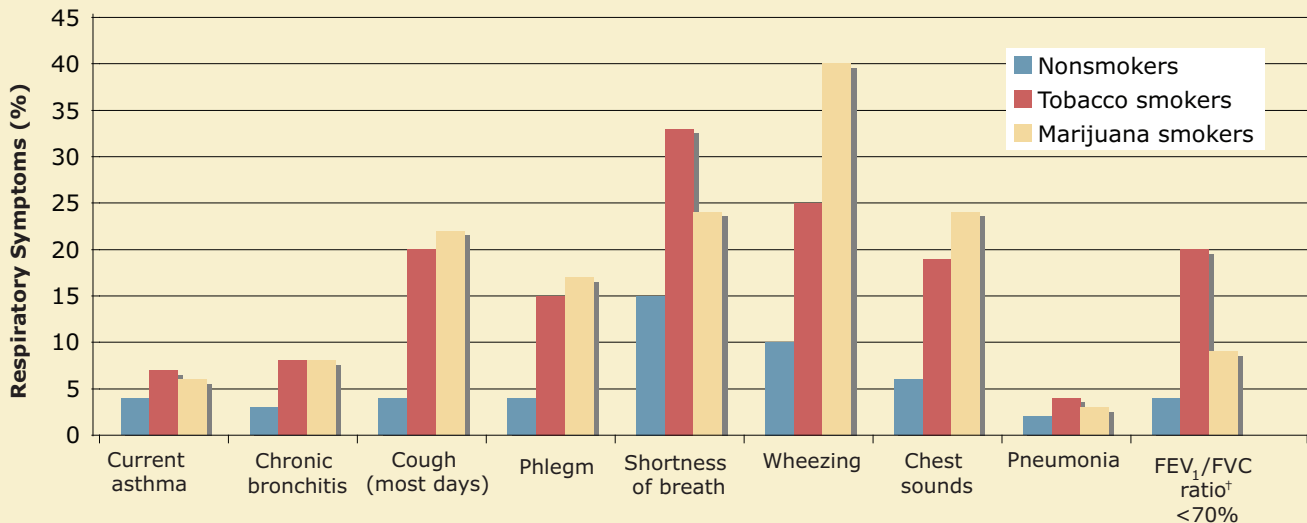
The researchers concluded that tobacco smokers who also smoked

marijuana had a higher prevalence of most respiratory symptoms than tobacco-only smokers. Compared with tobacco-only smokers, however, those who also smoked marijuana were less likely to have had pneumonia during the previous year or to show spirometric evidence of obstructive pulmonary disorder. Commenting on this finding, Dr. Moore says that it is important to note that the marijuana smokers in the sample were significantly younger (average age 31.2 years) than the tobacco smokers (average age 41.5 years). “The marijuana-related respiratory effects correspond to a relatively young population, and NHANES III did not ask participants older than age 59 about drug use,” he adds. “It is likely that respiratory effects will be higher in older

RESEARCHERS CITE PUBLIC HEALTH IMPACT More than 2 million adult Americans are heavy marijuana smokers, and increased efforts to prevent marijuana use may have significant public health benefits.



SURVEY TIES MARIJUANA ABUSE AND RESPIRATORY SYMPTOMS In a nationally representative sample of 6,728 U.S. adults, self-reported marijuana use was associated with chronic bronchitis, coughing on most days, phlegm production, wheezing, and chest sounds without a cold. Medical examinations provided overall chest findings and measures of pulmonary function.



SOURCE: National Health and Nutrition Examination Survey (NHANES III)
[†]FEV₁/FVC ratio measures lung obstruction or restriction.

marijuana smokers, and, because of the high prevalence of tobacco use among marijuana smokers, there appears to be an increased risk for illness due to cumulative effects of smoking both drugs.”

MARIJUANA’S LONG-TERM PULMONARY EFFECTS

Further evidence of marijuana’s respiratory toxicity emerged from a study conducted by Dr. Donald Tashkin at the University of California, Los Angeles. Dr. Tashkin conducted an extensive review of clinical and epidemiological research to determine the extent to which chronic marijuana smoking might lead to long-term pulmonary effects and diseases similar to those caused by tobacco. Unlike the NHANES III data examined by Dr. Moore, the studies evaluated by Dr. Tashkin made it possible to assess a possible association between marijuana smoking and respiratory cancers.

The results of animal and cell culture studies are mixed with respect to the carcinogenic effects of THC, some studies showing that THC promotes lung cancer growth and others showing an anti-tumoral

effect on a variety of malignancies. Although the results of epidemiological studies are also mixed, a large, recently completed case-control study has failed to find a direct link between marijuana use (including heavy use) and lung, throat, or other head and neck cancers. “Nevertheless, there is evidence that suggests precarcinogenic effects in respiratory tissue,” Dr. Tashkin says. “Biopsies of bronchial tissue provide evidence that regular marijuana smoking injures airway epithelial cells, leading to dysregulation of bronchial epithelial cell growth and eventually to possible malignant changes.” Moreover, he adds, because marijuana smokers typically hold their breath four times as long as tobacco smokers after inhaling, marijuana smoking deposits significantly more tar and known carcinogens within the tar, such as polycyclic aromatic hydrocarbons, in the airways. In addition to precancerous changes, Dr. Tashkin found that marijuana smoking is associated with a range of damaging pulmonary effects, including inhibition of the tumor-killing and bactericidal activity of alveolar macrophages, the primary immune cells within the lung.

Taken together, Dr. Tashkin’s survey of clinical and epidemiological studies and Dr. Moore’s assessment of self-reported and clinically observed effects provide an extensive catalog of respiratory and pulmonary damage associated with marijuana smoking. Smokers are subject to:

- Coughing and phlegm production on most days;
- Wheezing and other chest sounds;
- Acute and chronic bronchitis;
- Injury to airway tissue, including edema (swelling), increased vascularity, and increased mucus secretion; and
- Impaired function of immune system components (alveolar macrophages) in the lungs. ■

SOURCES

Moore, B.A., et al. Respiratory effects of marijuana and tobacco use in a U.S. sample. *Journal of General Internal Medicine* 20(1):33-37, 2005.

Tashkin, D.P. Smoked marijuana as a cause of lung injury. *Monaldi Archives for Chest Disease* 63(2):93-100, 2005.

Hashibe, M., et al. Marijuana use and aerodigestive tract cancers: a population-based case control study. *Cancer Epidemiology, Biomarkers & Prevention* (In Press).

NIDA's National Advisory Council Welcomes New Members



(L-R) NIDA Deputy Director Dr. Tim Condon, National Advisory Council members Ms. Janet Wood, Dr. Warren K. Bickel, Dr. Ellie E. Schoenbaum, Dr. Marina E. Wolf, and NIDA Director Dr. Nora D. Volkow

The National Advisory Council on Drug Abuse introduced four new members at its May meeting at NIDA headquarters in Rockville, Maryland.

Warren K. Bickel, Ph.D., is a professor in the College of Medicine and College of Public Health at the University of Arkansas for Medical Sciences (UAMS), Little Rock. He holds the Wilbur D. Mills Chair of Alcoholism and Drug Abuse Prevention and serves as director of the UAMS Center for Addiction Research and the Center for the Study of Tobacco Addiction. Dr. Bickel's recent research includes the application of behavioral economics to drug dependence.

Ellie E. Schoenbaum, M.D., is director of AIDS research, Department of Epidemiology and Population Health at Montefiore Medical Center in New York City. She is also professor of epidemiology and population health, medicine, and obstetrics-gynecology and women's health and vice chair, Department of Epidemiology and Population Health at Albert Einstein College of Medicine. Dr. Schoenbaum's research focuses on HIV, drug use, and women's health.

Marina E. Wolf, Ph.D., is chair of the Department of Neuroscience at the Chicago Medical School, Rosalind Franklin University of Medicine and Science. An elected member of the American College of Neuropsychopharmacology, Dr. Wolf conducts research on the role of neuronal plasticity in drug addiction.

Janet Wood, M.B.A., M.Ed., is director of behavioral health services, Colorado Department of Human Services in Denver, and the mental health commissioner for the State of Colorado.

The Council advises NIDA in its efforts to identify, review, and support scientific research that supports the Institute's mission. It comprises 18 members—12 experts in scientific fields and 6 members of the public, and ex officio members from other Government entities.

Walk the Line Is Among 10th Annual PRISM Awardees

Winners of the 10th Annual PRISM Awards include *Walk the Line*, a film portraying the life of singer Johnny Cash and his battle with drug addiction. The awards, cosponsored by NIDA, the Entertainment Industries Council, Inc., and Fox Broadcasting Company's FX Network, recognize accurate depictions of substance abuse and addiction in television, feature film, video, music, and comic book entertainment.

"What films and TV shows do is help to put a face on the issue of substance abuse and addiction, helping the public to better understand how addiction affects the addict and how treatment can lead to hope," says NIDA Director Dr. Nora D. Volkow, who cohosted the award ceremony in Los Angeles on April 27.

Walk the Line, a feature from Fox 2000 Pictures, Tree Line Films, and Catfish Productions, was singled out in the "feature film wide release" category.

Other award recipients include :

- The "Off the Tracks" episode of *Without a Trace* (TV drama episode);
- *Saturday Night Live* (TV comedy episode);
- Several episodes of *Reba* (TV comedy multi-episode storyline);
- *Behind the Camera: The Unauthorized Story of Mork and Mindy* (TV movie or mini series);
- *The Montel Williams Show* entitled "Drug Abuse: Rebuilding a Family" (TV talk show episode);
- Kelly Rowan in *The O.C.* (performance in a drama episode);
- Georgia Engel in *Everybody Loves Raymond* (performance in a comedy series);
- S. Epatha Merkerson in *Lackawanna Blues* (performance in a TV movie); and
- Lori Loughlin in *Summerland* (performance in a drama multi-episode storyline).

The 10th Annual PRISM Awards will air as a 1-hour TV special on the FX Network.



(L-R) Fox Broadcasting Company Entertainment President Mr. Peter Ligouri; NIDA Director Dr. Nora D. Volkow; and Entertainment Industries Council, Inc. President and CEO Mr. Brian Dyak

NIDA Launches Criminal Justice Publication in Chicago

NIDA Director Dr. Nora D. Volkow joined Chicago Mayor Richard M. Daley; Cook County, Illinois, Chief Judge Timothy Evans; and Illinois Treatment Alternatives for Safe Communities, Inc. (TASC) Director Melody Heaps at a July 24 press conference in Chicago to launch NIDA's *Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide*. The event also featured talks by six former clients of TASC, a not-for-profit organization that provides treatment management programs and services.

Principles of Drug Abuse Treatment for Criminal Justice Populations outlines 13 research-based principles of successful treatment of drug abusers who have entered the criminal justice system:

1. Drug addiction is a brain disease that affects behavior.
2. Recovery from drug addiction requires effective treatment, followed by management of the problem over time.
3. Treatment must last long enough to produce stable behavioral changes.
4. Assessment is the first step in treatment.
5. Tailoring services to fit the needs of the individual is an important part of effective drug abuse treatment for criminal justice populations.
6. Drug use during treatment should be carefully monitored.
7. Treatment should target factors that are associated with criminal behavior.
8. Criminal justice supervision should incorporate treatment planning for drug-abusing offenders, and treatment providers should be aware of correctional supervision requirements.



Cook County, Illinois, Chief Judge Timothy Evans addresses the conference

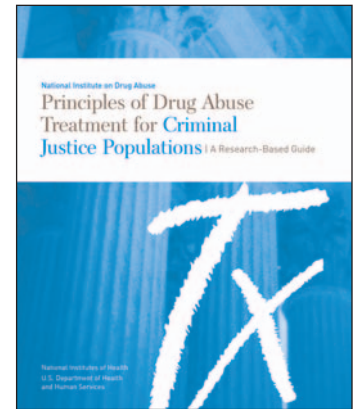


Mr. Tim Bell describes his journey and his ongoing sobriety

9. Continuity of care is essential for drug abusers reentering the community.
10. A balance of rewards and sanctions encourages prosocial behavior and treatment participation.
11. Offenders with co-occurring drug abuse and mental health problems often require an integrated treatment approach.
12. Medications are an important part of treatment for many drug-abusing offenders.
13. Treatment planning for drug-abusing offenders who are living in or reentering the community should include strategies to prevent and treat serious, chronic medical conditions, such as HIV/AIDS, hepatitis B and C, and tuberculosis.

The publication also provides answers to frequently asked questions about addiction as a chronic disease; co-occurring mental, emotional, and environmental conditions that make relapse more likely; recommendations for the components of treatment; cost-effectiveness of treatment; and the role of medication in treating substance-abusing offenders.

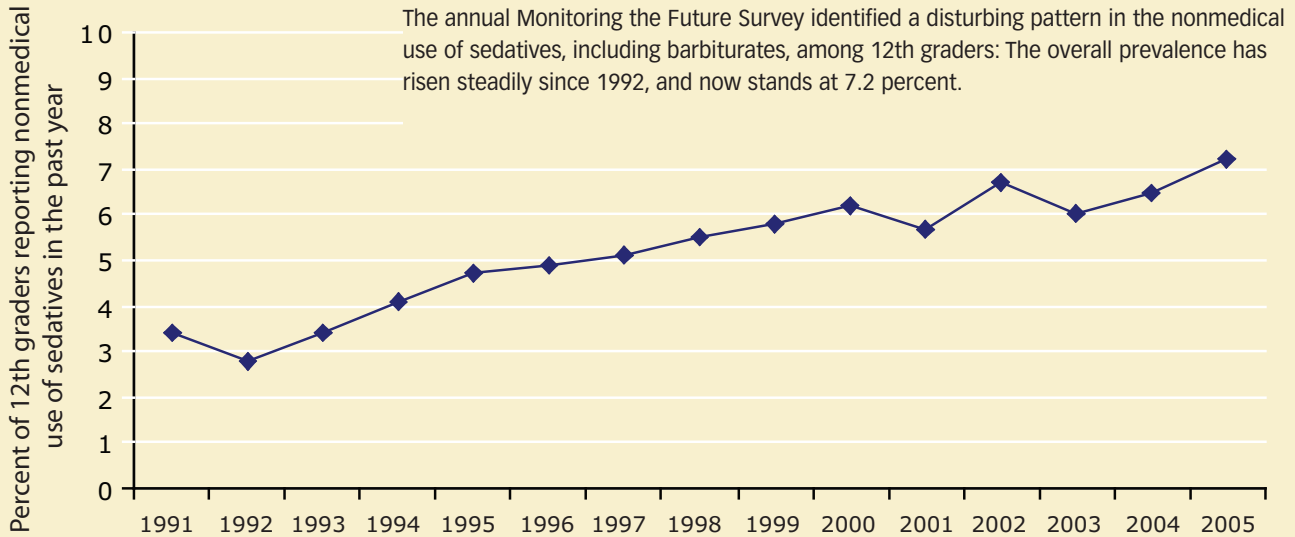
The press conference highlighted innovative substance abuse programs in Cook County, including a NIDA-sponsored project training judges about the neuroscience of addiction and treatment, so they can be better prepared to place addicted defendants in adequate treatment environments.



Celebrating the accomplishments of the TASC program: Chicago Mayor Richard M. Daley (third from left) with TASC program graduates Mr. Benny Lee, Ms. Cheryl Cline, Ms. Yvonne Thomas, Mr. Michorn Thompson, Mr. Tim Bell, and Mr. Angel Cruz

Principles of Drug Abuse Treatment for Criminal Justice Populations and its companion publication, *Principles of Drug Addiction Treatment* (issued in 1999) can be accessed on NIDA's Web site (www.drugabuse.gov) or by calling 800-729-6686. ■

High School Seniors Steadily Increase Nonmedical Use of Sedatives Over 15 Years



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