A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

Research on Heroin

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

NN0023

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Introduction

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA Notes*. Six times per year, *NIDA Notes* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA Notes* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA Notes* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 3 (April 2007)

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 maintenace reported reduced use and criminal activity.

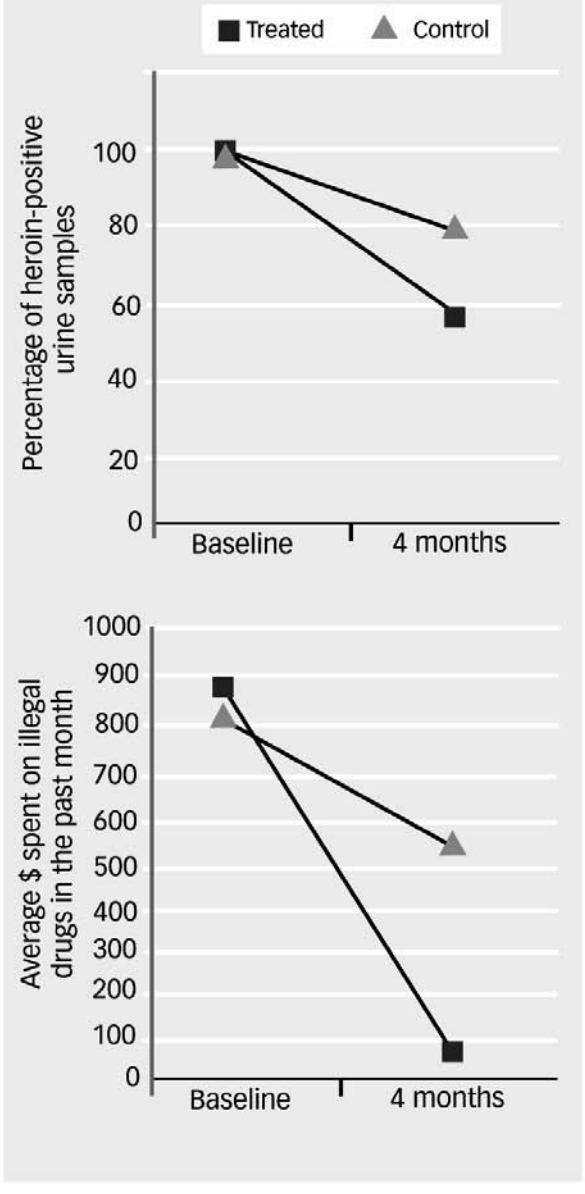
Across the Nation, full-to-capacity opioid treatment programs commonly put heroin-addicted men and women who present for treatment on waiting lists. By the time a treatment slot becomes available, the deferred applicants often have lost touch with the program or no longer desire treatment. The underlying 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 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.

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



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 of Vol. 21 No. 3). 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 controls. 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 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."

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 interm methadone—a program-wide rule that did not change for study participants. The clinic staff did not contact individuals who missed doses.

Sources

- Schwartz, R.P., et al. A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry* 63(1):102-109, 2006.
- Schwartz, R.P., et al. A randomized controlled trial of interim methadone maintenance: 10-month follow-up. *Drug and Alcohol Dependence* [June 19, 2006 Epub Ahead of Print]. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 3 (April 2007)

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.

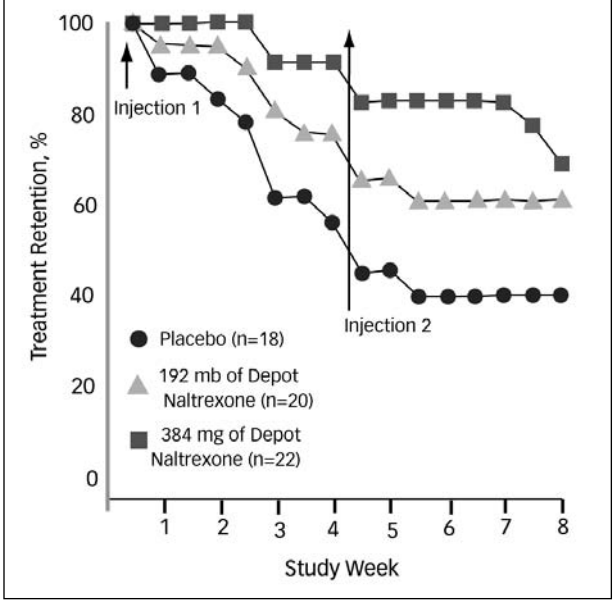
"What's exciting about this slow-release formula is that it provides continuous protection for a month at a time, freeing patients from having to decide to take or not take the medication every day," says Dr. Sandra Comer, lead investigator of the study. "By increasing treatment retention, depot naltrexone 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

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.



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."

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.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 1 (October 2006)

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

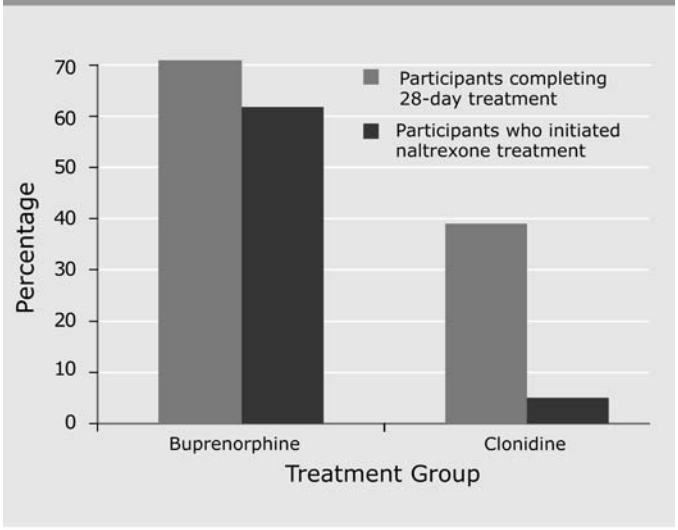
Adolescents addicted to opioids responded better to buprenorphine than clonidine in a clinical trial in which all patients also received behavioral therapy. In the NIDA-supported comparison trial at the University of Vermont, adolescents who received buprenorphine attended more scheduled counseling sessions 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 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 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.



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. NN

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Research Findings

Volume 21, Number 1 (October 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 remained awake and took a single dose of buprenorphine, a medication that eases

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)

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.

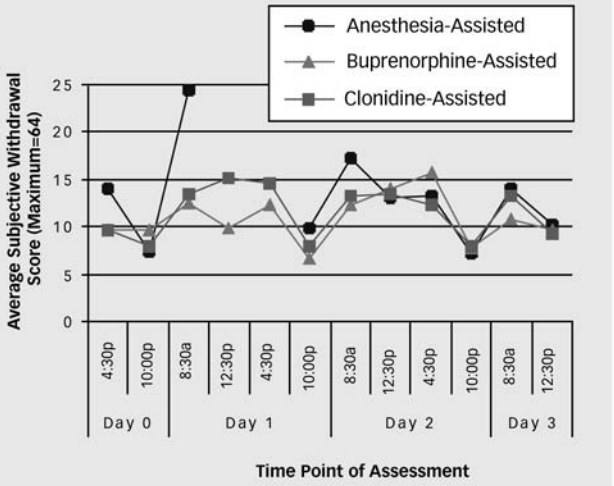
"No Advantage"

"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 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.

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.



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.

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Research Findings

Volume 20, Number 2 (August 2005)

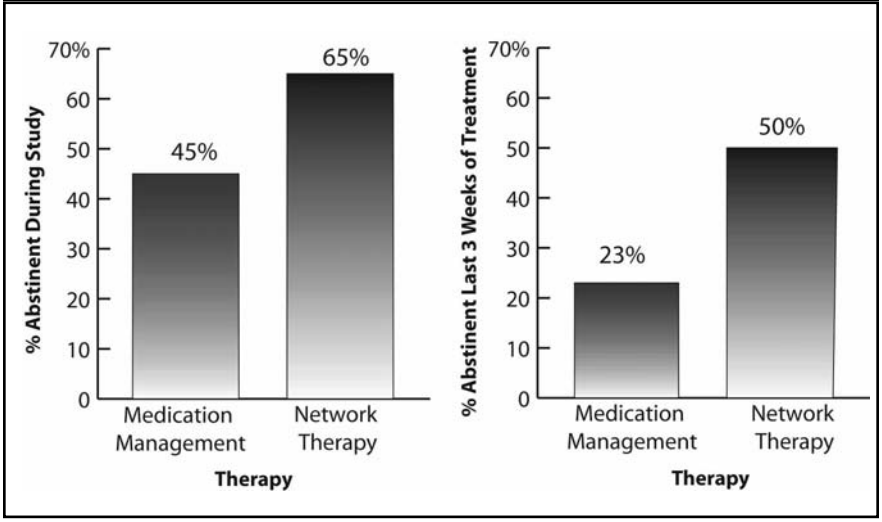
Network Therapy Enhances Office-Based Buprenorphine Treatment Outcomes

By Lori Whitten, *NIDA NOTES* Staff Writer

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

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

Network Therapy Increases Abstinence Among Patients Taking Buprenorphine



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

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

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

At the beginning of the study, patients chose people with whom they had an enduring relationship. Two people, on average, participated in each NT session with the patient. From the first NT session, therapists emphasized the primary guideline for this treatment approach: to focus on helping the patient achieve abstinence and to avoid discussions of relationship history, blaming, and emotional conflict. During sessions once a week, patients and their helpers communicated openly about events and people related to the patient's drug abuse and learned cognitive-behavioral techniques used widely in relapse prevention. As the supporters developed an understanding of relapse prevention, they helped the patient anticipate problem situations and develop recovery plans. They concentrated on creating an environment that helped the patient establish a drug-free residence, avoid substance-abusing peers, and stick to a medication regimen.

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

Patients participating in MM and NT spent the same amount of time in therapy, 70 days on average, but more NT participants achieved abstinence by the end of treatment. Half receiving NT attained this goal, confirmed by opioid-free urine tests, during the last 3 weeks of treatment, compared with 23 percent of MM patients. More NT than MM patients produced opioid-free urine samples during the study (65 percent versus 45 percent). NT patients participated in 10 network sessions on average; those who attended more sessions sustained abstinence longer during the study. Whether the network comprised family or friends did not affect treatment outcomes.

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

An Office-Based Approach

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

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

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

Studies show that many heroin-addicted patients in treatment continue to abuse some form of opioids, with only about 20 percent of those on buprenorphine medication demonstrating opioid-negative urine tests at the end of 1 month of treatment. Extending the therapy to 2 to 6 months increases the percentage of opioid-negative urine tests to 50 to 60 percent. Dr. Dorynne Czechowicz of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment says, "It's impressive that NT therapy enhanced the results typically seen with short-term buprenorphine medication." She emphasizes that the researchers should examine whether NT reduces abuse of other drugs among opioid-addicted patients, particularly cocaine, which puts people who are in recovery at high risk for opioid abuse relapse. She adds that investigators should also conduct longer-term studies to determine whether patients maintain these treatment gains and demonstrate NT's effectiveness in general medical practice.

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

Source

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

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Research Findings

Volume 20, Number 1 (August 2005)

Institute of Medicine Report Recommends NIDA Research Agenda for New Addiction Therapies

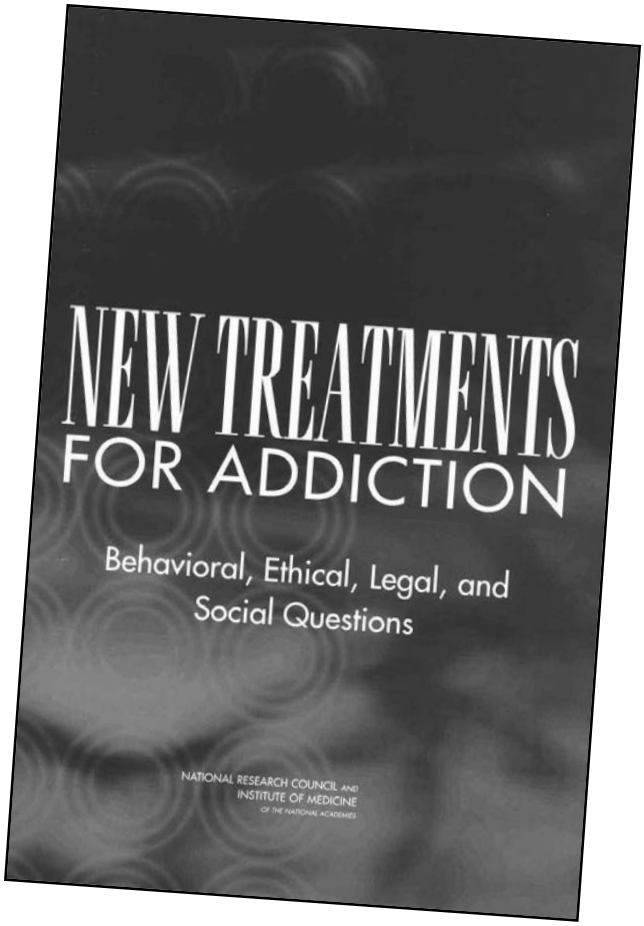
By Patrick Zickler, *NIDA NOTES* Staff Writer

A mother asks a pediatrician to vaccinate her child against nicotine's pleasurable effects, practically eliminating the possibility that the child will become a smoker. A patient in treatment for heroin addiction receives an injection of sustained-release medication that will prevent her from feeling the drug's euphoric effects for a year. As current drug abuse research brings such scenarios closer to realization, NIDA has begun to study the broad implications of these and other new types of preventive treatment. These therapies underscore the need to balance therapeutic benefits and ethical considerations, particularly if the person receiving treatment—a minor child or a person involved in the criminal justice system, for example—is not the person who chooses it.

At NIDA's request, the National Research Council's Institute of Medicine (IOM) identified ethical, legal, and behavioral issues that must be considered in the development and application of active and passive immunotherapies and sustained-release medication. The Institute's 306-page report recommends a set of guiding principles as NIDA-supported research pursues the development of these potentially powerful new preventive interventions.

Immunotherapies destroy drug molecules before they reach the brain. Active immunotherapy involves a vaccine that stimulates the body's immune system to create antibodies against drugs in the same way that an inoculation creates antibodies against polio or measles virus. Passive immunotherapy involves periodic injections of antibodies rather than stimulation of the immune system; an example of this type of therapy is tetanus immune globulin, which contains antibodies to provide short-term protection for someone whose injury may have exposed them to soil-borne tetanus bacteria. Sustained-release therapies involve injection or implantation of long-acting formulations of medications that are released over a period of weeks or months to block the effect of drugs in the brain.

The IOM report identifies ways to meet the challenges these interventions are likely to pose for researchers, treatment providers, policymakers, parents, and the public. Because the treatments may have lifelong effects, IOM recommends long-term studies involving animals of different ages, as well as their offspring, before human studies are undertaken.



IOM also recommends studies that can be used to establish clear guidelines for use of the new therapies in circumstances that are inherently coercive or nonconsensual, such as in the criminal justice system, child welfare cases, or the protective immunization of minor children. What, for example, are the possible legal consequences of administering immunotherapy medications to children or adolescents? Competent adults have the right to decline medical treatment, but the legal situation is more complicated when the patient is a minor and decisions made by others on his or her behalf may have a lifelong effect. Immunotherapies will leave long-lasting biological traces that can be detected in routine blood or urine tests. Such markers could label patients as drug abusers long after they have entered sustained recovery, which could discourage some from utilizing these treatments. In its report,

IOM says the development of immunotherapy and sustained-release medications highlights the need to understand addiction as a chronic medical condition that requires long-term management, a partnership between primary medical care and addiction treatment, and integration of psychosocial services into the treatment environment. The IOM report recommends that NIDA support models that integrate the new pharmacotherapies with psychosocial services in addiction treatment and primary care settings that reduce the stigma of substance abuse treatment.

The full report, *New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions*, is available online at www.nap.edu/catalog/10876.html. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 3 (September 2004)

Once-A-Month Medication for Heroin Addiction?

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

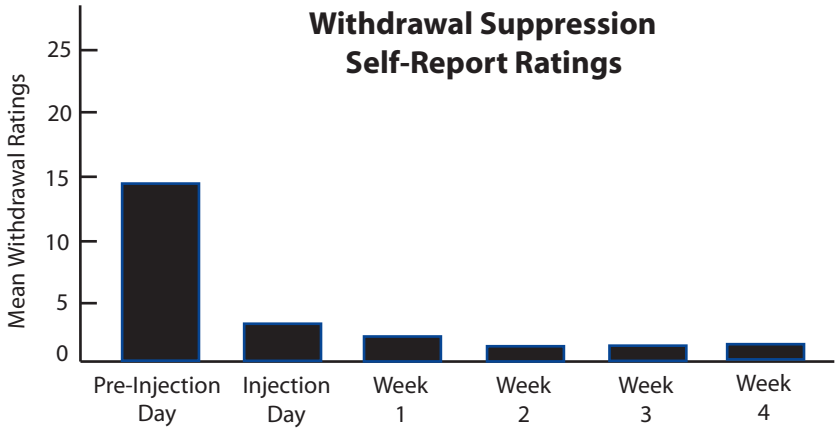
A single injection of a new sustained-release formulation of buprenorphine substantially blocked heroin's effects and relieved heroin craving and withdrawal symptoms for up to 6 weeks, report researchers at the Behavioral Pharmacology Research Unit at The Johns Hopkins University School of Medicine in Baltimore.

The study, the first to test sustained-release buprenorphine in human opioid addicts, affirms the promise of a formulation designed to increase patient adherence to treatment, ease the burden of visits to treatment providers, and reduce the risk of buprenorphine misuse.

Dr. George Bigelow and colleagues evaluated the formulation with five patients, two men and three women aged 33 to 42, who had been using heroin more than 6 years on average and were current daily users. The day before initiating buprenorphine, the researchers administered oral doses of hydromorphone as clinically needed to suppress the patients' withdrawal symptoms. The amount of hydromorphone needed to alleviate withdrawal symptoms is an objective measure of opioid dependence severity. The patients' average opioid addiction was approximately equivalent to 50 mg/day of methadone. Buprenorphine treatment consisted of a single injection of biodegradable polymer microcapsules containing 58 mg of the medication. During the following 6 weeks—a 4-week residential phase and a 2-week outpatient phase—researchers assessed the patients for signs of heroin withdrawal and patients rated their withdrawal symptoms using a standard questionnaire. No patient needed additional medication for withdrawal relief.

To test sustained-release buprenorphine's power to block the effects of heroin-like opioids, patients received weekly challenge test injections of 3 mg hydromorphone or saline under double-blind procedures. Patients' subjective ratings of various hydromorphone effects—such as feeling high, sick, or any effect—stood at zero in the first 2 weeks after buprenorphine treatment. Drug effect ratings in subsequent weeks of the study remained low—less than 25 on a 100-point scale. Moreover, the buprenorphine formulation appeared to be safe and well tolerated, with no significant side effects or signs of opioid intoxication or respiratory depression. These results suggest that sustained-release buprenorphine may prove an appealing and effective treatment option for opioid-addicted patients and their physicians.

Long-Lasting Buprenorphine Reduces Withdrawal Symptoms in Heroin-Dependent Patients



A new long-lasting, sustained-release form of buprenorphine given by a single injection reduced patients' heroin withdrawal symptoms for 4 weeks after treatment.

Source

- Sobel, B.F.; Sigmon, S.C.; Walsh, S.L.; Johnson, R.E.; Liebson, I.A.; Nuwayser, E.S.; Kerrigan, J.H.; and Bigelow, G.E. Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug and Alcohol Dependence* 73(1):11-22, 2004.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

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Successful Trial Caps 25-Year Buprenorphine Development Effort

By Arnold Mann, *NIDA NOTES* Contributing Writer

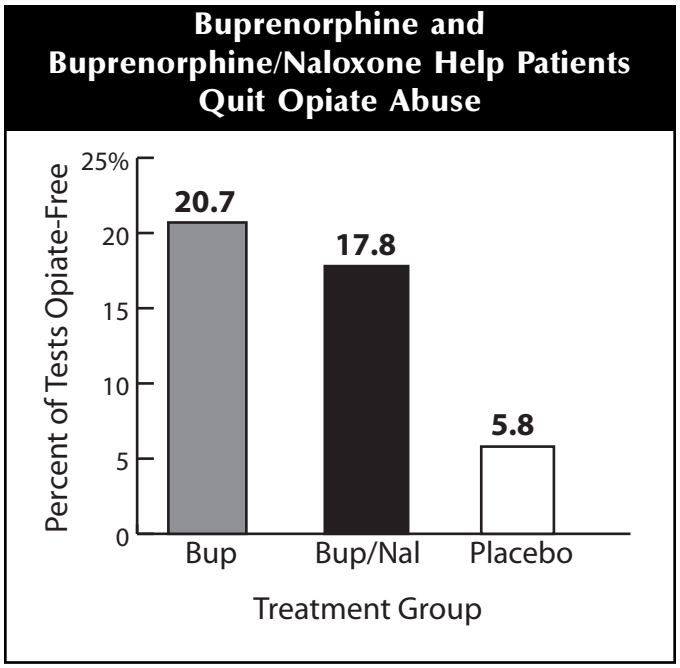
Twenty-five years ago it would have been almost impossible to imagine a treatment for opiate addiction that could be prescribed in a physician's office, picked up at a pharmacy, and taken at home. But that scenario has been achieved after a quarter-century of collaborative effort—and the overcoming of several barriers—by NIDA's medication development program and Reckitt Benckiser Pharmaceuticals, Inc.

Dr. Don Jasinski, a scientist at NIDA's Intramural Research Program (IRP), was the first to recognize the characteristics of buprenorphine—developed in the 1970s as an injectable pain medication—as useful for addiction treatment. He led the initial 1978 study demonstrating the drug's effectiveness and its acceptability to patients as a treatment for opiate dependence.

Early on, NIDA scientists realized that medications for addiction not only had to be safe and efficacious, but also had to be available in a form that would be practical for therapeutic use over the long term. NIDA worked with Reckitt Benckiser (then Reckitt & Colman) to develop noninjectable formulations of buprenorphine; by 1990, Dr. Ed Johnson and colleagues at the IRP demonstrated that a solution form of the drug administered under the tongue was safe, effective, and acceptable to patients as an opiate dependence treatment.

As with any opioid, however, there were concerns about buprenorphine diversion and the potential for abuse. NIDA again collaborated with the manufacturer, and by the mid-1990s, developed a combination tablet of buprenorphine and naloxone that would minimize the potential for abuse—a development that put the vision of take-home treatment for opiate dependence within reach. In the next decade, scientists at NIDA and Reckitt Benckiser conducted clinical trials with more than 2,400 patients that established buprenorphine's safety and efficacy in treating opiate dependence. And finally, a NIDA-funded collaborative clinical trial, codirected by Dr. Paul Fudala of the Veterans Affairs Medical Center and the University of Pennsylvania in Philadelphia, established the safety and effectiveness of the buprenorphine-naloxone combination as a prescribed take-home treatment. Data from this study and two other pivotal trials formed the basis for the U.S. Food and Drug Administration's (FDAs) approval of buprenorphine and the combination medication in 2002.

"People at NIDA knew of the great need to move opiate addiction treatment from the traditional clinic settings to individual physicians' offices. But we had to address concerns about diversion and unprescribed use. Drs. Jasinski, Johnson, and Fudala deserve a great deal of credit for their contributions to this collaborative achievement—a safe and effective take-home treatment with minimal likelihood for abuse," says Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development.



Patients undergoing treatment for opiate addiction who received buprenorphine or buprenorphine plus naloxone were more likely to test negative for opiate abuse than patients given placebo. Craving for opiates also was reduced in the two treatment groups.

Dr. Fudala's research, a nationwide study of 472 opiate-addicted men and women, was codirected by Dr. T. Peter Bridge, then of NIDA, and was recently published. The study confirmed that the efficacy and safety of the combined therapy are equivalent to those of buprenorphine alone and superior to placebo. The combination reduces craving for and use of opiates, presents limited potential for abuse, and is suitable for office-based use, the investigators concluded.

Initial Treatment Outcomes

The study began with a double-blind phase in which 323 opiate-addicted individuals (ages 18 to 59) received one of three treatments for 4 weeks. One group of 109 patients received tablets totaling 16 mg buprenorphine and 4 mg naloxone; the second group (105 patients) received tablets totaling 16 mg buprenorphine only; and the third group (109 patients) received placebo tablets. All tablets were identical in appearance and taste. Patients reported to the clinics for dosing every weekday and took their medications home for weekends and holidays. Study patients and placebo patients also participated in up to 1 hour of individualized counseling per week. Opiate use was monitored through urine tests every Monday, Wednesday, and Friday.

The plan for the initial double-blind, 4-week arm of the study was to recruit 384 patients and provide each patient with 4 full weeks of therapy. However, recruitment was halted at 323 subjects because the patients receiving either medication clearly were doing better than the placebo patients. Both medication groups showed significant reductions in opiate use and craving and significant improvements in perceptions of overall health compared with those receiving placebo.

In the buprenorphine-naloxone group, the proportion of opiate-free tests was 17.8 percent; the buprenorphine group had 20.7 percent opiate-free tests; and the placebo group, 5.8 percent. The presence of cocaine, the non-opiate drug most commonly found in urine samples in this study, did not vary significantly among the three groups. Nor was there a noticeable difference among the treatment groups in drug-positive results for amphetamines, barbiturates, or methadone.

"The number of urine samples negative for drugs probably would have been higher if investigators had used the results to counsel patients. Such feedback is known to further reduce patients' drug use, but that information was not revealed to the researchers to prevent bias. The urine test results reflect higher use at the beginning of the study—when patients are ambivalent about treatment and in the grip of addiction. It's positive that opioid use decreased over the course of the study," says Dr. Vocci.

Patients in both medication groups also reported reduced craving for opiates. All groups showed the same average self-reported craving level before treatment—approximately 60 on a 100-point scale. By week 4 of the study, the average craving scores fell by half for both medication groups but did not change for the placebo group. Patients receiving medications reported greater improvement in overall health and well-being than those in the placebo group—perceptions confirmed by higher weekly clinician ratings of patients' overall health and well-being for the two buprenorphine-treated groups. Because both medications were clearly effective, the researchers halted the first phase of the study. Patients receiving placebo during this phase went on to receive buprenorphine-naloxone combination treatment in the second phase of the study.

Longer-term Efficacy

The goal of the study's second phase was to evaluate the safety of the combination tablet in more natural conditions and over a longer term, without the restrictions associated with the double-blind condition. In this open-label portion of the study, which lasted up to 52 weeks, all patients received the combination tablet. Weekly counseling was available along with a daily dose of up to 24 mg buprenorphine and 6 mg naloxone, tailored to each patient's individual response. The sublingual tablet was administered at the clinic each weekday for the first 2 weeks; after that, patients could take home up to a 10-day medication supply at the discretion of the investigator.

Of the 472 patients who began this phase of the study, 385 received at least 8 weeks of treatment, and 261 were treated for at least 6 months. Fourteen patients discontinued therapy because of adverse events, of which detoxification or withdrawal symptoms were the most common. Opiate-free urine samples in the open-label phase of the study ranged from 35.2 percent to 67.4 percent in multiple assessments. The overall rate of opiate use was lower than in the first phase of the study, but cocaine and benzodiazepine use remained relatively constant, the researchers reported.

The study concluded that the addition of naloxone to protect against illicit use of the treatment medication did not reduce the efficacy of buprenorphine. "This new treatment option is historic," says Dr. Vocci. "Congress passed the Drug Abuse Treatment Act of 2000 so that buprenorphine products, and other Schedule III, IV, and V medications approved for opioid treatment by FDA, can be prescribed by qualified doctors for the treatment of opioid addiction. This represents a change to a level of prescribing privileges that American doctors have not had since the Harrison Narcotic Act of 1914."

Who Can Benefit

In the two years since the medication was approved, clinicians have gained an understanding of which patients are most likely to benefit from a take-home treatment option. Dr. Fudala cautions that buprenorphine is not likely to work well for every patient. Those less likely to benefit may include patients who require very high doses of methadone. Buprenorphine is a partial agonist, which means that in severely addicted people, it may not provide enough opiate agonist activity to treat them adequately.

Dr. Fudala says the combined agent may be especially useful for patients who do not have extremely high levels of addiction and for younger individuals, who typically have a shorter abuse history and may be using smaller amounts of an addictive substance. "We're seeing younger and younger heroin addicts these days," says Dr. Fudala. "It may be a good initial treatment for them, either as a medical detoxification or, if necessary, as a longer term treatment. We'll have a better understanding of this as we gain more experience." Another suitable population may be addicted professionals, including those in health care, who could be motivated to seek treatment in the privacy of a physician's office setting.

Buprenorphine's suitability for office-based prescribing is based on its pharmacologic profile. Like methadone, buprenorphine activates opiate receptors, but its effects level off as the patient takes higher and higher doses; this reduces the likelihood of dangerous side effects such as severe respiratory depression.

The addition of naloxone reduces the potential for abuse by illicit injection. If a combination tablet is crushed and injected by a heroin-addicted individual in an attempt to intensify buprenorphine's euphoric effect, naloxone kicks in to induce the symptoms of opiate withdrawal. Finally, buprenorphine has a relatively long duration of action and causes comparatively mild withdrawal discomfort on cessation, affording flexibility in dosing regimens and a margin of convenience for patients and physicians.

As of March 2004, 3,951 U.S. physicians were eligible to prescribe buprenorphine. Of that group, 2,848 were granted waivers of a Federal requirement for previous experience in addiction medicine. This number is growing, according to Dr. Vocci. "We had estimated that about 6,000 physicians would eventually take the training and get the waiver. So we're at about 50 percent," he says. At this time, he notes, certified physicians are restricted to treating no more than 30 patients. In October 2005, 3 years from the approval of the new drug combination, the Department of Health and Human Services and the Drug Enforcement Administration will evaluate the program and possibly adjust the restrictions. The overall picture, however, is positive, says Dr. Vocci. "Very little diversion has been reported with this new combination," he says.

Source

- Fudala, P.J., et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 349(10):949-958, 2003. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 1 (April 2004)

Researchers Adapt HIV Risk Prevention Program for African-American Women

By Jill Schlabig Williams, *NIDA NOTES* Contributing Writer

The HIV/AIDS epidemic has taken a disproportionate toll on racial and ethnic minority populations, especially women. In its surveillance report on the number of Americans living with HIV/AIDS in 2002, the Centers for Disease Control and Prevention estimates that among women with HIV/AIDS, non-Hispanic African-American women outnumbered non-Hispanic white women by three to one—a racial disparity not found among men.

African-American drug-using women were addressed in two recent studies by NIDA-funded researchers in Atlanta. Dr. Claire E. Sterk of Emory University, Dr. Kirk W. Elifson of Georgia State University, and colleagues developed and tested gender-tailored, culturally specific adaptations of a standard NIDA HIV prevention intervention. They found that female African-American injecting drug users (IDUs) and crack cocaine users who received either of two targeted 4-week prevention programs reduced their risk behaviors related to drug taking and sex more than did women who received the standard intervention.

"These studies are examples of research that is responsive to community needs," says Dr. Dionne Jones of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "When it comes to designing a prevention program, it's not one-size-fits-all. You have to consider social context, be culturally sensitive and appropriate, and tailor your message to the group."

Tailored Interventions Build on NIDA Intervention To Help Drug-Using Women Reduce HIV Risk

	Behavior in Past 30 days	NIDA Standard Intervention Group		Motivation Intervention Group		Negotiation Intervention Group	
		Baseline	Six-Month Followup	Baseline	Six-Month Followup	Baseline	Six-Month Followup
Injecting Drug Users	Number of days injected powder cocaine	8.2	3.1	6.4	0.1	4.7	0.2
	Number of days injected heroin	16.4	8.9	12.7	1.5	9.8	3.2
	Percentage who traded sex for drugs	70.4	40.7	50.0	20.0	42.9	10.0
Crack Cocaine Users	Mean number of days crack used	17.7	12.9	18.2	15.6	18.7	13.8
	Percentage who had vaginal sex with one or more paying partners	43.9	24.6	34.3	19.2	30.8	20.5

African-American drug-using women in three intervention groups reduced behaviors that heightened their risk of HIV infection. However, women receiving the culturally specific, gender-tailored motivation and negotiation interventions generally reported greater reductions in risky behaviors after their participation than women in the NIDA standard intervention.

The researchers' goal was to develop culturally appropriate programs grounded in the reality of the daily lives of women most at risk and the difficulties they face in their individual, social, family, and sexual relations and activities. "We worked hard to develop interventions with input from this target population, deliver the interventions in a setting where they feel comfortable, and involve them in planning, implementing, and evaluating the interventions," says Dr. Sterk.

Over 1 year, using one-on-one interviews and small focus groups, the researchers sought to define the key issues in the women's lives and identify ways to address those issues, including such factors as gender dynamics, economic stressors, gender-specific norms and values, and power and control. Two interventions came out of this research phase. One, a motivation intervention, was designed to motivate the participants to change

their behavior. The other, a negotiation intervention, recognized that women may fear verbal or physical abuse if they propose safer sex or safer needle use and thus sought to strengthen their negotiation and conflict-resolution skills.

"Our goal in the motivation intervention was to reduce risk based on what's realistic in the context of the participant's life," explains Dr. Sterk. "We worked with the women to set short- and long-term goals, celebrate successes, analyze failures, and identify and overcome barriers." The negotiation intervention recognizes that many of the women's challenges dealt with the need to resolve conflict and that negotiation skills are key to reducing risk.

Once the interventions were ready, more than 300 African-American women ages 18 to 59 years—68 IDUs and 265 crack cocaine users—were enrolled in the studies. All were HIV-negative and heterosexually active. The women were randomly assigned to one of the three interventions. The NIDA standard intervention was delivered in two one-on-one sessions; the motivation and negotiation interventions each involved four one-on-one sessions. (See textbox, below, for descriptions of each intervention.) At the 6-month followup, both IDUs and crack cocaine users in all three groups reported lower levels of drug-using behavior and risky sexual behaviors than they had reported before receiving the interventions. Reductions were greater among women who received the tailored interventions.

Injecting Drug Users. The motivation and negotiation interventions were equally effective in reducing the incidence of needle and injection-works sharing. At 6 months, there was no sharing of drug injection paraphernalia in these groups; in the standard intervention group, 13 percent reported sharing needles and 18 percent reported sharing injection works. Although women in all intervention groups reduced their number of injections over time, only those in the tailored interventions reported statistically significant decreases. Participants in the motivation intervention were most likely to attend drug treatment, whereas women in the negotiation intervention reported more changes in their sexual behavior than did women in other interventions.

Crack Cocaine Users. All three interventions were associated with a drop in crack use in the 30 days preceeding followup. About 40 percent of the women in each group reported no use during that period. Among those still abusing crack at followup, women in the motivation intervention were more likely to have reduced their use of crack in risky settings, such as outside or in a crack house, hotel room, or car. Women in the standard and motivation intervention groups significantly decreased the number of paying partners for vaginal sex and the frequency of sex with paying partners.

Dr. Sterk suggests that the study's results show it may be optimal to create an intervention that combines skills taught in both the negotiation and motivation

Protocols for Standard, Motivation, and Negotiation Interventions

All interventions include discussion of the local HIV epidemic, sex and drug-related risk behaviors, safer sex and drug use, and HIV risk-reduction strategies. The two tailored interventions also include a discussion of the impact of race and gender on HIV risk and protective behaviors.

The NIDA standard intervention is an HIV/AIDS education program that was developed in the early 1990s. It builds on standard HIV testing and counseling developed by CDC and adds discussion of the principles of HIV prevention for drug users and their sex partners. The intervention involves testing, counseling, and educating participants through use of cue cards on such topics as the definition of HIV/AIDS, who is at risk, and ways to reduce risk. Also offered are demonstrations on condom use and equipment-bleaching techniques for IDUs. Referrals to counseling and other services are provided.

The motivation intervention follows the format of the standard intervention for the first session but ends with asking participants to consider what they are motivated to change in their lives. During the second session, this list is reviewed and short- and long-term goals are set. The third and fourth sessions involve discussion of experiences with behavior change, including the woman's sense of control and feelings of ambivalence about behavior change. Risk-reduction messages tailored to the participant's level of readiness to change are also delivered in the fourth session.

The negotiation/conflict-resolution intervention also follows the NIDA standard intervention for the first session, but it ends with a discussion of intended behavior changes. The second session reviews the list of possible behavior changes and the level of control the participant believes she has and introduces general communication skills and strategies to develop assertiveness. Short-term goals are set for strengthening communication, gaining control, and developing assertiveness. Negotiation and conflict-resolution strategies are introduced during the third session and tailored to the individual during the final session.

interventions. While participants in the negotiation intervention were generally more successful at reducing sexual risk behaviors, including decreasing the number of paying partners and increasing condom use with steady partners, participants in the motivation intervention had more success at changing drug-use behaviors.

Efforts were also made to assist program participants in their lives outside of the program, with success extending well beyond the study's parameters, notes Dr. Sterk. "A lot of the women who received the one-on-one support available through the tailored interventions said the program served as a re-entry into society. For example, they were encouraged to obtain a photo ID. Many reported that this simple act made them feel more connected to society again, part of the larger world." Program graduates returned to school, earned their GED, found jobs, joined the project to become counselors or interviewers, and stopped using drugs.

"Over and over, researchers are finding that we need to take a more holistic approach to intervention programs," says NIDA's Dr. Jones. "We can't just focus on drugs and sex. We must look at the big picture. It involves childcare, education, employment, housing, and job training. Community stakeholders need to develop programs that address multiple needs."

The project maintained a high retention rate—96 percent of the women enrolled in the studies completed the 6-month followup interview. Dr. Sterk attributes this success to the fact that the project was grounded in the community and to the value of involving community consultants—residents, both former drug users and others, who played key roles in recruiting, interviewing, and counseling participants.

In future research, Dr. Sterk intends to examine the cost-effectiveness of various intervention formats. "It appears that individual sessions may be more desirable and cost-effective," she predicts. Dr. Sterk would like to continue the research, assessing the long-term effects of specific interventions. She wants to develop an intervention that focuses on women's households, targeting both the woman and her main partner, and she is interested in capacity-building—translating her research into other settings and training people to develop similar programs in more communities.

Sources

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- Sterk, C.E.; Theall, K.P.; Elifson, K.W.; and Kidder, D. HIV risk reduction among African-American women who inject drugs: A randomized controlled trial. *AIDS and Behavior* 7(1):73-86, 2003. NN

Principles That Guide Format, Content of Interventions

The interventions used by Dr. Sterk and her colleagues in this study are firmly based in theoretical research. The researchers conducted a series of one-on-one interviews and focus groups with the target population. These interviews yielded the following key principles that guided both the format and the content of the interventions.

- **Offer counseling sessions on an individual basis.** "It was very clear that women wanted to start with one-on-one sessions," says Dr. Sterk. "HIV risk behaviors involve so many private, personal issues—previous abuse experiences, actions to support their drug habits, things they'd never before discussed. They found it easier to discuss these experiences with one person, not a group."
- **Adopt a holistic approach.** Along with this research project, a clothing fair was conducted and clothes made available to program participants. Food for breakfast was provided; daycare was close by; and ongoing services, such as help preparing for job interviews, were provided.
- **Make programs community-based.** The project was headquartered in a house in the community, which was key to participants' convenience and comfort. Researchers also found it important for the women to link participation in this project to local social and health services, including local drug treatment, daycare centers, health services, and other community-based organizations. Community consultants played a key role in the project.
- **Address women's multiple social roles in the intervention.** Participants insisted that they didn't want to be labeled simply as drug users. Instead, they wanted the social context of their daily lives to be addressed, including their roles as mothers and steady partners.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 6 (March 2003)

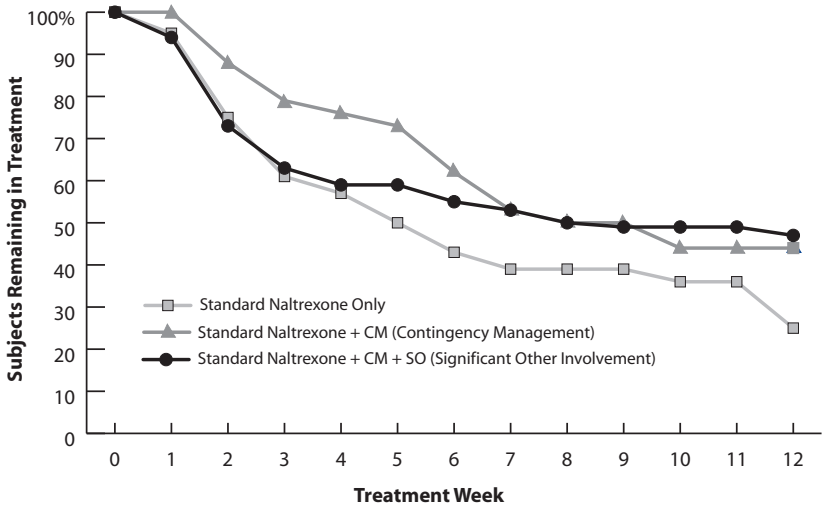
New Approaches Seek To Expand Naltrexone Use in Heroin Treatment

By Robert Mathias, *NIDA NOTES* Staff Writer

Naltrexone, an opiate treatment medication, is used to help patients make the transition from illicit opiate use to a drug-free life. Patients in naltrexone treatment are first detoxified from their dependence on opiates and then take thrice-weekly doses of naltrexone and participate in weekly group therapy sessions.

The medication provides a safety net for patients because it blocks the euphoric effects they normally would feel if they slip and use heroin or any other opiate. As a result, even relapse, which is common in addiction treatment, may have a therapeutic effect as repeated failure to get high may eventually break the neurobiological and behavioral links between taking drugs and the rewards that lead patients to resume regular drug use. With successful naltrexone treatment, slips to drug use become less frequent, the medication is discontinued, and patients continue behavioral treatment if needed.

Voucher Incentives Increase Retention In Naltrexone Treatment



Source: *Archives of General Psychiatry*, August 2001.

In a study with 127 heroin-addicted patients receiving naltrexone therapy, the 12-week dropout rate was about 50 percent among those in two groups that received voucher-based contingency management, and about 75 percent among those who did not.

Naltrexone treatment has been successful mainly with patients who are highly motivated to stop using opiates. Such patients include health care professionals who must stop using opiates to retain their licenses to practice medicine and individuals subject to criminal justice sanctions for relapse to illicit opiate use. The severe penalties that these patients would incur if they fail treatment enable them to overcome naltrexone's main drawback: It eliminates the powerful rewarding effects of opiates without any replacement to help patients cope with lingering effects of withdrawal.

Naltrexone's lack of a reinforcing effect has made it an unattractive treatment option for other patients who lack a strong external incentive to stop using drugs and do not want to go through detoxification and withdrawal from opiates. Most of these patients opt for treatment with medications such as LAAM and methadone, both of which help them to cope with the absence of the intense and rapid high that they are accustomed to getting from heroin by replacing it with a more moderate, stabilizing effect that can help them to maintain a nonaddicted lifestyle.

Despite its limited clinical use, naltrexone has many qualities that make it an attractive option for treating a broader range of opiate-dependent patients. It is not addicting, has few adverse effects, can be prescribed without concerns about diversion to the illicit drug market, and is not subject to the restrictive regulatory requirements that limit the use of methadone and LAAM to specialized clinics. Thus, like the recently approved opiate treatment medication buprenorphine, naltrexone can be administered in many settings, including private physicians' offices, making it more attractive to individuals who are reluctant to enter clinics.

Naltrexone's desirable therapeutic traits have continued to spark interest in finding new ways to expand its usefulness and application in practice. Two recent studies show that adjunctive behavioral and new pharmacological approaches may help to increase naltrexone's effectiveness for a wider range of opiate-addicted patients.

Voucher Reinforcement Increases Naltrexone's Effectiveness

A NIDA-supported treatment study that rewarded heroin-dependent patients with vouchers whenever they took their naltrexone or tested negative for drug use has found that this basic behavioral reinforcement approach achieved significantly better results than standard naltrexone treatment alone in keeping patients in treatment longer, having them complete treatment, and reducing their opiate use.

"A significant boost in treatment adherence was achieved not with highly motivated patient groups that have generally responded well to naltrexone treatment, but with predominantly unemployed 'street addicts,' most of whom had a history of extensive involvement with drug abuse treatment and the legal system," says Dr. Dorynne Czechowicz of NIDA's Division of Treatment Research and Development. She also maintains that the results are

Long-Lasting Formulation Also May Increase Naltrexone Compliance

NIDA-supported researchers have been testing a long-lasting "depot" formulation of naltrexone that is aimed at reducing the three-times-a-week frequency with which patients must now take the medication to prevent them from getting high if they use heroin. The formulation is packaged in microcapsules injected under the skin that slowly release medication for several weeks. The sustained release of naltrexone is meant to maintain enough medication in the patient to suppress heroin's euphoric effects for an extended time.

Clinical trials now under way are assessing the safety and efficacy of depot naltrexone. In a recent trial, Dr. Sandra D. Comer and a team of researchers from the New York State Psychiatric Institute and Columbia University tested depot naltrexone in an 8-week inpatient study with 12 heroin-dependent subjects to see how long the medication remains active in the human body and blocks heroin's effects. After detoxification, six patients received a low dose (192 mg) and six received a high dose (384 mg) of the medication. Patients in both groups subsequently were given a placebo or intravenous heroin once a day from Monday through Friday for 6 weeks. Each week, daily doses of heroin started at 6.5 mg and increased to 12.5, 18.75, and 25 mg; the placebo was administered randomly on one of the days.

Researchers assessed subjective, performance, and physiological effects after each dose of heroin or placebo and measured plasma levels of naltrexone over the course of the study. They found that both doses of depot naltrexone substantially suppressed the patients' ratings of heroin's pleasurable effects and how much they "liked" the drug and wanted to take it again. With the high dose of naltrexone, patients' positive ratings of heroin's pleasurable effects remained low for 5 weeks. In the 6th week, ratings increased significantly relative to week one after patients received the 18.75- and 25-mg injections of heroin. The low dose suppressed positive ratings of heroin for 3 weeks. Plasma levels of naltrexone remained above 1 ng/mL for 4 weeks with the high dose and 3 weeks with the low dose. Though these levels are low compared to those resulting from standard naltrexone treatment doses, other studies have reported that even with negligible plasma levels, naltrexone continues to counter heroin's effects. Other than initial discomfort at the site of naltrexone injection, there were no untoward side effects.

The results suggest that once-a-month administration of the depot formulation can provide safe, long-lasting blockade of the effects of intravenous "streetlevel" heroin doses in patients who have undergone detoxification. Future studies will address questions that remain about optimal dose levels for naltrexone treatment of heroin dependence, such as what effects different doses have on withdrawal, craving, and the ability to reduce heroin use.

Source

- Comer, S.D., et al. Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology* 159:351-360, 2002.

promising for expanding the types of patients who would benefit from naltrexone treatment.

The 12-week study, led by Dr. Kathleen Carroll of the Yale University School of Medicine, randomly assigned 127 recently detoxified opioid-dependent patients to 1 of 3 treatment conditions: standard treatment with naltrexone 3 times a week; standard naltrexone treatment plus a behavioral reinforcement approach called contingency management (CM); or standard naltrexone treatment and CM plus involvement of a significant other (SO) in up to 6 family counseling sessions. SO treatment was added to CM for patients in the third group to test the idea that encouragement and positive reinforcement from a significant other might help patients cope with any protracted drug withdrawal symptoms and remain in treatment longer. Patients in all three groups participated in weekly cognitive-behavioral group counseling sessions.

Patients in the CM groups could earn vouchers, which they could exchange for goods and services, in separate tracks for naltrexone compliance or drug-free tests. In each track, the voucher value started at $0.80, escalated in $0.40 increments for continuous compliance or abstinence, and were reset to the starting point for each failure to take the medication or pass a drug test. Over the course of the study, patients in the CM groups earned an average of $189 in vouchers out of the maximum $561 that could be earned for perfect medication compliance and all negative drug tests.

The researchers found that on average, patients in the two CM groups stayed in treatment 7.4 weeks, significantly longer than the 5.6 weeks for those in standard treatment. A much higher percentage of CM patients also completed the full 12-week treatment period—47 percent of CM plus SO patients, 42.9 percent in the CM group, and 25.6 percent of patients in the standard treatment group. These retention rates with CM added to standard treatment also compare favorably with rates achieved in previous studies of standard naltrexone treatment, which have reported that 60 to 70 percent of patients dropped out of treatment over a 12-week period, Dr. Carroll notes.

Patients in the CM groups also had significantly better treatment outcomes than those in the standard naltrexone group—more days of abstinence, longer periods of continuous abstinence, more opiate-free tests, and a higher percentage of drug-free specimens. Additional analyses suggested CM patients made greater reductions than standard treatment patients in the frequency with which they used opiates as the study progressed. Thus, 100 percent of patients reported weekly opioid use at the beginning of the study, but fewer than 10 percent of those who completed treatment reported weekly use over the last 4 weeks of the study. Although adding SO to CM did not improve most treatment outcomes, further analysis suggested it did produce a significant reduction in family problems over time.

"Our study shows you can really bump up medication compliance and outcomes with very simple behavioral interventions," Dr. Carroll says. "It doesn't take much effort or cost for treatment programs to do this, particularly if you look at the potential savings from keeping patients in treatment longer where they can learn how not to be drug users."

Source

- Carroll, K.M., et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. *Archives of General Psychiatry* 58(8):755-761, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 5 (January 2003)

Opening the Door to Mainstream Medical Treatment of Drug Addiction

By Glen R. Hanson, Ph.D., D.D.S., NIDA Acting Director

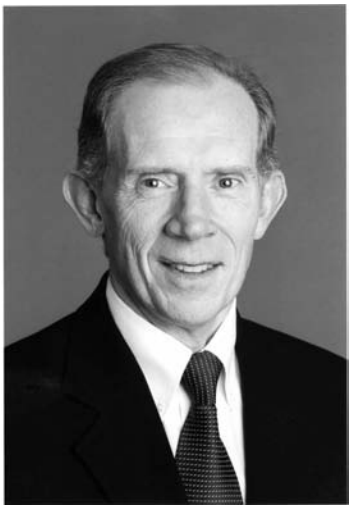
The October approval of buprenorphine by the U.S. Food and Drug Administration for treatment of opiate dependence marks a historic milestone for drug abuse research and treatment. Buprenorphine crowns more than two decades of NIDA-supported research on the neurobiology of drug addiction with a medication that has the potential to increase the safety, availability, and acceptance of opioid abuse treatment in the United States.

As the first medication for opioid maintenance treatment that physicians can dispense in their offices to patients addicted to heroin and prescription pain relievers, buprenorphine creates a new therapeutic option whose convenience and relative privacy should appeal to many patients and may facilitate the integration of drug abuse therapy with attention to patients' other medical needs.

Buprenorphine's availability culminates the collaborative efforts of NIDA's medications development program and the pharmaceutical division of the firm Reckitt Benckiser. Over the last decade, these entities conducted clinical trials with more than 2,400 patients that established buprenorphine's safety and efficacy in treating opiate dependence. At the same time, Federal legislators enacted the Drug Abuse Treatment Act of 2000 (DATA), which removed numerous regulatory barriers to the use of approved opiate treatment medications in doctors' offices. More than 2,000 physicians already have qualified under DATA to use buprenorphine in their practices.

Buprenorphine's distinctive pharmacology gives it the safety margin and low potential for diversion to illicit use required for office-based use.

Buprenorphine's distinctive pharmacology gives it the safety margin and low potential for diversion to illicit use required for office-based use. The medication's unique mechanism of action—how it works to achieve its therapeutic effect and reduce the likelihood it will be abused—is grounded in decades of basic and clinical research on the biological and behavioral underpinnings of drug addiction.



Using fundamental knowledge derived from NIDA-funded research about where and how opiates such as heroin work to achieve their euphoric effects, NIDA researchers identified buprenorphine as a potential opiate treatment medication in the late 1970s. Subsequent research with the compound showed that it interacts in similar but significantly different ways at the same mu opioid receptor in the brain where heroin, morphine, and prescription pain relievers as well as the treatment medication methadone initiate their effects.

As a partial agonist at this receptor, buprenorphine blocks heroin's effects, reduces cravings for the drug, and prevents unpleasant withdrawal symptoms. Moreover, its potential for abuse is limited because it produces less stimulation and physical dependence than full agonist medications, such as methadone, and its euphoric effect peaks at a moderate level no matter how much is taken.

NIDA's medications development program further refined buprenorphine by developing two formulations for use at different stages of treatment for opiate addiction. Patients generally will make the transition from illicit opiate drugs to Subutex—a medication containing only buprenorphine—in a few days under their physician's direct supervision when they begin treatment. Once they adjust to Subutex, patients will be switched to Suboxone, which contains buprenorphine and an opiate antagonist called naloxone. This combination of ingredients further reduces the medication's potential for illicit injection; if a Suboxone tablet is crushed and injected in an attempt to accelerate and intensify buprenorphine's agonist effects, naloxone blocks the mu receptor and can induce opiate withdrawal. Suboxone will be the main prescription medication

patients take home for long-term treatment of the physiological changes wrought by chronic opiate abuse, for use in conjunction with counseling and support services to help them live stable, productive lives.

Office-based treatment with buprenorphine will give clinicians a powerful new tool to treat opiate addiction; it will not replace medications now used to treat this disorder. Much research and clinical experience has shown that methadone, administered regularly in a comprehensive treatment program, can reduce or eliminate heroin injection and the attendant risk of AIDS and other infectious diseases. A longer lasting form of methadone, LAAM (the first medication developed by NIDA's medications development program) gives clinicians additional flexibility in managing opiate dependence. As full agonists at the mu opioid receptor, both methadone and LAAM address heroin's harmful effects but also produce strong physical dependence and, compared to buprenorphine, have a higher potential for abuse and greater danger of overdose. As a result, they remain subject to strict Federal, State, and local regulations that limit their use to licensed narcotic addiction treatment clinics.

Methadone clinics will continue to play a crucial role in treating heroin addiction, but they are able to treat only one-fifth of the estimated 1 million Americans who are dependent on opiates.

Methadone clinics will continue to play a crucial role in treating heroin addiction, but they are able to treat only one-fifth of the estimated 1 million Americans who are dependent on opiates. Office-based treatment with buprenorphine will help fill this treatment gap by providing more treatment options for the 800,000 opiate-addicted individuals not now being treated. People who abuse heroin or prescription pain medications but have avoided methadone clinics because of the stigma associated with them, and likewise, adolescents and young adults who have become addicted to heroin through snorting the drug are among the prospective new patients expected to get the medical help they need from their physicians. In addition, some stable methadone patients may transfer from clinic care to office-based treatment to eliminate the burden of daily methadone clinic visits. As a result of such transfers, methadone treatment slots will open up for the many heroin abusers waiting to enter treatment.

The public-private initiatives that have made it possible for patients to be treated with buprenorphine in their doctors' offices are based on scientific understanding of drug addiction as a chronic, relapsing brain disease that can be treated medically as we treat other chronic diseases, such as diabetes or hypertension. Office-based treatment with buprenorphine advances the day when all distinctions between drug abuse and other medical treatment disappear and primary care physicians and treatment professionals work together to provide patients with the most effective medications and psychosocial treatments available for their disease. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 4 (November 2002)

Buprenorphine Approval Expands Options for Addiction Treatment

Roughly two decades of NIDA-sponsored research and clinical trials have culminated in the Food and Drug Administration's (FDA) approval of buprenorphine as a treatment for opiate dependence and addiction. The medication was developed through a Cooperative Research and Development Agreement between NIDA and the firm Reckitt Benckiser, Inc.

Buprenorphine and the combination buprenorphine/naloxone are the first medications approved under the Drug Abuse Treatment Act of 2000 (DATA), which allows for office-based treatment of opiate addiction. Under the terms of DATA, physicians providing treatment must complete special training to dispense the medications, must agree to treat no more than 30 patients at a time in an office setting, and must refer patients to appropriate counseling and support services to enhance pharmacological treatment.

The FDA action will permit physicians to prescribe buprenorphine as part of office-based practice, making it possible for patients dependent on heroin or prescription painkillers such as OxyContin to receive treatment in their doctors' offices rather than requiring daily visits to a centralized methadone clinic. Patients entering or continuing treatment in clinic settings would also be eligible to receive the new medications.

"We are hopeful bupenorphine will be the first of many new drug addiction medications eligible for use under the Drug Abuse Treatment Act of 2000 legislation."

—Senator Orrin Hatch (R-Utah), coauthor of DATA.

"Approval of this new drug will allow for the long-awaited and appropriate conventional, office-based approach to addiction treatment in this country."

—Senator Carl Levin (D-Michigan), coauthor of DATA.

The availability of an effective medication that can be provided in an office-based setting will significantly increase the number of patients receiving treatment, according to Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development. "Nearly 1 million Americans are dependent on opiates, but only 200,000 of them are getting treatment in licensed methadone clinics. Approval of this medication means that many more people who want treatment can get it," Dr. Vocci says. "FDA approval of this medication marks a truly great moment in the treatment of drug dependence and addiction, and it clearly shows the value of collaborative partnerships between legislators, Federal agencies, and private industry."

Buprenorphine is pharmacologically related to morphine and is a partial opioid agonist—it has the same effect on mu opiod receptors in the brain as does heroin or other

opiate drugs, but it has a lower maximum effect. Buprenorphine reduces or eliminates withdrawal symptoms associated with opioid dependence but is not strong enough to produce the euphoria and sedation caused by heroin or other opiates. Increasing the dose of buprenorphine does not enhance the drug effects, however, so the medication is unlikely to be abused.

FDA approved two forms of the medication. Buprenorphine alone will be prescribed (under the trade name Subutex) for patients in the early stages of treatment. Buprenorphine combined with naloxone, an opioid antagonist, will be prescribed (as Suboxone) for long-term maintenance therapy that will allow patients to resume and maintain normal, productive lives during treatment. Combining the antagonist naloxone with buprenorphine further reduces the potential that the medication could be abused; injecting the combined formulation triggers withdrawal symptoms. Subutex and Suboxone will be provided in tablet form as take-home medications. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 3 (October 2002)

Combining Medications May Be Effective Treatment for "Speedball" Abuse

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

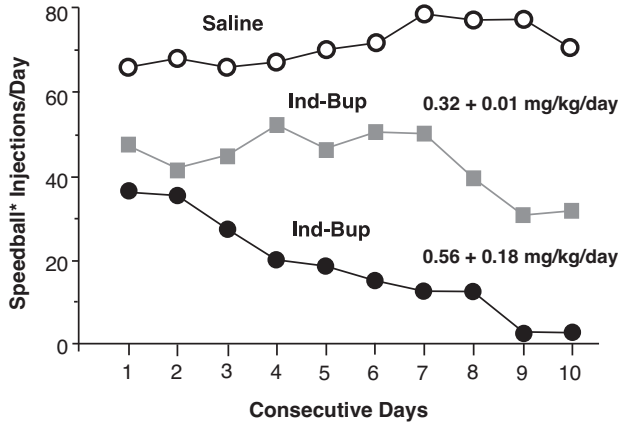
NIDA-supported researchers from Harvard Medical School-McLean Hospital, in Belmont, Massachusetts, discovered that a combination of the drugs buprenorphine and indatraline reduced the self-administration of "speedball" by monkeys. Speedball is a cocaine-heroin mixture that is taken by some injecting drug users and may increase the adverse consequences of drug abuse, such as greater severity of psychiatric disorders, higher incidence of failure in drug abuse treatment, and increased risk of contracting HIV infection.

Speedball abuse presents special challenges for drug abuse treatment. Cocaine and heroin exert different effects on the brain, and little is known scientifically about how the two drugs interact. Current medications for heroin abuse, such as methadone, are only moderately effective in reducing speedball abuse and at present there are no effective medications for cocaine abuse. Combinations of medications that target the effects of either cocaine or heroin have shown promise in reducing speedball self-administration in preclinical studies.

"Clinical experience has shown that the most effective medications currently available to treat drug abuse have two distinguishing characteristics," said co-investigator Dr. Nancy K. Mello. "First, these medications produce behavioral effects that are similar to the abused drug and minimize or prevent withdrawal symptoms. Second, these medications have a slow onset and long duration of action, resulting in a lower potential for abuse than rapid-onset, short-acting drugs such as heroin or cocaine. Indatraline, a dopamine reuptake inhibitor, and buprenorphine, an opioid mixed agonist-antagonist, each meet both of these criteria. Both drugs have a long duration of action; buprenorphine produces behavioral and physiological effects similar to heroin; indatraline is an experimental drug that produces cocaine-like effects."

Dr. Mello and Dr. S. Stevens Negus compared the effects of chronic treatment with indatraline and buprenorphine separately and in combination on speedball self-administration by rhesus monkeys. Five monkeys previously trained to self-administer cocaine were given access to speedball combinations (3:1 ratios of cocaine to heroin), which they began to self-administer more than 70 times a day.

Indatraline-Buprenorphine Combination Reduces Self-Injection of Speedball by Monkeys



*Speedball: Cocaine 0.01 + heroin 0.0032 mg/kg/inj

Before treatment with a combination of indatraline and buprenorphine, monkeys injected speedball an average of 66 to 78 times per day. After treatment, speedball self-administration was reduced and the decreases were sustained throughout 10 days of treatment. After 5 days of treatment with the highest dose of the combined medications, speedball self-administration decreased to between zero and five injections per day.

Over four 10-day periods, the monkeys were treated daily with saline, with indatraline or buprenorphine alone, and with the indatraline-buprenorphine combination in three increasing concentrations. Saline and the lowest concentration of the combined medications had little effect on speedball self-administration; the highest doses of the combined medications significantly decreased the number of times the monkeys self-administered speedball.

By the fifth day of treatment with a combination of indatraline and buprenorphine, speedball injections decreased by more than 90 percent, to fewer than five injections per day in four of the five monkeys studied. The same doses of indatraline or buprenorphine alone did not significantly reduce speedball self-administration.

"The combination of indatraline and buprenorphine not only reduced speedball self-administration, but these effects were sustained across the 10-day treatment period and over a range of doses," says Dr. Mello. "These findings underline the importance of exploring medication combinations as a novel approach for treatment of polydrug abuse."

"Although this study used an animal model, the results are intriguing and suggestive of potential clinical efficacy," said Dr. Jane Acri of NIDA's Division of Treatment Research and Development. "There is evidence that buprenorphine can reduce opiate use in humans, but the data supporting the use of compounds such as indatraline for reducing cocaine use by humans are more limited. The selection of a combination mechanism strategy is reasonable; further study is needed to determine the effectiveness of these compounds in the treatment of speedball abuse in humans."

Sources

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 2 (May 2002)

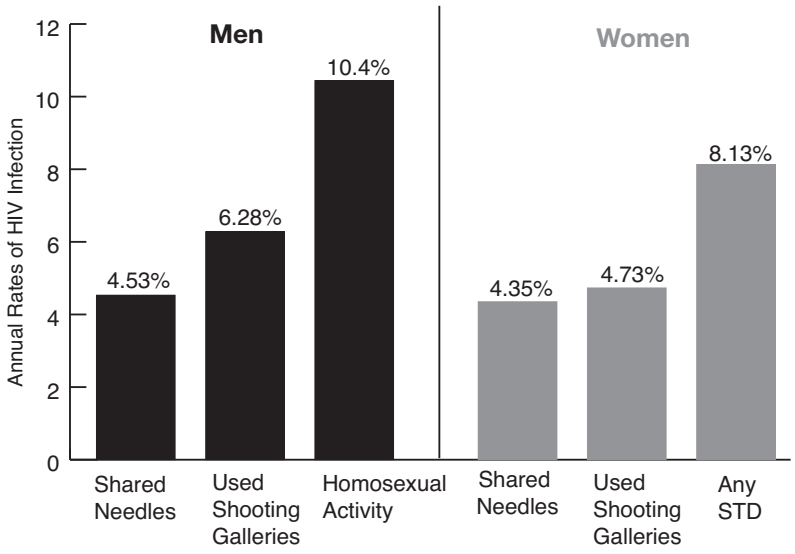
High-Risk Sex Is Main Factor in HIV Infection for Men and Women Who Inject Drugs

By Robert Mathias, *NIDA NOTES* Staff Writer

A 10-year study has found that the biggest predictor of HIV infection for both male and female injecting drug users (IDUs) is high-risk sexual behavior, not sharing needles used to inject drugs. High-risk homosexual activity was the most important factor in HIV transmission for men; high-risk heterosexual activity was most significant for women. Risky drug-use behaviors also were strong predictors of HIV transmission for men but were less significant for women, the study found.

"In the past, we assumed that IDUs who were HIV-positive had been infected with the virus through needle-sharing," says Dr. Steffanie Strathdee of the Johns Hopkins University Bloomberg School of Public Health in Baltimore, who conducted the NIDA-funded study. "Our analysis indicates that sexual behaviors, which we thought were less important among IDUs, really carry a heavy weight in terms of risks for HIV seroconversion for both men and women."

High-Risk Sexual Behavior Leading Cause of HIV Infection Among Injection Drug Users in 10-Year Study



High-risk sexual behavior played the biggest role in HIV infection for both male and female injection drug users (IDUs) in this study of 1,800 IDUs. Significant risk factors for men were high-risk homosexual activity, using shooting galleries, and sharing needles used to inject drugs with multiple partners. For women, high-risk heterosexual activity, as indicated by reporting a recent sexually transmitted disease (STD), was the most significant cause of HIV infection.

In the study, Dr. Strathdee led a team of researchers who analyzed data collected every 6 months from 1,800 IDUs in Baltimore from 1988 to 1998. Participants had to be at least 18 years of age when they entered the study, have a history of injection drug use within the previous 10 years, and not have HIV infection or AIDS. More than 90 percent of the participants said they had injected drugs in the 6 months prior to enrolling in the study. In their semi-annual interviews, study participants reported their recent drug use and sexual behavior and submitted blood samples to determine if they had become HIV-positive since their last visit.

Researchers analyzed the role of homosexual activity in HIV seroconversions among male IDUs in the study, after taking into account other factors that increased their risk of acquiring HIV, such as their drug injection practices.

This analysis revealed that the incidence of HIV infection among male IDUs who had engaged in homosexual activity within the previous 6 months was 10.44 percent a year, compared to 3.01 percent among men who did not report having homosexual sex.

Visiting "shooting galleries," where drug abusers gather to obtain and inject drugs, sharing needles used to inject drugs with multiple partners, and injecting drugs daily also were independently linked to significantly higher rates of HIV infection among men in the study. Men who said they had used shooting galleries had an HIV incidence rate of 6.28 percent per year, and men who shared needles with more than one partner had a rate of 5.52 percent per year. These infection rates were more than double those found among men who had not engaged in these

behaviors. Men who injected drugs at least once a day had HIV infection rates of 4.68 percent, more than one and one-half times the rate among men who had injected less than once a day.

Sharing needles also increased risk of HIV infection among women IDUs. However, high-risk heterosexual activity was a much more important risk factor for these women, the study found. In fact, other than being younger than 30 years—which independently predicted HIV infection for both sexes—high-risk heterosexual activity was the main predictor of HIV seroconversion among women. Women who reported having a recent sexually transmitted disease (STD), an indicator of unprotected sex, had more than 2.5 times the rate of HIV infection of women who did not have an STD.

"Both homosexual men and heterosexual women IDUs appear to be at dual risk for becoming infected with HIV," Dr. Strathdee says. "In previous studies by our group, being a gay male IDU was closely linked to visiting shooting galleries and sharing needles. Heterosexual women IDUs tend to have more of an overlap in their sexual partners and their drug use than men do. This puts them at increased HIV risk because they are sharing needles and having unprotected sex with a partner who is more likely to be infected with the virus."

"HIV prevention programs have done a good job in reducing needle-sharing and other drug-use behaviors that spread the virus among IDUs," Dr. Strathdee says.

"However, our study indicates that HIV prevention programs can achieve better results by also addressing sexual risk behaviors among IDUs. A multifaceted approach is needed that screens both men and women IDUs for STDs at places where they go, such as needle-exchange programs and methadone treatment programs, and provides comprehensive treatment at those sites."

"HIV prevention efforts also should be gender-specific, targeting the important differences we have found in sexual and drug-use behaviors among men and women that increase their risk of acquiring and transmitting HIV," Dr. Strathdee says. "For example, women IDUs in stable relationships could be shown how to negotiate condom use with their partners and offered couple counseling to educate both partners about HIV risks associated with their drug use and sexual behaviors. We need more research to identify and evaluate HIV prevention approaches for male IDUs who have sex with men to determine what kinds of interventions might work."

Source

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

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 4 (October 2001)

Buprenorphine Taken Three Times per Week Is as Effective as Daily Doses in Treating Heroin Addiction

By Patrick Zickler, *NIDA NOTES* Staff Writer

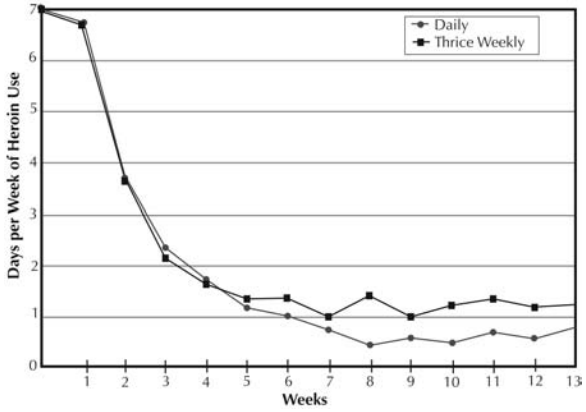
Buprenorphine, a medication developed through NIDA-funded research, has been shown in clinical trials to be an effective treatment for opioid addiction when taken in daily doses. Research at Yale University School of Medicine in New Haven, Connecticut, now suggests that buprenorphine taken three times per week is similarly effective. This finding, says NIDA-supported investigator Dr. Richard Schottenfeld, makes buprenorphine an even more flexible alternative to methadone, a medication that has been used for decades to treat opioid addiction.

Methadone is the most widely used medication for opioid addiction, yet fewer than one in five heroin users now receive methadone treatment for their addiction, Dr. Schottenfeld says. A daily dosing requirement and distressing symptoms of withdrawal that can result from a missed dose cause some heroin users to drop out of or to forgo methadone treatment programs. "Buprenorphine has relatively mild withdrawal symptoms, and a treatment schedule that does not require daily dosing could significantly increase the number of heroin users seeking treatment when buprenorphine becomes available," he says. Buprenorphine is in the final stages of the Food and Drug Administration (FDA) approval process.

Dr. Schottenfeld and his colleagues compared the effectiveness of daily versus thrice-weekly administration of buprenorphine in a 12-week trial involving 92 participants (73 percent white, 75 percent male) who met diagnostic criteria for opioid dependence and FDA criteria for eligibility in methadone maintenance treatment, but who were not currently in treatment. Forty-five participants were assigned to receive daily buprenorphine in an average daily dose of 16 mg per 70 kg of body weight. Forty-seven participants received doses of 34 mg per 70 kg of body weight on Fridays and Sundays, 44 mg per 70 kg of body weight on Tuesdays, and a placebo on other days. All 92 study participants provided urine samples on Mondays, Wednesdays, and Fridays. All samples were analyzed for opioids and cocaine metabolites, and one sample per week from each participant was tested for benzodiazepines.

"There were no significant differences between groups in reduction of opioid use, in retention in the treatment program, or in cocaine use," Dr. Schottenfeld says. "Interviews with the participants suggest that they couldn't reliably tell whether they were receiving the medication daily or three times each week."

Daily or Thrice-Weekly Buprenorphine Doses Yield Similar Declines in Days of Drug Use



Patients in treatment for opioid addiction received either daily or thrice-weekly doses of buprenorphine. Both groups showed reductions in reported days of heroin use during a 13-week treatment program.

Roughly three-quarters of the participants (77 percent of those receiving thrice-weekly and 71 percent of those receiving daily medication) completed the full 12-week program. The proportion of opioid-positive urine samples dropped consistently through the course of treatment (to 57 percent in the daily and 58 percent in the thrice-weekly group), and participants in both groups reported substantial reductions in illicit drug use. The similarity in drug use is evidence that the participants felt no stronger urge to use opioids than those on the daily schedule, Dr. Schottenfeld says. Equally important, he notes, is the fact that both groups were equally likely to stay in treatment, to show up on time for treatment, and to attend regularly scheduled counseling sessions.

In this study, all participants made daily clinic visits even though the thrice-weekly group received medication only every third day. Additional research is needed to determine the effectiveness of thrice-weekly dosing on a schedule that does not require daily contact, Dr. Schottenfeld says. Still, he adds, the finding that thrice-weekly dosing can be as effective as daily dosing in treatment outcome is an important step forward that builds on previous research indicating that some patients would prefer less-than-daily dosing of medication.

"This schedule of treatment could substantially reduce the cost to clinics and the inconvenience to patients. It can also help move use of buprenorphine beyond the traditional narcotic treatment programs and into new treatment settings, such as primary care clinics or physicians' offices," Dr. Schottenfeld says.

Source

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 4 (October 2001)

33-Year Study Finds Lifelong, Lethal Consequences of Heroin Addiction

By Patrick Zickler, *NIDA NOTES* Staff Writer

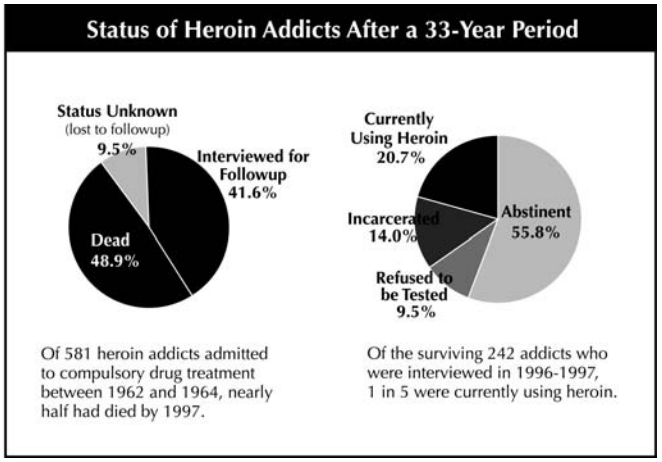
Heroin addiction exacts a terrible toll. For many addicts the condition lasts a lifetime—a lifetime shortened by health and social consequences of addiction. NIDA-supported researchers at the University of California, Los Angeles (UCLA), examined the patterns and consequences of heroin addiction over 33 years in nearly 600 heroin-addicted criminal offenders and found that their lives were characterized by repeated cycles of drug abuse and abstinence, along with increased risk of crime or incarceration, health problems, and death.

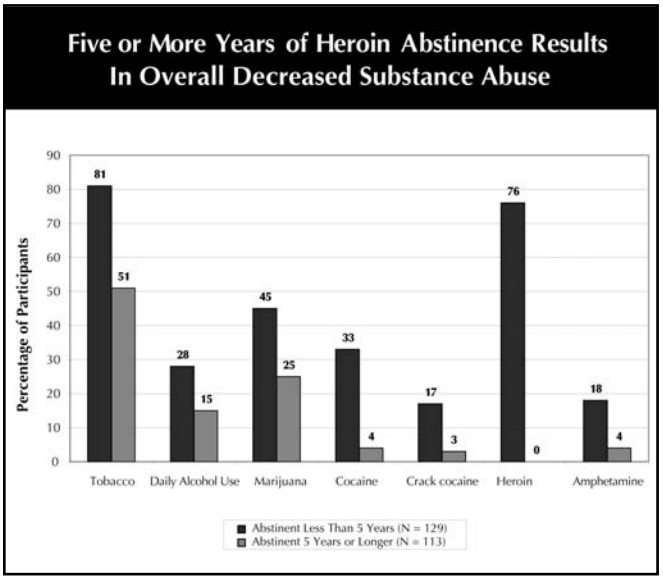
Drs. Yih-Ing Hser, Valerie Hoffman, Christine Grella, and Douglas Anglin of UCLA's Drug Abuse Research Center studied a group of 581 male heroin addicts admitted between 1962 and 1964 to the California Civil Addict Program (CAP), a compulsory drug treatment program for criminal offenders. By 1997, nearly half of the group had died, roughly 40 percent of those still living reported using heroin within the past year, and fewer than 10 percent of the survivors were currently enrolled in methadone treatment.

The death rate among the members of the group is 50 to 100 times the rate among the general population of men in the same age range. "The high mortality rate is evidence of the severe consequences of heroin use," Dr. Hser says. "Even among surviving members of the group, severe consequences such as high levels of health problems, criminal behavior and incarceration, and public assistance were associated with long-term heroin use."

Researchers first interviewed the participants during the period 1962 through 1964 and conducted followup interviews at roughly 10-year intervals–in 1974 and 1975, 1985 and 1986, and 1996 and 1997. In the most recent interviews, the UCLA researchers found that 284 (49 percent) of the 581 addicts enrolled in CAP between 1962 and 1964 had died. The most common cause of death (21.6 percent) was accidental poisoning or drug overdose. Homicide, suicide, or accident accounted for 19.5 percent of deaths, and the next most common causes were liver disease, cancer, and cardiovascular diseases (15.2, 11.7, and 11.7 percent, respectively). Fifty-five original participants could not be located, refused to be interviewed, or could not be interviewed.

Of the 242 surviving members interviewed in 1996 and 1997, 135 (55.8 percent) were not currently using heroin, 50 (20.7 percent) were actively using heroin, and 23 (9.5 percent) refused to provide urine samples for testing. In addition, urine samples were not available from 34 men who were incarcerated at the time of the interviews.





During interviews conducted in 1996 and 1997, heroin abusers who had been continuously abstinent for at least the last 5 years were less likely than other abusers to have used other drugs in the past year.

During any given year, roughly 10 percent of participants were in treatment, according to Dr. Hser. "Although many of the survivors reported that they had been able to stop using heroin for extensive periods, fewer than half reported abstinence for periods of more than 5 years," Dr. Hser

says. "Abstinence for 5 years significantly reduced the likelihood of relapse, but even among those who achieved 15 years of abstinence, a quarter still relapsed." Those who achieved abstinence for more than 5 years were more likely to be employed and less likely to report that they had health problems that prevented them from working, were receiving public assistance, or had been involved in criminal activity than were the rest of the cohort. Rates of HIV, hepatitis, and sexually transmitted diseases did not differ very much between those who had achieved more or less than 5 years of abstinence.

Dr. Hser adds that the results of the 33-year followup study should be considered in light of the fact that all members of the study originally were selected from a corrections-based treatment program and may not be representative of addicts who would have voluntarily sought treatment in community-based facilities had those programs been available 30 years ago. "Nevertheless, we believe the findings on patterns of heroin use and related consequences have important implications for the study of heroin addicts generally," Dr. Hser says. "These results suggest that heroin addiction treatment programs should prepare addicts for the fact that relapse is a very real possibility. Most people go into treatment thinking that they will be cured and not return to addiction, but abstinence is very difficult to maintain."

Heroin addicts and treatment providers should understand that treatment is a way to achieve abstinence and that recovery consists of improvements resulting from those periods when they are free of addiction, Dr. Hser says.

Source

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NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 2 (May 2001)

Buprenorphine Proves Effective, Expands Options For Treatment of Heroin Addiction

By Josephine Thomas, *NIDA NOTES* Contributing Writer

NIDA-supported researchers continue to expand treatment options for heroin addicts. A recent clinical trial showed that buprenorphine can be as effective as levo-alpha-acetyl-methadol (LAAM) and high-dose methadone in the treatment of heroin addiction. All three of these medications are more effective than low-dose methadone.

Dr. Rolley Johnson of The Johns Hopkins University in Baltimore led the research team that compared the different types of opioid addiction treatment medications. The team randomly assigned 220 heroin-addicted volunteers between the ages of 21 and 55 to 1 of 4 treatments: 16 to 32 mg of buprenorphine 3 times a week; 75 to 115 mg of LAAM 3 times a week; high-dose (60 to 100 mg daily) methadone; or low-dose (20 mg daily) methadone.

Effectiveness of Four Treatment Medications for Opioid Addiction

	Buprenorphine n=55	LAAM n=55	High-Dose Methadone n=55	Low-Dose Methadone n=55
Average number of days that patients remained in treatment	96	89	105	70
Percentage of patients with 12 or more consecutive drug-free urine samples	26	36	28	8

n=number of patients in treatment group

Buprenorphine proved as effective as LAAM and high-dose methadone in treating patients addicted to heroin. All three medications were more effective than low-dose methadone.

Treatment effectiveness was measured through participants' reports of heroin use, medication and drug levels in participants' urine samples, and how long participants remained in the study. Participants in the buprenorphine, LAAM, and high-dose methadone groups who completed the study reported that their heroin use decreased 90 percent on average. Urine tests conducted 3 times a week revealed that LAAM produced the longest period of abstinence; 36 percent of these patients had 12 consecutive heroin-free urine samples. A total of 26 percent of buprenorphine and 28 percent of high-dose methadone patients, but only 8 percent of the low-dose methadone patients, had 12 consecutive negative tests. Overall, 50.9 percent of the study's participants completed the 17-week study. The retention rates ranged from a high of 72.7 percent in the high-dose methadone group to 58.2 percent in the buprenorphine group, 52.7 percent in the LAAM group, and 20 percent in the low-dose methadone group.

"This study illustrates that there is more than one alternative for the effective treatment of heroin addiction," says Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development. "Although methadone remains the 'gold standard,' the new medications do not have to be administered in public clinics and closely supervised in the way high-dose methadone administration has been in the past. The results of this research thus open the door to medical mainstreaming—treatment in doctors' offices and private facilities, rather than only in narcotic treatment programs—for individuals addicted to heroin."

"This research demonstrates that these three medications are effective for the treatment of heroin addiction and that a one-size-fits-all model is no longer necessary," says Dr. Johnson. "Future research will help clinicians identify which patients will benefit most from which medications.

"Heroin addiction is a chronic brain disease, and we can treat it like any other chronic medical condition—considering alternatives for treatment and planning that treatment based on individual patient needs," Dr. Johnson continues. "Since it is difficult to have this kind of medical model of treatment with only one medication, expanding the numbers and types of potential treatment medications should help bring the treatment of opiate addiction into mainstream medical practice."

Source

- Johnson, R.E., et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine* 343(18):1290-1297, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 5 (October 2000)

Nicotine Craving and Heavy Smoking May Contribute to Increased Use of Cocaine and Heroin

By Patrick Zickler, *NIDA NOTES* Staff Writer

People who abuse drugs are also likely to be cigarette smokers. More than two-thirds of drug abusers are regular tobacco smokers, a rate more than double that of the rest of the population. NIDA researchers have found that craving for nicotine appears to increase craving for illicit drugs among drug abusers who also smoke tobacco, and this relationship suggests that smokers in drug treatment programs may be less successful than nonsmokers in staying off drugs.

At NIDA's Intramural Research Program in Baltimore, Dr. Stephen Heishman and his colleagues examined the interaction of craving for nicotine and craving for other drugs and found that situations that increased desire to smoke also increased desire to use drugs. The study involved male and female adult smokers who were not trying to stop smoking and had histories of abusing alcohol, cocaine, heroin, marijuana, and/or other substances.

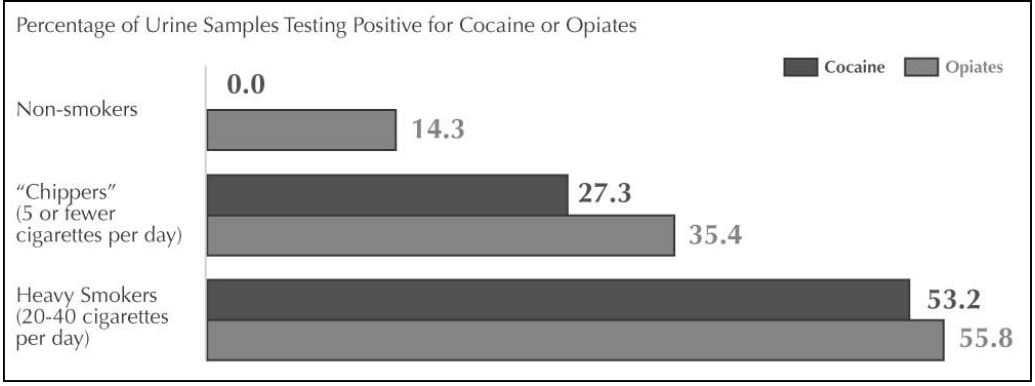
The researchers asked participants to listen to recorded scripts describing scenes and then to rate their urge to smoke and their desire to use other drugs. In the first part of the study, which involved 18 participants, the scripts had content that was generally pleasant (watching children on a sunny beach), unpleasant (a friend asking to borrow money), or neutral (doing household chores). Some scripts also included people expressing a desire to smoke, while others did not mention smoking at all (see "Cues Trigger Craving"). Both the scripts including a mention of smoking and those containing negative emotional content increased the participants' craving for drugs, as well as for smoking.

In the second part of the study, 24 participants heard scripts with only pleasant content (enjoying the beach, talking on the phone with an old acquaintance, or visiting friends). These scripts also contained descriptions of tobacco craving that increased in intensity from no mention of smoking to asking the question, "How could you really enjoy yourself fully unless you were smoking?" Participants reported that craving for both drugs and tobacco increased as the intensity of the tobacco craving messages in the scripts increased.

"One of our more interesting findings was that scripts that elicited craving for tobacco also elicited craving for the subject's drug of choice. This suggests that real-world situations that produce tobacco craving also may result in craving for drugs of abuse," Dr. Heishman says. The findings also suggest that treatment for heroin, cocaine, or alcohol addiction might be more effective if it included concurrent treatment of tobacco addiction, he says.

In a NIDA-supported study at the University of California, San Diego, doctoral candidate Dominick Frosch and his colleagues at the Integrated Substance Abuse Program at the University of California, Los Angeles, investigated the relationship between levels of cigarette smoking and levels of cocaine and heroin use among 32 individuals who had been in a methadone treatment program for at least 4 months. The participants included 10 nonsmokers (6 female, 4 male) and 22 smokers (16 female, 6 male). The smokers were equally divided among heavy smokers (20 to 40 cigarettes per day) and "chippers" who smoked 5 or fewer cigarettes per day.

Cigarette Smoking Associated With Use of Cocaine and Opiates



Among patients in a methadone treatment program for opiate addiction, levels of cocaine or opiate use were directly related to levels of cigarette smoking.

"Compared with heavy smokers, chippers have less intense craving for their first cigarette of the day and can more comfortably avoid smoking in situations where it is not permitted," Mr. Frosch explains.

The researchers evaluated the connection between tobacco smoking and illicit drug use among the smokers and nonsmokers by using breath and urine samples from the participants over a 7-day period. They found that the amount of cocaine and heroin use was closely related to the level of tobacco use. "The more cigarettes smoked, the more likely the person was to use illegal drugs," Mr. Frosch says. "These findings provide compelling reasons for implementing smoking cessation programs for patients in methadone treatment, as the benefits of smoking cessation may extend to opiate addiction as well."

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Cues Trigger Craving

To evaluate the impact of the urge to smoke on craving for other drugs, Dr. Stephen Heishman and his colleagues asked participants to rate their desires for tobacco and other drugs after listening to recorded "scripts" of scenes involving pleasant, unpleasant, or neutral situations and containing "urge" or "no-urge" smoking cues. The scripts were originally developed by Dr. Stephen Tiffany and colleagues at Purdue University.

Pleasant, no-urge script: You're at the beach, lying on a blanket. The warm sun penetrates your skin and relaxes you thoroughly. A fresh breeze blows over your body as you run your hands through the clean white sand and let the grains fall through your fingers. You're feeling refreshed and at ease, and pleasant thoughts run through your mind. You can hear the sound of waves splashing rhythmically against the shore. Nearby there are some children playing a game. A bright red beach ball lands near your blanket. You look up and see two of the children running toward you to get their ball. You stand up, pick up the ball, and toss it to them. They laugh and giggle and run back to their game. You go to the blanket and lie down. You're enjoying this day completely.

Pleasant, urge script: You're at a friend's house sitting in a big comfortable chair. You're with people you've known a long time, and you're enjoying yourself very much. You're sipping a drink, and you're feeling totally at ease. Many of your friends are smoking cigarettes, just as you used to do. You've gone an entire week without smoking. As you sit there listening to the conversation and laughter, you begin to wonder what a cigarette would taste like. The more you think about smoking, the stronger your desire becomes. Maybe just tonight when you're with your friends and having a good time, it would be okay to smoke. How could you really enjoy yourself fully unless you were smoking? Your desire to smoke becomes intense, and you know that there's no good reason not to ask one of your friends for a cigarette.

Sources

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 3 (August 2000)

Drug Abuse Treatment Programs Make Gains in Methadone Treatment and HIV Prevention

By Steven Stocker, *NIDA NOTES* Contributing Writer

Drug abuse treatment programs have substantially improved their methadone treatment practices and increased their HIV prevention efforts since the late 1980s, according to recent NIDA-funded research. These improvements appear to be partly the result of NIDA's efforts to improve drug abuse treatment and HIV/AIDS outreach.

Clinical studies conducted in the late 1980s and early 1990s indicated that methadone treatment is more likely to reduce heroin use if the dose level is at least 60 milligrams per day (mg/day), if patients are given a voice in determining their dose levels, and if no restriction is placed on treatment duration. Subsequent research, however, indicated that the majority of the Nation's methadone treatment facilities were dispensing methadone doses less than 60 mg/day, were not giving patients a voice in dosage decisions, and were encouraging patients to stop taking methadone in 6 months or less.

In response to this situation, NIDA and other Federal agencies took steps to improve methadone treatment. NIDA funded an Institute of Medicine report that recommended changes in heroin addiction treatment practices and their regulation. NIDA also funded the development of a quality assurance program that evaluates methadone treatment facilities in terms of patient outcomes. In addition, the Center for Substance Abuse Treatment (CSAT) developed a set of methadone treatment guidelines and distributed them to State substance abuse agencies and treatment providers around the country.

To determine whether these efforts were in fact improving methadone treatment practices, in 1995 Dr. Thomas D'Aunno of the University of Chicago and his colleagues at the University of Michigan in Ann Arbor collected data from 116 methadone treatment facilities located throughout the country and compared them with data collected on these same facilities in 1988 and 1990. Results showed improvement during the 7-year period, particularly regarding methadone dosage. The average dose was 45 mg/day in 1988 and 46 mg/day in 1990. By 1995, however, the average dose had increased to 59 mg/day. Also, more programs were allowing patients to participate in dosage decisions, and more programs were waiting at least a year before encouraging patients to stop taking methadone.

The treatment facilities most likely to conduct HIV prevention activities were those that had more patients at high risk of HIV infection, more resources, and lower patient-to-staff ratios.

"Although these results show that methadone treatment facilities have made substantial improvements, we still need to make more progress," says Dr. D'Aunno. "We found an average dose of 59 mg/day in our sample of treatment facilities, but recent research indicates that doses between 80 and 100 mg/day may be the most effective in reducing heroin use." (See "High-Dose Methadone Improves Treatment Outcomes" on page 41 of this collection.)

The study found differences in treatment practices in different areas of the country and for different population groups. Dr. D'Aunno suggests that efforts targeted at particular groups of programs may be a further step to improve treatment.

Dr. Bennett Fletcher of NIDA's Division of Epidemiology, Services, and Prevention Research agrees that efforts to improve methadone treatment practices should continue but adds that misunderstandings some patients have about methadone may also contribute to the problem. For example, he says, some patients attribute adverse effects to methadone that it actually does not cause. "These patients may develop medical or dental problems while taking heroin, but they don't notice them either because of heroin's analgesic effect or because they are distracted by withdrawal symptoms during abstinence," he says. "Once they're in methadone treatment and physiologically stabilized, the medical or dental problems are unmasked. It is easy to blame methadone for these problems, when in fact they were pre-existing." These misunderstandings may cause some patients to request lower methadone doses or to stop methadone prematurely, says Dr. Fletcher.

The Bandwagon Effect

Dr. D'Aunno, along with colleagues at the University of Iowa in Iowa City and the Centers for Disease Control and Prevention in Atlanta, also evaluated treatment facilities' HIV prevention efforts, including HIV testing, counseling, and outreach. For this project, they used data collected from the sample of methadone treatment facilities plus other substance abuse treatment facilities for a total of 618 facilities.

As with the methadone treatment practices, the investigators found that the facilities had made substantial improvements in their HIV prevention efforts over the period from 1988 to 1995. In both 1988 and 1990, only 39 percent of the facilities provided HIV testing and counseling, but by 1995, 61 percent were providing these services. Also, 51 percent of the facilities in 1988 and 65 percent in 1990 were engaging in HIV outreach, but by 1995 this had increased to 75 percent.

The investigators found that the treatment facilities most likely to conduct HIV prevention activities were those that had more patients at high risk of HIV infection, more resources, and lower patient-to-staff ratios. Also, these facilities generally were publicly rather than privately funded and had clinical supervisors who supported HIV prevention practices.

Perhaps the most important factor in promoting HIV prevention practices, however, seemed to be pressure from people in the drug abuse treatment field. "When the HIV epidemic first started, many treatment facilities were uncertain how to react," says Dr. D'Aunno. "As some facilities began conducting HIV testing, counseling, and outreach, pressure began to mount for other facilities to do the same. This eventually created a bandwagon effect."

NIDA helped get the bandwagon going by supporting research programs in which scientists worked together with practitioners to develop effective HIV/AIDS outreach techniques, according to Dr. D'Aunno. "These programs set a good example for treatment providers," he says. "The providers saw local researchers and other providers working together on HIV prevention, and they decided to follow their lead."

Sources

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 6 (March 2000)

Recovery Harder for Addicts Who Start Young

A NIDA-funded study has demonstrated that the relapse rate for heroin addicts increases with time and that the probability of long-run abstinence depends on the age of first drug use. Those who start daily heroin use at a younger age are more likely to relapse than those who start later.

The study, conducted by Dr. Marnik G. Dekimpe of the Catholic University Leuven in Belgium and his colleagues in Belgium and at the University of California, Los Angeles, examined the treatment histories of 846 patients at methadone clinics in central and southern California. The researchers looked at males and females, whites and Chicanos, most of whom started using heroin between the ages of 17 and 25. Subjects were interviewed over a 4-year period during and after treatment to determine the probability of their relapse to heroin use.

The finding that relapse is connected to time suggests the need for long-term periodic monitoring of a former heroin user's abstinence, Dr. Dekimpe says. The researchers also found drug relapse odds were significantly different across the sociodemographic groups studied, suggesting that prevention resources could be directed to groups at higher risk. No significant differences in relapse probability were associated with either gender or education. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 5 (December 1999)

High-Dose Methadone Improves Treatment Outcomes

By Patrick Zickler, *NIDA NOTES* Staff Writer

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

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

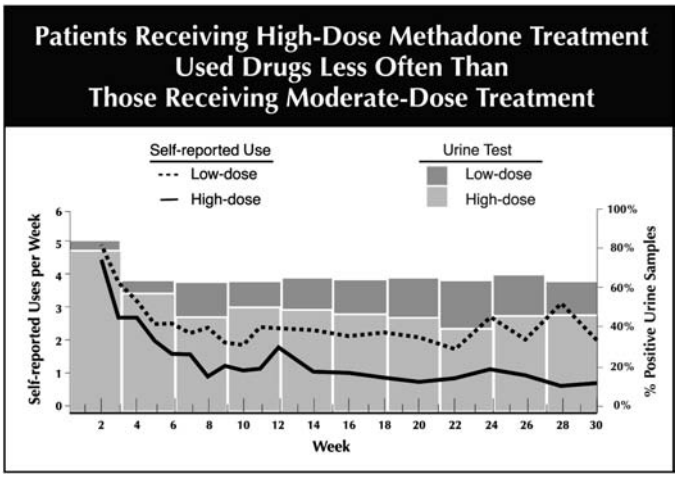
Dr. Strain and his colleagues investigated the effectiveness of high-dose—80 to 100 mg per day—methadone treatment and found this dosage to be more effective in reducing heroin use than treatment with a moderate dose of 40 to 50 mg per day. The study involved 192 patients. Sixty-five percent of participants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

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

Dr. Strain and his colleagues evaluated the effectiveness of treatment through analysis of twice-weekly observed urine testing, weekly patient reports of heroin use, and the length of time patients remained in treatment. "The high-dose group used opiates significantly less during treatment than did the moderate-dose group on average," Dr. Strain says. "Patients in the high-dose group reported using opiates no more than once a week. The moderate-dose group reported using drugs two to three times per week on average." Among patients who completed the 30-week active phase, 33 percent of high-dose patients remained in treatment throughout a 10-week methadone phase-out, compared with 20 percent of moderate-dose patients. There were no gender-related differences in outcome for high- or moderate-dose groups, and no difference was reported between the high- and moderate-dose patients for side effects such as grogginess or constipation.

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

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



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

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 2 (August 1999)

Heroin Snorters Risk Transition To Injection Drug Use and Infectious Disease

By Robert Mathias, *NIDA NOTES* Staff Writer

Heroin users who think they can avoid the harmful consequences of drug injection by snorting or smoking the drug may be dangerously mistaken. A NIDA-funded study indicates that noninjecting heroin users (NIUs) are at considerable risk of becoming drug injectors, thereby incurring risks for HIV, hepatitis, and other serious diseases. Moreover, regardless of whether they go on to inject drugs, a significant number contract hepatitis, the study shows.

"Becoming a drug injector is not inevitable for heroin snorters who have never injected drugs, but the risk of making the transition to injection drug use is fairly substantial," says Dr. Alan Neaigus of National Development and Research Institutes (NDRI), Inc., in New York City. Dr. Neaigus and his colleagues at NDRI have been examining rates of transition to injection drug use and disease incidence among 560 NIUs recruited from March 1996 through April 1998. The study group consists of heroin users who have never injected drugs and former heroin injectors who had not injected drugs for at least 6 months prior to the study. Data from followup interviews conducted with 331 study participants show that more than 15 percent transitioned to drug injection during an average period of a little more than a year. The researchers found no significant difference in the transition rate between NIUs who had never injected heroin and the 31 percent of the study group who were former injectors.

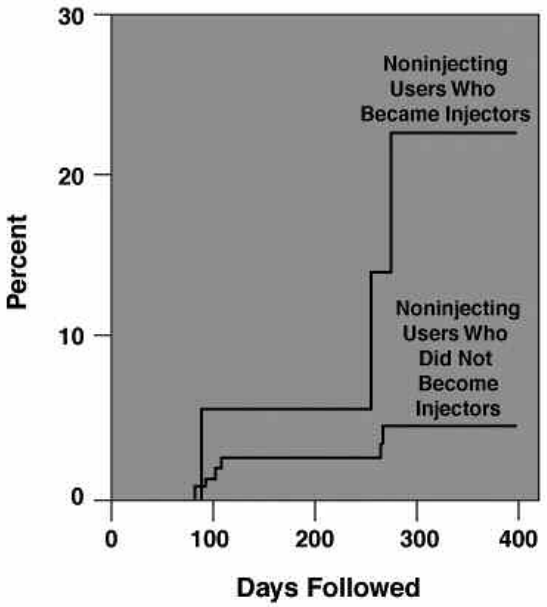
Previous studies have found higher rates of transition from noninjection to injection drug use, particularly among former injectors. However, Dr. Neagius says a number of factors may now be slowing the rate at which heroin snorters are initiating or resuming injection of the drug. First, a dramatic increase in the purity of heroin during the 1990s has made it possible for snorters to achieve a high that is similar to what they can obtain from injection. Second, greater awareness of the risk of contracting AIDS from injecting drugs may be dissuading more users from the practice.

The NIU study supported earlier research findings that NIUs who socialize, use drugs, or have sex with IDUs significantly increase their risk of crossing the line from snorting to injecting drugs. Preliminary analysis further suggests that being in the presence of an IDU who is injecting drugs may play an important role both in the initiation and resumption of injection drug use, Dr. Neaigus says. This finding suggests that the direct transfer of information and techniques used to inject drugs may be an important factor in the transition to injection drug use.

> ***"This is the era of AIDS, and everyone knows about the risks from needles. When you sniff, you don't have to worry about AIDS."***
>
> **—Noninjecting heroin user interviewed in New York City**

The level of heroin addiction is another major factor in the transition to injection. The NIU study participants' levels of addiction ranged from snorting heroin occasionally on weekends through using several bags a day,

Hepatitis C Among Noninjecting Heroin Users



Drug injection is the primary mode of hepatitis C transmission. In a New York City study, a large percentage of noninjecting heroin users who transitioned to injection drug use contracted the disease.

Dr. Neaigus says. Previous research has suggested that even with the availability of high-purity heroin, more heavily addicted heroin snorters may turn to drug injection because it remains a more effective way to take the drug. For example, in a study conducted between 1991 and 1993 by Dr. Samuel R. Friedman, also of NDRI, 30 percent of 755 IDUs in Brooklyn, New York, reported they started to inject to get a better high.

NIUs and Infectious Disease

The health risks associated with noninjecting heroin use are substantial, both for NIUs who become IDUs and for those who don't, the study found. All study participants received counseling about the risks of drug injection, hepatitis, and HIV. Nevertheless, almost 23 percent of the NIUs who began to inject drugs contracted hepatitis C (HCV) over the average followup period of a little over a year. HCV leads to chronic liver infection in about 80 percent of patients, most of whom eventually develop fatal liver diseases such as cirrhosis and liver cancer, says Dr. Henry Francis, who directs NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse.

Because injection drug use is the primary mode of HCV transmission, "the rapid rate of transmission of hepatitis C among NIUs who initiate or resume injecting was expected," Dr. Neaigus says. "However, it is still alarming," he adds. What was unexpected was that some NIUs who did not begin to inject drugs—about 4 percent—also contracted HCV during the followup period. NDRI researchers now are attempting to determine how these NIUs contracted the infection, Dr. Neaigus says.

NIUs who did not transition to injection drug use were also at substantial risk of becoming infected with hepatitis B (HBV), the study shows. About 9.5 percent contracted HBV during the followup period. Though it receives less attention than HCV, HBV can develop into chronic infection and serious liver disease in up to 20 percent of cases, says NIDA's Dr. Francis.

NIUs who socialize, use drugs, or have sex with IDUs significantly increase their risk of crossing the line from snorting to injecting drugs.

The considerable amount of HBV found among NIUs, particularly among those who have never injected, reflects substantial sexual transmission of this disease, Dr. Neaigus says. Though the study only measured sexual activity over a 30-day period, "we found a lot of sexual risk in this group," he says. For example, about 70 percent of NIUs were sexually active during this period with two-thirds of them engaging in unprotected sex, many with partners who had HIV or were IDUs, says Dr. Neaigus.

To date, the study has not found any new cases of HIV either among NIUs who began injecting drugs or among those who did not. However, Dr. Neaigus says that the high rates of new HBV and HCV infections found among NIUs may serve as markers for sexual behaviors and drug injection practices that continue to put NIUs at risk for infection with HIV. In addition to finding extensive high-risk sexual activity among NIUs, the study found NIUs who had recently transitioned to injection drug use commonly shared injection equipment, such as cookers, cotton, and rinse water. However, they infrequently shared syringes and over half obtained all their syringes from syringe exchange programs.

Noninjection drug use is two-edged in its effect on heroin users' risk of contracting infectious diseases, Dr. Neaigus concludes. On the one hand, the considerable numbers of former IDUs who are now snorting heroin instead of injecting it have reduced their risk of AIDS and HCV considerably. On the other hand, NIUs who have never used heroin before have increased their risk of heroin addiction, transition to injection drug use, and contracting HIV, HCV, and HBV.

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Research Findings

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Linking Medical Care With Drug Abuse Treatment Stems Tuberculosis Among HIV-Infected Drug Users

By Robert Mathias, *NIDA NOTES* Staff Writer

Injecting drug users with HIV/AIDS can be treated successfully for tuberculosis (TB) in methadone treatment programs that provide comprehensive medical care, according to NIDA-supported research. Integrating medical care and drug abuse treatment also has been effective in preventing new cases of TB from developing among HIV-positive patients, the research indicates.

"A key to dealing successfully with infectious diseases, such as TB and HIV, among drug abuse patients is the linkage of primary care and drug abuse treatment in a drug abuse treatment setting," says Dr. Paul A. Coulis of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "In places where this has been done, such as New York City, it has been effective, so we know it works," he says.

TB is a chronic and infectious lung disease. People with latent tuberculosis infection do not have symptoms, may not develop active disease, and cannot spread TB. However, if such individuals do not receive preventive therapy, they may develop active TB, which is contagious.

Research has shown that injecting drug users have high rates of latent tuberculosis infection. NIDA-supported studies among injecting drug users have shown that HIV can activate this latent TB infection and increase the risk that active TB will develop. In New York City, which was hard hit by the linked epidemics of HIV and TB during the mid-1980s and early 1990s, 30 percent of persons with active TB were injecting drug users, according to the Centers for Disease Control and Prevention (CDC).

Rates of TB have declined both nationally and in New York City since 1992. However, injecting drug users continue to be at high risk for HIV and tuberculosis. For example, about one-third of the 900 methadone treatment patients in the Montefiore Medical Center's Substance Abuse Treatment Program in The Bronx, New York, have HIV, and TB rates are much higher than they are in the general population, says Dr. Marc Gourevitch, who directs a NIDA-funded study of TB infection in drug users enrolled in the program. "Almost all the active TB cases we see among drug users in our program are among those who are HIV-positive," Dr. Gourevitch notes.

To respond to the complex health needs of its patients, the Montefiore treatment program used funding from NIDA and the Health Resources and Services Administration to begin providing medical care on site along with methadone treatment in 1989. In addition to general and HIV-related primary care, on-site services now include mental health and social support services; HIV testing and counseling; and TB testing, prevention, and treatment.

"Our model has been to build comprehensive primary care services into the same site at which people are receiving their drug treatment to make it easier for them to get their medical care," Dr. Gourevitch says. This treatment model has enabled the program to achieve excellent success in getting drug abuse treatment patients to complete the full course of TB therapy needed to curtail the spread of the disease, he says.

Patients must follow demanding medication regimens to prevent and treat TB. To complete the full course of TB prevention, injecting drug users with latent TB infection must take one medication, isoniazid, daily for up to a year. Patients with active tuberculosis require an initial hospitalization with a 4-medication regimen and then must take 2 to 4 medications daily or several times a week for up to a year. Failure to complete the full course of TB treatment can spawn an even more deadly form of the disease, one that is resistant to tuberculosis medications.

In 1989, the Montefiore treatment program implemented a strategy called directly observed therapy (DOT) that was designed to increase patients' adherence to TB therapy. With DOT, treatment personnel observe patients taking each dose of their TB prevention and treatment medications. Now a widely accepted TB treatment practice, DOT, along with improved management of TB cases to ensure completion of a full course of therapy, has been credited by the CDC as playing a major role in the overall reduction in TB rates in the United States since 1992 (see "The Rise and Fall of TB in the United States."). Methadone treatment programs offer an ideal setting to implement DOT and ensure that injecting drug users complete the full course of treatment because patients are coming in daily for their methadone anyway, Dr. Gourevitch says. "It's a natural process to administer the

anti-TB medications and methadone at the same time under direct supervision," he says.

Directly observed tuberculosis prevention and treatment are voluntary at Montefiore. No incentives are offered for participating in supervised preventive therapy, and methadone is not withheld if drug abuse treatment patients do not accept TB therapy. "Yet, almost everyone opts for observed therapy because it eliminates the hassle of having to remember to take TB medications at other times of the day," Dr. Gourevitch says.

Research conducted by Dr. Gourevitch shows that a high percentage of patients receiving directly observed prophylaxis and treatment in the context of their methadone treatment adhere to and complete TB therapy. In one study, more than 80 percent of 114 eligible patients had completed or were still receiving prophylaxis or treatment at the end of a 2-year period. Additional research by Dr. Gourevitch indicates that completion of TB prophylaxis was associated with a 75-percent reduction in the TB rate in this high-risk population and that providing on-site directly observed prophylaxis is cost-effective in terms of preventing the costs of treating active TB.

"What we've learned is that having primary care integrated with drug abuse treatment is a very effective way to treat and prevent various diseases among drug users," concludes NIDA's Dr. Coulis.

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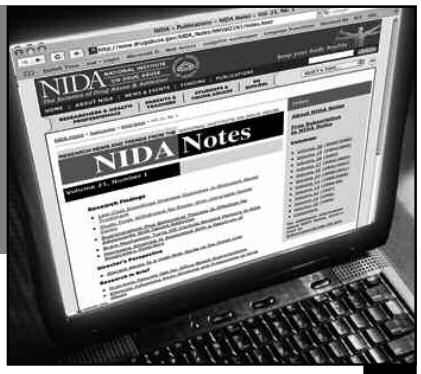

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