Depot Naltrexone Appears Safe and Effective for Heroin Addiction

Research Findings
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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.

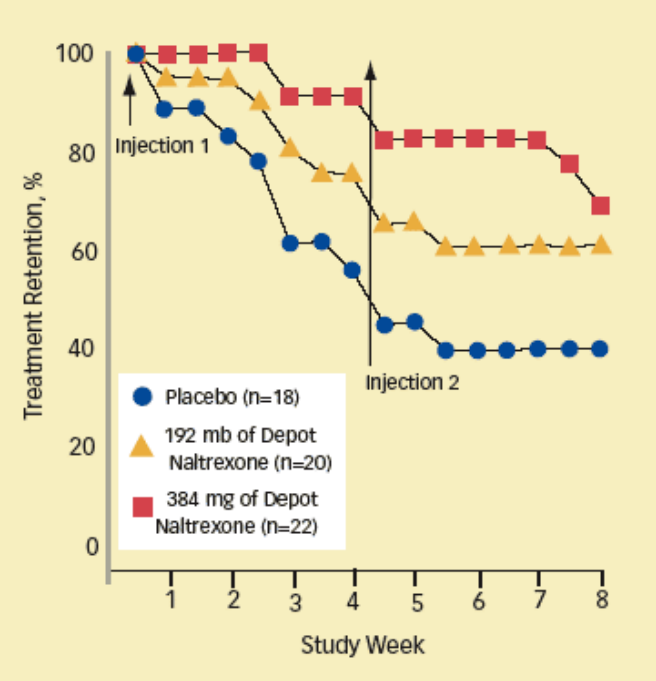
"What's exciting about this slow-release formula is that it provides continuous protection for a month at a time, freeing patients from having to decide to take or not take the medication every day," says Dr. Sandra Comer, lead investigator of the study. "By increasing treatment retention, depot naltrexone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

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.

was highest for the group receiving 384 mg of naltrexone (62 percent) and lowest for the placebo group (25 percent). After receiving the medication, patients in the naltrexone groups reported "needing heroin" significantly less than those taking placebo.



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

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

Dr. Richard Hawks of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse, says pharmaceutical companies are developing even longeracting 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. [Abstract]

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Interim Methadone Raises Odds of Enrolling in Comprehensive Treatment

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

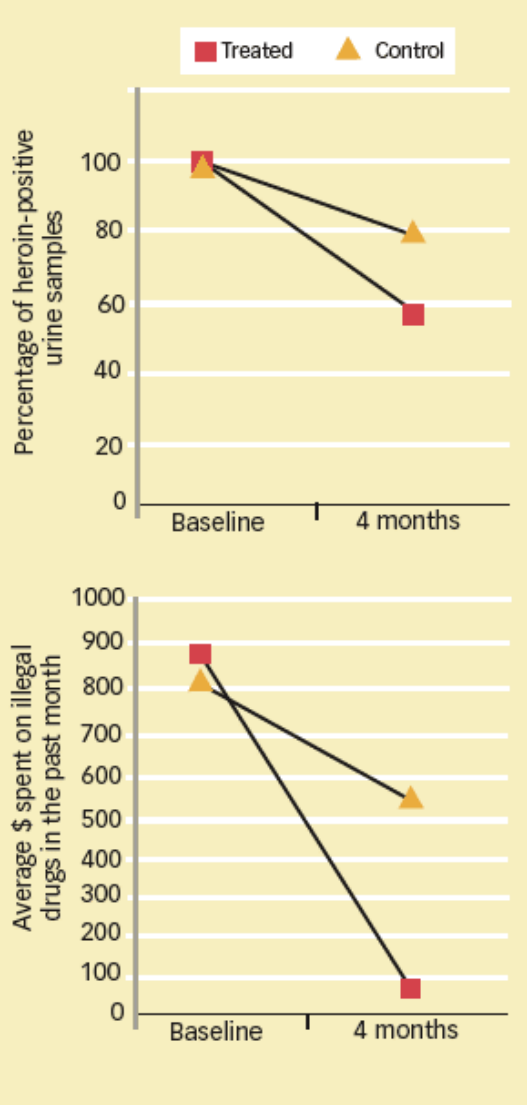
BY SARAH TEAGLE, *NIDA Notes* Contributing Writer

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.

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

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.

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). 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 highermotivated subgroup—they actively sought it out using the local program information we gave them."

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

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."

SOURCE

Schwartz, R.P., et al. A randomized controlled trial of interim methadone maintenance. Archives of General Psychiatry 63(1):102-109, 2006. [Abstract]

Schwartz, R.P., et al. A randomized controlled trial of interim methadone maintenance: 10-month followup. Drug and Alcohol Dependence [June 19, 2006 Epub Ahead of Print] [Abstract]

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Buprenorphine Plus Behavioral Therapy Is Effective For Adolescents With Opioid Addiction

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

BY PATRICK ZICKLER, *NIDA Notes* Contributing Writer

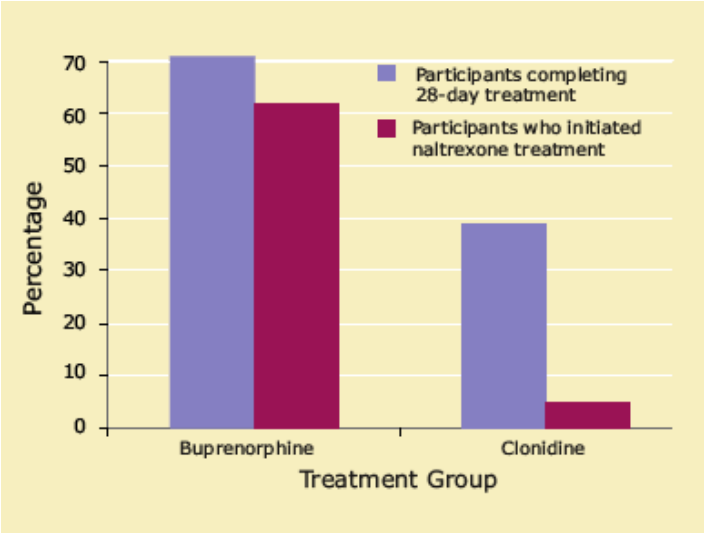
Adolescents addicted to opioids responded better to buprenorphine than clonidine in a clinical trial in which all patients also received behavioral therapy. In the NIDA-supported comparison trial at the University of Vermont, adolescents who received buprenorphine attended more scheduled counseling sessions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

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.

Medication dosages varied depending on each participant's weight and the amount of drug he or she reported abusing before beginning treatment; dosages of buprenorphine were in the low to moderate range of those typically given to opioid-addicted adults.



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

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

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

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

SOURCE

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

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