ORIGINAL ARTICLE

Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders

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ABSTRACT

BACKGROUND

Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited.

METHODS

In this five-site, open-label, randomized trial, we compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78.

RESULTS

A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the 24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P=0.91). The rates of other prespecified secondary outcome measures — self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration — were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (P=0.02).

CONCLUSIONS

In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation. (Funded by the National Institute on Drug Abuse; ClinicalTrials.gov number, NCT00781898.)

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This article was updated on April 14, 2016, at NEJM.org.

N Engl J Med 2016;374:1232-42.
DOI: 10.1056/NEJMoa1505409

Opioid-use disorder is a chronic relapsing condition that has serious public health consequences. Opioid dependence disproportionately affects U.S. criminal justice system populations, and relapse and overdose deaths occur at high rates after release from incarceration.[1] Evidence-based opioid-agonist maintenance therapies for opioid dependence (methadone and buprenorphine) are effective in prison, jail, and community reentry (i.e., parole) settings[2-5] but have historically been unavailable or discouraged among criminal justice clients.[6-8] Extended-release naltrexone (Vivitrol, Alkermes), a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, was approved by the Food and Drug Administration in 2010 for the prevention of relapse to opioid dependence. Extended-release naltrexone may be particularly appealing and beneficial to patients and providers who are unlikely to access opioid-agonist maintenance treatment or who prefer a relapse-prevention medication. As a noncontrolled substance with no known abuse or diversion potential, extended-release naltrexone has gained increasing acceptance in the criminal justice system despite limited data on effectiveness.

Extended-release naltrexone gradually releases sufficient naltrexone to block the euphoric effects of opioids for approximately 1 month after injection and is efficacious as compared with placebo.[9-12] A pilot study that was performed at the same five sites that participated in this trial used a single-group observational cohort design and showed the feasibility of using Depotrex, an alternative formulation of extended-release naltrexone, as a treatment option for outpatient parolees and probationers.[13] We conducted a large, multisite, randomized trial to examine the effectiveness of extended-release naltrexone among community-dwelling criminal justice offenders who were at high risk for opioid relapse and related adverse outcomes.

METHODS

TRIAL DESIGN, SITES, AND OVERSIGHT

This open-label, randomized, controlled effectiveness trial compared six monthly injections of extended-release naltrexone (Vivitrol, Alkermes) with usual treatment (brief counseling and referrals for community treatment programs) for the prevention of opioid relapse among criminal justice offenders. We hypothesized that the likelihood of an opioid-relapse event would be lower, the time to relapse longer, and overall rates of opioid use lower with extended-release naltrexone than with usual treatment.

Five independently funded sites implemented a common collaborative protocol: University of Pennsylvania (Philadelphia), New York University School of Medicine and Bellevue Hospital Center (New York), Rhode Island Hospital and Brown University (Providence, Rhode Island), Columbia University Medical Center (New York), and Friends Research Institute (Baltimore). The University of Pennsylvania, which was the lead site, hosted the regulatory and data management cores and the data and safety monitoring board.

The rationale, protocol development, design, and methods of this trial are described in full elsewhere.[14] All sites obtained approval from the local institutional review board and the U.S. Office for Human Research Protections for the common trial protocol. The authors alone designed and implemented the trial; collected, accessed, and analyzed the data; and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The first author wrote the initial draft of the manuscript, and all the authors participated in revisions and approved the final draft. The sponsor (National Institute on Drug Abuse) and the manufacturer of extended-release naltrexone (Alkermes) did not have editorial control or access to trial data. The manufacturer contributed Vivitrol in kind through an investigator-initiated trial contract, which allowed for review of and comment on the manuscript before submission for publication.

PARTICIPANTS

We recruited community-dwelling adult volunteers who were criminal justice offenders and who had a history of opioid dependence. Eligibility criteria were current (within the previous 12 months) or lifetime (any previous) opioid dependence (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV])[15]; a stated goal of opiate-free treatment rather than opioid-agonist or partial-agonist maintenance therapy; an opioid-free status as confirmed by negative urine toxicologic screening for all opioids before randomization; residence in the community and receipt of an adjudicated sentence that included

supervision (e.g., parole, probation, outpatient drug-court programs, or other court-mandated treatment) or, in the previous 12 months, release from jail or prison, a plea-bargain arrangement, or any community supervision as above; general good health as determined by history and physical examination; an age of 18 to 60 years; and the ability to provide written informed consent.

Exclusion criteria were other drug or alcohol dependence requiring a level of care that would interfere with trial participation; pregnancy or a plan to conceive during the 24-week treatment phase, lactation, or an inability to use adequate contraceptive methods; an untreated psychiatric disorder or medical condition that might make participation hazardous, including liver-enzyme levels more than three times the upper limit of the normal range and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of more than 40; allergy to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the diluent; a current diagnosis of chronic pain for which opioids were prescribed; or a drug overdose in the previous 3 years requiring inpatient hospitalization.

We recruited participants by standard outreach to community-dwelling at-risk populations through print, radio, and online publicity and provider detailing (e.g., letters to clinic directors); in an effort to minimize potential coercion, we did not recruit through direct referrals from criminal justice authorities, including departments of corrections, probation, or parole and drug courts or other diversion programs. Prescreening questionnaires were used to briefly evaluate potential participants and to schedule an in-person screening visit at which written informed consent was obtained; participants were required to establish their comprehension of consent information by passing an informed-consent quiz.

RANDOMIZATION AND TRIAL TREATMENTS

Participants were randomly assigned, in a 1:1 ratio, to extended-release naltrexone or usual treatment for opioid-relapse prevention. An urn randomization procedure ensured balance with respect to trial site, sex, and status regarding the need for opioid detoxification.[16] An independent, centralized, automated telephone system made the treatment assignments after eligibility of the participants was confirmed.[17]

Trial physicians or nurses administered extended-release naltrexone by injection and provided medication-management counseling. Extended-release naltrexone, at a dose of 380 mg, was administered by intramuscular injection once every 4 weeks during medical management visits, the first of which occurred at the time of randomization. A standard naloxone challenge (i.e., administration of >0.8 mg of naloxone intravenously, intramuscularly, or subcutaneously and assessment of opioid-withdrawal symptoms) had to be negative before the initial injection. At one site (Friends Research Institute), 12.5 mg of oral naltrexone was also administered as a low-dose challenge, followed by a 2-hour observation period, before injection of extended-release naltrexone; this additional challenge reflected the preferences of the local site and institutional review board. Medical management counseling focused on medication side effects, support for recovery and treatment participation, and counseling to reduce the risk of relapse and overdose.[18] Participants in the usual-treatment group received similar counseling that was focused on adverse events, the prevention of relapse and overdose, and support for community treatment involvement from the same trial personnel.

Incentives, follow-up visit schedules and procedures, and community treatment referrals were the same in the two groups; all participants were encouraged by the same trial staff to access appropriate community treatment and relapse-prevention resources, including buprenorphine or methadone treatment if preferred or indicated during the trial and after the treatment phase (no extended-release naltrexone was provided after the end of the 24-week treatment phase). All participants were compensated for attendance at individual visits; total cash or voucher compensation across 17 visits varied according to site ($385 to $820).

CLINICAL ASSESSMENTS

Follow-up and assessment procedures were the same in the two groups. Visits occurred at screening, randomization, and then every 2 weeks for 24 weeks during the treatment phase. Post-treatment follow-up assessments occurred at weeks 27, 52, and 78 (three visits only). The visits occurring every 2 weeks and at weeks 27, 52, and 78 included urine toxicologic screening and self-report of opioid, cocaine, alcohol, and intrave-

nous drug use with the use of the Timeline Followback calendar method for count data.[19] Urine samples were tested for opiates (a level >300 ng per milliliter was considered to indicate a positive test), oxycodone, methadone, buprenorphine, and cocaine metabolites. Data on unsafe sex were captured every 6 months with the use of the Sex Risk subscale of the Risk Assessment Battery (on which scores range from 0 to 18, with higher scores indicating a greater risk of contracting and spreading human immunodeficiency virus [HIV] infection through sexual behaviors).[20] Self-reported information about criminal activity, rearrests, and days of reincarceration was collected every 2 weeks with the use of the Timeline Followback method for days in controlled environments, monthly with the use of the Crime and Legal Activities Report,[21] and every 6 months with the use of the legal-status items in the Addiction Severity Index Lite.[22]

OUTCOMES

The primary outcome was the time (in weeks) to an opioid-relapse event during the 24-week treatment phase. A relapse event was defined as 10 or more days of opioid use in a 28-day (4-week) period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Relapse was considered to be a one-time event and corresponded to the loss of persistent opioid abstinence after randomization, when all participants had been opioid-free and had endorsed a goal of opioid abstinence. Related opioid-use outcomes were rates of opioid-negative (vs. opioid-positive or missing) urine samples, the percentage of 2-week intervals with no opioid use as assessed by self-report or by testing of urine samples (confirmed abstinence), the percentage of days with self-reported opioid use, and post-treatment rates of opioid use as assessed by self-report (percentage of 2-week intervals with any opioid use vs. no opioid use) and by testing of single urine samples at weeks 52 and 78. The primary relapse outcome used during the treatment phase, defined by assessments performed every 2 weeks, self-report, and testing of urine samples, was not available during long-term follow-up because visits were scheduled only at weeks 52 and 78. Secondary outcomes of interest were rates of alcohol and nonopioid drug use, HIV risk behaviors, rearrests and reincarcerations, and adverse events including opioid overdose.

STATISTICAL ANALYSIS

We calculated that a sample size of 164 participants per group, with an assumed loss to attrition of approximately 5% per month, would provide the trial with 80% power to detect a hazard ratio for relapse with usual treatment of 1.53 or higher, equivalent to an estimated difference in relapse rates of 15 percentage points (45% vs. 30%).[9,13] The primary outcome analysis tested whether extended-release naltrexone resulted in a longer time to relapse than that with usual treatment, with the use of Cox proportional-hazards regression models. We compared overall relapse rates using intention-to-treat mixed-effects logistic-regression models and compared rates of positive urine tests and days with self-reported opioid use using a linear mixed-effects model for count data. Missed visits and missing data on urine samples were counted as positive for opioid use; thus, dropouts contributed to a relapse event. Missing data for secondary outcomes (cocaine, alcohol, and intravenous drug use; score on the Sex Risk subscale of the Risk Assessment Battery; and reincarceration) were estimated from available data only.

At the week 52 and week 78 visits, participants provided 6 months of self-reports on opioid use and a single urine sample. We analyzed the percentage of opioid-negative (vs. opioid-positive or missing) urine samples at both visits using mixed-effects logistic models. We used a logistic mixed-effects model for repeated measures to analyze self-reported opioid use from week 1 to week 78 and to test for differences in the treatment groups over time with the use of an interaction term between group and time.

RESULTS

SCREENING AND RANDOMIZATION

Recruitment began in February 2009 and continued through November 2013. The five sites obtained consent from and screened 437 persons, of whom 308 underwent randomization; 153 were assigned to extended-release naltrexone and 155 to usual treatment (Fig. 1). Common reasons for exclusion were an incomplete screening visit, incomplete detoxification or a lack of opioid abstinence before randomization, and

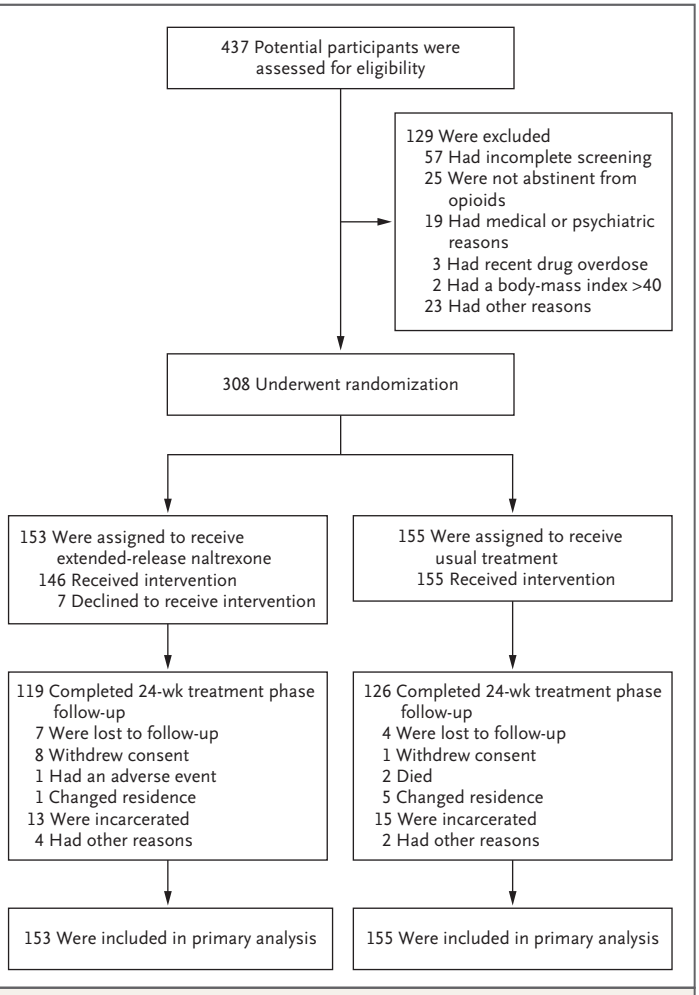

Figure 1. Screening, Randomization, and Follow-up.

serious medical or psychiatric coexisting conditions. Two potential participants were excluded because of a BMI of more than 40 and therefore a potentially elevated risk of a severe injection-site reaction.

PARTICIPANTS

The characteristics of the trial groups were similar at baseline. The mean age was 44 years; 85% of the participants were male, 77% were black or Hispanic, 74% were on parole or probation, and 65% had not used heroin or other opioids in the previous 30 days (Table 1). All reported a history of DSM-IV opioid dependence. A total of 88% of the participants reported heroin use and 41% reported injection-drug use during their lifetimes; 34% reported any opioid (heroin or other) use in the previous 30 days. A total of 9% of the participants required opioid detoxification to enter the trial.

ATTENDANCE AT SCHEDULED VISITS AND ADHERENCE TO MEDICATION

Most of the visits that were scheduled every 2 weeks (3096 of 4004, 77%) were attended; participants assigned to extended-release naltrexone attended 79% of the scheduled visits, and those assigned to usual treatment attended 75%. A total of 75% of the participants completed an end-of-treatment-phase visit at week 27. Overall, participants assigned to extended-release naltrexone completed 711 of the 918 planned monthly injections (77%). Seven participants (5%) declined any injections after randomization; 146 (95%) completed the first injection, 132 (86%) the second injection, 119 (78%) the third injection, 111 (73%) the fourth injection, 100 (65%) the fifth injection, and 93 (61%) the sixth injection.

PRIMARY OUTCOME AND RELATED OPIOID-USE OUTCOMES

During the 24-week treatment phase, the time to relapse was significantly longer in the extended-release naltrexone group than in the usual-treatment group: 10.5 weeks versus 5.0 weeks ($P<0.001$; hazard ratio for relapse, 0.49; 95% confidence interval [CI], 0.36 to 0.68) (Fig. 2). A relapse event was detected in 66 participants assigned to extended-release naltrexone (43%) as compared with 99 assigned to usual treatment (64%) ($P<0.001$; odds ratio, 0.43; 95% CI, 0.28 to 0.65); this finding is consistent with the higher rate of opioid-negative urine samples, the lower percentage of days with self-reported opioid use, and the higher percentage of 2-week intervals with confirmed abstinence that we observed with extended-release naltrexone than with usual treatment (Table 2). An alternative analysis of missing urine data, in which only two consecutive confirmed positive urine screening results or self-reports of opioid use contributed to a "confirmed relapse outcome," also favored extended-release naltrexone (rate of relapse, 15% vs. 37%; $P<0.001$; hazard ratio, 0.33; 95% CI, 0.21 to 0.54). The treatment effect did not differ significantly according to site.

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