General Purpose Standing Committee No. 2
Inquiry into drug and alcohol treatment
Legislative Council – Committees
Parliament of New South Wales
Parliament House
Macquarie Street
Sydney NSW 2000

1st May, 2013

Questions taken on notice:

1. Life skills training program – program details

The Life Skills Training (LST) program is a multi-component competence enhancement based preventive intervention that emphasises drug resistance skills training within the context of a generic personal and social skills training model. The LST program is one of the most thoroughly evaluated evidence-based drug abuse prevention programs for middle school students. Over the past two decades, the LST program has been shown to be highly effective in a series of randomised, controlled efficacy studies and two large-scale effectiveness trials. Evaluation studies have consistently shown reductions in smoking, alcohol use, and cannabis use of 50% or more in students receiving the LST program relative to controls, as well as improvements in a host of important risk and protective factors for adolescent drug abuse.

Program Overview and Core Components
The LST prevention program consists of three major components. The first component is designed to teach students a set of general self-management skills, and the second focuses on general social skills. These two components are designed to enhance personal and social competence and to decrease motivations to use drugs and vulnerability to social influences that support drug use. The third component of LST focuses on information and skills that are specific to drug use in order to promote drug resistance skills, antidrug attitudes, and antidrug norms. Below is a brief description of the major components of the LST program.

Component 1: Personal Self-Management Skills
The personal skills component of the LST program is designed to influence a broad array of self-management skills. To accomplish this, the personal skills component contains material to foster the development of decision-making and problem-solving (e.g., identifying problems, defining goals, generating alternative solutions, considering consequences), teaches skills for identifying, analysing, and resisting media influences, and provides students with self-control skills for coping with anxiety (e.g., relaxation training) and anger/frustration (e.g., inhibiting impulsive reactions, reframing, using self-statements). Furthermore, students are encouraged to design a "self-improvement" project in which they select something about themselves that they would like to improve or change (e.g., a skill or behaviour). Students learn how to set realistic goals and sub goals, evaluate and record their progress, and how to handle success and failure along the way. A goal of teaching these basic principles of personal behaviour change and self-improvement is to enhance self-esteem.

Component 2: Social Skills
The social skills component is designed to improve several important interpersonal skills in order to enhance general social competence. This social skills component contains material designed to help students improve general interpersonal skills such as how to overcome shyness, how to give and receive compliments, how to initiate social interactions, as well as skills related to dating relationships and assertiveness (verbal and nonverbal).

Component 3: Drug-Related Information and Skills
This component is designed to have an impact on knowledge and attitudes concerning drug use, normative expectations, and skills for resisting drug use influences from peers and the media. This material is similar to that contained in many psychosocial drug abuse prevention programs that focus on the teaching of social resistance skills. This component of the LST program includes a focus on the short-term consequences of drug use, knowledge about the actual levels of drug use among adolescents and adults in order to correct normative expectations about drug use, information about the declining social acceptability of cigarette smoking and other drug use, information and class exercises demonstrating the immediate physiological effects of cigarette smoking, and material concerning peer and media pressures to smoke, drink, or use drugs and techniques for resisting these pressures.

Program Materials and Methods
Curriculum materials have been developed to standardise the implementation of the LST program and increase its exportability. These materials consist of a Teacher's Manual and Student Guide for each year of the program (published by Princeton Health Press). The Teacher's Manual contains detailed lesson plans that describe the overall goals and objectives for each intervention session and provide the appropriate content and activities. The Student Guide contains class exercises, homework assignments, and reference material for each session.

The LST program is intended for high school students (in the USA: middle or junior high school students) and is implemented during 15 class periods (about 45 minutes each) in the first year which is typically year seven. An additional two years of booster intervention are designed to reinforce the material covered during the first year. There are 10 booster sessions in year eight and five booster sessions in year nine. There are additional (optional) sessions on violence prevention: three during year one, and two each in year two and three.

The LST program is taught using cognitive-behavioural skills training techniques, facilitated group discussion, classroom demonstrations, and traditional didactic teaching methods. The material is most effectively taught through facilitated group discussion and skills training exercise, although conventional teaching methods are appropriate for some of the content. Because the major emphasis of the LST program is on the teaching of personal self-management skills, social skills, and drug resistance skills, the most important intervention method is skills training. The cognitive-behavioural skills in the LST program are taught using a combination of instruction, demonstration, behavioural rehearsal, feedback, social reinforcement, and extended practice in the form of behavioural homework assignments. Provider training typically consists of a one- or two-day training workshop to familiarise intervention providers with the prevention program and its rationale, and to provide an opportunity for trainees to learn and practice the skills needed to implement the prevention program successfully.

Taken from: Botvin, G. J., & Griffin, K. W. (2004). Life skills training: Empirical findings and future directions. *The Journal of Primary Prevention, 25*(2), 211-232. http://link.springer.com/article/10.1023/B%3AJOPP.0000042391.58573.5b#

2. Recent Russian trials of naltrexone, peer reviewed academic publications

Krupitsky, E., Zvartau, E., Blokhina, E., Verbitskaya, E., Wahlgren, V., Tsoy-Podosenin, M., et al. (2012). Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Archives of General Psychiatry, 69*(9), 973-981.

Krupitsky, E., Nunes, E.V., Ling, W., Illeperuma, A., Gastfriend, D.R., & Silverman, B.L. (2011). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. *The Lancet, 377*, 1506-1513.

Tiihonen, J., Krupitsky, E., Verbitskaya, E., Blokhina, E., Mamontova, O., Föhr, J., et al. (2012). Naltrexone implant for the treatment of polydrug dependence: A randomized controlled trial. *American Journal of Psychiatry, 169*(5), 531-536.

Copies of the papers attached

3. Other more recent naltrexone publications (peer reviewed)

Lobmaier, P.P., KunØe, N., Gossop, M., Katevoll, T., & Waal, H. (2010). Naltrexone implants compared to methadone: Outcomes six months after prison release. *European Addiction Research, 16*(3), 139-145.

KunØe, N., Lobmaier, P., Ngo, H., & Hulse, G. (2012). Injectable and implantable sustained release naltrexone in the treatment of opioid addiction. *British Journal of Clinical Pharmacology*. DOI:10.111/bcp.12011

Copies of the papers attached

I would be pleased to provide any additional information to the Inquiry.

Yours sincerely

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ORIGINAL ARTICLE

Randomized Trial of Long-Acting Sustained-Release Naltrexone Implant vs Oral Naltrexone or Placebo for Preventing Relapse to Opioid Dependence

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Context: Sustained-release naltrexone implants may improve outcomes of nonagonist treatment of opioid addiction.

Objective: To compare outcomes of naltrexone implants, oral naltrexone hydrochloride, and nonmedication treatment.

Design: Six-month double-blind, double-dummy, randomized trial.

Setting: Addiction treatment programs in St Petersburg, Russia.

Participants: Three hundred six opioid-addicted patients recently undergoing detoxification.

Interventions: Biweekly counseling and 1 of the following 3 treatments for 24 weeks: (1) 1000-mg naltrexone implant and oral placebo (NI+OP group; 102 patients); (2) placebo implant and 50-mg oral naltrexone hydrochloride (PI+ON group; 102 patients); or (3) placebo implant and oral placebo (PI+OP group; 102 patients).

Main Outcome Measure: Percentage of patients retained in treatment without relapse.

Results: By month 6, 54 of 102 patients in the NI+OP group (52.9%) remained in treatment without relapse compared with 16 of 102 patients in the PI+ON group (15.7%) (survival analysis, log-rank test, $P<.001$) and 11 of 102 patients in the PI+OP group (10.8%) ($P<.001$). The PI+ON vs PI+OP comparison showed a nonsignificant trend favoring the PI+ON group ($P=.07$). Counting missing test results as positive, the proportion of urine screening tests yielding negative results for opiates was 63.6% (95% CI, 60%-66%) for the NI+OP group; 42.7% (40%-45%) for the PI+ON group; and 34.1% (32%-37%) for the PI+OP group ($P<.001$, Fisher exact test, compared with the NI+OP group). Twelve wound infections occurred among 244 implantations (4.9%) in the NI+OP group, 2 among 181 (1.1%) in the PI+ON group, and 1 among 148 (0.7%) in the PI+OP group ($P=.02$). All events were in the first 2 weeks after implantation and resolved with antibiotic therapy. Four local-site reactions (redness and swelling) occurred in the second month after implantation in the NI+OP group ($P=.12$), and all resolved with antiallergy medication treatment. Other nonlocal-site adverse effects were reported in 8 of 886 visits (0.9%) in the NI+OP group, 4 of 522 visits (0.8%) in the PI+ON group, and 3 of 394 visits (0.8%) in the PI+ON group; all resolved and none were serious. No evidence of increased deaths from overdose after naltrexone treatment ended was found.

Conclusions: The implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation, but none are serious and all resolve with treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00218426

Arch Gen Psychiatry. 2012;69(9):973-981

NALTREXONE HYDROCHLORIDE competitively blocks μ-opioid receptors and reduces or eliminates the positive reinforcing effects of opioids. One 50-mg tablet blocks these effects for 24 to 36 hours; tolerance and withdrawal do not occur; and the medication prevents relapse if taken daily,[1,2] unless high doses of opioid are used.[3] Unfortunately, adherence to the treatment regimen has been poor except in highly motivated patients,[4,5] when family members monitor adherence,[6] or when patients face incarceration or job loss if they relapse.[2,7] A Cochrane review of sustained-release naltrexone for opioid dependence published in 2008 concluded that evidence was insufficient to evaluate its effectiveness,[8] but the review was conducted before publication of a more recent study showing significantly better out-

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comes with sustained-release injected naltrexone than a control treatment[9] and before publication of the findings from the study reported herein. An updated Cochrane review of oral naltrexone published in 2011 concluded that maintenance treatment with naltrexone has not been proven superior to other kinds of treatment.[10] However, this review was somewhat internally inconsistent in that the review described findings from the previous studies, in which oral naltrexone was superior to control treatments when used in situations where adoption of naltrexone was facilitated by personal or cultural factors.

One setting where the cultural situation facilitates adoption of naltrexone treatment for opioid dependence is the Russian Federation, where naltrexone is the only effective medication approved for preventing relapse. Addiction treatment in Russia typically begins with 7 to 10 days of inpatient detoxification in specialized addiction (narcology) hospitals using clonidine hydrochloride or other nonopioid medications followed by 2 to 4 weeks of inpatient therapy that includes relaxation and counseling. Patients are referred to a primary health care provider or health center after discharge, but most do not keep appointments. Relapse rates are high and patients are readmitted to repeat the same treatment in attempts to achieve sustained remission. Many patients are young and live with family members who can monitor and enforce adherence, which likely contributed to the positive results in 2 prior studies of oral naltrexone where only 10% to 12% of the placebo control group remained in treatment and did not relapse compared with 42% to 44% of the oral naltrexone group.[11,12]

Sustained-release formulations might improve these results, and the following 2 formulations have been approved: extended-release naltrexone,[9] administered as a monthly injection and approved by the US Food and Drug Administration for preventing relapse to opioid dependence in 2010; and an implant that blocks opioid effects for 60 to 90 days and is registered in the Russian Federation.[13] Another extended-release injected product that was developed but is no longer available increased retention in a study of 60 patients who were randomized to 192- or 384-mg doses or matching placebo with a second injection a month later.[14] Clinicians in Australia developed an extended-release implant that contains 2.3 g of naltrexone and is inserted subcutaneously every 6 months. The product is not registered but is manufactured under the Therapeutic Goods Administration Good Manufacturing Practice in a purpose-built facility inspected and approved by the Therapeutic Goods Administration of Australia (Gary Hulse, PhD, personal communication, September 2011). The implant reduced relapse in a study of 70 opioid-addicted patients who were randomized to the implant formulation or to oral naltrexone,[15] and in another study where 56 patients seeking nonagonist treatment were randomized to receive the implant before inpatient discharge or to usual outpatient follow-up care.[16]

Herein we present the results of a 6-month trial undertaken in Russia among 306 consenting, opioid-addicted patients who had undergone detoxification within the last 1 to 2 weeks. We compare the Russian extended-release implant with oral naltrexone and placebo. All patients received biweekly drug counseling. Our main objective was to assess the degree to which the 3 conditions retained patients in treatment and prevented relapse; secondary outcomes included negative results of opioid urine tests, relapse after treatment ended, and safety.

We hypothesized that patients who received the naltrexone implant would experience more retention and less opioid use and relapse than those receiving oral naltrexone or placebo, and that patients receiving oral naltrexone would have better outcomes than the placebo group. The trial was conducted in outpatient units at Pavlov State Medical University, St Petersburg (Pavlov), and the Leningrad Regional Addiction Treatment and Research Center, affiliated with Pavlov.

The study was conducted according to guidelines in the Helsinki Declaration and approved by the ethical review board at Pavlov and the institutional review board at the University of Pennsylvania before recruitment commenced; each committee reviewed its progress and reapproved it annually. A University of Pennsylvania staff member who is fluent in Russian and English checked the consent forms to verify that their contents were identical. Written informed consent in Russian was obtained before enrollment, and patients were free to withdraw from the study at any time without jeopardizing their access to other treatments. The principal investigator (G.E.W.) maintained weekly to monthly contact with Russian investigators via e-mail, Skype, and meetings (College on Problems of Drug Dependence and National Institute on Drug Abuse/Pavlov meetings in St Petersburg) to check study progress and visited the research sites on 4 occasions during the course of the study, when he viewed study case report forms, talked to patients, and observed study procedures.

METHODS

STUDY DESIGN

We conducted a randomized, double-blind, double-dummy, 24-week trial in which patients received biweekly drug counseling and (1) a bimonthly implant with naltrexone, 1000 mg, and daily oral naltrexone placebo (NI+OP group), (2) a bimonthly placebo implant and oral naltrexone hydrochloride, 50 mg/d (PI+ON group), or (3) a bimonthly placebo implant and daily oral naltrexone placebo (PI+OP group). Patients underwent assessment every 2 weeks during treatment with follow-up at months 9 and 12 for those who remained in treatment without relapse. The first patient was randomized on July 31, 2006; the last visit, January 4, 2009; and the last follow-up, June 10, 2009.

PARTICIPANTS

Inclusion criteria consisted of ages 18 to 40 years; *DSM-IV* criteria for opioid dependence with physiological features for at least 1 year as determined by results of clinical examination and the Composite International Diagnostic Interview[17]; abstinence from heroin and other substances for the past week or more; negative results of urine toxicology and alcohol breath tests; no psychotropic medication; ability to provide informed

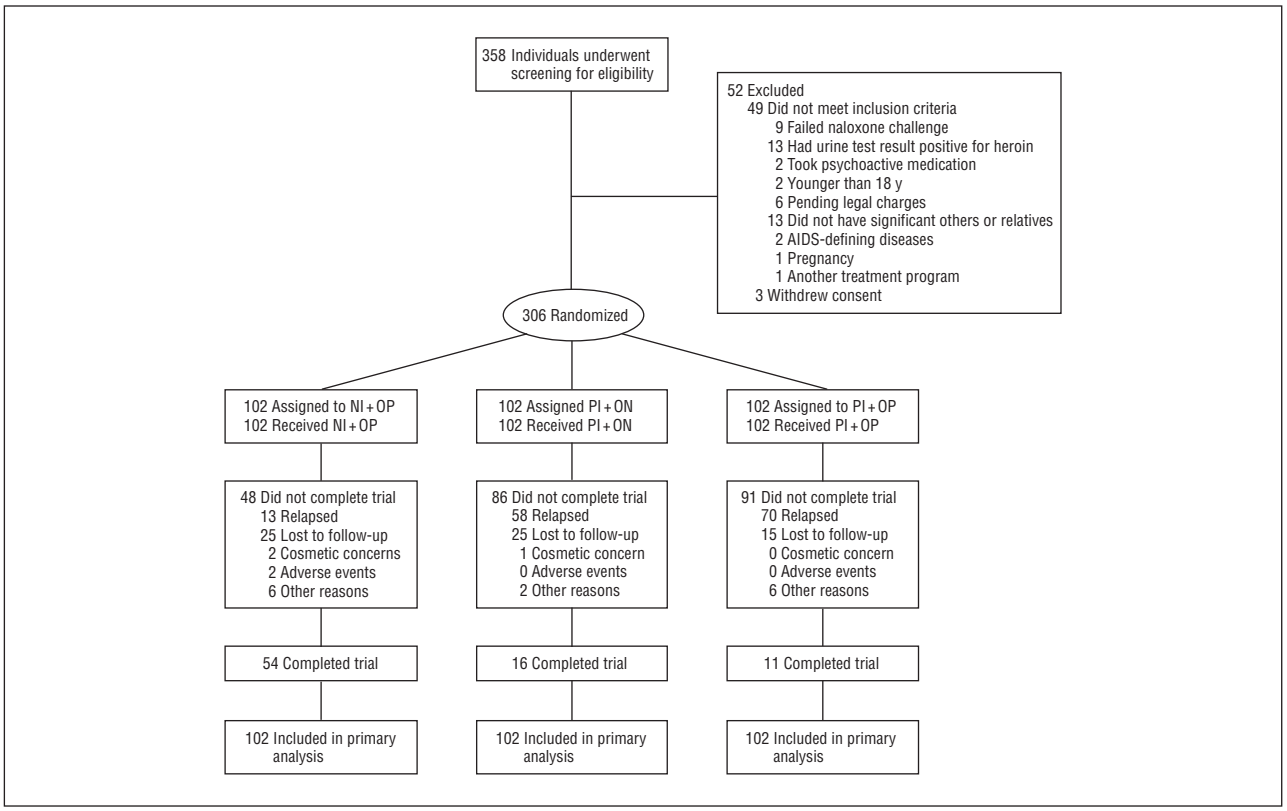

Figure 1. Study flow diagram. NI+OP indicates 1000-mg naltrexone implant and oral placebo; PI+NO, placebo implant and 50-mg oral naltrexone hydrochloride; PI+OP, placebo implant and oral placebo. The 2 adverse events in the NI+OP group include wound infection only.

consent; 1 or more relatives or significant others who are willing to encourage medication therapy adherence and provide follow-up information if contacted by research staff; agreement to allow research staff to contact these individual(s); stable address in the St Petersburg/Leningrad region; ability to provide a home telephone number; negative pregnancy test results and use of adequate contraception for women of childbearing age; and negative results of a naloxone challenge. Exclusion criteria included a major psychiatric disorder (ie, dementia, schizophrenia, paranoia, bipolar disorder, or seizure disorder); advanced neurological, cardiovascular, renal, or hepatic disease; active tuberculosis or current febrile illness; AIDS-defining illness; significant laboratory abnormality (severe anemia, unstable diabetes, alanine aminotransferase/aspartate aminotransferase [ALT/AST] levels of >3 times the top reference limit); pending incarceration; and participation in another treatment study or substance abuse program.

SCREENING: NALOXONE CHALLENGE AND ENROLLMENT

Clinical staff on inpatient units at the St Petersburg City Addiction Hospital and the Leningrad Regional Center for Addictions referred potential subjects to research assistants who were assigned to these units; a few (n=25) were referred by local practitioners after completing outpatient detoxification. Research assistants explained the study, obtained informed consent, and scheduled appointments for additional screening at 1 of the 2 outpatient sites.

Three hundred fifty eight patients reported for outpatient screening where the medical history and laboratory test results from their recent addiction treatment were checked to confirm eligibility and a urine sample was obtained for drug screening. If the result of the urine screening was negative for opioids and no evidence of physiological dependence or other exclusionary criteria was found, the patient was scheduled for a naloxone challenge and the first dose of study medications. Among the 52 who were excluded from participation, 13 did not have relatives or significant others who could supervise them and provide follow-up information. Patient flow, including reasons for study exclusion, is seen in **Figure 1**. Those patients found ineligible were referred to usual treatment.

The naloxone challenge was administered in a room set aside for minor surgical procedures at a time that a study surgeon was available to insert the implant. On arrival, the patient was given another urine drug test and checked for signs or symptoms of opioid dependence. Those with a urine test result negative for opioids and no evidence of dependence were given 0.8 mg of naloxone intramuscularly and observed for 1 hour. Those who experienced withdrawal were treated symptomatically and invited to return in 2 to 3 days for a repeat challenge. Failure to pass the challenge on 3 occasions disqualified patients from study enrollment.

Those who passed the challenge underwent randomization. The surgeon inserted the implant, the first dose of oral medication was administered, and the patient was given an appointment for outpatient counseling and a 1-month supply of tablets for availability in case the appointment was missed. At each counseling session, patients were asked if they had used opiates (heroin) since the last appointment, given a urine drug test, and observed for signs of withdrawal or recent use. Relatives often accompanied patients and provided information to supplement self-reports or were contacted by telephone to determine patient status in case of missed appointments. A naloxone challenge was repeated if a urine test result was positive for opioids or other evidence of relapse; patients who showed evidence of relapse were referred to usual treatment and not eligible to continue to receive study medication. Others were given a 2-week supply of study

tablets and scheduled for the next counseling session. A naloxone challenge was repeated before each implantation unless clear evidence indicated relapse.

INTERVENTIONS

Implant Naltrexone and Implant Placebo Naltrexone

The implant contains 1000 mg of naltrexone embedded in a magnesium stearate matrix with a small dose of triamcinolone acetonide added to prevent inflammation. The implant is inserted under the skin of the abdominal wall to a depth of 3 to 4 cm using a sterile, prepackaged disposable syringe through a 1- to 2-cm incision that is closed with 1 to 2 sutures. Plasma levels during 30 to 60 days are 20 ng/mL for naltrexone and 60 ng/mL for 6β-naltrexol, naltrexone's active metabolite.[18] This implant has been shown to block opioids for 2 months, is biodegradable, and does not require removal.[18]

Oral Naltrexone and Oral Placebo

Pavlov pharmacy staff made visually identical oral naltrexone and placebo capsules containing a 50-mg riboflavin marker for monitoring adherence. Studies of 50-mg tablets have shown plasma levels peaking in 1 to 3 hours at 10.0 to 20.0 ng/mL and declining to approximately 0.5 to 1.0 ng/mL at 24 hours with a half-life of 4 hours; 6β-naltrexol reached roughly 8 times the peak naltrexone concentration and declined with a half-life of about 14 hours.[19,20]

Blinding

Pavlov pharmacy staff prepared medication kits containing the oral and implant medication combinations for individual patients, placed them in numbered containers, and transported them to outpatient sites. Research assistants, treating physicians, other project staff, and participants were blind to group assignment. A master code was kept off-site, and the blind could be broken in case of emergency (this option was never used). Formal procedures to assess the success of blinding were not undertaken.

Randomization

Randomization was completed in the data management unit at Pavlov using a generator of random numbers into commercially available software (SPSS, version 17; SPSS, Inc).

Individual Drug Counseling

Individual drug counseling was based on a modified version of the treatment used in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study[21] as described on the National Institute on Drug Abuse web site (http://archives.drugabuse.gov/TXManuals/IDCA/IDCA16.html). Modifications involved emphasizing adherence to medication and counseling, dealing with persistent withdrawal, and de-emphasizing self-help group participation because it is not widely used in St Petersburg. The manual was revised to reflect these changes and translated into Russian. Therapists were experienced masters' level psychologists and addiction psychiatrists (narcologists) and were provided with a copy of the manual, given an overview of counseling techniques by the manual's authors, and supervised by one of us (E.K.). All patients received human immunodeficiency virus (HIV) risk reduction information as part of usual treatment before enrolling in the study. Counseling sessions lasted about 45 minutes and were not recorded or rated for adherence.

MEASURES

Routine blood tests (complete blood cell counts, electrolytes, and levels of ALT/AST) and urinalysis were completed as part of usual treatment before study enrollment. Assessments added for the study included a detailed history of drug use and psychiatric interview to confirm current opioid dependence; urine testing for opiates, cocaine, amphetamines, marijuana, benzodiazepines, and barbiturates; alcohol breath test; Addiction Severity Index[22]; Risk Assessment Battery[23]; Time Line Follow-Back for alcohol and drugs[24]; pregnancy test; monthly measurements of ALT and AST levels while receiving medication; heroin craving (visual analog scale); Global Assessment of Functioning[25]; Beck Depression Inventory[26]; Brief Psychiatric Rating Scale[27]; Spielberger State-Trait Anxiety Test[28]; Scale of Protracted Withdrawal Syndrome[29]; Chapman Scale of Physical and Social Anhedonia[30]; Ferguson Anhedonia Scale[31]; and visual inspection of the site 5 to 7 days after implantation. No measure for differences in swelling, redness, and tenderness was used. Urine drug testing was performed at biweekly counseling sessions.

Adherence to the tablet regimen was assessed by pill counts at each appointment, visual inspection for the presence of riboflavin in the urine using UV light at 444 nm in a room with low ambient light, and information from the family member or significant other whom the patient agreed to allow research staff to contact.

Interviews and urine drug screens were completed at 9 and 12 months to assess for relapse in patients who remained in treatment and did not relapse. Patient safety was assessed by inspection of the implant site 5 to 7 days after implantation and at subsequent visits, asking patients if they were having problems at biweekly counseling sessions, testing for liver enzyme levels at week 24, and contacting patients or significant others approximately 18 months after randomization to find out if they were alive and, if not, the cause of death.

Patients were counted as early terminators if they missed more than 2 consecutive biweekly appointments and as having a relapse if they reported daily heroin use, had signs and symptoms of withdrawal, or a positive result of a naloxone challenge. Patients who reported occasional heroin use but did not have physiological dependence were considered to have had a slip rather than a relapse and continued to receive study medication if they passed a naloxone challenge. Patients were reimbursed for time and transportation with the ruble equivalent of $10 for each study visit for a total of $120 if all study appointments were kept.

STATISTICAL ANALYSIS

Data were double entered and checked for errors and analyzed using commercially available software (SPSS, version 17; SPSS, Inc). Survival analysis (Kaplan-Meier survival functions with log-rank Cox-Mantel criteria for group comparison[32]) was used to determine the primary outcome of retention, defined as not missing 2 consecutive counseling sessions and not having a relapse. Because this outcome combined patients who failed to keep appointments with those who kept appointments but relapsed, the proportion of nonsurvivors attributable to proven relapse was also determined. Secondary outcomes reported herein are the cumulative percentages of negative results of urine screening for opiates during the 24-week medication phase, relapse at 9 and 12 months among patients who completed treatment without relapse and returned for follow-up, and safety. Safety assessments included adverse effects (AEs) using Fisher

exact tests with Monte-Carlo modeling for more than 2 groups, liver enzyme levels at 24 weeks, and overdose deaths 18 months after randomization.

The sample size provided 80% power to detect a difference of 20% or greater between the groups for the primary outcome assuming an α value of .025 (2 contrasts) and a survival rate of approximately 60% in the NI+OP group. The major study statistician (E.V.) was not blinded to group assignment; however, another statistician who was blinded to group assignment and working on genetics issues of this study verified the major biostatistician's findings on survival analyses and urine test results (Nina Alexeyeva, PhD, personal communication, September 2011).

RESULTS

DEMOGRAPHIC AND CLINICAL FEATURES

All patients were dependent on intravenous heroin; prescription opioids are highly restricted, expensive, and difficult to obtain in Russia. Patients' mean (SE) age was 28.2 (0.2) years; most (n=222 [72.5%]) were male; average (SE) duration of opioid dependency was 8.0 (0.2) years; and average number of previous treatments ranged from 3.8 to 4.9. Among 306 study patients, the baseline assessment showed that 144 (47.1%) were seropositive for HIV; 292 (95.4%) were seropositive for hepatitis C virus; and 47 (15.4%) were seropositive for hepatitis B virus. Past 30-day self-reported substance use at baseline showed that 82 (26.8%) used marijuana; 36 (11.8%), amphetamines; 34 (11.1%), sedatives, mostly benzodiazepines; and none, cocaine. Average (SD) alcohol use was 9.6 (1.0) g/d. There were no significant baseline differences between groups in demographics or clinical variables.

ORAL MEDICATION ADHERENCE

Urine samples were collected biweekly from patients who remained in treatment; the proportion of riboflavin-positive samples varied from 70% to 100%. These data were consistent with capsule counts and information from informants, indicating that those who remained in treatment were taking the oral study medication.

PRIMARY OUTCOME: RETENTION WITHOUT RELAPSE

By month 6, 54 of 102 patients in the NI+OP group (52.9%) remained in treatment without relapse, compared with 16 of 102 patients in the PI+ON group (15.7%) and 11 of 102 patients in the PI+OP group (10.8%). **Figure 2** shows the Kaplan-Meier survival curves for these comparisons. Log-rank tests showed a significant overall effect for treatment group (log-rank statistic, 62.16; $df=2$ [$P<.001$]). We found significant differences between the NI+OP and PI+OP groups (log-rank statistic, 68.4; $df=1$ [$P<.001$]) and between the NI+OP and PI+ON groups (log-rank statistic, 45.2; $df=1$ [$P<.001$]). The PI+ON vs PI+OP comparison showed a nonsignificant trend favoring oral naltrexone (log-rank test, 3.44; $df=1$ [$P=.07$]), as seen in Figure 2.

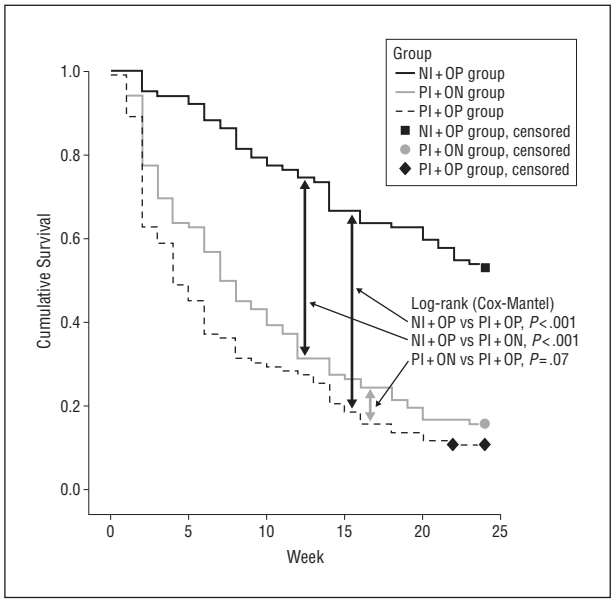

Figure 2. Kaplan-Meier survival evaluating treatment dropout and relapse. NI+OP indicates 1000-mg naltrexone implant and oral placebo (n=102); PI+NO, placebo implant and 50-mg oral naltrexone hydrochloride (n=102); PI+OP, placebo implant and oral placebo (n=102).

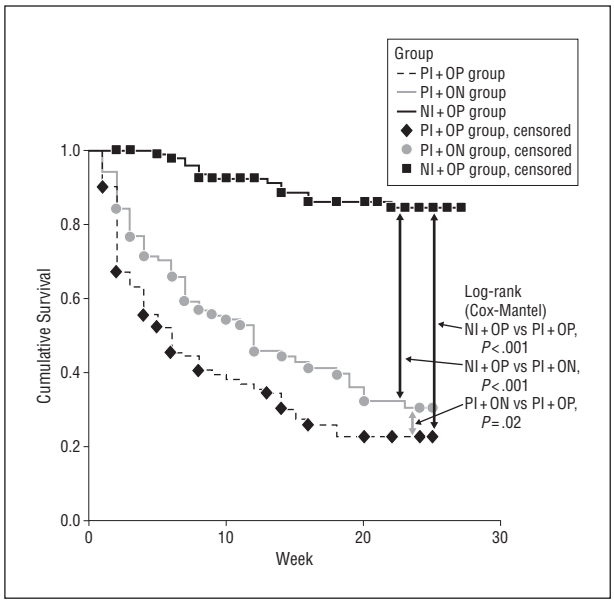

Figure 3. Kaplan-Meier survival evaluating verified relapse. NI+OP indicates 1000-mg naltrexone implant and oral placebo (n=102); PI+NO, placebo implant and 50-mg oral naltrexone hydrochloride (n=102); PI+OP, placebo implant and oral placebo (n=102).

Figure 3 shows the Kaplan-Meier survival curves for the event of verified relapse. The results were very similar to those in Figure 2; however, in this analysis we found a significant difference between the PI+ON and PI+OP groups (log-rank test, 5.08; $df=1$ [$P=.02$]).

SECONDARY OUTCOMES

Opiate Urine Test Results

Results of missed urine tests were imputed to be positive for opiates. The cumulative urine tests with results

negative for opiates in the NI+OP group was 908 of 1428 (63.6%), significantly greater than in the PI+ON (610 of 1428 [42.7%]; odds ratio, 0.43 [95% CI, 0.38-0.50; $P<.001$]) and PI+OP groups (487 of 1428 [34.1%]; odds ratio, 0.30 [95% CI, 0.25-0.35; $P<.001$]). The cumulative proportion of urine tests with results negative for opiates in the PI+ON group was greater than in the PI+OP group (odds ratio, 0.69 [95% CI, 0.60-0.81; $P<.001$]). The results of self-reported opiate use were very similar to the urine drug test results.

Relapse at Follow-up

At 9 months, 35 of 306 patients returned for follow-up assessments. Among these, 20 were in the NI+OP group (12 of 102 in remission), 7 in the PI+ON group (4 of 102 in remission [$P=.14$]), and 8 in the PI+OP group (5 of 102 in remission [$P=.07$]). At 12 months, 28 of the 306 patients underwent assessment and among these, 16 were in the NI+OP group (7 of 102 in remission); 6, the PI+ON group (2 of 102 in remission [$P=.17$]); and 6, the PI+OP group (3 of 102 in remission [$P=.33$]).

Safety

Adverse events at the implant site were wound infections and local reactions (redness and swelling). Infections were observed in 9 of 102 patients (8.8%) in the NI+OP group (twice in 3 patients, after the first and second implantations); in 2 of 102 patients (2.0%) in the PI+ON group ($P=.02$, Fisher exact test); and in 1 of 102 patients (1.1%) in the PI+OP group ($P=.008$, Fisher exact test). Because the number of implantations was different in each group owing to attrition, we calculated AEs per number of implantations. Results were 12 wound infections of 244 implantations (4.9%) in the NI+OP group, 2 of 181 implantations (1.1%) in the PI+ON group ($P=.02$, Fisher exact test), and 1 of 148 implantations (0.7%) in PI+OP group ($P=.02$, Fisher exact test). All infections were observed within the first 2 weeks after implantation and successfully treated with antibiotics within 1 week; however, 2 patients in the NI+OP group left the study owing to wound infections. Four patients had local-site reactions (redness and swelling), all in the NI+OP group ($P=.12$, Fisher exact test). All were observed in the second month after implantation and successfully treated with chloropyramin (an antiallergic medication) during the next month. Other (nonlocal-site) AEs among patients who remained in treatment were reported by 8 of 102 patients in the NI+OP group (7.8%), 4 of 102 patients in the PI+ON group (3.9) ($P=.19$ compared with the NI+OP group, Fisher exact test), and 3 of 102 patients in the PI+OP group (2.9%) ($P=.1$ compared with the NI+OP group, Fisher exact test). However, more NI+OP than PI+ON or PI+OP patients remained in treatment. Thus, nonlocal-site AEs were reported in 8 of 886 visits in the NI+OP group (0.9%), 4 of 522 in the PI+ON group (0.7%), and 3 of 394 in the PI+ON group (0.8%) (all differences were nonsignificant). The most common AEs were abdominal discomfort, nausea, and drowsiness. Most AEs were in the first 3 months; none were severe; and all resolved without medication. The only known severe AE during the treatment phase was a cholecystectomy in the PI+OP group.

At baseline, the mean ALT level varied from 45.9 to 54.1(SE, 3.08) IU/L and AST, from 45.8 to 52.6 (SE, 2.58) IU/L with no significant differences between groups (to convert ALT and AST to microkatals per liter, multiply by 0.0167). End of treatment measures were only available for patients who remained in treatment and did not relapse. For these patients, ALT levels varied from 47.4 to 96.5 (SE, 8.84) IU/L and AST, from 43.2 to 89.5 (SE, 8.3) IU/L; differences were not significant across groups or from baseline to 6 months. We found no evidence of increased risk of death due to overdose after naltrexone treatment.[33]

COMMENT

Methadone is a schedule I drug in Russia, and the Ministry of Health has not accepted Western data on the benefits of agonist maintenance therapy. This approach is similar in many ways to the United States from the mid-1920s to late 1960s, when physicians could lose their licenses or be arrested and jailed if they used opioids to treat opioid addicts. However, unlike the United States during those years, Russia has committed significant resources to detoxification and residential treatment. For example, state-supported alcohol and drug treatment is provided in 138 dispensaries (115 of which have inpatient units) and 12 addiction hospitals with more than 25 000 beds in total and from 50 to 2000 beds per hospital depending on the region. In addition, several hundred commercial and nongovernmental organizations and more than 5600 psychiatrist-narcologists work in the addiction field (Evgenia Koshkina, MD, PhD, personal communication, September 2011). This treatment is readily available, as seen in the **Table**, where study patients averaged 4 to 5 prior treatment episodes.

Starting naltrexone therapy for these patients and under these conditions is easy because the patients undergo routine detoxification. Study findings show that an extended-release implant can alter the course of the addiction, at least for 6 months in about half the patients; however, the degree to which patients will accept longer courses of treatment is a topic for future studies. Unfortunately naltrexone, in the oral or extended-release form, is not widely available in Russia owing to costs, but this situation could change. Whatever the future may bring, patients in this study likely received better treatment than they otherwise would have, including those in the placebo group who received counseling from experienced therapists that was integrated into the study procedures and available immediately after completing detoxification and residential treatment.

Although results clearly favored the implant, patients who received oral naltrexone had fewer urine tests yielding results positive for opiates compared with the placebo group. In addition, the primary outcome showed a nonsignificant trend ($P=.07$) favoring oral naltrexone compared with placebo that might be significant with a larger sample size. This difference was significant ($P=.02$)

Table. Baseline Demographics and Clinical Characteristics[a]

	Medication Group			
	NI+OP (n = 102)	PI+ON (n = 102)	PI+OP (n = 102)	All Patients (n = 306)
Age, y	28.0 (0.4)	27.9 (0.4)	28.7 (0.5)	28.2 (0.2)
Sex, No. (%)				
Male	74 (72.5)	74 (72.5)	74 (72.5)	222 (72.5)
Female	28 (27.5)	28 (27.5)	28 (27.5)	84 (27.5)
Duration of heroin abuse, y	7.8 (0.4)	7.9 (0.4)	8.3 (0.4)	8.0 (0.2)
Average dose of heroin, mg/d	1.1 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.04)
Use of amphetamines, No. (%)	12 (11.8)	6 (5.9)	18 (17.6)	36 (11.8)
Use of cocaine, No. (%)	0	0	0	0
Use of marijuana, No. (%)	35 (34.3)	22 (21.6)	25 (24.5)	82 (26.8)
Use of sedatives or benzodiazepines, No. (%)	15 (14.7)	10 (9.8)	9 (8.8)	34 (11.1)
Use of alcohol, g/d	10.2 (1.7)	9.0 (1.7)	9.6 (1.6)	9.6 (1.0)
No. of previous treatments	4.9 (0.4)	4.3 (0.4)	3.8 (0.3)	4.3 (0.2)
Employment, No. (%)	47 (46.1)	42 (41.2)	51 (50.0)	140 (45.8)
Seropositive for HIV, No. (%)	44 (43.1)	53 (52.0)	47 (46.1)	144 (47.1)
Seropositive for hepatitis B virus, No. (%)	18 (17.6)	16 (15.7)	13 (12.7)	47 (15.4)
Seropositive for hepatitis C virus, No. (%)	98 (96.1)	98 (96.1)	96 (94.1)	292 (95.4)
RAB drug risk	8.0 (0.47)	8.1 (0.44)	8.7 (0.49)	8.2 (0.27)
GAF score	64.7 (0.8)	62.8 (0.7)	62.5 (0.9)	63.3 (0.5)
ASI subscales				
Medical problems	0.13 (0.02)	0.07 (0.01)	0.09 (0.01)	0.10 (0.01)
Work problems	0.68 (0.03)	0.72 (0.03)	0.76 (0.03)	0.73 (0.02)
Alcohol use problems	0.11 (0.01)	0.08 (0.01)	0.10 (0.01)	0.10 (0.01)
Drug use problems	0.29 (0.01)	0.29 (0.01)	0.29 (0.01)	0.29 (0.004)
Legal problems	0.11 (0.02)	0.07 (0.01)	0.10 (0.02)	0.09 (0.01)
Family problems	0.34 (0.03)	0.31 (0.02)	0.30 (0.02)	0.32 (0.01)
Psychiatric problems	0.15 (0.02)	0.19 (0.02)	0.18 (0.02)	0.17 (0.01)

Abbreviations: ASI, Addiction Severity Index; GAF, Global Assessment of Functioning; HIV, human immunodeficiency virus; NI+OP, 1000-mg naltrexone implant and oral placebo; PI+ON, placebo implant and 50-mg oral naltrexone hydrochloride; PI+OP, placebo implant and oral placebo; RAB, Risk Assessment Battery.

[a] Unless otherwise indicated, data are expressed as mean (SE). Differences between groups were nonsignificant.

when survival was measured for verified relapse; thus, oral naltrexone appeared to improve on the results of usual treatment with a few patients. These findings differ from earlier Russian studies where patients receiving oral naltrexone treatment had better outcomes than those of the placebo control group starting in the first month and continuing through month 6.[11,12] A possible reason for these differences is that the older patients in the implant study (average age, 28.2 years) may have been less influenced by and dependent on close relatives for support than the younger patients (aged 21-23 years) in the earlier oral naltrexone studies. Genetic differences in μ-receptors may also play a role, and we are exploring this possibility in collaboration with other investigators.

These findings are similar to those from the recent trial of sustained-release injected naltrexone, where about half of the patients in the medication group remained in treatment for 6 months and had fewer urine tests with results positive for opioids than the placebo control group.[9] From follow-ups on the limited sample of patients who remained in treatment without relapse and who returned for 9- and 12-month follow-ups, we can determine that approximately half relapsed after treatment ended. However, by counting missed appointments as relapses, almost all patients had a relapse, suggesting that for most patients, naltrexone therapy probably needs to be continued for an extended period.

Fourteen patients who received the naltrexone implant (13.7%) experienced a relapse between implantations, and 12 relapses occurred in weeks 6 through 8. The following 5 possibilities might account for this finding: fibrosis around the implant reduced dissemination of naltrexone; the patients metabolized naltrexone rapidly; patients had access to large amounts of high-grade heroin that they used to overcome the blockade as blood levels dropped toward the end of the dosing cycle; the implant released naltrexone more quickly than intended, resulting in low blood levels toward the end of the dosing cycle; or the subcutaneous tissue where the implant was placed did not have enough blood supply to absorb the naltrexone and maintain opioid blockade.

The possibility of patients unmasking the study by using heroin is not as likely as it may appear. In Russia, a sort of placebo effect is associated with getting an injection: patients often think injections are stronger regardless what is injected. In addition, the quality of heroin is sometimes poor, which might reduce the effect of a single heroin injection, and the effect also depends to some extent on expectation and setting. Thus lack of an effect from a single injection may not necessarily be attributable to opioid blockade. In addition, the placebos were not active and had only a visual similarity to the active medication.

Similar to earlier studies, we saw no evidence of increased depression, anxiety, or anhedonia associated with naltrexone.[34] In fact these symptoms, along with crav-

ing, appeared to drop for patients who continued treatment without relapse, as seen in other naltrexone studies with opioid-dependent patients[35,36] and in studies of alcohol-dependent patients treated with extended-release injected naltrexone who did not experience dysphoria or lack of pleasurable stimuli.[37]

Tolerability of the implant was generally good, and no serious AEs attributable to the study medications were reported; however, AEs at the implant site were more common among patients who received the naltrexone implant. This finding could reflect contamination in some of the implants, local irritation caused by naltrexone or other components of the implant, or patients' attempts to remove the implant, although none were reported. The proportion of other AEs was comparable across groups and also to those in a study using the Australian implant[16]; however, in that study, 3 of the 56 patients had implants removed at their request.

Previous studies have shown that any effective treatment for opioid dependence reduces risk of HIV due to injections.[38] This finding is very relevant to countries such as Russia, where HIV is being spread largely by injected drug use as reflected by these and other data from St Petersburg showing that more than 40% of opiate-addicted patients are seropositive for HIV.[39,40] Given the potential for reduction in HIV risk among patients who remained in naltrexone treatment and did not relapse, combined with the apparent unshakable resistance to using agonist therapies in Russia and the widespread availability of inpatient detoxification, naltrexone and in particular extended-release formulations could play a meaningful role in reducing the spread of HIV if the treatment was more readily available throughout the network of state and private treatment facilities.

The limitations of naltrexone implants include the surgical procedure, possibility of wound infection or local irritation, cosmetic defects (scars), need for high opioid doses if the patient develops a medical condition that requires opioid therapy, and possible removal of the implant by the patient within 7 to 14 days after receiving it. Limitations of the study include the limited amount of data on patients who did not remain in treatment, thus making it difficult to obtain more accurate information on the proportions with relapse at 9- and 12-month follow-ups and other secondary outcomes. Strengths include the randomized, prospective, double-dummy design; the large number of participants; involvement of close relatives to provide additional information; and determination of the primary outcome by objective data.

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Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

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Summary

Background Opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences. We aimed to assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification.

Methods We did a double-blind, placebo-controlled, randomised, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and gender in a centralised, permuted-block method. Participants also received 12 biweekly counselling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00678418.

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002). Patients in the XR-NTX group self-reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in craving was –10·1 (95% CI –12·3 to –7·8) in the XR-NTX group compared with 0·7 (–3·1 to 4·4) in the placebo group (p<0·0001). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0·0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

Interpretation XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

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Introduction

Opioid dependence is a potentially life-threatening illness[1] associated with adverse societal effects including increased morbidity and mortality, poor social functioning, economic dependence, and crime.[2–4] The worldwide incidence of opioid dependence has increased during the past decade, and many patients are not receiving treatment for the disorder, although rates of treatment are increasing in many countries.[1,5,6] The main treatments consist of either maintenance pharmacotherapy with counselling or drug-free psychosocial treatment. Although abstinence is the primary goal, drug-free treatment is associated with high rates of relapse.[7] Agonist maintenance, such as with the μ-opioid receptor agonist methadone or the partial agonist buprenorphine, has an established role in the management of opioid dependence, with studies, reviews, and meta-analyses reporting a variety of public-health and safety benefits. These benefits include decreases in illicit drug use; reduced rates of HIV seroconversion, and improved morbidity, mortality, HIV risk behaviours, and patient functioning.[5,7–10] However, in 122 of 192 UN member states, agonist therapy is restricted or unavailable because of philosophical preferences for opioid-free treatment or policy concerns about physiological dependence or abuse and illegal drug diversion.[5,6] Furthermore, agonist therapy might be less suitable for certain subgroups of patients, particularly young people, patients with a brief history of addiction or who are new to treatment, and patients whose employment might prohibit opioid use (eg, health-care providers, pilots, and police, fire, emergency and military personnel).

An alternative pharmacotherapy that supports abstinence is naltrexone, a μ-opioid receptor antagonist that does not have opioid agonist effects, produces no euphoria or sedation, and is not addictive. Antagonist pharmacotherapy is particularly appropriate for patients who have achieved abstinence during inpatient treatment or incarceration and are at risk of relapse after discharge. Naltrexone cessation causes no symptoms of withdrawal because patients are not physically opioid dependent. However, apart from when dosing is supervised, such as for recovering physicians[11] or in the context of intensive behavioural treatments,[12] oral naltrexone has generally been ineffective because of poor adherence.[13]

In 1976, the US National Institute on Drug Abuse requested development of a long-acting opioid antagonist. Responses to this request consisted of subcutaneous naltrexone implants, which have shown efficacy[14,15] but are associated with adverse events related to surgical insertion; and a long-acting injectable naltrexone formulation, which was effective in a small, 2-month long controlled trial.[16] A once-monthly extended-release formulation of injectable naltrexone (XR-NTX, Vivitrol, Alkermes, Waltham MA, USA) has been approved in the USA and Russia for treatment of alcohol dependence. This formulation, administered via intramuscular injection by a health-care provider, gradually releases naltrexone from microspheres composed of medical-grade poly-(d,l-lactide-co-glycolide)—a polymer used in dissolvable surgical sutures. In patients with alcohol dependence, XR-NTX reduced the incidence of heavy drinking[17] and increased the rate of total abstinence over 6 months in those with initial abstinence compared with placebo,[18] with associated improvements in health and social functioning.[19]

We did a multicentre, randomised, placebo-controlled 24-week trial to assess the efficacy, safety, and patient-reported outcomes of once-monthly XR-NTX for the treatment of opioid dependence.

Methods

Patients

Men and women aged 18 years or over who met the Diagnostic and Statistical Manual of Mental Disorders 4th edition[20] criteria for opioid dependence disorder, who were completing inpatient opioid detoxification (≤30 days), and who were off opioids for at least 7 days were enrolled at 13 clinical sites in Russia. Patients were voluntarily seeking treatment and were excluded if they were under justice system coercion—ie, parole or probation, or pending legal proceedings with potential for incarceration. Every patient also had a significant other (eg, spouse or relative) who supervised their compliance with the visit schedule and study procedures. Women of childbearing potential agreed to use contraception during the study.

Exclusion criteria were pregnancy or breastfeeding; significant medical conditions (eg, acute renal failure, endocarditis, and tuberculosis); positive naloxone challenge (increases in vital signs or opioid withdrawal symptoms); hepatic failure; past or present history of an AIDS-indicator disease; active hepatitis or aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal; known intolerance or hypersensitivity to naltrexone, carmellose, or polylactide-co-glycolide; psychosis, bipolar disorder, major depressive disorder with suicidal ideation, or present dependence on substances other than opioids or heroin, including alcohol; positive urine test for cocaine or amphetamines; and naltrexone use within the past 6 months.

Each site's independent ethics committee or institutional review board approved the protocol and participants gave written, informed consent in accordance with the Declaration of Helsinki.

Randomisation and masking

We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and sex with a centralised, permuted-block method with a block size of four. This system was also used to manage the supply of masked study drugs. Participants, investigators, staff, and the sponsor were masked to treatment allocation. To ensure masking, amber vials and syringes were used, and different personnel did counselling and data collection.

Procedures

Patients received an injection of XR-NTX or placebo within 1 week after detoxification and then every 4 weeks thereafter, for a total of six injections over 24 weeks. Participants were also offered 12 biweekly sessions of individual drug counselling, adapted for opioid dependence.[21] Psychologists or psychiatrists who were trained in individual drug counselling reviewed patients' substance use, recovery efforts, functioning, and adverse events, and provided support and advice to patients. Upon completion of the 24-week treatment period, all patients were offered open-label XR-NTX treatment for an additional year. All treatment was offered at no expense to patients. Urine drug testing for opioids (immunochromatography-based one-step in-vitro tests) was done weekly for 24 weeks and detected urine morphine and methadone at concentrations greater than 300 ng/mL.

The following drugs were prohibited during the study: naltrexone, buprenorphine, levacetylmethadol, methadone, other prescription opioids, antipsychotics, anticonvulsants, antidepressants, and anxiolytics. Permitted drugs were anticonvulsants if dosing was stable and short-acting insomnia drugs, such as zopiclone, as required.

The primary endpoint was the response profile for confirmed abstinence during weeks 5–24. We prospectively omitted weeks 1–4 from this endpoint because participants might challenge the blockade during this period, after which abstinence should stabilise.

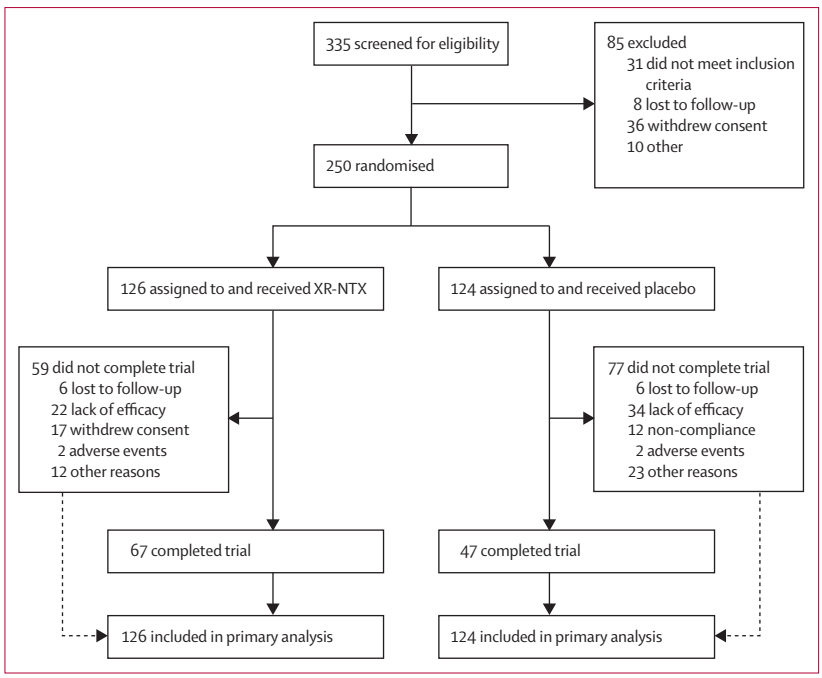

Figure 1: **Trial profile**
XR-NTX=extended-release naltrexone.

	XR-NTX (n=126)	Placebo (n=124)
Age (years)	29·4 (4·8)	29·7 (3·6)
Men	113 (90%)	107 (86%)
White	124 (98%)	124 (100%)
Duration of opioid dependence (years)	9·1 (4·5)	10·0 (3·9)
Days of pre-study inpatient detoxification	18 (9)	18 (7)
Opioid craving scale	18 (23)	22 (24)
HIV serology positive	51 (40%)	52 (42%)
Hepatitis C positive	111 (88%)	117 (94%)

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.

Table 1: **Demographics and baseline clinical characteristics**

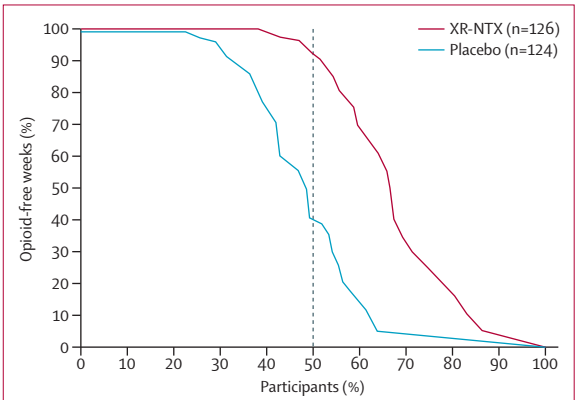

Figure 2: **Percent of confirmed opioid-free weeks (cumulative) among participants treated with XR-NTX compared with placebo**
XR-NTX=extended-release naltrexone.

Confirmed abstinence was defined as a negative urine drug test and no self-reported opioid use on the timeline follow-back (TLFB) survey.[22] The TLFB survey uses calendars and daily recall of substance use on specific days to record quantity or frequency of opioid use. Omission of any of these criteria resulted in failure to confirm abstinence for the week.

Secondary a-priori endpoints were self-reported opioid-free days according to the TLFB, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Because use of opioids might produce relapse to physiological opioid dependence, measurement of both opioid use and physiological dependence was important. Craving was assessed with a weekly self-report visual analogue scale (VAS) of need for opioids (scale 0–100, 0=not at all; 100=very much so).[23] Physiological dependence was assessed via naloxone challenge at baseline, upon any positive urine drug screen, at treatment discontinuation, and at week 24. Patients were removed from the study if the naloxone challenge test was positive, to protect the patient from the possibility of a prolonged precipitated withdrawal with XR-NTX. Other health outcomes that were also assessed included the HIV risk assessment battery,[24] the 36-item short form health survey (version 2),[25] patients' VAS assessments of their general health on the EuroQol-5 dimensions questionnaire,[26] and investigators' revised clinical global impression ratings.[27]

Safety was assessed by weekly monitoring of treatment-emergent adverse events, vital signs, biochemistry and haematology on urine and blood samples, including liver function tests, monthly physical examination of injection sites, and baseline and endpoint electrocardiographs.

Statistical analysis

Before the trial, we calculated that a sample size of 125 patients per treatment group would provide 85% and 96% power to detect an effect size of Cohen's d 0·4 and 0·5, respectively, by a Wilcoxon rank-sum test at a two-sided significance level of 0·05. Intent-to-treat analyses of efficacy endpoints were done with all randomised patients. We created response profiles by calculating the number of confirmed abstinence weeks for weeks 5–24 for each patient and then dividing by the number of scheduled tests (20). The response profile for each treatment group is the cumulative distribution function of percent of opioid-free weeks. For between-group comparisons we used a two-sided Van der Waerden test[28]—a non-parametric test of whether k population distributions are equal. To assess the effect of baseline characteristics, the rate of opioid-negative urine drug tests were analysed with ANCOVA, containing factors for treatment group, sex, and sex-by-treatment interaction, and with age, duration of opioid dependence, and duration of last pre-study inpatient detoxification as covariates. Consistency of the effects of treatment on opioid-free weeks across subgroups

	XR-NTX (n=126)	Placebo (n=124)	Treatment effect*	p value
Primary endpoint				
Proportion of weeks of confirmed abstinence	90·0% (69·9 to 92·4)	35·0% (11·4 to 63·8)	55·0 (15·9 to 76·1)	0·0002
Patients with total confirmed abstinence	45 (35·7%, 27·4 to 44·1)	28 (22·6%, 15·2 to 29·9)	1·58 (1·06 to 2·36)	0·0224
Secondary endpoint				
Proportion of self-reported opioid-free days over 24 weeks	99·2% (89·1 to 99·4)	60·4% (46·2 to 94·0)	38·7 (3·3 to 52·5)	0·0004
Craving: mean change in VAS score from baseline	−10·1 (−12·3 to −7·8)	0·7 (−3·1 to 4·4)	−10·7 (−15·0 to 6·4)	<0·0001†
Number of days of retention	>168‡	96 (63 to 165)	0·61 (0·44 to 0·86)	0·0042†
Participants with positive naloxone challenge test	1 (0·8%, 0·0 to 2·3)	17 (13·7%, 7·7 to 19·8)	17·3 (2·3 to 127·8)	<0·0001
Other outcomes				
Patients who completed double-blind treatment period	67 (53·2%, 44·5 to 61·9)	47 (37·9%, 29·4 to 46·4)	1·40 (1·06 to 1·85)	0·0171
Risk for HIV: mean change in behaviour scores from baseline	−0·187 (−0·224 to −0·150)	−0·130 (−0·173 to −0·087)	−0·057 (−0·113 to −0·001)	0·0212
Mean change from baseline in VAS self-ratings on EQ-5D	14·1 (9·6 to 18·7)	2·7 (−1·9 to 7·8)	11·4 (5·0 to 17·8)	0·0005
Proportion rated as much or very much improved on CGI	85·9% (77·8 to 94·0)	57·5% (45·7 to 69·5)	1·49 (1·19 to 1·87)	0·0002

Data are median (95% CI) or number (%, 95% CI), unless otherwise stated. XR-NTX=extended release naltrexone. VAS=visual analogue scale. EQ-5D=EuroQol-5 dimensions questionnaire. CGI=clinical global impression. *Difference between XR-NTX and placebo for location parameters and relative risk for proportions. Hazard ratio of early termination (Cox model) is shown for retention. †Adjusted for multiplicity by the Bonferroni-Holm method[29] to preserve family-wise type 1 error at 0·05. ‡95% CI cannot be calculated because median exceeds the study duration.

Table 2: **Clinical outcomes**

defined by baseline characteristics (sex, age, duration of opioid dependence, and duration of pre-study detoxification) and site was measured with ANCOVA models. Retention was assessed with Kaplan-Meier curves and a log-rank test. Changes from baseline in weekly craving scores were analysed with a generalised estimation equation model, assuming normal distribution and autoregressive correlation structure, with baseline craving as a covariate. For secondary endpoints, group differences were tested with the Van de Waerden test for continuous endpoints and χ^2 tests or Fisher's exact test for categorical endpoints. Adverse events were compared by Fisher's exact test.

Missing urine drug test results were imputed as positive for opioids; retention was censored upon discontinuation, craving was imputed using last observation carried forward, and missing TLFB data were imputed using patients' rates of opioid-free days during the 30 pre-detoxification days. For all other endpoints, all available data were included in analyses.

The primary endpoint was tested with a two-sided $\alpha=0\cdot05$. For craving and retention outcomes p values were adjusted for multiplicity using the Bonferroni-Holm method[29] to preserve family-wise type 1 error at 0·05.

A full statistical analysis was also done by an independent academic statistician who came to the same conclusions.

Role of the funding source

The sponsor designed the protocol in collaboration with participating investigators. The sponsor had the overall responsibility for the conduct of the study. Data were collected and monitored by Alkermes and PSI (Zug, Switzerland), a contract research organisation. Data were managed and analysed by Alkermes clinical and regulatory personnel, and staff at Cytel (Cambridge, MA, USA), and were interpreted by the authors with input from Alkermes clinical and statistical staff. The first author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between July 3, 2008, and Oct 5, 2009, 335 candidates were screened, 250 of whom were randomly assigned to XR-NTX or placebo (figure 1). Participants were predominantly young, white men (table 1) who had been addicted to heroin for about 10 years. High rates of HIV and hepatitis C infection were reported in the study population (table 1). In the 30 days before the first injection, heroin was used by 221 (88%) of 250 participants, methadone by 29 (12%), and other opioids or analgesics by 33 (13%). Demographic and baseline clinical characteristics showed no substantial inter-group differences (table 1).

Of 4285 urine drug tests and TLFB responses obtained, 4178 (97·5%) were in agreement. On 53 (1·2%) of 4285 occasions, participants self-reported using opioids despite opioid-negative urine tests. During weeks 5–24, there were 2098 of 5000 (42·0%) missing urine samples, 1255 (50·6%) of 2480 with placebo and 833 (33·1%) of 2520 with XR-NTX; 2096 of 2098 missing samples were because of early termination. Patients in the XR-NTX group received 1191 (99·7%) of 1194 scheduled counselling sessions (median 12; range 1–13) versus 922 (99·6%) of 926 for the placebo group (median 8; range 1–13).

The percentage of opioid-free weeks was significantly higher in the XR-NTX group than the placebo group (p=0·0002), with substantial separation between groups across all measured values of opioid-free weeks (figure 2). The median proportion of patients who had confirmed abstinence was higher in the XR-NTX group than the placebo group (p=0·0002; table 2). Total

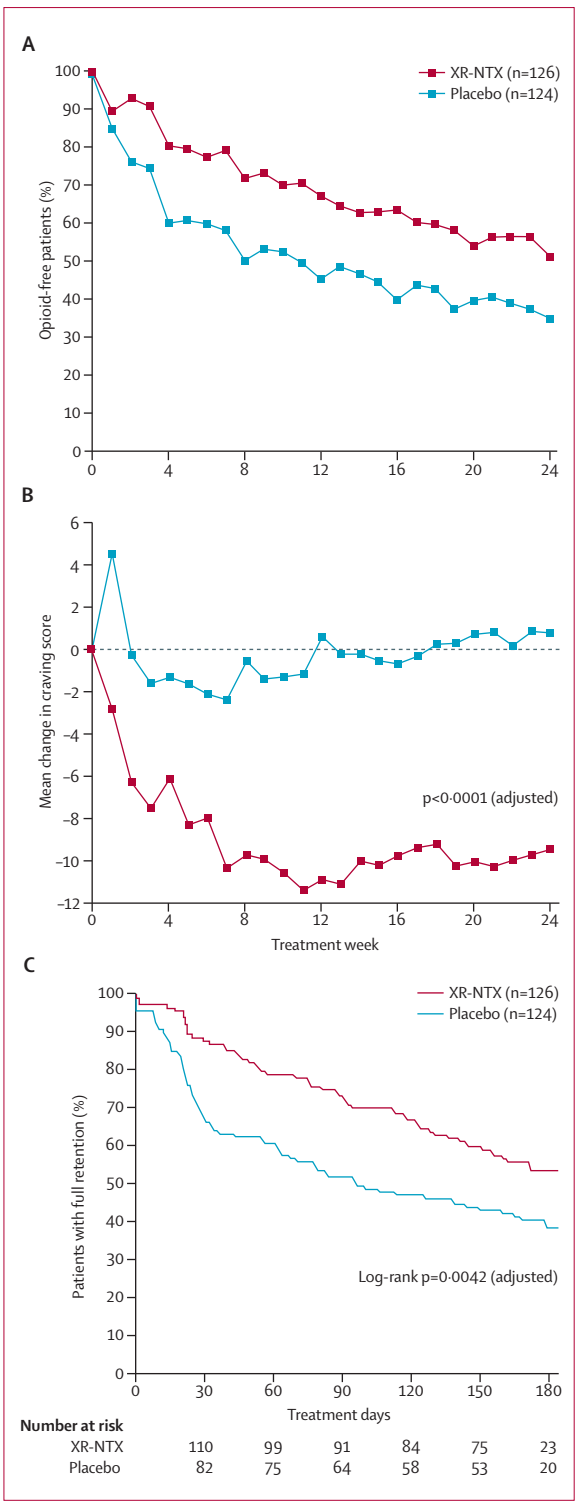

Figure 3: **Key secondary efficacy outcomes**
(A) Proportion of opioid-free patients by timeline follow-back self-report. (B) Mean change from baseline in craving. p value is based on a generalised estimating equation model assuming normal distribution and autoregressive correlation structure. (C) Time-to-discontinuation of study treatment. p values for analyses of craving (B) and retention (C) are adjusted for multiplicity. XR-NTX=extended-release naltrexone.

abstinence was reported in 36% of patients in the XR-NTX group compared with 23% in the placebo group (p=0·0224; table 2). When efficacy was analysed on the basis of the full 24-week period, including weeks 1–4, results were still significant (p=0·0001). 119 (94%) of 126 patients in the XR-NTX group were opioid free compared with 96 (77%) of 124 in the placebo group by week 2, and this separation persisted through to the end of the trial (figure 3). No significant relation was noted between age, sex, or duration of opioid dependence and the rate of opioid-free urine tests (data not shown). The treatment effect was consistent across baseline variables and study sites (data not shown).

All four secondary endpoints also showed significant differences between the treatment groups (table 2). Median self-report of opioid-free days over 24 weeks was 99% for the XR-NTX compared with 60% for the placebo group (p=0·0004; table 2; figure 3). There was a statistically and clinically significantly greater reduction in opioid craving in the XR-NTX group than the placebo group by week 8 (p=0·0048), which persisted every week through to week 24 (baseline to week 24: XR-NTX 18·2–8·8 *vs* placebo 21·8–22·5; p<0·0001, adjusted for multiplicity; table 2; figure 3). Median number of days of retention was 168 days (ie, still retained at the end of the study) in the XR-NTX group compared with 96 days for the placebo group (p=0·0042, adjusted for multiplicity; table 2; figure 3). All six injections were received by 73 (57·9%) of patients in the XR-NTX group compared with 52 (41·9%) of the placebo group (XR-NTX:placebo ratio 1·37, 95% CI 1·06–1·78; p=0·0171). Relapse to physiological opioid dependence was identified in one patient (who had missed two previous injections) in the XR-NTX group compared with 17 on placebo (p<0·0001; table 2).

Health outcome measures were similar between groups at baseline; however, the XR-NTX group had significantly greater improvement from baseline than placebo in reduction of HIV risk, increased general health, and investigators' clinical global impression improvement ratings. Baseline and post-treatment 36-item short form physical component summary scores were normal for both groups. The mental component score was well below US population norms (ie, score of 50) for both groups at baseline, but at study end the XR-NTX group (but not the placebo group) had normalised and was significantly better than placebo by 0·5 SD (mean 50·37 [SD 9·18] *vs* 45·28 [10·47]; difference 5·09, 95% CI 2·09–8·09; p=0·0043). Similar results were found on all four subscales, including vitality (58·13 [8·43]) and were similar to Russian normative population scores.[30]

XR-NTX was generally well tolerated; two patients in each group discontinued owing to adverse events (table 3). 103 (41%) of 250 patients experienced at least one adverse event; a higher proportion of patients in the XR-NTX group than the placebo group had at least one

	XR-NTX (n=126)	Placebo (n=124)	p value
Nasopharyngitis	9 (7%)	3 (2%)	0·14
Insomnia	8 (6%)	1 (1%)	0·036
Hypertension	6 (5%)	4 (3%)	0·75
Influenza	6 (5%)	5 (4%)	>0·99
Injection site pain	6 (5%)	1 (1%)	0·12
Toothache	5 (4%)	2 (2%)	0·45
Headache	4 (3%)	3 (2%)	>0·99
≥1 adverse event	63 (50%)	40 (32%)	0·005
≥1 drug-related adverse event	33 (26%)	12 (10%)	0·001
≥1 serious adverse event*	3 (2%)	4 (3%)	0·72
Discontinued owing to adverse events	2 (2%)	2 (2%)	..

Data are number (%). XR-NTX=extended-release naltrexone. *Three patients in the XR-NTX group reported four serious adverse events (infectious processes, eg, AIDS or HIV) and four patients in the placebo group reported five serious adverse events (two infectious, one drug dependence, one psychotic disorder, and one peptic ulcer).

Table 3: **Clinical adverse events**

adverse event (p=0·005). All non-serious adverse events were deemed mild or moderate by investigators and most were judged to be unrelated to the study drug. Serious adverse events were uncommon and no episodes of intractable pain management were reported. No overdose events, suicide attempts, or deaths, or other severe adverse events were reported.

The mean increase from baseline of alanine aminotransferase was 6·9 IU/L in the XR-NTX group and 5·6 IU/L in the placebo group, and for aspartate aminotransferase the mean increase from baseline was 3·8 IU/L in the XR-NTX group and 6·7 IU/L for placebo. Hepatic enzyme abnormalities were more common with XR-NTX (data not shown).

Discussion

Detoxified, opioid-dependent adults voluntarily seeking treatment who received XR-NTX had more opioid-free weeks than those who received placebo. Efficacy did not vary by age, sex, or duration of opioid dependence. There was a persistent anti-craving effect over weeks 8–24, 94% fewer naloxone-confirmed relapses to dependence, and nearly double the median length of retention in treatment in patients who received XR-NTX than those on placebo. Onset was rapid, with an anti-craving effect at week 1, an increase in abstinent days within 2 weeks, and improved retention at 1 month.

Although this study did not include a comparison with oral naltrexone, a meta-analysis of ten studies of oral naltrexone compared with placebo in multiple countries with 696 participants in total and a mean duration of 6 months did not find benefits for retention or prevention of relapse (panel).[13] Similarly, a study of oral naltrexone compared with treatment without naltrexone did not report an anti-craving effect,[31] whereas in the present study treatment with XR-NTX resulted in a rapid progressive decline in craving to 50% of baseline compared with no change with placebo. These differences might have been because oral naltrexone was self-administered daily and because XR-NTX has different release kinetics, which, compared with daily oral naltrexone, yields about four times the area-under-the-curve plasma concentration of naltrexone and reduced exposure to 6β-naltrexol.[32] Comparison of the present results with a small study of an injectable formulation of naltrexone are difficult because the previous study was only 8 weeks long, used a different psychosocial intervention, and was done in the USA.[16] However, both studies reported that extended-release, injectable naltrexone was superior to placebo for the outcome of opioid-negative urine.

XR-NTX was generally well tolerated and no new safety findings were reported. Adverse events of any kind were reported by half of patients in the XR-NTX group compared with a third of those in the placebo group; however, rates of discontinuations owing to adverse events and serious adverse events were similar in both groups. High baseline incidence of opioid dependence-related medical comorbidity, including hepatitis C and HIV infection, might have affected liver enzyme measurements. Abnormal liver function tests occurred only in patients with existing hepatitis C infection (data not shown). An FDA warning previously advised US providers of the occurrence of injection site reactions and the importance of proper injection technique; injection site pain was more prevalent in the XR-NTX group compared with the placebo group, although no severe adverse reactions were reported. No instances of intractable pain were reported, although patients with acute or chronic pain or anticipated pain episodes (eg, elective surgery) were excluded and study investigators were instructed in pain management alternatives to opioid analgesics. Previous studies have shown that the competitive blockade of naltrexone can be overcome: rats given XR-NTX, and then either hydrocodone or fentanyl at 10–20 times the usual doses achieved an analgesia response and did not have significant respiratory depression or sedation.[33]

A strength of this study was its geographic setting in Russia—one of the many countries where opioid agonist therapy is unavailable,[6] but where there is an alarming growth in availability of heroin and the fastest-growing HIV infection rate in the world.[34] The report of efficacy in these seriously ill patients is important both in Russia and as a model for the rest of the world. Patients included in this study share similarities with the opioid-dependent population in other countries, including relatively young age, predominantly male sex, and high rates of infection with HIV and hepatitis C. Nevertheless, given the population and treatment system differences, generalisability of these results beyond Russia is a topic for further research. However, in countries with a viable system of opioid agonist maintenance treatment, patient resistance

Panel: Research in context

Systematic review

In systematic reviews, opioid substitution treatment (buprenorphine and methadone) was effective in the treatment of opioid dependence,[8,9] but such agonist treatments are restricted or unavailable in many countries and might not be suitable for all patients. Systematic reviews of antagonist maintenance with oral naltrexone have generally reported the treatment to be ineffective because of poor adherence.[13]

Interpretation

In this study, once-monthly extended release naltrexone (XR-NTX) was superior to placebo with respect to the endpoints of confirmed abstinence, craving for opioids, retention, and prevention of relapse to opioid dependence. XR-NTX offers a new treatment option without risk of physical dependence or illegal diversion. This approach might aid community and cultural acceptance of opioid dependence pharmacotherapy.

to placebo treatment or ethical considerations might make it difficult to do a placebo-controlled trial. The extent of patient interest in XR-NTX when opioid substitution treatments are available remains a topic for future health services research; however, there might be interest among those whose employment prohibits opioid use, those with a relatively recent addiction to opioids, and those who wish to secure their recovery after a successful course of agonist therapy. In countries where both XR-NTX and opioid substitution treatments are available, the relative costs of such treatments might be an important factor in their clinical use and accessibility. Another strength of this study was the rigorous definition used for opioid abstinence, which included both self-report and urine testing. Furthermore, the imputation that patients who were lost to treatment represented treatment failures was a conservative interpretation that is consistent with the importance of treatment retention and abstinence.

There are several limitations of this study. There was a substantial clinical response to placebo; however, the treatment group still showed greater benefits than those in the placebo group. Retention in the placebo group might have been reduced by recognition upon opioid use that one was on placebo or—among patients in the placebo group who had relapsed to regular opioid use—by reluctance to return to the clinic and face a withdrawal reaction from a naloxone challenge test. Despite these possibilities, the placebo group showed a substantial retention and response profile, and a markedly higher rate of positive naloxone challenge tests. Drug use might have been under-reported on self-report; however, there was a high degree of agreement between results from urine tests and self-report and the urine data was a required confirmatory element of the primary efficacy measure. The high retention rate might have been influenced by the inclusion criterion that patients have someone available to supervise attendance, the provision of individual counselling, the absence of alternative treatments (eg, methadone or buprenorphine) in Russia, and the promise of active XR-NTX treatment for all patients after 6 months in the subsequent open-label extension safety study.

Additional research on the practical aspects of opioid antagonist treatment might support further improvement of patient outcomes.[35] Patients must be fully detoxified before receiving opioid antagonists to avoid precipitation of opioid withdrawal; thus, methods for antagonist induction and treatment transition need to be optimised. Studies are needed on the differential roles of agonist and antagonist maintenance therapies—eg, in early versus late stage illness, in the context of chaotic versus structured social supports, in patients with versus those without chronic pain, or in judicial or employment settings. The worldwide societal effects of this disease lend an urgency to the replication of these results and call for research into this treatment approach in different countries and settings, such as primary-care offices; in different populations, including those that might be less compliant than the patients included in this study; and on the appropriate duration of treatment, long-term benefits and safety, and the health economic and policy aspects.

The results of this study suggest that XR-NTX offers a new approach—distinct from opioid-agonist maintenance—that assists patients in abstaining from opioids and prevents relapse to opioid dependence. Given the heterogeneity of patient needs, to provide optimum care for patients who are opioid dependent, a comprehensive set of treatment options is needed, including existing agonist maintenance treatments, which are well validated both in efficacy and effectiveness research[7–10] and psychosocial management. The findings of the present study suggest that antagonist therapy could also play a part. A once-monthly supervised pharmacological treatment with proven efficacy that is free of physical dependence and is not subject to illegal diversion might aid community and cultural acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

Contributors

EK had full access to the original data, reviewed the data analyses, contributed to data interpretation, wrote the first draft of the manuscript, made final decisions on all parts of the report, and approved the final version of the submitted report. All other authors had access to the data used in the paper and additional data when requests were made and wrote the final draft. EK, EVN, AI, DRG, and BLS designed the study. EK enrolled patients. AI did the statistical analyses and generated tables and figures. EK, DRG, and BLS provided study supervision and administrative support.

Conflicts of interest

The Medisorb preparation used in XR-NTX was developed with support from the National Institute on Drug Abuse (grant R43DA013531) and National Institute on Alcohol Abuse and Alcoholism (grant N43AA001002). EK is a consultant for Alkermes and received research funding for this study from Alkermes. EVN was a member of the

Alkermes advisory board that designed this trial and was an unpaid consultant to an expert panel convened by Alkermes, with approval from the Columbia University Department of Psychiatry. WL has been an advisory board member for Alkermes and US World Med, has received research funding from Titan Pharmaceuticals, investigator initiated research funding from Hythiam, and research support, an unrestricted educational grant, and speaker support from Reckitt Benckiser. AI, DRG, and BLS are full-time employees of Alkermes.

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Article

Naltrexone Implant for the Treatment of Polydrug Dependence: A Randomized Controlled Trial

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Objective: The majority of drug addicts are polydrug dependent, and no effective pharmacological treatment is currently available for them. The authors studied the overall real-world effectiveness of naltrexone implant in this patient population.

Method: The authors assessed the effectiveness of a naltrexone implant in the treatment of coexisting heroin and amphetamine polydrug dependence in 100 heroin- and amphetamine-dependent outpatients in a 10-week randomized, double-blind, placebo-controlled trial. The main outcome measures were retention in the study, proportion of drug-free urine samples, and improvement score on the Clinical Global Impressions Scale (CGI). Analyses were conducted in an intent-to-treat model.

Results: At week 10, the retention rate was 52% for patients who received a naltrexone implant and 28% for those who received a placebo implant; the proportions of drug-free urine samples were 38% and 16%, respectively, for the two groups. On the CGI improvement item, 56% of the patients in the naltrexone group showed much or very much improvement, compared with 14% of those in the placebo group (number needed to treat=3).

Conclusions: Naltrexone implants resulted in higher retention in the study, decreased heroin and amphetamine use, and improved clinical condition for patients, thus providing the first evidence of an effective pharmacological treatment for this type of polydrug dependence.

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During the past four decades, the only substantially effective treatment for opioid dependence has been the substitution of another opioid for the initial opioid of abuse (1). This approach aims to reduce harm by replacing intravenous use of heroin with orally administered methadone or buprenorphine. Although such substitution therapy has resulted in a reduction of harm related to illicit drug use, such as crime and the spreading of HIV and hepatitis C (2–4), it has also caused severe problems. For example, in several countries, such as Finland, Georgia, and Mauritius, the vast majority of all opioid-dependent individuals now inject illicitly sold buprenorphine or buprenorphine-naloxone instead of heroin (5–7), which has also led to increased incidences of opioid dependence. Therefore, the misused treatment has occasionally become a bigger problem than the heroin use had been.

Naltrexone is an opioid receptor antagonist that has been used for the treatment of both alcohol and opioid dependence (1, 8–11). However, oral naltrexone has proved ineffective in the treatment of opioid dependence because of poor treatment adherence (1). Five recent randomized controlled trials indicate that naltrexone implant (12–14) and depot injection (15, 16) may be the first effective, nonaddictive pharmacological treatments for heroin dependence in patients who have no other coexisting drug dependence. However, the majority of drug addicts are polydrug dependent (17), and thus the real-world effectiveness of long-acting naltrexone formulations is unknown. Moreover, no effective pharmacological treatment is currently available for polydrug dependence (18). In this patient population, treatment with naltrexone might be useless in reducing drug-related harm if the putative compensatory increase in stimulant use outweighs the decrease in opioid use. Oral naltrexone has been reported to decrease amphetamine use compared with placebo (19) in selected amphetamine-dependent patients. Thus, naltrexone might also be a potential treatment for polydrug dependence, even in real-world settings, if the problem of treatment adherence could be solved. We studied the real-world effectiveness of a naltrexone implant in the treatment of heroin-amphetamine polydrug dependence.

This article is featured in this month's AJP Audio, is discussed in an Editorial by Dr. Penetar (p. 455), and is an article that provides Clinical Guidance (p. 536)

Method

Study Design

The trial was conducted at the St. Petersburg State Pavlov Medical University, Russia, and its affiliated hospital, Leningrad Regional Addiction Hospital. The recruitment of patients began in March 2008, and the study was completed in February 2011. An interim analysis of the first 50 patients was conducted to evaluate the putative harms and benefits of the interventions. Since no harmful effects were observed to be associated with the active treatment, the study was continued as planned. One hundred patients having coexisting amphetamine and opioid dependence (confirmed by a positive urine sample) were randomly assigned, in a 1:1 ratio in a double-blind protocol, to receive a naltrexone depot implant (N=50) or a placebo implant that was identical in appearance (N=50). A sample size of 100 was considered sufficient to reveal significance of an effect size of medium magnitude (20). Randomization was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial (E.V.). The study was approved by the Independent Ethical Committee of St. Petersburg State Pavlov Medical University.

Patients

The inclusion criteria were a primary DSM-IV diagnosis of concurrent amphetamine and opioid dependence, present for at least 1 year; age between 18 and 50 years; education level of high school graduate or above; negative urine toxicology and alcohol breath tests; no current use of psychotropic medications; at least one relative willing to participate in the treatment (e.g., to monitor the administration of medications, assist in follow-up, and provide outcome data); a stable address in St. Petersburg or in the nearest districts of Leningrad Region; a home telephone number at which the patient could be reached; willingness and ability to give informed consent and otherwise participate; and, for women of childbearing age, a negative pregnancy test and use of adequate contraception.

The exclusion criteria were clinically significant cognitive impairment, schizophrenia, a paranoid disorder, bipolar disorder, or a seizure disorder; advanced neurological, cardiovascular, renal, or hepatic disease; active tuberculosis; a current febrile illness; an AIDS-defining illness; a significant laboratory abnormality, such as severe anemia, unstable diabetes, or liver function test results greater than three times normal values; pregnancy; pending legal charges with potential impending incarceration; concurrent participation in another treatment study; and concurrent treatment in another substance abuse program.

Procedure

Treatment medication was labeled according to the randomization list, and all individuals involved with the clinical phase of the trial were blind to the intervention. Patients were examined by a psychiatrist at the beginning of the study and at visits throughout treatment. Psychiatrists who were trained in individual drug counseling (E.B., O.M.) enrolled the patients, assigned them to interventions, reviewed their substance use, recovery efforts, functioning, and adverse events, and provided them with psychological support and advice. Patients had to provide an opioid-negative urine sample and undergo a naloxone challenge test, after which they received the surgical naltrexone implant. This sustained-release naltrexone preparation (Prodetoxon) has been approved in the Russian Federation for preventing relapse to opioid dependence. Prodetoxon is a composite subcutaneous implant prepared in a cylinder that is 18 mm long and 8.5 mm in diameter. It contains 1000 mg of naltrexone and blocks opioid effects for 8–10 weeks. Patients gave urine samples (the pH of the urine was measured) once a week, under supervision, for up to 70 days (10 weeks). The cutoff for heroin-free urine was 300 ng/mL of morphine. With this procedure, heroin can be detected for up to 3–4 days after use, which may result in missing occasional heroin use in weekly urine tests. Opioid and amphetamine use was also assessed by self-reported use on the timeline follow-back survey (21). The severity of the addiction at baseline was measured by the Addiction Severity Index (22). Other health assessments included the HIV Risk Assessment Battery (23), visual analogue scales of craving for opioids and amphetamine, the Clinical Global Impressions Scale (CGI), and the Global Assessment of Functioning Scale (GAF). Safety was assessed by weekly monitoring of treatment-emergent adverse events, with vital signs and biochemistry and hematology of urine and blood samples, which included liver function tests. Adverse events were assessed through open questions during the weekly visits. At week 10, participants' relatives were contacted by telephone to investigate outcomes (including mortality) among patients who dropped out.

Outcomes

The primary outcomes assessed were retention in the study, proportion of urine samples that were free of both amphetamine and opioids during the treatment (missing samples were considered positive for both drug classes), and improvement on the CGI during treatment.

The secondary outcomes assessed were proportion of opioid-free urine samples during treatment (missing samples were considered opioid positive), proportion of amphetamine-free urine samples during the treatment (missing samples were considered amphetamine positive), GAF score, number of days per week that amphetamine was used during treatment, craving for opioids and amphetamine, and adverse events.

The study protocol was updated on December 22, 2009, for several reasons. Because of new legislation in Russia prohibiting the export of any biological samples to Finland, the quantitative amphetamine analyses could not be done in the laboratory of the National Public Health Institute, Helsinki. Also, funding was not sufficient for us to perform naloxone challenge tests to evaluate opioid dependence. Under these circumstances, we decided to use conventional urine tests to measure opioid and amphetamine use (our primary outcome measure). The updated protocol also included the addition of retention in the study and CGI improvement score as primary outcome measures (retention in the study and the patients' general well-being are considered the most important indicators of the effectiveness of the treatment in drug addiction trials). For the secondary outcomes, the update added adverse events and excluded cannabis and benzodiazepine use, since it had become evident that their use was not sufficiently common in the study population. The original sponsor, the National Research and Development Centre for Welfare and Health (Finland), merged with the National Public Health Institute on January 1, 2009, and the organization became the National Institute for Health and Welfare; thus, the name of the sponsor changed in the update. Finally, the start and end dates were delayed from the anticipated dates.

Statistical Analysis

The results were analyzed in an intent-to-treat model in which missing urine samples were classified as drug positive. Categorical variables were analyzed with the chi-square test or Fisher's exact test and continuous variables with the t test or Mann-Whitney U test, depending on the validity of distributional assumptions. Data management and analyses were conducted with SPSS, version 17.0 (SPSS, Inc., Chicago), and StatCalc (www.acastat.com). For patients lost to follow-up, the change in the CGI improvement score was defined as the change between baseline (week 0) and the last available observation.

TABLE 1. Baseline Characteristics of Opioid-Amphetamine Polydrug-Dependent Patients Treated With Naltrexone or Placebo Implant[a]

	Placebo (N=50)		Naltrexone (N=50)	
Characteristic	Mean	SD	Mean	SD
Age (years)	29.3	4.38	28.0	4.10
Duration of heroin addiction (years)	8.7	2.83	8.2	3.75
Duration of amphetamine addiction (years)	5.6	2.62	5.6	3.11
Amphetamine use (days per month)	24.3	14.35	27.4	13.50
Heroin use[b] (g/day)	1.0	0.64	0.9	0.49
Alcohol[b] (g/day)	6.8	10.18	8.2	10.11
Craving for heroin[c]	39.7	32.17	44.2	34.08
Craving for amphetamine[c]	45.0	28.77	47.5	31.39
Addiction Severity Index				
Medical status	0.09	0.085	0.11	0.085
Work	0.81	0.23	0.82	0.25
Opiates	0.24	0.085	0.24	0.091
Amphetamine	0.19	0.11	0.18	0.091
Legal status	0.06	0.078	0.07	0.071
Family	0.25	0.18	0.25	0.16
Drug HIV risk behavior[d]	9.14	3.73	10.34	4.48
Sexual HIV risk behavior[d]	5.22	2.72	5.76	2.92
Global Assessment of Functioning Scale score	66.4	7.92	67.8	7.64
Alanine aminotransferase (ALT) (U/L)	39.9	23.54	34.2	20.79
Aspartate aminotransferase (AST) (U/L)	57.0	29.76	50.0	17.39

[a] There were no significant differences between groups on any variable.
[b] Based on self-report on the timeline follow-back survey.
[c] Craving was assessed with a weekly self-report visual analogue scale of the need for opioids or amphetamine (scale ranges from 0 to 100; 0=not at all, 100=very much so).
[d] HIV risk behavior was measured with the HIV Risk Assessment Battery.

Results

The CONSORT flow diagram of the study is presented in Figure S1 in the online data supplement that accompanies the online edition of this article. The main baseline clinical measures are listed in Table 1; no statistically significant differences were observed between the two treatment groups. Most patients were men; the naltrexone arm included four women (8%), and the placebo arm included seven (14%). HIV status was available for 86 patients; in the placebo arm, 77% (34/44) were HIV positive, and in the naltrexone arm, 48% (20/42) were HIV positive (χ^2=8.09, df=1, p=0.004). Fifteen patients (30%) in the naltrexone group used marijuana, and 13 (26%) in the placebo group did so. The use of sedatives was rare in this sample (none in the naltrexone arm, and one in the placebo arm). The mean consumption of alcohol was only 7.5 g/day (SD=9.9) for the total study population, and therefore the putative reduction was not studied.

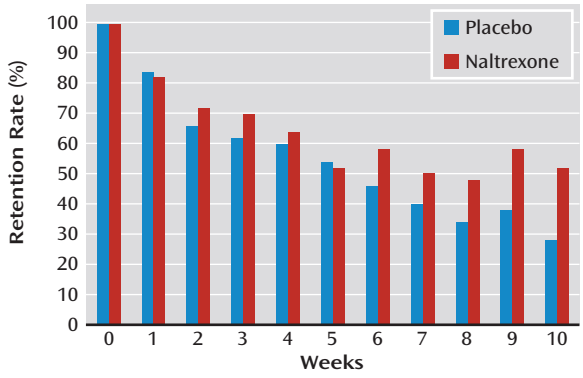
Primary Outcome Measures

Retention in the study is illustrated in Figure 1. At week 10, the retention rate was 52% (N=26) for the naltrexone group and 28% (N=14) for the placebo group (χ^2=6.00, df=1, p=0.01). The proportion of drug-free urine samples was 38% (N=19) in the naltrexone group and 16% (N=8) in the placebo group (χ^2=6.14, df=1, p=0.01). The changes in the CGI improvement score indicating the difference in treatment effect are summarized in Table 2. The naltrexone arm showed a substantially greater treatment effect than the placebo arm, with 56% of naltrexone patients showing much or very much improvement according to the CGI, compared with only 14% of the placebo patients (χ^2=19.4, df=1, p<0.001; number needed to treat=3, 95% CI=2–4).

Secondary Outcome Measures

At week 10, patients in the naltrexone group had significantly more heroin-free urine samples (52% compared with 20%; χ^2=11.1, df=1, p<0.001) and more amphetamine-free urine samples, although the difference fell short of significance (40% compared with 24%; χ^2=2.94, df=1, p=0.09). In the weekly urine analyses, a statistically significant difference in heroin-free samples was also observed at week 6 (χ^2=8.1, df=1, p=0.005), at week 8 (χ^2=4.3, df=1, p=0.04), and at week 9 (χ^2=4.2, df=1, p=0.04), with patients in the naltrexone arm having more heroin-free samples. No statistically significant differences were observed in amphetamine-free urine samples. At week 10, the mean number of amphetamine use incidents (times/week) was 4.5 times in the naltrexone group and 5.7 times in the placebo group (Mann-Whitney U test=1030.5, p=0.06). The rating of subjective effects of amphetamine was available for 18 patients in the placebo group and 22 patients in the naltrexone group. Fifteen patients in the placebo group (83.3%) and three in the naltrexone group

FIGURE 1. Study Retention Among Opioid-Amphetamine Polydrug-Dependent Patients Treated With Naltrexone or Placebo Implant During the 10-Week Treatment Period[a]



[a] At week 10, retention was 52% (26/50) for patients in the naltrexone group, compared with 28% (14/50) for patients in the placebo group (significantly different at p=0.01). Since patients were permitted to continue in the trial despite missing previous visits, the retention rate increased at weeks 6 and 9, when patients who missed visits the previous week resumed participation.

(13.6%) reported full effect for amphetamine use, indicating that naltrexone suppressed the euphoric effect more than did placebo (p<0.001, Fisher's exact test). The mean GAF scores at week 10 were 82.0 for the naltrexone group (N=20) and 71.9 for the placebo group (N=28) (Mann-Whitney U test=145.5, p=0.004), indicating a better outcome among patients receiving naltrexone.

Craving for opioids or amphetamine, as well as HIV-drug and HIV-sex risk behaviors, decreased in both groups over the study period (Figure 2). However, no significant differences in craving, for either opioids or amphetamine, were observed between the groups.

Adverse Events

Adverse events are listed in Table 3. No severe adverse events were reported, and no significant differences were observed between groups. No significant differences were seen between groups in change in the alanine aminotransferase (ALT) level from baseline to week 10 (from 39.9 U/L to 36.2 U/L for the placebo group compared with 34.2 U/L to 30.3 U/L for naltrexone group; reference range, 10–45 U/L for females and 10–70 U/L for males), but the aspartate aminotransferase (AST) level decreased in the naltrexone group (N=13) and increased in the placebo group (N=26) (from 50.0 U/L to 48.7 U/L in the naltrexone group and from 57.0 U/L to 65.0 U/L in the placebo group; reference range, 10–35 U/L for females and 10–45 U/L for males; difference between groups, Mann-Whitney U test=92, p=0.02). All patients or their relatives were contacted by telephone at the end of the study. All patients in the study were alive at week 10.

Discussion

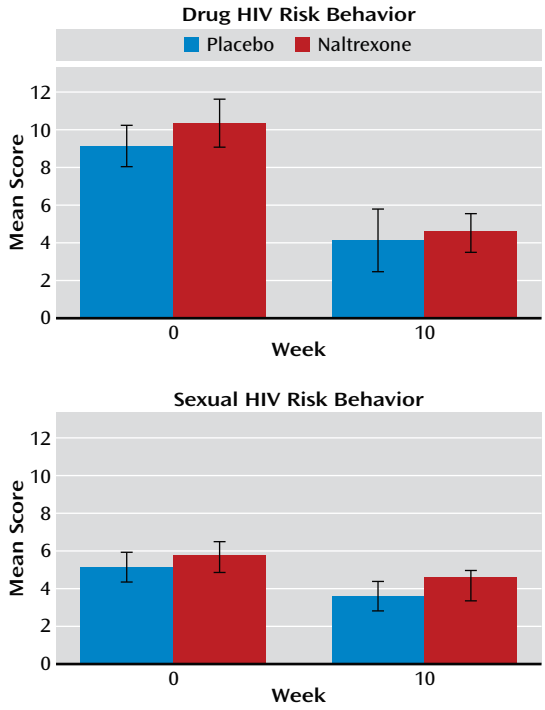
Our results show that relative to placebo, the naltrexone implant resulted in higher retention in the study, decreased heroin and amphetamine use, and improved clinical condition of patients, thus providing the first evidence of an effective pharmacological treatment for this type of polydrug dependence. Because the majority of drug-dependent patients use more than one drug (17), treatment of only one dependence, such as intravenous heroin use by oral methadone or buprenorphine, would not be sufficient for injection-related harm reduction if the patient continued to inject other drugs, such as amphetamine. Since long-acting naltrexone effectively decreases opioid use, it might lead to compensatory increases in the use of nonopioid drugs, such as amphetamine, among polydrug-dependent patients, resulting in zero net benefit. However, our results indicate that this is not the case. The effectiveness of polydrug dependence treatment with naltrexone implants or depot injections should be studied and confirmed in other patient populations who use combinations of heroin, buprenorphine, amphetamine, and cocaine. Preliminary evidence from a study by Comer et al. (15) suggests that naltrexone depot formulations might have a beneficial effect on cocaine abuse and even on cannabis and benzodiazepine abuse. This suggests that the opioidergic system may be the common pathway for the effects of all these drugs of abuse. A recent meta-analysis that included 10 randomized controlled trials comparing oral naltrexone and placebo detected no beneficial effect on retention or relapse rates for opioid-dependent patients (24). However, a significant treatment effect was observed in a Swedish study (19) that compared oral naltrexone and placebo in the treatment of amphetamine dependence in selected and highly motivated patients (more than 70% of the assessed individuals were excluded from the study). In the present study, our sample was a typical treatment-seeking patient population (only 16% of assessed individuals were excluded), which suggests that our results reflect the real-world effectiveness of the naltrexone implant treatment. The duration of our trial was 10 weeks, which is a short period when considering the chronic nature of concurrent opioid and amphetamine dependence. It is likely that in clinical practice, patients

TABLE 2. Change From Baseline in Clinical Global Impression Scale Improvement Score in Opioid-Amphetamine Polydrug-Dependent Patients Treated With Naltrexone or Placebo Implant[a]

	Placebo (N=50)		Naltrexone (N=50)	
Rating	N	%	N	%
Much improved	7	14	28	56
Moderately improved	11	22	6	12
Minimally improved	8	16	6	12
No change	24	48	10	20

[a] The proportion of patients with much improvement was substantially greater in the naltrexone arm than in the placebo arm (χ^2=19.4, df=1, p<0.001). The evaluations were done at week 0 and week 10 among those patients who completed the study per protocol, and at week 0 and the last visit among those stopping the study prematurely. If the patient could not be evaluated after week 0, the change was rated as "no change."

FIGURE 2. Drug and Sexual HIV Risk Behavior



should be treated with several successive implants in 2- to 3-month intervals to achieve long-term recovery from dependence.

The naltrexone implant was generally well tolerated. It was not associated with increased levels of ALT or AST, and it was actually associated with a reduction in AST levels compared with placebo. Two patients (4%) experienced mild surgical side effects. The implant used in this study results in naltrexone serum levels of around 2 ng/mL for 10 weeks, which is somewhat higher than levels provided by the currently available depot injection (Vivitrol) during 4-week injection intervals (25). Vivitrol has been shown to be effective for the treatment of heroin dependence, and on the basis of the results of our previous trial (16), it was recently approved by the U.S. Food and Drug Administration for the treatment of opioid dependence. However, whether it is also effective for the treatment of amphetamine dependence is unknown.

It has been suspected that oral naltrexone treatment could lead to an increased risk of death due to accidental overdose (26). However, a large follow-up study (27) that included all patients in Western Australia starting methadone (N=553) or naltrexone implant (N=341) found that naltrexone implant was associated with a slightly lower age-standardized mortality rate ratio compared with methadone (0.65, 95% CI=0.12–1.17). This suggests that while oral naltrexone may be ineffective in treating opioid dependence, because of low treatment adherence and the increased risk of concomitant opioid overdose, a naltrexone implant is at least as safe as methadone. In our study, no deaths were reported in the survey of all patients at the end of the study.

TABLE 3. Adverse Events in Opioid-Amphetamine Polydrug-Dependent Patients Treated With Naltrexone or Placebo Implant[a]

Event	Placebo (N=50)	Naltrexone (N=50)
Surgical implantation	0	2
Diarrhea	0	3
Nervousness	1	0
Insomnia	3	3
Fatigue	1	1
Irritability, nervousness	2	2
Dry mouth	1	0
Loss of appetite	1	2

[a] No significant differences between groups.

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Dr. Tiihonen has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon, has received fees for giving expert opinions to Bristol-Myers Squibb and GlaxoSmithKline, and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, and Pfizer. Dr. Krupitsky has served as a consultant to Alkermes. The other authors report no financial relationships with commercial interests.

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Clinical Guidance: Implantable Naltrexone for Mixed Heroin-Amphetamine Dependence

A placebo-controlled study of 100 outpatients with mixed heroin-amphetamine addiction showed that implanted naltrexone, designed to block opiate effects for 8–10 weeks, led to 52% of patients remaining in treatment and 38% having urine samples free of both drugs at 10 weeks, compared to 28% remaining and 16% drug free for the placebo implant. Tiihonen et al. report that use of other substances, such as alcohol, did not increase. The number needed to treat, i.e., number of patients who have to be treated for one to benefit, was three. In an editorial, Penetar (p. 455) points out that a puzzling aspect of the study is that craving decreased in both treated and placebo groups, even though remission rates differed. Naltrexone did decrease euphoria in patients who continued to use amphetamine.

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Naltrexone Implants Compared to Methadone: Outcomes Six Months after Prison Release

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Key Words
Prison release · Relapse · Methadone · Naltrexone implants · Heroin

Abstract
Background: After prison release, offenders with heroin use problems are at high risk of relapse and overdose death. There is a particular need for treatments that can be initiated in prison and continued after release into the community. Methadone maintenance treatment has been shown to reduce heroin use, criminality and mortality. Naltrexone implant treatment has not previously been evaluated in prison settings. ***Methods:*** This study compares the effects of naltrexone implants and methadone treatment on heroin and other illicit drug use, and criminality among heroin-dependent inmates after release from prison. ***Results:*** Forty-six volunteers were randomly allocated to naltrexone implants or methadone before release. Intention-to-treat analyses showed reductions in both groups in frequency of use of heroin and benzodiazepines, as well as criminality, 6 months after prison release. ***Conclusions:*** Naltrexone implants may be a valuable treatment option in prison settings.

Introduction

In prison populations throughout the world, substance use disorders are over-represented compared to the general population. Studies from several countries have found that between 60 and 70% of inmates report drug use before incarceration [1, 2]. Access to specialised substance abuse treatment in prisons is limited and further evaluations of the effectiveness of programmes are needed [3–5].

For treatment of opioid dependence, methadone maintenance is an effective treatment and has become widely available in the community during the last four decades [6]. Methadone maintenance in the community reduces heroin and polydrug use, mortality and crime [7–10]. Until recently, prison-based methadone programmes were scarce, but they are now being increasingly implemented in criminal justice settings [11].

A different approach to preventing relapse to heroin use involves naltrexone treatment, an opioid receptor antagonist developed by the National Institute on Drug Abuse in the 1970s [12, 13]. Studies on oral naltrexone treatment in criminal justice settings have shown re-

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duced heroin use and crime [14–16]. In spite of these promising results, an important limitation of oral naltrexone treatment in community settings has involved high treatment attrition and low medication compliance rates [17, 18].

Sustained-release naltrexone as a depot or implant formulation may offer one option to overcome these compliance issues [19–21]. Naltrexone depot and implant treatment has been found to lead to reduced heroin use and mortality [22–24]. Recently, a number of papers have reviewed the possible beneficial effects of sustained-release naltrexone for criminal justice populations [25–28]. However, trials of sustained-release naltrexone in criminal justice settings are still lacking. After release from prison, drug-involved offenders are at high risk of rapid relapse to drug use [29, 30] and are more likely to commit new crimes than other offenders [31]. Thus, prison-based substance abuse treatment should extend beyond release. Continuity of care when treating drug-involved offenders is regarded as crucial and should be emphasized in any prison-based treatment effort [32–34].

The present study investigates naltrexone implants compared to methadone treatment in an opioid-dependent inmate population. The objectives were to initiate treatment before prison release, and to investigate effects in terms of heroin use, non-opioid drug use and criminal activity after release from prison. This paper reports drug use and criminal recidivism outcomes for the 6-month period after prison release.

Methods

Participants

This study was a 2-arm, open-label trial comparing randomly allocated naltrexone implants with methadone. Treatments were initiated among inmates prior to release from prison. Participants were recruited from 4 prisons for male and 1 for female inmates. First contact was established through prison staff, prison health services or self-referral. Inclusion criteria were pre-incarceration heroin dependence and at least 2 months sentence time remaining. Individuals were excluded if they presented with untreated major depression or psychosis, severe hepatic impairment, or if they were already in agonist maintenance treatment or pregnant. Eligibility criteria were assessed by trained interviewers according to DSM-IV diagnostic criteria with the Mini-International Neuropsychiatric Interview (M.I.N.I. Plus) [35]. First follow-up was scheduled at 6 months after prison release.

Procedures

Participants initiated treatment about 1 month before release. Participants received 20 pellet naltrexone implants, which were previously shown to release naltrexone for 5–6 months [36–38]. Methadone induction started at 30 mg per day and the recommended daily dose of 80–130 mg was reached typically during a period of 3 weeks. Methadone treatment was provided according to the WHO guidelines [39] and the standard Norwegian programme regulations free of charge. An evaluation of the Norwegian high-threshold methadone programme has been published in a previous paper [40]. All participants were free to seek additional support such as inpatient institution treatment, outpatient psychotherapy or Narcotics Anonymous. Regular individual meetings for counselling with social services, a general practitioner and other drug treatment providers were encouraged.

Outcomes were heroin use, days to heroin relapse, use of illicit non-opioid drugs, treatment retention and criminal activity. Outcomes were assessed by trained interviewers with the European version of the Addiction Severity Index [41]. At baseline, it was explicitly stated that the periods 'during the last 6 months' and 'during the last 30 days' applied to the time prior to incarceration.

At 6 months follow-up, heroin use was additionally assessed by timeline follow-back for each month after release [42]. Cumulative numbers of days used (0–180) were then standardised to the number of days used during those months spent outside of prison, resulting in values between 0 and 30 days. Heroin use of 7 or more days per month was defined as relapse. In case of re-incarceration during the follow-up period, drug use was reported for the preceding time. Data on days re-incarcerated in any Norwegian prison during the follow-up period was provided by the Correctional Services.

Participants were randomly allocated to open-label treatment. Prior to trial enrolment, the random treatment allocation sequence was generated by a statistician from an independent centre for clinical research using a permuted block protocol. The treatment sequence was concealed until baseline assessment in sequentially numbered opaque envelopes sealed by study-independent staff. The treatment condition was then randomly assigned during baseline assessment.

Statistical Analyses

Intention-to-treat analyses were performed on the randomised sample. This was done regardless of medication initiation or treatment retention. Missing data at follow-up was replaced with baseline observations on the assumption of relapse. A mixed between-within subjects analysis of variance (ANOVA) on outcomes was performed to assess time and group effects. Outcome measures in the two completer groups were compared with t tests or non-parametric statistics if the assumption of normal distribution was violated. Survival analyses of time to heroin relapse were based on timeline follow-back data and performed using the Kaplan-Meier method [43]. For the intention-to-treat analyses, missing data was replaced on the assumption of relapse on day 1 after prison release. The survival analyses were repeated without replaced data. Group differences were assessed by the Mantel-Cox (or log-rank) test. Statistical analyses were performed using SPSS for Windows version 16.

Ethics and Approvals

Prison inmates are afforded special human rights protection when participating in clinical research [44]. In our study, all participation was voluntary and independent of decisions by the criminal justice system regarding terms of sentence or release

Table 1. Drug use and criminal activity before imprisonment and 6 months after release, intention-to-treat

	Naltrexone group		Methadone group		Effect of time, p value
	before imprisonment	at follow-up	before imprisonment	at follow-up	
Heroin	27.8 (4.96)	15.6 (14.97)	25.0 (9.18)	20.2 (12.56)	<0.001
Benzodiazepines	14.5 (11.69)	11.9 (10.96)	15.9 (12.48)	9.9 (10.97)	0.010
Amphetamines	11.0 (12.90)	10.5 (11.08)	9.5 (11.91)	8.0 (10.45)	0.617
Criminal activity	20.3 (12.11)	14.9 (12.34)	18.5 (12.15)	14.4 (13.11)	0.009

Values indicate mean days per month (SD).

date. All inmates were systematically granted confidentiality and offered the possibility of refusing further participation at any stage. The study was approved by the Norwegian Regional Committee for Medical Research Ethics, the Norwegian Correctional Services and the Norwegian Medicines Agency. Beginning in January 2006, a protocol amendment allowed for compensating participants who met for follow-up with ca. EUR 38. No other incentives or compensation were used. The study was funded by the Research Council of Norway and registered publicly at http://clinicaltrials.gov, identifier NCT00204243.

Results

Prior to recruitment, 111 eligible inmates were screened: 65 refused the offer of participation. Of the 46 volunteers, 43 were men and 3 were women. One male inmate from each treatment group withdrew consent before treatment initiation. Thus, the final sample for the intention-to-treat analyses comprised 44 individuals. Twenty-three inmates were randomly allocated to receive naltrexone implant treatment and 21 were allocated to receive methadone. The mean age at study inclusion was 35.1 years (SD 7.0). The mean age at which the participants commenced using heroin regularly was 23.4 years (SD 6.6). Most participants (86.4%) were regular polydrug users. They had spent a mean of 5.0 years (SD 4.2) in prison during their lifetime and 36.4% were homeless before the current sentence. Their current sentence length was on average 9.4 months (SD 5.4). There were no differences in these personal and social demographic characteristics between the two treatment groups. The mean time to follow-up was 167 days (SD 22.1). Participants in the naltrexone group were followed up between 160 and 197 days after the start of treatment. Participants in the methadone group were followed up between 169 and 227 days after prison release.

Treatment acceptance, initiation and dropout differed between the two groups for several reasons. Before random allocation, 43% of the sample reported that methadone would have been their preferred treatment, 34% reported that their preferred intervention would have been naltrexone implant treatment, and the remaining 23% expressed no preference for either treatment. In the naltrexone implant arm of the trial, 7 of 23 inmates did not initiate treatment: all 7 reported a preference for methadone or a non-study treatment. In the methadone treatment arm, 10 of 21 inmates did not initiate treatment and dropped out before release: 60% of the methadone group drop-outs reported that they intended to start, but were not granted the possibility to continue with methadone maintenance upon release by community treatment providers. Of the 11 methadone treatment starters, 9 reached the target dose of 80 mg per day before prison release, whereas 2 participants discontinued methadone due to side effects while still in prison. For virtually all inmates, it was not possible to predict with any certainty the exact release dates, either due to new verdicts pending or due to unexpectedly pearly release on parole. This uncertainty impeded preparation of aftercare arrangements, such as establishing contact with community treatment providers and housing. Participants' treatment preferences, the impact of the uncertainty of their release dates and its implications for conducting this study are described in detail in a previous paper [45].

Statistically significant reductions in the use of heroin and illicit benzodiazepines were found in both groups at follow-up (table 1). Use of amphetamines was slightly, but not significantly, lower at follow-up. Criminal activity was significantly lower at follow-up than during the period before arrest. There were no statistically significant differences between the naltrexone and methadone groups in terms of changes in substance use and criminal activity.

Kaplan-Meier survival estimates were calculated for rates of heroin relapse in both groups. No differences between groups were found when missing data were replaced on the assumption of immediate relapse after release. Without data replacement, the Kaplan-Meier estimates suggest that relapse to heroin use was significantly less likely in the naltrexone group ($p = 0.012$). Re-incarceration rates were comparable in both groups with 21.7% of the participants in the naltrexone and 23.8% in the methadone group spending 1 or more days in a Norwegian prison during follow-up.

A statistically significant reduction of drug use and criminal activity was detected in the per-protocol completer analyses of both groups, which further showed that 50.0% of participants in the naltrexone and 36.4% in the methadone group attended aftercare arrangements until the 6-month follow-up. None of the completers reported participation in other treatment modalities such as Narcotics Anonymous, psychotherapy or residential treatment. Six months after prison release, 69.6% of the participants in the naltrexone implant group were receiving study treatment compared to 23.8% in the methadone group. This difference was statistically significant ($p = 0.003$).

Adverse Events

None of the 16 naltrexone implants was surgically removed due to site reactions or patient request. Two participants reported itching and skin rash at the implantation site, which resolved with oral antihistamines on the one and oral antibiotics on the other occasion. Adverse effects not related to the implant-site were generally rated as being short in duration and of minor intensity. Headache, reduced appetite, nausea, sleep disorders, restlessness and irritability were reported by more than half of those who received naltrexone implants. Constipation, diarrhoea and muscle or joint pain were sporadically reported. All symptoms were transient and deemed possibly related to study medication. Methadone treatment was terminated in 2 participants due to unspecific gastrointestinal discomfort after a few days in the one, and oedema after 3 weeks in the other case.

Five hospital admissions were deemed unrelated to study medication: 1 for lung tuberculosis in the naltrexone group, and 2 for drug detoxification, 1 for multiple abscess infections and 1 for a traffic accident in the methadone group. Information on deaths was available for 41 of 44 participants, and among these, none had died during the 6 months follow-up. One individual (not initiated methadone treatment, not contacted for follow-up) died of an unclear cause 8.5 months after prison release. None of the remaining 3 participants with unavailable information on death had initiated treatment; 2 individuals had been randomly assigned to methadone and 1 to naltrexone implant treatment.

Discussion

At the 6-month follow-up, both treatment groups showed reductions in the use of heroin and illicit benzodiazepines and in criminal activity after prison release. For these outcomes, and for time to heroin relapse, patients allocated to naltrexone implants and methadone treatment showed similar levels of reductions in problem scores, and in these respects the two treatments may be regarded as being of comparable effectiveness.

The two study groups showed different treatment performance. In the naltrexone implant group, treatment retention was higher than in the methadone group, but naltrexone acceptance was lower. Some methadone group participants also refused to initiate treatment due to non-acceptance, but the main contributing factors to unsatisfactory methadone initiation were the programme's application process that relied on community treatment providers and the complicating prison routines. Retention in the methadone treatment programme was low. This may have been due to the requirement of daily dose pickup which proved difficult to comply with for many individuals. The differences in treatment retention at 6 months may be partly attributed to the very different formulations of the two medications. All participants who started treatment in the naltrexone implant group were receiving this treatment 6 months after prison release: none had the implant surgically removed. For participants who started methadone treatment, the majority were not receiving medication at 6 months after release. The low medication compliance rate in our methadone group differs from methadone programme evaluations in Sydney and Baltimore, where medication compliance after prison release was generally high [46–49]. These dissimilar findings may be explained by the fact that agonist maintenance treatment was available in all of our five cooperating prisons, independent of study participation. A considerable number of inmates may have preferred regular methadone treatment instead of random assignment as offered in our trial.

The aftercare attendance rates were comparable in both groups, and these are in line with the highly structured programme described by Cornish et al. [16]. They

report a 6-month attendance rate of 52% for the oral naltrexone group and of 33% for the control group receiving counselling only. In the present study and in the trial by Cornish et al. [16], a high proportion of polydrug users were enrolled and the impact of naltrexone treatment on the use of illicit non-opioid drugs was less evident than for opioid use.

Naltrexone implants have not previously been compared to methadone treatment. Several studies on orally administered naltrexone have been conducted in prison settings. In the most recent one, Shearer et al. [50] reported low acceptance of oral naltrexone in Sydney. In their sample, 68% of the participants who were randomly allocated to naltrexone were already receiving agonist maintenance treatment and the majority were reluctant to accept detoxification and naltrexone induction. Further, a high proportion of the few treatment starters ceased oral naltrexone during the first few weeks after release. This finding is consistent with another study on oral naltrexone in US criminal justice settings, where noncompliance occurred most frequently during the first week after release [16]. Our study shows that medication compliance during this vulnerable post-release period may be improved by the provision of naltrexone implant treatment. Avoiding noncompliance and unblocked heroin use with sustained-release formulations have been considered crucial within naltrexone maintenance therapy for decades [51, 52]. Noncompliance with oral naltrexone permits heroin effect, and a few episodes of unblocked heroin use will typically lead to relapse to dependent use [21].

Several study limitations should be acknowledged. The dropout rates in the methadone group after prison release were high. This indicates that the advantages of methadone maintenance that are described for community populations were harder to achieve for our inmate population. Strengthened post-release care, such as more frequent counselling or release on parole with meeting requirements, could have substantially increased the compliance with methadone treatment and thus improved outcomes in our population. Further, life quality, dysphoria or other psychiatric symptoms were not frequently assessed. The first follow-up visit at the research centre was scheduled at about 6 months after prison release for methadone participants. Naltrexone participants were scheduled to meet 6 months after treatment start, taking into account the implants' expected naltrexone release time of 5–6 months. Earlier and more frequent follow-up visits including urinalyses and the evaluation of psychiatric symptoms, such as dysphoria, could have improved treatment adherence, assessment of drug use and, thus, outcomes substantially.

The treatment conditions were not blind, which may have increased the risk of performance bias, i.e. the novelty of naltrexone implant treatment may have contributed to the reporting of advantageous outcomes. Blinding was judged unethical for two reasons: dummy implants require surgery with the risk of adverse events such as infection. Also, the distinct nature of methadone and naltrexone impede effective blinding, as the rewarding effects of opioid agonists will be detectable. These reasons also supported our rationale for opting against dummy naltrexone implants that are needed for a placebo-controlled study design. Placebo comparison with naltrexone has reportedly failed [53] because heroin-dependent individuals are likely to reveal the allocated treatment condition by testing the blockade with heroin, thus running a considerable risk of relapse and overdose death.

A further limitation is that the number of participants in this study may have been too small to detect any differences between the two treatment conditions. Larger trials are required to confirm our findings and to assess possible advantages of one treatment over the other. Also, drug use or relapse to dependent heroin use was not assessed by objective measures such as urinalyses or a naloxone challenge. However, the self-reported data were collected by interviewers who were independent from treatment providers and criminal justice staff, and such data have previously been found to be reliable and valid [54–56]. Finally, a large number of eligible inmates did not wish to participate in the study, and despite random treatment allocation, the risk of selection bias cannot be ruled out. The reasons for not giving consent are not known. However, other studies have shown that a high proportion of opioid-dependent individuals tend not to be willing to accept antagonist treatment, and this is a known drawback of naltrexone [17, 23, 57].

Despite these limitations, our results provide evidence that naltrexone implants and methadone treatment appear to be of comparable effectiveness in leading to reductions in the use of heroin and illicit benzodiazepines, as well as leading to reduced criminal activity after prison release. Both medications may contribute to relapse prevention programmes in criminal justice settings. Although the issue of mortality was not investigated in the present study, a further potential advantage of initiating such pharmacotherapies with opioid-dependent offenders in prison concerns the risk of death from drug overdoses during the immediate post-release period. During the first 2–3 weeks following prison release, the risk of

overdose death is greatly increased [29, 30, 58–60]. Methadone maintenance is effective in reducing opioid overdose death [7] and it is the preferred treatment for many opioid-dependent individuals [6]. During incarceration, access to methadone maintenance should be facilitated, taking into account the high risk of relapse and overdose death after release.

Our findings support the need for implementation of more comprehensive treatment programmes for criminal justice populations [27, 61], and particularly for treatments that can be initiated in prison and continued after release into the community. Naltrexone implant treatment showed promising results and was not found to have severe adverse events in our study with volunteers. This treatment merits further evaluation in criminal justice populations as it may have particular advantages in such settings. Access to opioids during incarceration is limited [62], so naltrexone induction, which requires abstinence from opioid use, is facilitated. Sustained-release naltrexone formulations may improve medication compliance to a greater extent than oral naltrexone. This is of particular importance during the first couple of weeks following prison release, when heroin-involved inmates are most vulnerable for relapse and subsequent overdose death.

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Injectable and implantable sustained release naltrexone in the treatment of opioid addiction

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Summary

Background

Sustained release technologies for administering the opioid antagonist naltrexone (SRX) have the potential to assist opioid-addicted patients in their efforts to maintain abstinence from heroin and other opioid agonists. Recently, reliable SRX formulations in intramuscular or implantable polymers that release naltrexone for 1-7 months have become available for clinical use and - research.

Methods

This qualitative review of the literature provides an overview of the technologies currently available for sustained release naltrexone (SRX) and their effectiveness in reducing opioid use and other relevant outcomes.

Results

The majority of studies indicate that SRX is effective in reducing heroin use, and the most frequently studied SRX formulations have acceptable adverse events profiles. Registry data indicate a protective effect of SRX on mortality and morbidity. In some studies, SRX also seems to affect other outcomes like concomitant substance use, vocational training attendance, needle use, and risk behaviour for blood-borne diseases like Hepatitis or HIV. There is a general need for more controlled studies, in particular comparing SRX with agonist maintenance treatment, combinations of SRX with behavioural interventions, and with at-risk groups like prison inmates or opioid addicted pregnant patients.

Conclusion

The literature suggests that sustained release naltrexone is a feasible, safe and effective option for assisting abstinence efforts in opioid addiction.

Introduction

Heroin is used by an estimated 0.4% of the world's population, but heroin-related problems account for nearly 60% of the treatment demand in Europe and Asia (1). The best candidate explanation for this lies in the comprehensive nature of heroin addiction: the sedative effects of the opioid agonist heroin greatly increases the risk of fatal or near-fatal overdose, while a high incidence of injecting use greatly increases the risk of introducing bacterial, viral or fungal agents due to non-sterile injecting practices. Regular heroin users also have an increased occurrence of mental health disorders, and often engage in the regular use of at least two other illicit drugs (2). In the United States of America, diversion and misuse of prescription opioids is an increasing problem (3). Environmental factors associated with illicit opioid use, such as engagement in criminal activities, poor living standards and 'less stable environments' (i.e. exposure to violence, accidents, injury and suicide) (4). All these factors contribute to increase the risk of death from regular illicit opioids to a rate of about 8.6 deaths per 1000 person-years (5). This risk is heightened following detoxification and discharge from a controlled environment, as opioid receptors are thought to readjust to function without exogenous opioid intake. For example, one study found risk of overdose death was 12 times that of the pre-admission risk following discharge from inpatient treatment like detoxification (6). Another study found mortality risk was up to 34 times elevated during the first two weeks following release from a prison setting (7). Recovery from heroin addiction often takes several years with at least occasional relapse and setbacks; it is thus often understood as a chronically relapsing disease (8). While most of our present knowledge on opioid addiction comes from experience with illicit heroin users, all types of opioid agonists

share the same basic neurophysiological pathways and thus the risk of dependence, tolerance, withdrawal, intoxication and abuse.

Present treatment alternatives

Until recently, treatment options for heroin addiction were limited to three main alternatives: ***Detoxification*** followed by long-term residential treatment; ***Opioid maintenance treatment*** (OMT) and ***Oral Naltrexone.***

Detoxification followed by long-term residential treatment has been found to result in some reduction in drug use for a large minority of patients, but suffers from problems with retention in treatment and risk of overdose upon discharge (9). ***Opioid maintenance treatment*** maintains or substitutes dependence on heroin via the supervised administration of opioid agonist medications including methadone, buprenorphine or medically dispensed heroin (10). While OMT is effective in reducing mortality, morbidity and drug-related criminal activity, chief concerns are dropout during the initial months of treatment and that only a minority of patients are able to achieve normal vocational and social functioning. For those who do achieve such integration, there is currently no validated alternative to life-long dependence on the opioid agonists administered daily in OMT.

Naltrexone - an opioid antagonist

Naltrexone induces a competitive antagonism at all main types of opioid receptors, with some preference for the mu receptor. Although both naltrexone and naloxone were developed based on modifications of oximorphan, naltrexone's overall affinity for opioid receptors is higher and its half-life significantly longer than that of naloxone. Thus naloxone is better suited for acute purposes like reversing the effects

of opioid-induced sedation, while naltrexone is better for scenarios that require prolonged antagonism, e.g. assisting abstinence from opioid agonists following detoxification and/or reducing addiction-related craving. While a full review of these latter types of effects is beyond the scope of this article, the high prevalence of comorbid substance use problems makes them relevant to the overall therapeutic effect, especially for heroin users.

Naltrexone has long been known to cause a reduction in craving sensation for many types of addictive substances including alcohol (11) and amphetamine (12). There has also been reports of a similar effect on certain types of compulsive behaviours, such as bodily self-harm (13) and gambling addiction (14). The precise mechanism for craving reduction has not been determined, but the most likely is that naltrexone causes antagonism of opioid pathways to the nucleus accumbens, reducing the total amount of dopamine released. Naltrexone at very low doses (0.25 mg/day) seems to reduce the severity and/or longevity of opioid withdrawal during detoxification (15), possibly assisting a restoration of normal opioid receptor functioning (16) and attenuating noradrenergic withdrawal systems (17). In addition, opioid antagonists like naltrexone affects other biological systems like G-receptor second messenger systems (18), the immune system (19), and the HPA axis (20).

Compliance problems with oral naltrexone

Studies of oral naltrexone tablets taken daily or bi-daily have generally failed to show superiority over placebo, mostly due to rapid dropout in the active naltrexone group. However, modestly improved results can be achieved when oral naltrexone is taken as part of a compliance-reinforcing scheme like contingency management (21). The lack

of clinical success with oral naltrexone were recognized in the first clinical studies of oral naltrexone (22,23). Consequently, research efforts were started in order to develop sustained release technologies that would decrease compliance problems by reducing the number of dropout opportunities. As part of development efforts for a sustained release formulation, two central SRX characteristics were formulated: 1) for blocking street heroin doses, the minimum plasma level of naltrexone was estimated to be about 1 ng/ml, although some of this blockade is also provided by the metabolite 6-beta naltrexol (24). And 2) A clinically useful SRX formulation was thus considered to release naltrexone at levels of 1ng/ml plasma or above for the duration of at least four weeks, with an acceptable rate of tissue-related adverse events. Following more than 30 years of development efforts, this goal has recently been achieved.

Sustained release naltrexone (SRX) formulations

Currently two main types of sustained release technologies are used to release naltrexone: injectable intramuscular suspension and surgically implantable pellets. This section provides a summary of the data from the literature on the currently available SRX technologies, and their ability to block opioid agonists such as heroin or morphine. While there are other sustained release technologies available e.g. for buprenorphine (25), these have not been developed for naltrexone.

Polylactide suspension

The naltrexone release of this class of SRX medications is based on the slow biodegrading of a 380 mg poly-lactide and naltrexone suspension providing therapeutic blood levels of naltrexone over a period of 28 days. An intramuscular

SRX suspension of this type was recently FDA-approved for prescription for opioid dependence in the US, after being approved for the treatment of alcohol dependence in 2006. The intramuscular suspension is administered via injection into the gluteus muscle, alternating sides every 4 weeks. A research-only formulation can be injected subcutaneously. With the latter formulation, a heroin challenge study was conducted where participants were administered a 380 mg dosage of subcutaneous and then received IV dosages of heroin at 0, 6.25, 12.5 or 25 mg of heroin in a double-blind design. The suspension provided satisfactory blockade of both self-rated and objective measures (e.g pupil diameter) of heroin for between four and five weeks (26). Recently, a similar experiment was conducted using the FDA-approved intramuscular suspension in reduced dosages of 75, 150 or 300 mg of naltrexone and using hydromorphone instead of heroin for the challenge tests; 3 mg of hydromorphone was blocked by the 300 mg SRX formulation for 28 days, whereas the lower SRX dosages blocked this challenge for a correspondingly shorter duration (27).

Surgically implanted capsules

The other main type of SRX technology consists of pellets with biodegradable solid polymer surgically inserted or implanted under the skin or fatty tissue with the use of local anaesthetic. The wound is then sealed with 1-3 sutures, with the wound inspected after about one week. The two formulations of surgically implanted naltrexone that have been used in the majority of controlled studies are an Australian type with release periods as long as 7 months when 30 pellets are inserted (28) and a Russian type with a release period of 2-3 months (29). Other manufacturers of naltrexone implants exist, but little research has been published on their reliability or production methods (see (30) for an exception to this). Case data support the view that

SRX implants releasing naltrexone at or above 1ng/ml blood will block normal dosages of laboratory-administered heroin as well as high dosages of illicit heroin (24,31,32).

Effect on opioid use

The majority of RCTs on SRX have shown promising increases in heroin abstinence in the SRX group relative to controls, despite diversity in sample composition, study design, and cultural settings. Two studies have been conducted of 4-week intramuscular SRX suspensions: An eight-week double-blind study from the US of a selected sample divided into a high-dosage to low-dosage and placebo (33), and a 24-week double-blind trial of SRX vs placebo in a sample of Russian heroin users (34). Both studies found significant increases in the proportion of urine samples negative for heroin use. On implantable naltrexone, five RCTs will be reviewed here: Three RCTs utilized a six-month version of the Australian implant: One open-label study randomizing to treatment as usual in a Norwegian treatment setting (35) and a placebo-controlled, double-dummy design with oral naltrexone in Western Australia (36) both found significant decreases in heroin use. A Norwegian open-label study randomizing to methadone OMT or naltrexone implant in probationer settings experienced dropout problems, and found similar reductions in opioid use among the patients who remained (37).

Two randomized studies have been conducted in Russia using a Russian naltrexone implant: A 10-week study of n=100 patients (n=50 in the SRX and placebo groups, respectively) who were both amphetamine and heroin dependent found significant reductions in heroin use (29). A larger study that followed n=306 opioid dependent

patients over 6 months in a three-group, double-dummy design found a significantly larger proportion of urine samples were opioid-negative in the active SRX group compared to both oral naltrexone and placebo (38).

The magnitude of the reduction in opioid use with SRX is typically about 50% at a group level when compared to oral naltrexone or usual-treatment controls, although there is considerable individual variation among patients. In summary, sustained release naltrexone seems to succeed in assisting patients in achieving abstinence from opioids. The consistency of this finding despite diversity in study designs, cultural setting, and SRX formulation reinforces the impression that SRXs' effect on heroin use is a clinically robust finding. There are few data regarding the effectiveness of SRX in the treatment of addiction to prescription opioids.

SRX and heroin-related overdose

Naltrexone's ability to compete against heroin for opioid receptors means it should provide protection against overdose and – death. The RCTs thus far completed have an insufficient number of participants to permit meaningful analyses of mortality rates. A series of registry cohort studies from Western Australia have used samples of several thousand patients; these studies suggest SRX reduces the number of deaths among heroin users compared to methadone users and oral naltrexone (39–41). The same open cohort was used for the SRX implant patients in two of these studies. Case reports have been published of patients 'breaking the naltrexone blockade' with large doses of opioids (e.g. (42)), as well as post-mortem cases (43) often do not account for potential confounding factors. Data from Norwegian SRX patients confirm that a minority of patients report 'breakthrough'-like experiences, but that the use of non-

opioid illicit drugs makes it difficult to verify which substance induced the experience (32). The concept of true receptor agonism or 'breakthrough' in the presence of naltrexone also appear inconsistent with case stories of naltrexone blocking large quantities of heroin (24,32).

An extension of this question is whether death from an overdose of heroin can occur in active SRX patients. Like any pharmacotherapy, naltrexone's binding at the receptor site is of a competitive type that it is technically possible to outperform using extreme quantities of normal-affinity opioids or high-affinity synthetic opioids like fentanyl. In clinical settings, obtaining and self-administering agonists of the right type or quantity would be very difficult; deaths in patients treated with a reliable SRX formulation are thus more likely to be caused by exposure to the many non-opioid mortality sources common in the heroin demographic.

Retention in SRX for heroin users

Ambivalence between remaining in treatment and recommencing heroin use means heroin users are often tempted to drop out from treatment. Thus retention in treatment is considered a highly important measure of the clinical feasibility of any treatment for heroin addiction, including OMT and SRX. For naltrexone treatment, the inability to retain patients in oral naltrexone regimens has strongly contributed to why oral naltrexone treatment has seen minimal adoption in clinical settings with heroin users (21). A central clinical advantage of sustained release – over oral naltrexone – is the reduction in dropout opportunities, e.g. one intramuscular injection every 28th day instead of a tablet every day. In one RCT (33), retention was 62% between the first and second 28-day intramuscular SRX administration. In the Russian study of

intramuscular SRX (28 days' naltrexone release), attrition at the end of six months' administration of intramuscular SRX administrations was about 50% (34). This is similar to retention between the first and second administration of six-month implantable SRX (44). For patients receiving the 10-week Russian implant, retention was 63% over 6 months among Russian heroin users (38) and 52% in the study of patients with both opioid and amphetamine dependence (29). Differences in study design and - setting, as well as differences in readministration frequencies and adverse event profile make it difficult to infer beyond that retention rates for SRX are within a clinically acceptable range and tend to be better than their comparison group. Thus in this respect SRX seems to confirm hopes that it would constitute an improvement over oral naltrexone (21).

Integration with other behavioural interventions

A study from the Johns Hopkins behavioural laboratory found that when entry into a voucher-based workplace system was contingent on acceptance of a monthly intramuscular SRX, compliance and retention was improved when patients could enter the workplace freely versus those who were simply prescribed SRX monthly: 74% of contingency patients accepted all six injections, whereas only 26% of prescription patients did the same (45). This is consistent with previous findings from contingency management with oral naltrexone (46). This suggests that the retention in SRX can be greatly improved when combined with behavioural interventions in order to maximise its clinical usefulness.

SRX administered as part of a planned release from prison is another area of considerable interest, in particular due to the increase in overdose mortality reported

in several studies (e.g. (7,47)). As heroin is less available in prison, inmates are more likely to maintain abstinence from heroin that greatly facilitates naltrexone induction (48). Several studies on oral naltrexone for opioid dependent inmate populations concluded with beneficial outcomes when naltrexone was integrated with psychosocial support to enhance external motivation, e.g. work-release programmes and parole including follow-up by criminal justice staff (49–52). Although treatment attrition was still high in these trials, those who stayed on oral naltrexone were less likely to relapse to heroin and less likely to engage in criminal activity than comparison groups not receiving naltrexone. A recent pilot study suggests intramuscular SRX is feasible in probationers with participants displaying reductions in opioid use (53). This is consistent with findings from a Norwegian OMT-SRX randomized study (37), where heroin abstinence rates were equivalent between the two groups six months post release. There is debate regarding the ethical aspects of mandating SRX for heroin users as part of sentencing or parole conditions (e.g. (54)).

Concomitant substance use

Several studies have examined whether SRX also reduces concomitant use of non-opioid illicit drugs. Naltrexone has been known to reduce craving for a number of addictive substances (see elsewhere in this issue), often resulting in a subsequent reduction in substance use. Of the available studies, RCTs with stricter inclusion criteria seem to confirm a change in non-opioid drug use (33,34); this effect does not reach significance in studies with less strict inclusion criteria (28,34,35). This indicates that SRX may have an effect on concomitant drug use in heroin users, but less dramatic than the effect seen on heroin consumption; the division along inclusion criteria may also indicate that a reduction in concomitant substance use is more likely

to occur in subgroups of heroin users that are pre-screened to reduce the incidence of potential confounders.

Somatic & mental health outcomes

A registry cohort study in Australia followed cohorts of both SRX and methadone patients, and found their rate of mental health related hospitalization similarly reduced (55). In a similar study, SRX patients presented with fewer psychiatric hospital admissions after entering SRX (56). For somatic hospitalizations, overdose admissions were reduced to zero among SRX implant patients in a registry linkage study, and continued to be reduced compared to pre-admission levels for an additional six months following the expiry of naltrexone from the SRX implant (39).

Adverse events

Moderate adverse effects such as nausea, vomiting, and muscle twitches are experienced by heroin users in both SRX and oral naltrexone treatment (22,57). The majority of adverse effects are described as mild to moderate (35), and are more likely to occur in active SRX groups than in placebo patients (29,33,34). As SRX releases naltrexone into the bloodstream gradually at concentrations typically in the 1-5 ng/ml range, the intensity of adverse effects is much reduced compared to oral naltrexone, where blood naltrexone levels can remain at 10-30 ng/ml for several hours every day following tablet intake. The blockade of endogenous opioids thought to result from treatment with SRX has not been reported to have consequences for the occurrence of mood disorders in any of the RCTs thus far published, even though the majority of them administered instruments to measure depression. While there have been reports of depression in users of oral naltrexone (58,59), subsequent investigations failed to

confirm any effects on mood (60,61). Clinicians should perhaps be more concerned that naltrexone blocks the effects of opioid-agonist based analgesics in an accident-prone population, although increasing the dosage or using other types of analgesics will often resolve the problem. It has also been suggested that naltrexone increases the sensitivity of the opioid receptor system, making patients more vulnerable than usual to heroin overdose once SRX is concluded (62). However, findings from toxicological examinations of heroin-related deaths comparing patients with or without prior naltrexone exposure do not support this hypothesis (63). In addition, a recent database study found a reduction in deaths among SRX patients during the first months following treatment when compared to oral naltrexone patients (41).

An important difference between SRX and oral naltrexone is the occurrence of site-related adverse events (64). For implantable SRX, these may appear as mild allergic itching or redness around the implantation site, infection of the skin, stitching or underlying tissue (65). These events are reported to occur in 2-5% of patients (e.g. (29,35)) and usually resolve with symptomatic treatment but in extreme cases may require removal of the implant. Some patients have cosmetic concerns with the fact that some implantable SRX formulations may take months or years to biodegrade completely (66). Similarly, recipients of SRX with intramuscular suspension can often experience some site pain, while a few percent experience more serious site reactions like induration and infection.

Hepatic health is sometimes a concern with heroin users, especially for patients recently infected with Hepatitis C. There is little evidence that SRX in ordinarily administered doses is hepatotoxic. Intramuscular SRX has been found to be well tolerated in alcohol dependent patients with hepatic impairment requiring no dose

adjustments (67,68). A pilot study of implantable SRX in heroin users found key hepatic indicators such as ALT to improve over the course of treatment (31), and the influence of SRX on indicators in other studies have generally been below levels of clinical significance. A clinical study of 50 SRX implant patients undergoing antiviral therapy for Hepatitis C found 62% were HCV negative following completion of HCV treatment and 6 months of SRX (69). Still, caution may be warranted in administering SRX to patients who present with severely reduced hepatic functioning, e.g. who qualify for an impairment classification corresponding to Child-Pugh grade C.

Pregnancy is a debated topic in SRX research, as with heroin users in general (70–72). SRX medication is now available for regular prescription in the US, and there is an interest among pregnant drug users despite a general lack of knowledge about SRX's effects on foetal health. While this lack of knowledge is unfortunate from a medical point of view, the risk of return to heroin use upon discontinuation of SRX may be considered an even worse outcome. Historically, the solution most often adopted has been to continue the pharmacotherapies for pregnant heroin users and initiating short- and long-term studies on adverse effects following delivery of the child (73). Only one case has been reported following this approach, with no adverse effects detected in mother or child (74).

Conclusions

Since a Cochrane review in 2008 (75) concluded there were too few studies to conduct any meaningful assessment of sustained release naltrexone (SRX) in the opioid addicted, the amount of research published on SRX has accumulated to the point where this conclusion seems gradually less valid. SRX is showing promising,

consistent effects in supporting opioid users' efforts to achieve abstinence across different clinical study design and - treatment settings. The SRX formulations that have been the subject of the majority of research articles appear to have a satisfactory rate of consistency in naltrexone release and an acceptable adverse effects profile. The literature on SRX for opioid addiction still requires more studies in order to confirm initial findings on effects. There is a particular need for more knowledge on SRX compared with current standard treatments, the impact on poly-drug dependence, the use of SRX during pregnancy, and the combination of SRX with other interventions in order to maximise the impact on recovery.

Declaration of interests

The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request) and declare: no support from any organisation for the submitted work; GKH had entered into a contractual arrangement (via the University of Western Australia) with Go Medical Industries (who manufactures the Australian naltrexone implant) to conduct a number of research studies in the previous 3 years; GKH had co-authored with Dr. George O'Neil (Director, Go Medical Industries) on a number of previous publications.

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