Long-acting depot formulations of naltrexone for heroin dependence: a review

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Purpose of review
The major problem with the oral formulation of naltrexone for heroin dependence is poor compliance (adherence). Long-acting sustained release formulations of naltrexone (implantable and injectable) might help to improve compliance and, thus, increase the efficacy of abstinence-oriented treatment of heroin dependence with naltrexone.

Recent findings
There have been several implantable and injectable formulations of naltrexone developed within the last decade. It was demonstrated that some of them are effective and relatively well tolerated medications for relapse prevention in heroin addicts. However, advantages and disadvantages of these new medications have never been systematically analyzed.

Summary
Long-acting sustained release formulations of naltrexone are well tolerated and more effective for relapse prevention in heroin addicts than the oral ones.

Keywords
heroin dependence, long-acting sustained release formulations, naltrexone

Introduction

Naltrexone was approved by the Food and Drug Administration (FDA) as an opioid antagonist to treat heroin dependence in 1984 on the basis of its pharmacological profile. Naltrexone blocks heroin effects by competitive antagonism at the μ-opioid receptors [1]. The degree of blockade depends on the concentration of agonists to antagonists and their affinity to opioid receptors. Naltrexone is a perfect antagonist to treat heroin dependence: 50 mg (one tablet) of naltrexone blocks the subjective effects of heroin for 24–36 h, it is easy to administer (one tablet per day or two tablets every other day), it is well tolerated (has a relatively small number of side effects), and tolerance does not develop to the opioid antagonism. However, there is one problem that makes naltrexone relatively low in effectiveness in heroin dependence management: heroin addicts do not like it and they do not take it on the regular daily basis that is required. The dropout rate with oral naltrexone is high, but it is significantly better under the limited number of conditions in which there is a substantial external motivation, such as in physicians whose performance is being impaired, those involved with the criminal justice system, and those facing loss of an important job [1]. Retention in treatment and related efficacy of oral naltrexone are also better in Russia, where heroin addicts are often young adults living with their parents, who monitor intake and no agonist maintenance is permitted [2].

Long-acting sustained release formulations seem to be the most efficient way to solve the problem of poor adherence to oral naltrexone in heroin addicts. There are two major groups of long-acting sustained release formulations: injectable formulations and implantable ones.

Injectable formulations

We will consider general information, effectiveness, and safety issues.

General information

There were three injectable formulations of sustained-release naltrexone developed during the late 1990s to early 2000s: Vivitrol (manufactured by Alkermes, Cambridge, Massachusetts, USA), Depotrex (manufactured by Biotech, Bethesda, Maryland, USA), and Naltrel (manufactured by Drug Abuse Sciences, Hayward, California, USA) [3]. Currently, only Vivitrol is available in the United States and Europe. Intramuscular injectable formulations of naltrexone were developed to address the challenge of poor adherence by providing a therapeutically relevant plasma concentration of naltrexone over the course of 4 weeks following a single injection. Following intramuscular injection, naltrexone is

released from the microspheres in multiple phases by a combination of diffusion and polymer erosion. Drug release under in-vitro conditions can be described as occurring in three distinct phases: an initial release of surface drug within 24 h of injection, a hydration phase that occurs during the first week following injection, and a sustained-release phase with a near constant rate of release during weeks 2–4 postinjection [4]. This release provides sustained naltrexone plasma concentrations and minimizes the peaks and troughs that occur with once-daily oral naltrexone administration. As the polymer erodes, the resulting lactide and glycolide monomers are metabolized and eliminated from the body as carbon dioxide and water [4].

Each of the injectable formulations can produce a plasma level of naltrexone that is stable and pharmacologically effective for approximately 1 month. In a randomized, placebo-controlled trial using the injectable sustained-release naltrexone Depotrex with 60 heroin-dependent adults receiving placebo or one of two doses of depot naltrexone, the mean $\pm$ SD peak naltrexone plasma levels measured approximately 1 week after the administration of 192 and 384 mg of depot naltrexone were 1.9 ± 0.6 and 3.2 ± 0.7 ng/ml, respectively. Across the 8-week study, plasma naltrexone levels tended to be fairly constant, with a slight decline during the fourth week after drug administration. Plasma levels of 6-β-naltrexol, the primary pharmacologically active metabolite of naltrexone, tended to be higher than naltrexone levels and more variable across time [5]. Similarly, in a study with Vivitrol, the mean plasma naltrexone concentration remained higher than 1 ng/ml for longer than 35 days at the 380 mg dose level [6]. For comparison, a single oral dose of 50 mg of naltrexone produces mean peak naltrexone plasma concentrations of approximately 9 ng/ml 1 h after drug administration. In general, many investigators agree that doses that maintain naltrexone plasma levels of approximately 2 ng/ml are sufficient for antagonizing the effects of 25 mg intravenous heroin. Other findings suggest that a plasma concentration of less than 1 ng/ml is sufficient to antagonize heroin-induced effects [6].

Effectiveness
Injectable depot naltrexone has mostly been used for the treatment of alcohol dependence. One inpatient study has demonstrated the safety and clinical effectiveness of the sustained-release naltrexone Depotrex for the treatment of opioid dependence. In a randomized, double-blind, placebo-controlled clinical trial, heroin-dependent adults received placebo ($n = 18$) or 192 ($n = 20$) or 384 mg ($n = 22$) of injectable depot naltrexone monthly for 2 months, in addition to twice weekly relapse prevention therapy [5]. The 192 and 384 mg injectable naltrexone groups had a significantly higher (60 and 68%, respect-

ively) percentage of patients remaining in treatment at the end of 2 months than the placebo group (39%). Time to dropout had a significant main effect of dose, with mean time to dropout of 27, 36, and 48 days for the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively. The mean percentage of urine samples negative for opioids across the study was lowest for the placebo group (25.3%) and highest for the 384 mg of naltrexone group (61.9%). However, when the data were recalculated without the assumption that missing urine samples were positive, there were no significant differences between the groups in percentage of negative urine tests for opioids. This is the only published study to evaluate the advantage of injectable naltrexone depot over placebo. But it is limited by the number of participants recruited.

The effectiveness of another injectable depot formulation of naltrexone – Vivitrol – for the treatment of opioid dependence is currently being studied with positive preliminary results from a large phase 3 (250 patients), double-blind, placebo-controlled, randomized, multicenter clinical trial released very recently by the pharmaceutical company Alkermes (http://investor.alkermes.com/phoenix.zhtml?c=92211&p=irol-newsArticle&ID=1355632&highlight). The 6-month phase 3 study met its primary efficacy endpoint and data showed that patients treated once monthly with Vivitrol demonstrated statistically significant higher rates of clean (opioid-free) urine screens than patients treated with placebo, as measured by the cumulative distribution of clean urine screens ($P < 0.0002$). In addition to meeting the primary efficacy endpoint, the 6-month phase 3 study met all secondary efficacy endpoints. Retention in treatment in the Vivitrol group was significantly higher than in the placebo group. Data from the intent-to-treat analysis showed that the median patient taking Vivitrol had 90% opioid-free urine screens during the evaluation phase of the study and patients treated with Vivitrol demonstrated a significant reduction in opioid craving compared with placebo, as measured by a visual analogue scale.

Dunbar *et al.* [4], in an article devoted to the pharmacokinetics of extended-release injectable naltrexone, mentioned two clinical studies conducted by Alkermes Inc. One is a phase 2 single-dose clinical trial on healthy and opioid-dependent individuals ($n = 25$) and the second a phase 3 double-blind multidose trial evaluating the safety of 380 mg extended-release naltrexone intramuscular injections every 4 weeks compared with 50 mg oral daily naltrexone in alcohol-dependent and/or opioid-dependent individuals ($n = 367$). The results of these studies are not yet published. However, in a case report of a 17-year-old girl receiving extended-release naltrexone (Vivitrol) for opioid dependence, Vivitrol precipitated withdrawal following her third serial monthly dose of

the medication, several days after using oxycodone with mild intoxication [7•]. This case demonstrates that it is possible to overcome opioid blockade with Vivitrol on the third week after the injection.

To summarize everything mentioned above, the effectiveness of injectable naltrexone seems to be superior to placebo; however, this had never been compared with oral naltrexone.

Safety
According to the published literature, extended-release naltrexone is free of serious side effects. In the recent Vivitrol study mentioned above, it was generally well tolerated and no patients on Vivitrol discontinued the study owing to adverse events. The most common adverse events experienced by patients receiving Vivitrol during the study were nasopharyngitis and insomnia. Still, there is a concern that clinical use of this formulation is limited by patient safety and tolerability concerns. One potential concern with a long-lasting antagonist is that patients will attempt to override the blockade by using large amounts of heroin, thereby placing themselves at increased risk for overdose, especially during the period when naltrexone blood levels are decreasing. This concern is particularly relevant given the clinical case with Vivitrol described above, when the effect of this injectable formulation was overcome with oxicodone on the third week after Vivitrol administration [7•]. However, we should mention that the risk of overdose is not specifically related to any naltrexone formulation but rather to detoxification and any abstinence-oriented treatment in general which brings about a decrease in the tolerance to opioids.

Another potential concern is that the use of nonopioid drugs may increase. A recent finding did not confirm this concern [5], though future studies with an opioid-abusing population should carefully assess potential changes in the amount and patterns of other drug use.

Potential adverse events that may be unique to injectable sustained-release formulations of naltrexone include the tissue reactions around the site of drug administration. Thus, in a pharmacokinetic study with Vivitrol ($n = 42$), tenderness and indurations at the injection site were reported in three participants over a period of 2–23 days after receiving the first intramuscular dose of long-acting naltrexone. All injection site-related events were not clinically significant [6].

Impairment in liver function is a common concern with naltrexone therapy because early studies suggested that high doses of naltrexone may produce hepatotoxicity, and opioid-dependent patients often have elevations in liver enzymes through hepatic infection such as hepatitis B and C. However, several clinical trials on patients with severe liver impairment generally have not shown significant changes in liver function after treatment with naltrexone [4–6].

Implantable formulations
We will consider general information, effectiveness, and safety issues.

General information
Except injectable formulations of long-acting naltrexone, there are four different forms of naltrexone implant: the first manufactured by GoMedical Industries, Australia; the second was developed by Dr Lance Gooberman and the Wedgewood Pharmacy in New Jersey, USA [3]; the third formulation was developed by Fidelity Capital in Russia [8]; and web advertising provides information about the fourth product manufactured by Civil Life, China. The only implantable formulation of naltrexone that is officially registered at the moment is the Russian one (Prodetoxone). According to the information from the manufacturers, Russian and American implants are made using a similar technology based on the magnesium stearate matrix, whereas Australian and Chinese implants are manufactured with a technology involving special biodegradable polymers. It was declared by the manufacturers that naltrexone implants maintain a therapeutically effective level of naltrexone (more than 2 ng/ml) for 2–2.5 months (American formulation), 2–3 months (Russian implant), 6 months (implant from Australia), and 6–10 months (Chinese formulation). Several biorelevant studies investigated in-vitro and in-vivo drug release from a naltrexone implant. The real-time data generated over 6 months indicated stable drug release for the Australian implant with a 48% lower rate at the end of the investigated period. No macroscopic or clinical toxicity signs were observed during the in-vivo implantation study [9–11]. Russian pharmacokinetic studies with Prodetoxone also demonstrated its long-lasting effects in terms of a therapeutically significant naltrexone blood level [12,13].

Effectiveness
The clinical efficacy for long-acting implantable naltrexone for opioid dependence has been demonstrated in several clinical trials. In particular, Reece [14] conducted a retrospective comparative review of experience with a 1-month depot device from the USA, the implant from Perth, Australia, and the historical group treated with oral naltrexone. The parameter of interest was opiate-free success, which was 82, 58, and 52% for the Perth implant, the USA implant, and the historical group, respectively. There are several limitations of this study. First, it was not randomized; second, the investigators used historical controls; and third, the small number of patients with the

Australian implant did not allow a significant difference between the two implant types to be determined.

In a recent 6-month, double-blind, double placebo-controlled, randomized clinical trial, oral naltrexone was compared with a single dose of 2.3 g of the Australian naltrexone implant. Seventy heroin addicts received oral naltrexone with placebo implant or naltrexone implant and oral placebo. The major finding in this study was that more participants treated with oral naltrexone returned to regular heroin use by 6 months ($P = 0.003$) and at an earlier stage (median/SE 115/12.0 days) than participants in the implant naltrexone group (158/9.4 days) [15•]. The limitations of this study are the limited number of patients (35 per group) and the lack of a double placebo group.

Kunoe et al. [16•] presented a study done in Norway comparing oral and Australian implant naltrexone. A total of 56 patients were randomly but openly assigned to receive either a 6-month naltrexone implant or their usual care (outpatient counseling, application for entry to the Norwegian maintenance treatment program, readmission to detoxification or residential treatment). The study demonstrated that the patients receiving naltrexone had an average of 45 days less heroin use and 60 days less opioid use than the control group in the 180-day period. The major limitation of this study is lack of masking; this factor could alter the efficacy results.

A rigorous study with implantable Russian naltrexone (Prodetoxne) was recently completed by Krupitsky et al. [17]. A total of 306 recently detoxified heroin addicts were randomized to a 6-month course of biweekly drug counseling and one of three medication groups (102 patients per group): naltrexone implant (1000 mg, three times – every other month) + oral placebo daily (NI+OP), placebo implant + oral naltrexone (PI+ON) (50 mg/day), and double placebo (implant and oral; PI+OP). Medications were administered under double-dummy/double-blind conditions. Urine drug testing and brief psychiatric evaluations were done at each biweekly visit. Oral medication compliance was evaluated using a urine riboflavin marker. Interim analysis of the data from this study demonstrated high efficacy of the naltrexone implant. The treatment effectiveness score (TES – the sum of heroin positive and missed urines) revealed a clear advantage of the naltrexone implant group over the two others (oral naltrexone and double placebo). At the end of 6 months, the TES in the NI+OP group was 63% compared with 87% in the PI+ON group and 86% in the PI+OP group. Survival analysis also revealed a significantly greater retention in the NI+OP group than in the two other groups ($P < 0.01$).

The major study comparing the safety and effectiveness of the Australian naltrexone implant with buprenorphine was conducted by Reece [18]. This study was structured as a naturalistic clinical audit and so did not have the advantages conferred by randomization. An additional limitation is that the effectiveness of the naltrexone implant was assessed prior to its formal registration in Australia. A total of 255 naltrexone implant therapy and 2518 buprenorphine patients were assessed. The study demonstrates that the naltrexone implant can be used with low mortality rates, involves fewer patient treatment episodes than buprenorphine, demonstrates superior patient retention, is flexible enough to accommodate dose variation, and is accompanied by relatively minor morbidity.

Another study compared drug-related hospital morbidity in heroin users at 6 months and 3.5 years after receiving a naltrexone implant with outcomes from a similar cohort treated with methadone maintenance therapy. This investigation revealed the naltrexone implant to be effective for long-term management of heroin dependence without compromising safety concerns; particularly, it, more effectively than methadone, decreased the opioid-related risk of overdose [18]. However, certain limitations of this study need to be acknowledged. First, the methadone cohort is only included as a reference group and, therefore, any between-group comparisons must be interpreted with great caution. Also the study did not control for several important factors inherently differentiating the two cohorts, such as motivation level, situational influences, socioeconomic background, and preexisting illness. Another related issue is the unavailability of medication dosage and treatment retention data on individual patients receiving methadone, which prevents a complete assessment of the drug-related health outcomes of these patients.

Safety
Naltrexone implants are generally well tolerated but the major concerns remain the same as with injectable naltrexone. The first concern is that a long-acting naltrexone implant may increase suicide rates during treatment and fatal overdose rates in the posttreatment period. However, in a large retrospective study in which Tait and coworkers [19,20] assessed the mortality rate in independent cohorts who received either the sustained-release Australian naltrexone implant ($n = 341$) or methadone maintenance treatment ($n = 553$) in the same period, methadone was found to increase mortality during induction into the maintenance treatment, whereas evidence relating naltrexone to an increase in either suicide or overdose was not found.

Overdose is the second concern. A nonlethal overdose related to overriding the naltrexone implant blockade had been described in a case report [8].

Surgical adverse events are another concern related to implant technology. In the above mentioned study with

the Russian naltrexone implant, the number of nonsurgical adverse events was limited with no difference between groups; however, surgical side effects (wound infections, local site reactions) were higher in the naltrexone implant group [17]. Limitations of the naltrexone implant technology related to surgical procedure apart from wound infections and local site reactions include cosmetic defects (scar) and specific sterile conditions required in the procedure itself. Another limitation is the possibility of removing the implant soon after its insertion. We should also mention critical comments on the widespread use of some unregistered naltrexone implants before controlled trials were published or the products approved [21].

Conclusion

In general, long-acting sustained release naltrexone formulations (implantable and injectable) seem to be well tolerated and more effective than oral naltrexone and placebo for relapse prevention to heroin dependence. However, studies comparing an injectable formulation with oral naltrexone are needed. Also, studies comparing the safety and efficacy of different naltrexone implant technologies as well as comparing implantable and injectable formulations seem to be important.

Conflict of interests

Evgeny Krupitsky is a consultant with the pharmaceutical company Alkermes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 285).

1 Kleber H. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. Dialogues Clin Neurosci 2007; 9:455–470.

2 Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. J Subst Abuse Treat 2006; 31:319–328.

3 Volpicelli RG, Fenton M. Sustained-release naltrexone formulations for the treatment of alcohol and opioid dependence. Future Neurol 2006; 1:389–398.

4 Dunbar JL, Turncliff RZ, Hayes SC, et al. Population pharmacokinetics of extended-release injectable naltrexone (XR-NTX) in patients with alcohol dependence. J Stud Alcohol Drugs 2007; 68:862–870.

5 Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence. Arch Gen Psychiatry 2006; 63:210–218.

6 Dunbar JL, Turncliff RZ, Dong Q, et al. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. Alcohol Clin Exp Res 2006; 30:480–490.

7 Fishman M. Precipitated withdrawal during maintenance opioid blockade with
• extended release naltrexone. Addiction 2008; 103:1399–1401.
This clinical case demonstrates that it is possible to overcome opioid blockade with Vivitrol and precipitate withdrawal in some circumstances.

8 Kruptisky EM, Burakov AM, Tsoy MV, et al. Overcoming opioid blockade from depot naltrexone (Prodetoxon®). Addiction 2007; 102:1164–1165.

9 Iyer SS, Barr WH, Karnes HT. A 'biorelevant' approach to accelerated in vitro drug release testing of a biodegradable, naltrexone implant. Int J Pharm 2007; 340 (1–2):119–125.

10 Iyer SS, Barr WH, Dance ME, et al. A 'biorelevant' system to investigate in vitro drug released from a naltrexone implant. Int J Pharm 2007; 340 (1–2):104–118.

11 Ngo HTT, Arnold-Reed DE, Hansson RC, et al. Blood naltrexone levels over time following naltrexone implant. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:23–28.

12 Arzamastsev EV, Malinovskaya KI, Golubyh VL, et al. Preclinical toxicological study of new depot formulation of naltrexone – prodetoxon. Novye Lekarstvennye Preparaty (New Medications) 2006; 33:31–39. (in Russian).

13 Boiko EO. The long term use of Prodetoxone in the treatment of opiate dependence. Narcologiya (Addict Med) 2007; 3:21–24. (in Russian).

14 Reece AS. Psychosocial and treatment correlates of opiate free success in a clinical review of a naltrexone implant program. Subst Abuse Treat Prev Policy 2007; 2:35.

15 Hulse GK, Morris N, Arnold-Reed D, et al. Improving clinical outcomes
• in treating heroin dependence. Arch Gen Psychiatry 2009; 66:1108–1115.
This first double-blind, placebo-controlled, randomized clinical trial showed the effectiveness of a single dose of the Australian naltrexone implant in comparison with oral naltrexone.

16 Kunoe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient
• treatment for opioid dependence: randomized controlled trial. Br J Psychiatry 2009; 194:541–546.
This study done in Norway compares oral naltrexone and Australian implantable naltrexone.

17 Krupitsky E, Zvartau EE, Woody G. Long acting naltrexone implants for heroin dependence. Eur Neuropsychopharmacol 2009; 19:192.

18 Reece AS. Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. J Subst Abuse Treat 2009; 37:256–265.

19 Ngo HTT, Tait RJ, Hulse GK. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance therapy or naltrexone implantation. Arch Gen Psychiatry 2008; 65:457–465.

20 Tait RG, Ngo HTT, Hulse GH. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. J Subst Abuse Treat 2008; 35:116–124.

21 Degenhardt L, Gibson A, Mattick RP, et al. Depot naltrexone use for opioid dependence in Australia: large-scale use of an unregistered medication in the absence of data on safety and efficacy. Drug Alcohol Rev 2008; 27:1–3.