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Use of Naltrexone to Treat Opioid Addiction in a Country in Which Methadone and Buprenorphine Are Not Available

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Abstract

Opioid dependence is one of the most severe drug dependencies. Naltrexone is a medication that completely blocks the subjective and other effects of opioids and, when administered to detoxified opioid addicts and taken as directed, prevents relapse and helps maintain abstinence. The major problem with naltrexone is poor compliance, particularly in countries in which there is a treatment alternative based on substitution of illicit opioids such as heroin with orally administered opioid agonists (methadone) or partial agonist/antagonists (buprenorphine). In Russia, substitution therapy is forbidden by law, and naltrexone is the only available pharmacotherapy for heroin dependence. Due to the lack of alternatives to naltrexone and stronger family control of compliance (adherence), naltrexone is more effective for relapse prevention and abstinence stabilization in Russia than in Western countries. Long-acting, sustained-release formulations (injectable and implantable) seem particularly effective compared with oral formulations. This article summarizes the results of studies conducted in Russia during the past 10 years that demonstrate these points.

Keywords

Naltrexone; Opiate dependence; Pharmacotherapy

Introduction

Naltrexone, an opioid antagonist, was approved by the US Food and Drug Administration to treat opioid dependence in 1984. Approval was based primarily on its pharmacologic profile, as it blocks opioid effects by antagonism at the μ-opioid receptors [1•]. The

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blockade is competitive, and the degree of blockade depends on the relative concentration of agonists to antagonists and their affinity for opioid receptors. Naltrexone is a perfect antagonist for treating heroin dependence, as 50 mg (one tablet) blocks the subjective effects of heroin for 24 to 36 h; it is easy to administer (one tablet per day or two tablets every other day), safe (no common serious adverse events if used in recommended doses), well-tolerated (a relatively small number of side effects), and does not have addictive potential; and tolerance does not develop to the opioid antagonism.

However, one problem markedly reduces naltrexone's efficacy and has limited its use for treating heroin and other forms of opioid dependence worldwide: patients often do not like it and do not take it on a daily basis. The dropout rate with oral naltrexone has been better in the limited number of patients in whom there is substantial external motivation to remain abstinent, such as physicians who are in monitoring programs and could lose their license if they relapse, those involved in the criminal justice system who could go to prison if they relapse, and those facing loss of employment [1•, 2–4].

A few US studies have shown positive effects with psychosocial or behavioral therapies. In two, contingency management combined with naltrexone was helpful [5, 6]. In another, naltrexone combined with individual [7] and group [2] psychotherapy yielded positive effects. A third tested a behavioral therapy that used rewards for negative urine tests [8]; however, it had a relatively limited effect and was identified by Nunes et al. [9] as one of several examples indicating that there appears to be a ceiling effect on the degree to which behavioral interventions can be used to improve naltrexone treatment outcomes.

Recent World Health Organization guidelines for the pharmacologic treatment of opioid dependence suggest that the limited evidence available demonstrates that in dependent opioid users who have withdrawn from opioids, those treated with naltrexone are less likely to use heroin or engage in criminal activity than those who do not take naltrexone, but the proportion who continue taking naltrexone has been very low [10••]. However, our recent studies of naltrexone for treating opioid dependence in St. Petersburg, Russia, have shown that in some cultural settings, naltrexone may be much more effective. In particular, Russian law forbids substitution therapy for opioid dependence with methadone or buprenorphine. Naltrexone is the only specific pharmacotherapy that is currently approved for use in the Russian Federation and is available as an oral tablet in extended-release formulations. The results of studies using these formulations are summarized below.

Studies of Oral Naltrexone

Naltrexone Only

Our first relatively small (*n*=52 patients), double-blind, placebo-controlled, randomized trial of naltrexone for opioid dependence began in the late-1990s [11]. At that time, Russia faced a dual epidemic of HIV and heroin addiction that had been spreading rapidly. Treatment of opioid dependence consisted of detoxification and drug-free rehabilitation, but relapse rates were high. We hypothesized that naltrexone may be an effective treatment in Russia for several reasons: 1) heroin addicts are mostly young people living with their parents, who are usually the initiators of treatment and can control the daily process of taking naltrexone; 2) heroin addiction is generally not accompanied by use of other drugs; and 3) use of agonists for addiction treatment is illegal. Thus, naltrexone is the only pharmacotherapy available for treating this disorder. That pilot study evaluated the efficacy of naltrexone for preventing relapse to heroin addiction and reducing HIV risk in a Russian cultural setting. A total of 52 heroin addicts who completed detoxification at addiction treatment hospitals in St. Petersburg and provided informed consent (mean age, 22 years; dependent on heroin for 2.5 years on average) were randomly assigned to a double-blind, 6-month course of biweekly

manualized drug counseling and oral naltrexone, 50 mg/d, or counseling and identical-looking placebo. A close family member (e.g., mother, spouse) agreed to supervise daily dosing. Drug testing and brief evaluations were done at each biweekly visit. Medication compliance was evaluated using a riboflavin marker; more extensive psychometric evaluations were done at 3 and 6 months. A total of 81 patients were asked if they would be interested in participating: 62 gave informed consent, and 52 met study entrance criteria and were randomly assigned. Significant differences in retention and relapse favoring naltrexone were seen beginning at 1 month and continuing throughout the study. At the end of 6 months, 12 of the 27 naltrexone patients (44.4%) remained in the study and had not relapsed, compared with 4 of 25 placebo patients (16%) ($P<0.05$). Among patients who remained in the study, compliance with medication measured by riboflavin in the urine was high (85%–95%), probably a result of the family involvement. Reductions in HIV risk, alcohol use, anxiety, depression, and anhedonia, and improvement in overall function were substantial and about equal in both groups among those who were retained in treatment. However, the proportion of those retained in treatment was significantly higher in the naltrexone group. Thus, the study demonstrated that cultural factors unique to Russia are associated with greater interest and compliance with naltrexone than in the United States [11]. Because heroin addiction is the main route of transmission of HIV in Russia, naltrexone seemed likely to improve treatment outcome and in turn help reduce the spread of HIV if it could be made more widely available. The major limitation for its widespread use is cost: a monthly supply costs about $100 (United States).

Thus, although our first study showed a clear advantage for naltrexone, the number of patients was relatively small, dropout continued to be a problem, and naltrexone did not reduce protracted withdrawal-related psychiatric symptoms. Because an earlier study showed that a selective serotonin reuptake inhibitor (SSRI; citalopram) reduced anxiety, depression, and other protracted withdrawal-related symptoms but did not prevent relapse [12], we hypothesized that combining naltrexone with an SSRI might be additive, with the antidepressant alleviating protracted withdrawal-related symptoms and improving adherence to naltrexone and treatment outcome.

Naltrexone in Combination with Other Psychoactive Medications

Naltrexone and a Selective Serotonin Reuptake Inhibitor—Although our first double-blind pilot study demonstrated that naltrexone was more effective than placebo for relapse prevention in heroin addicts in Russia [11], it provided no data to indicate that naltrexone itself reduced the depression, anxiety, and anhedonia that are typically associated with heroin dependence and withdrawal following detoxification. It is possible that psychiatric symptoms increase the risk for dropout and relapse, and, therefore, antidepressants might alleviate these symptoms and thus improve results of naltrexone therapy. Our next study aimed to test this hypothesis using fluoxetine with and without naltrexone [13]. We chose fluoxetine, as it is approved for use in Russia and was offered at reduced cost by Gideon Richter (Budapest, Hungary), a pharmaceutical company that has provided psychiatric medications to Russia since the end of World War II. This second study was much larger: 280 heroin addicts who completed detoxification at addiction treatment hospitals in St. Petersburg and provided informed consent were included in a 6-month course of biweekly drug counseling and randomly assigned under double-dummy and double-blind conditions to one of four medication groups of 70 participants each: naltrexone (N, 50 mg daily) plus fluoxetine (F, 20 mg daily); naltrexone plus fluoxetine placebo (FP); naltrexone placebo (NP) plus fluoxetine; or naltrexone placebo plus fluoxetine placebo. The primary outcome was relapse to opioid (heroin) dependence. Urine drug testing and brief psychiatric evaluations were conducted at each biweekly visit, and medication compliance was evaluated biweekly using a riboflavin marker; more extensive psychiatric evaluations

were done at 3 and 6 months. Results showed that 414 patients were asked if they would be interested in participating, 343 agreed, and 280 met study entrance criteria and were randomly assigned. At the end of 6 months, 43% of participants in the N plus F group remained in the study and had not relapsed, as compared with 36% in the N plus FP group, 21% in the NP plus F group, and 10% in the NP plus FP group. Based on the survival analysis and retention rate in 6 months, both N plus F and N plus FP were more effective than NP plus FP ($P<0.001$) and NP plus F ($P< 0.01$). Fluoxetine (NP + F) did not differ significantly from NP plus FP, and N plus F did not differ from naltrexone alone (N + FP; $P=0.2$). However, women in the N plus F group showed a trend toward an advantage when compared with women receiving naltrexone and fluoxetine placebo (N + FP; $P=0.08$), probably due to a higher level of depression, anxiety, and anhedonia in women at study intake compared with men. Thus, it was confirmed in this larger study that naltrexone was more effective than placebo for relapse prevention in opioid addicts in Russia. In addition, naltrexone and fluoxetine, or naltrexone alone, were both more effective than fluoxetine alone, although the combination of naltrexone and fluoxetine had a tendency to be more effective than naltrexone alone in women [13]. Overall, the antidepressant did not dramatically improve the naltrexone treatment outcome. It should be added that oral naltrexone was generally well-tolerated, the number of side effects was limited, and neither serious adverse events nor lethal overdose occurred.

Naltrexone and Presynaptic, α-adrenergic Agonists—A small pilot study of opioid-dependent patients ($n=18$) found that a combination of naltrexone and lofexidine (a presynaptic α-adrenergic agonist that has antihypertensive and stress protective properties and reduces opioid withdrawal) may improve naltrexone outcome [14]. The antihypertensive medication lofexidine is used commonly in the United Kingdom and less often in the United States to alleviate symptoms of opiate withdrawal. A pilot study by Sinha and colleagues [14] at Yale University School of Medicine suggested that lofexidine can enhance success rates among patients taking maintenance naltrexone and help them avoid relapse to opioids. After obtaining informed consent that explained all study procedures, the researchers stabilized 18 opioid-detoxified men and women on naltrexone (50 mg) and lofexidine (2.4 mg) daily for 1 month. They then continued all patients on naltrexone for four more weeks but kept eight on lofexidine and gave ten others identical-looking pills containing lofexidine doses that were tapered to zero over several days. Of the 13 patients who completed the study, 80% of those who continued to receive combination therapy submitted opiate-free urine samples throughout the 4-week period, compared with 25% of those tapered to placebo. A follow-up laboratory session that exposed ten of the patients to stressful and opiate-related stimuli showed that lofexidine—but not placebo lofexidine—reduced the patients' reaction to stress, stress-induced opiate craving, and negative emotions (e. g., anger), all of which can trigger relapse [14]. However, these results are considered very preliminary because of the small sample size.

We are presently conducting a large ($n=300$ opioid-dependent patients), randomized, double-blind, double-dummy, placebo-controlled, four-cell study of naltrexone and guanfacine (another presynaptic α-adrenergic ligand used to treat hypertension) in collaboration with Dr. T. Kosten of Baylor College of Medicine. An interim analysis of half the sample did not find a significant additive effect of guanfacine on preventing relapse; however, final conclusions cannot be drawn until analyses have been completed on the entire sample.

In summary, combining naltrexone with fluoxetine (an SSRI) or an α-adrenergic agonist has not demonstrated a significant improvement in treatment outcome, and we have decided to change the direction of our naltrexone research and study long-acting, sustained-release formulations, as they may help solve the problem of compliance.

Studies with Long-Acting, Sustained-Release Formulations

Implantable Naltrexone

The first long-acting, sustained-release naltrexone formulation available in Russia was an implant (Prodetoxon; Fidelity Capital, Moscow, Russia). It contains 1000 mg of naltrexone that is slowly released after being inserted subcutaneously in the abdominal wall via a small incision. It was registered in Russia in 2005 and shown to block opioids for 2 months, but this time frame was extended to 3 months during the past year, based on clinical experience. As of this writing, it is the only officially registered naltrexone implant in the world. We are currently completing a double-blind, double-dummy, placebo-controlled, randomized study of this naltrexone formulation. The final group of patients (n=306) has completed treatment, and outcome data are not yet available. However, we completed an interim analysis of 190 patients in December 2008 [15].

In this study, recently detoxified heroin addicts were randomly assigned to a 6-month course of biweekly drug counseling and one of three medication groups: naltrexone implant every other month plus oral naltrexone placebo (NI + OP, n=66); placebo implant plus oral naltrexone, 50 mg/d (PI + ON, n=62); or double-placebo (PI + OP, n= 62). Medications were administered under double-blind, double-dummy conditions. Urine drug testing and brief psychiatric evaluations were done at each biweekly visit, with more extensive assessments at 3 and 6 months. Oral medication compliance was evaluated using a urine riboflavin marker. An interim analysis showed a clear advantage favoring the implant over oral naltrexone and placebo implant. In particular, the treatment effectiveness score (a sum of heroin-positive and missed urines) favored the implant group over the other two (P<0.01): at the end of the 6-month treatment phase, the treatment effectiveness score in the NI plus OP group was 63%, compared with 87% in the PI plus ON group and 86% in the PI plus OP group. Survival analysis also revealed significantly greater retention in the NI plus OP group compared with the other two groups. The percentage of nonsurgical adverse events (unrelated to minor surgery required to insert the implant) was less than 1%, with no difference between groups; however, surgical side effects (wound infections, local site reactions) were higher in the NI plus OP group (6% of all implantations) compared with the two other groups (1%). All adverse events were successfully treated, and no serious adverse events occurred.

No significant differences were detected between groups in physical and social anhedonia, thus implying that the long-acting naltrexone did not interfere with normal pleasurable stimuli. Similar to our studies with oral naltrexone, psychiatric symptoms (anxiety, depression, opioid craving) were markedly reduced in patients who remained in treatment and did not relapse, and no differences were noted between groups for those who remained in treatment and did not relapse. The efficacy of oral naltrexone was lower in this implant study compared with the previous oral naltrexone studies [11, 13], which may be related to the age of opioid addicts and the degree to which family members could supervise compliance. For example, the mean age of patients in the implant study was 28–29 years, significantly higher than previous studies, in which the average was 21–23 years. These older patients were less likely to be living with relatives, which made it more difficult for the relatives to supervise compliance.

In summary, the Russian long-acting, sustained-release naltrexone implant (Prodetoxon) appears to be safe and more effective than the oral naltrexone and placebo implant for prevention of relapse to heroin dependence [15]. The blockade provided by Prodetoxon is very difficult to override. However, it is possible to accomplish it with a very high dose of heroin (~10-fold compared with the usual daily dose) [16•]. Attempts to overcome the naltrexone implant blockade are not common and are usually unsuccessful because

naltrexone has high affinity for the μ-opioid receptor. If a patient can obtain a large dose of heroin or other opiate, he or she may be able to feel the opioid effects, but they are usually attenuated. Patients on naltrexone have survived even a very high dose of heroin [16•]. Of course, a patient who stops naltrexone and then returns to his or her pre-naltrexone dose of heroin will have diminished tolerance and could suffer a serious or fatal overdose.

Results of two recent randomized trials of another naltrexone implant developed in Australia also demonstrated its advantages over oral naltrexone [17•] and usual-treatment aftercare [18•]. However, these studies did not have a placebo group. Other long-acting, slow-release naltrexone formulations (implantable and injectable) for opioid dependence are being developed and tested [19••].

Implantable naltrexone formulations have several limitations. First, they require a minor surgical procedure that carries with it the risk of wound infections and cosmetic defects. Second, it is possible for the patient to remove the implant within the first few weeks, as Prodetoxon slowly dissolves and can be removed reasonably intact within the first few weeks. Third, in some patients (< 10%), the implant appeared to block opioids for less than 2 months. Therefore, a long-acting, slow-release formulation that is injectable and simple to use and does not require surgery might have some advantages over an implant formulation.

Injectable Naltrexone

Three sustained-release, injectable naltrexone formulations have been developed in the past 10–15 years: Vivitrol (Alkermes, Waltham, MA), Depotrex (Biotech, Bethesda, MD), and Naltrel (DrugAbuse Sciences, Hayward, CA) [20]. Only Vivitrol has US Food and Drug Administration approval. It is administered via a monthly intramuscular injection and approved for prevention of relapse to alcohol dependence. It is available in the United States, Europe, and Russia, and recent studies have found that a monthly intramuscular injection also blocks the subjective effects of opioids [21].

The first published controlled study of a sustained-release formulation for preventing relapse to opioid dependence in the United States was conducted with Depotrex [22]. In a randomized, double-blind, placebo-controlled clinical trial, 60 detoxified, heroin-dependent adults received placebo (n=18), 192 mg (n=20), or 384 mg (n=22) of injectable depot naltrexone monthly for 2 months along with twice-weekly relapse prevention therapy [22]. The 192-mg and 384-mg naltrexone groups had a significantly higher (60% and 68%, respectively) percentage of patients remaining in treatment at the end of 2 months than the placebo group (39%). Time to dropout had a significant dose-related effect, 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 on percentage of negative urine tests for opioids.

The effectiveness of Vivitrol for preventing relapse to opioid dependence is currently being studied in Russia in a phase three, double-blind, placebo-controlled, randomized, multicenter trial whose preliminary results have not yet been published but were released very recently by Alkermes on its corporate website [23]. This study was designed to assess the efficacy and safety of injectable naltrexone compared with placebo in opioid-dependent individuals who were recently detoxified and abstinent from opioids for a minimum of 7 days prior to treatment initiation. A total of 250 participants were randomly assigned to receive once-monthly injections of injectable naltrexone, 380 mg, or placebo in combination with counseling for 6 months. The primary efficacy end point was the response profile based

on the rate of urine drug screens that were free of opioids during the last 20 weeks of the 24-week, double-blind treatment period, as measured by the cumulative distribution of negative urine screens. Secondary efficacy end points were treatment retention, craving, self-reported opioid use, and relapse to physiologic opioid dependence. All participants who completed the randomized portion of the study were eligible to continue in an open-label extension phase and receive Vivitrol once monthly for an additional 13 months in combination with counseling. Safety measures included the number of adverse events and number of serious advised events [23]. Results of this study had not been published as of this writing; however, a press release recently posted to the Alkermes website indicated that this study met all its primary and secondary efficacy end points, with the Vivitrol generally well-tolerated [23]. As earlier with the implantable naltrexone formulation [16•], one case report demonstrated that it is possible to overcome opioid blockade with the injectable formulation; this event occurred during the third week after an injection [24•].

Conclusions

Studies conducted in St. Petersburg, Russia, for more than a decade have demonstrated the efficacy and safety of different naltrexone formulations (oral, implantable, injectable) for relapse prevention and maintenance of abstinence in detoxified opioid addicts. The positive results from different formulations seem related to two cultural factors. One is that relatives can be recruited to supervise daily dosing of the oral formulation. However, this advantage is decreasing as the addicted population ages. The second is that substitution therapy is not available; thus, naltrexone is the only effective medication available, which makes it easier to motivate patients to use it. Preliminary findings from studies of long-acting, slow-release formulations of naltrexone (implantable and injectable) suggest that they are more effective than the oral formulations and are likely to be important additions to current treatments. How they compare with maintenance treatment using methadone or buprenorphine in settings in which these three treatment options are available is a topic for future studies.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1•. Kleber H. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. Dialogues Clin Neurosci. 2007; 9:455–470. This an excellent review of pharmacologic treatments for opioid dependence. [PubMed: 18286804]

2. Roth A, Hogan I, Farren C. Naltrexone plus group therapy for the treatment of opiate-abusing health-care professionals. J Subst Abuse Treat. 1997; 14:19–22. [PubMed: 9218232]

3. O'Brien C, Cornish JW. Naltrexone for probationers and parolees. J Subst Abuse Treat. 2006; 31:107–111. [PubMed: 16919734]

4. Washton AM, Pottash AC, Gold MS. Naltrexone in addicted business executives and physicians. J Clin Psychiatry. 1984; 45:39–41. [PubMed: 6088468]

5. Preston KL, Silverman K, Umbricht A, et al. Improvement in naltrexone treatment compliance with contingency management. Drug Alcohol Depend. 1999; 54:127–135. [PubMed: 10217552]

6. Carroll KM, Ball SA, Nich C, et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. Arch Gen Psychiatry. 2001; 58:755–761. [PubMed: 11483141]
7. Rounsaville, B. Can psychotherapy rescue naltrexone treatment of opioid addiction?. In: Onken, L.; Blaine, J., editors. Potentiating the Efficacy of Medications: Integrating Psychosocial Therapies With Pharmacotherapies in the Treatment of Drug Dependence. Rockville, MD: National Institute on Drug Abuse; 1995. p. 37-52.NIDA Research Monograph series no. 105, NIH publication no. 95-3899
8. Rothenberg JL, Sullivan MA, Church SH, et al. Behavioral naltrexone therapy: an integrated treatment for opiate dependence. J Subst Abuse Treat. 2002; 23:351–360. [PubMed: 12495797]
9. Nunes EV, Rothenberg JL, Sullivan MA, et al. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? Am J Drug Alcohol Abuse. 2006; 32:503–517. [PubMed: 17127538]
10••. World Health Organization. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva, Switzerland: World Health Organization; 2009. The guidelines review the use of medications such as methadone, buprenorphine, naltrexone, and others in combination with psychosocial support in the treatment of individuals dependent on heroin or other opioids. Based on the systematic review of the literature, the guidelines contain specific recommendations on the range of issues faced in organizing treatment systems, managing treatment programs, and treating those who are dependent on opioids
11. Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. J Subst Abuse Treat. 2004; 26:285–294. [PubMed: 15182893]
12. Krupitsky EM, Burakov AM, Didenko TY, et al. Effects of citalopram treatment of protracted withdrawal (syndrome of anhedonia) in patients with heroin addiction. Addict Disord Their Treat. 2002; 1:29–33.
13. 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. [PubMed: 17084785]
14. Sinha R, Kimmerling A, Doebrick C, Kosten TR. Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. Psychopharmacology. 2007; 190:569–574. [PubMed: 17136399]
15. Krupitsky E, Zvartau E, Woody G. Long acting naltrexone implants for heroin dependence. Eur Neuropsychopharmacol. 2009; 19:192.
16•. Kruptisky EM, Burakov AM, Tsoy MV, et al. Overcoming opioid blockade from depot naltrexone (Prodetoxon). Addiction. 2007; 102:1164–1165. This case describes a situation in which an opioid-dependent patient overcame naltrexone implant blockade. [PubMed: 17498182]
17•. 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 the single-dose Australian naltrexone implant in comparison with oral naltrexone. [PubMed: 19805701]
18•. Kunøe 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 Norwegian study compared the Australian implantable naltrexone with usual-treatment aftercare. [PubMed: 19478295]
19••. Krupitsky EM, Blokhina EA. Long acting sustained release formulations of naltrexone for heroin dependence: a review. Curr Opin Psychiatry. 2010; 23:210–214. This is a review of the most recent data on the variety of long-acting, sustained-release formulations of naltrexone (implantable and injectable) and their use for opiate dependence, including their efficacy and safety. [PubMed: 20224403]
20. Volpicelli RG, Fenton M. Sustained-release naltrexone formulations for the treatment of alcohol and opioid dependence. Future Neurol. 2006; 1:389–398.
21. 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. [PubMed: 16499489]

22. 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. [PubMed: 16461865]

23. Alkermes announces positive results from phase 3 clinical study of naltrexone for extended-release injectable suspension for the treatment of opioid dependence. Cambridge, MA: Alkermes; November 16. 2009 Available at http://investor.alkermes.com/phoenix.zhtml?c=92211&p=irol-newsArticle&ID=1355632&highlight

24•. Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. Addiction. 2008; 103:1399–1401. This clinical case demonstrated that it is possible to overcome opioid blockade with Vivitrol and precipitate withdrawal in some circumstances. [PubMed: 18855831]