REVIEW

Long-Acting Injectable Naltrexone for the Management of Patients with Opioid Dependence

Kimberly L. Kjome and F. Gerard Moeller

Department of Psychiatry and Behavioral Sciences, University of Texas-Houston Medical School, Houston, Texas, USA.
Corresponding author email: kimberly.l.kjome@uth.tmc.edu

Abstract: Opioid dependence is a condition with serious clinical ramifications. Treatment has focused on detoxification, agonist therapy with methadone or buprenorphine, or remission maintenance with the opioid antagonist, naltrexone. Treatment with oral naltrexone has been limited by poor treatment adherence and relapse. Studies with long-acting formulations have shown increased treatment adherence. Extended-release injectable naltrexone has been used for the treatment of alcohol dependence, and has recently received an indication for treatment of opioid dependence from the US Food and Drug Administration. Dosing occurs once monthly and existing data with long-acting naltrexone supports efficacy of treatment for opioid dependence; however published data is sparse. Treatment with long-acting naltrexone should be monitored for hepatotoxicity, and patients should be made aware of increased risk of overdose with administration of opioids during and immediately after discontinuation of long-acting naltrexone.

Keywords: opioid dependence, naltrexone, Vivitrol, opioid, heroin

Introduction

Opioid dependence is a prevalent condition in the United States, causing high rates of morbidity among the people afflicted with it. Two main types of psychopharmacological agents have been employed for its treatment, use of mu-opioid agonists to treat withdrawal and prevent illicit use, as well as mu-opioid antagonists, aimed at blocking the euphoric and physiological manifestations of opioid intoxication. Successful treatment is closely linked with compliance, which is higher in treatment with agonist therapy. Poor compliance with treatment has limited the utility of opioid antagonists such as naltrexone as a mainline treatment for opioid dependence.

Numerous studies have tried to enhance adherence to naltrexone in this population, including intensive follow up with different psychotherapeutic modalities, as well as long-acting implants to insure consistent blood levels over longer periods of time. The development of long-acting injectable naltrexone allows for monthly dosing, and has been used to treat alcohol dependence since 2006. Opioid dependence in the United States is no longer limited to heroin use, and is currently characterized by a growing number of people who are dependent on prescription opioids. For this population, treatment is limited to agonist therapy with methadone or buprenorphine, only available through approved distribution centers and specially trained practitioners, respectively. An indication for the treatment of opioid dependence has recently been approved for extended-release injectable naltrexone. This would provide another option in the treatment of opioid dependence, a chronic mental health condition with serious consequences.

Opioid Dependence

Dependence to opioids is defined as the desire to take, difficulty controlling ingestion, manifestation of physiological withdrawal upon cessation or reduction, tolerance to, and loss of function related to the use of a μ-opioid antagonist.[1] Substances ingested in opioid dependence can be illicit, like heroin or opium, or illicitly acquired/misused prescription medications, such as hydromorphone, morphine, hydrocodone, oxycodone, fentanyl, methadone, buprenorphine and codeine. Dependence to opioids has been linked with increased rates of morbidity and mortality, infection, increased health care, criminal consequences, as well psychological suffering for the dependent individual as well as others in their lives.[2] Neurobiologically, opioid dependence develops after ingestion of a μ-opioid receptor agonist in the CNS, elevating dopamine levels in the mesolimbic reward system.[3] Association of ingestion of opioids to sensations of reward can lead increased desire to use, and possibly to opioid misuse and abuse, and over time dependence if other individual and environmental factors are in place. With time, continued use results in tolerance, or need to ingest more opioids to provide same level of euphoria, as well as withdrawal manifestations with cessation of use. Symptoms of opioid withdrawal are unpleasant and include diaphoresis, pain, myadriasis, piloerection, anxiety, diarrhea, nausea, vomiting. Manifestation of withdrawal symptoms is also a driving factor in continuation of opioid dependence.

The rates of opioid dependence in the United States are deceptive. Practitioners classically link opioid dependence to heroin, which has dependence prevalence at about 0.14% in the United States.[4] Rates of prescription opioid abuse are higher, with a prevalence of abuse in the United States at approximately 2 million and rising.[4]

Opioid dependence has classically been treated pharmacologically by maintenance therapy, detoxification and antagonist therapy. Essentially providing a safer substitution for illicit opioids and ability to make opioid detoxification more comfortable, agonist maintenance therapy and detoxification is the most popular form of treatment. Maintenance treatment utilizes μ-opioid agonists or partial agonists to occupy receptor sites, preventing withdrawal manifestations when illicit opioids are stopped, and preventing intoxication by blocking μ-receptor binding of illicit opioids. Methadone maintenance is currently the most successful treatment for opioid dependence, and has high rates of treatment retention and reduces IV opioid use, criminal activity and HIV infection.[5–7] More recently, buprenorphine, a μ-opioid partial agonist, has been used more for maintenance and opioid detoxification due to the ability to dispense it in outpatient clinical settings by specially trained providers rather than specialized clinics, as well as the reduced risk of overdose compared to methadone. The partial agonist properties that make it desirable as a safer alternative for detoxification or maintenance limits its effect at the μ-opioid receptor, resulting in a "ceiling

effect" in efficacy.[8,9] Problems related to treatment with agonist therapy include access limitations, ambiguous treatment protocols, diversion of medications and social stigma.

Treatment with opioid antagonists has been less prevalent, and until recently utilizes daily or every-other day oral doses of naltrexone. Naltrexone is a μ-opioid antagonist that blocks euphoric effects from illicit opioid use, and causes no euphoric effects itself. Oral daily dosing with naltrexone is characterized by low compliance with medication, and poor treatment retention,[10] probably due to naltrexone's lack of reinforcing properties and lack of withdrawal manifestations when treatment is stopped. Compliance with antagonist dosing is lower than agonist therapy, so treatment has been limited to externally motivated patients such as physicians and parolees.

Naltrexone

Originally approved for use in the treatment of opioid dependence by the United States Food and Drug administration (FDA) in 1984, naltrexone is a competitive μ-opioid receptor antagonist with negligible agonist effects, blocking euphoric and physiological effects of opioid agonists.[11,12] Naltrexone does not cause the development of dependence or tolerance over time, and dosing cessation does not result in withdrawal.[13]

Orally dosed naltrexone is subject to first pass metabolism, where it is converted to active (6-β naltrexol) and inactive metabolites.[14] First-pass metabolism of orally dosed naltrexone is high, evidenced by the peak dose of naltrexone and its metabolites 1 hour after oral dosing.[15] Serum half-life for chronic oral administration is approximately 10 hours.[15] The half-life, when compared to naloxone, another μ-opioid antagonist, is longer, and naltrexone is able to block the agonist effects of other opioids for 48 hours.[16] Oral dosing is accomplished by either 50 mg daily dosing or three times weekly dosing with two 100 mg doses and one 150 mg dose.

Naltrexone Use for Opioid Dependence: The Issue of Compliance

The value of naltrexone for the treatment of opioid dependence has been investigated, and has been limited by its ability to maintain patients in treatment for illicit opioids compared with agonist therapies.

Long-lasting injectable formulations of naltrexone have been developed, based on improved compliance and outcome from trials using sustained-release formulations of naltrexone. With compliance, naltrexone has shown success for relapse prevention.[17–19] Patients who continue to take naltrexone have also shown improvement in employment status and reduction of legal and social problems stemming from dependence.[20]

Despite the ease of outpatient dosing and its ability to effectively block the euphoric effects of μ-opioid agonists, naltrexone has had limited success for relapse prevention when compared with maintenance therapy with methadone or buprenorphine. Studies have shown that fewer patients choose to start treatment with naltrexone,[21] and few of those remain compliant with medications.[22,23] Patients who have been treated previously with methadone are also less likely to sustain opioid abstinence with naltrexone compared with individuals who had only had naltrexone for treatment of opioid dependence.[24–26] Poor compliance with naltrexone is also associated with higher dosages of heroin used daily.[26] Of patients in treatment with naltrexone, many drop out quickly within the first few weeks, especially if they used opioids again after missing naltrexone doses.[27] The numbers of drop-outs from naltrexone treatment are very high, with over one quarter dropping out after a few days,[28] and almost one-half dropping out in first few weeks.[29]

Mitigating factors for poor compliance with oral naltrexone include contingency management and other forms of therapy, which are found to increase compliance with oral naltrexone.[30,31] However, treatment of opioid dependence with oral naltrexone and contingency management is still characterized by high drop-out rates.[31]

Naltrexone has been more useful in treating opioid dependence in populations with external motivation to remain in treatment, including people in the criminal justice system, physicians, and other individuals with employment in jeopardy.[12] Despite the ability to induce abstinence from opioids with consistent naltrexone dosing and corresponding consistent μ-opioid receptor blockade, lack of compliance with oral dosing has limited the application of oral naltrexone as a treatment for opioid dependence, especially when effective and more popular agonist therapies are present.

Sustained-Release Naltrexone Implants

In order to overcome the issues of poor treatment adherence with oral naltrexone, a number of sustained-release implants have been developed internationally for use in alcohol and opioid dependence. A non-randomized retrospective review examined two types of sustained-release naltrexone implants, oral naltrexone, and historical controls revealed a significant difference between immediate and sustained-release injectable naltrexone in individuals opioid-free 12 months after initiating treatment. Rates combined for the two types of naltrexone implants were 82% opioid free at 12 months compared to 58% opioid free for the oral naltrexone group, and 52% for the historical control group.[32]

Due to legal limitations on agonist therapy for the treatment of opioid dependence, Russian research has focused on antagonist treatment, especially treatments using sustained-release formulations for naltrexone. A randomized, controlled trial over 6 months examined 3 medication groups (n = 102 per group) receiving naltrexone implant (1000 mg, implanted every two months) and oral placebo, oral naltrexone (50 mg/d) and placebo implant, or double placebo was conducting using urine drug testing and oral medication compliance markers as measures. Opioid positive urines at 6 months were lowest in the naltrexone implant group (63%), and higher in the oral naltrexone and placebo trials (87 and 86%, respectively). Retention was also significantly higher in the naltrexone implant group compared to the other groups ($P < 0.01$).[33]

In part related to compliance, the maintenance of consistent blood levels of naltrexone may be an important factor in the success of sustained release formulations over daily doses of naltrexone. A randomized, double-blind, double placebo controlled trial examined naltrexone sustained-release implants versus daily oral naltrexone in heroin dependent individuals.[34] The study examined safety and efficacy over a 6-month period of time and enrolled 70 heroin dependent adults to receive either 50 mg/d oral naltrexone plus placebo implants for 6 months or single dose 2.3 g naltrexone implant plus placebo tablets. More patients enrolled in the oral naltrexone group had plasma naltrexone levels less than 2 ng/ml in month one ($P = 0.001$) and month two ($P = 0.01$).

In the implant group, patients maintained plasma naltrexone levels between 1 and 2 ng/ml longer in the naltrexone implant group. More patients receiving oral naltrexone had also resumed heroin use by the end of 6 months compared to the naltrexone implant group ($P = 0.003$), and had resumed heroin use earlier (115 days versus 158 days). This study illustrates the relationship of consistent plasma naltrexone levels to opioid abstinence, due to a more effective μ-opioid receptor blockade.

Pharmacodynamic and Pharmacokinetic Characteristics of Extended-Release Injectable Naltrexone

On October 12, 2010, the US Food and Drug Administration (FDA) approved the use of naltrexone for extended-release injectable suspension (Vivitrol, Alkermes) for relapse prevention in opioid dependent patients after detoxification treatment. The approval was in response to poor compliance with oral naltrexone and promising outcomes with the use of sustained-release formulations of naltrexone for relapse prevention in opioid dependence. Extended-release injectable naltrexone is not a new pharmacological agent, and has had FDA approval for relapse prevention in alcohol dependent patients since 2006.

After intramuscular injection, naltrexone is released from the proprietary polymer microspheres in phases via diffusion and polymer erosion. Release of naltrexone into blood plasma takes place in phases. The initial phase occurs in the first 24 hours and releases surface drug from the injection site. Afterward, the injection site undergoes hydration within 48 hours of injection, and a sustained-release phase occurs over 30 days post-injection release drug via polymer microsphere erosion.[35] Plasma levels are not significantly dependent on weight, creatinine clearance, age, gender, or hepatic function.[36] Another significant issue related to extended-release injectable naltrexone is the avoidance of first-pass metabolism to 6-β-naltrexol.[35] This metabolic step is significant in oral dosing, since the ratio of naltrexone to 6-β-naltrexol quickly reaches 1:10, with the much less active metabolite more predominant than naltrexone.[37] Plasma naltrexone levels after dosage with long-acting naltrexone formulations consistently stays above 2 ng/ml longer, a cited

therapeutic level for opioid relapse prevention.[35,38,39] Injections are given intramuscularly every four weeks, in alternating gluteal regions.

Results of Clinical Studies Examining Long-Acting Injectable Naltrexone for Opioid Dependence

A randomized, double-blind, placebo-controlled trial examined the treatment efficacy of long-acting inject-able naltrexone (Naltrel, DrugAbuse Sciences) for relapse prevention in 60 heroin-dependent individuals. Patients were stratified by sex and years of heroin use and randomized to receive placebo, 192 mg, or 384 mg of long-acting naltrexone intramuscular injections dosed on weeks 1 and 5. In addition to medication, patients received relapse prevention therapy and had urine monitored for drug relapse. At the end of 2 months, 39%, 60% and 68% of the placebo, 192 mg naltrexone and 384 mg naltrexone groups, respec-tively were still in treatment. Mean treatment drop-out occurred in 27 days, 36 days, and 48 days for the placebo, 192 mg naltrexone and 384 mg naltrexone groups. Assuming that missing urine samples were positive, patients receiving placebo had the lowest mean percentage of negative urine samples (25.3%), with the highest mean percentage of negative urine samples in the patient group receiving 384 mg of naltrexone (61.9%). There was a significant main effect of group ($P = 0.03$), but without assumption of miss-ing urines being positive, was no longer significant. This study highlighted the issues of treatment reten-tion with long-acting injectable naltrexone, but was limited by small sample size, and direct comparison to treatment retention with oral naltrexone.[40]

Another study utilizing a quasi-experimental design compared early treatment retention and opioid use confirmed by urine in opioid-dependent patients in two concurrent randomized clinical trials of oral (n = 69) and extended release injectable naltrexone (n = 42). Patients receiving long-acting injectable naltrexone (Depotrex, BioTek) had higher mean days retained in treatment ($P = 0.012$), and in subanaly-sis found that patients with more severe heroin use had better treatment retention with oral naltrexone and therapy than long-acting injectable naltrexone and therapy. The therapeutic modalities employed in the two studies were different, and the authors attributed the improved retention in the severe heroin use group to the intensive psychosocial treatments they received in addition to oral naltrexone. This study is a prelimi-nary study, and limited by the different study designs employed with the different routes of dosing. Further studies with more subjects, consistent use of psycho-therapeutic modalities for different pharmacologic treatment arms, comparison of efficacy with oral nal-trexone, and efficacy not only in heroin dependence but other types of opioid dependence are necessary to characterize the efficacy of long-acting injectable naltrexone.[41]

In a small non-controlled case series, Fishman et al examined the use of extended-release injectable nal-trexone (Vivitrol, Alkermes) in opioid dependent adolescents. Of 16 cases where the subject received extended-release naltrexone, 10 were retained for at least four months in treatment (63%), and 9 (56%) had a good outcome defined by decreased use of opi-oids, improved psychosocial function, and no new substance use problems. This study is a small, pre-liminary study to look at feasibility of treatment with extended-release injectable naltrexone in an adoles-cent population, and does not provide comparison of treatment outcomes with this agent compared with oral naltrexone or buprenorphine, the other agents administered at their treatment site. The study is useful in regards to the treatment population, given the limited means of treating opioid dependence in adolescence.[42]

Findings from a 24-week randomized controlled trial comparing extended-release injectable naltrex-one (Vivitrol, Alkermes) to placebo in individuals with current opioid dependence have been consid-ered in the recent indication for extended-release injectable naltrexone for the treatment of opioid dependence. In this trial, subjects having completed 30-day detoxification were recruited from 13 sites in Russia received either 380 mg intramuscular injec-tions of extended-release naltrexone (n = 126) or pla-cebo injection (n = 124) every 4 weeks for 24 weeks. Primary outcome data of opioid abstinence, mea-sured by urine and self-report as well as secondary data including opioid craving, dependence relapse and study retention were measured. Opioid-free weeks from week 5 to 24 were significantly differ-ent between treatment groups ($P < 0.0002$), with a median of 90% percent of opioid-free urines in the

extended-release naltrexone group and 35% in the placebo group. Total abstinence measured as 100% opioid-free weeks in weeks 5 through 24 was 35.7% in the extended-release naltrexone group versus 22.6% in the placebo group. With extended-release naltrexone, subjects reported a 50% mean reduction in subjective craving compared with no change in craving for subjects receiving placebo, and retention in the extended-release naltrexone group was significantly longer compared to the placebo group (168 days vs. 96 days, $P = 0.0042$).[43]

Long-acting Injectable Naltrexone Formulations and Safety

At this point, long-acting injectable naltrexone is well tolerated, with one of the studies above reporting no significant difference in overall adverse events, treatment related adverse events or discontinuations due to adverse events between the group receiving placebo, 192 mg injectable naltrexone, or 384 mg injectable naltrexone (Naltrel, DrugAbuse Sciences).[40] Most treatment related events were related to administration site conditions and "general disorders" and included fatigue, injection site induration, and injection site pain, and were reported in all three groups. Common adverse reactions related to long-acting naltrexone injection are injection site reactions, nausea, vomiting, headache, insomnia, anorexia, elevated liver enzymes, and depressed mood. Serious adverse reactions related to naltrexone are depressed mood and suicidality, opioid withdrawal in patients who have not undergone appropriate withdrawal prior to starting naltrexone, hepatotoxicity, injection site reactions, abscess and necrosis, anaphylaxis, cholelithiasis, cholecystitis, and eosinophilic pneumonia. Hepatotoxicity and issues related to treatment with naltrexone and opioid use patterns will be addressed further.

Naltrexone in all forms carries a black-box warning for hepatotoxicity, and warnings for use in patients with elevated hepatic enzymes and acute hepatitis. Oral and injectable naltrexone is also indicated for alcohol dependence, a condition that can lead to chronic hepatic disease. One study examining the tolerability of oral naltrexone in 74 alcohol dependent individuals over a 12 week period showed that therapeutic dosages of oral naltrexone (25 mg daily the first week, then 50 mg daily) did not result in increased levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) for all but one patient. What was observed was a significant decrease in AST and ALT levels throughout the study in subjects who continued naltrexone use, prompting the authors to hypothesize that as alcohol dependence improved with therapeutic dosages of naltrexone, hepatic function improved.[44] This study did have one patient with significantly elevated liver enzymes which may indicate that hepatotoxicity may occur in some patients receiving therapeutic dosages of naltrexone.

Hepatotoxicity resulting from extended-release injectable naltrexone (Vivitrol, Alkermes) has also been examined in alcohol dependence. Patients were randomly assigned to receive extended-release injectable naltrexone at a dose of 380 mg (n = 205), 190 mg (n = 210), or placebo (n = 209). All groups had infrequent elevation in hepatic enzymes greater than three times the upper limit and/or hepatic events. No significant difference was seen in levels of ALT, AST, or bilirubin between groups at initiation or at other timepoints. Of interest were decreases in gamma-glutamyltransferase (GGT) in the group receiving 380 mg of injectable naltrexone after initiation of treatment compared with placebo. The study also identified higher risk subject-patients who were drinking heavily throughout the study, obese patients

Table 1. Long-acting injectable naltrexone formulations.[50]

Name	Maker	Duration	Route	Formulation	Dosage	Clinically available
Vivitrol	Alkermes	4 weeks	Gluteal IM	Microsphere suspension, single use administration mechanism	380 mg	Yes
Depotrex	BioTek	3–4 weeks depending on dosage	Gluteal IM	Microcapsule suspension, single use vial	192 and 394 mg	No
Naltrel	DrugAbuse sciences	4 weeks	Gluteal IM	Microsphere suspension, single use vial	150 and 300 mg	No

and those taking NSAIDS. There was no increase in hepatic enzymes or hepatic-related adverse events with injectable naltrexone compared to placebo.[45]

Information about hepatotoxicity with naltrexone in alcohol dependence is helpful and applicable to treatment of opioid dependence with naltrexone. Though opioids are not as hepatotoxic as alcohol, patients who have used opioids may have used them intravenously, putting them at increased risk for hepatitis C infection and resultant hepatic disease. Controversy has surrounded the use of naltrexone in patients with existing hepatitis and liver disease. A literature review characterizing the relationship of naltrexone to hepatic function found that no evidence exists to suggest that naltrexone causes liver disease or exacerbates pre-existing liver disease, and has been safely used in case reports of patients with severe cirrhosis and liver disease. Also noted in their review, naltrexone had not caused a case of clinically significant liver disease.[46]

Another concerning issue related to use of naltrexone in general as well as long-acting injectable naltrexone is opioid overdose with relapse. With chronic opioid use, there is a down-regulation in μ-opioid receptors throughout the body, which leads to symptoms of tolerance and an increased need to consume more opioids to achieve the same levels of euphoria. Naltrexone functions as a μ-opioid antagonist, and consistent dosing can lead to increased sensitivity to opioids in an individual previously tolerant to larger doses of opioids. Naltrexone is also believed to antagonize euphoric effects of opioid agonists more than respiratory and cardiovascular effects.[47] This would be an issue for an individual who may try to override a naltrexone-induced antagonism with higher doses of opioids, leading to respiratory depression and death before full euphoric effects are reached. Individuals who cease treatment with naltrexone are at significantly increased risk of overdose and resulting death from opioid use compared to those continuing treatment, especially in the first two weeks out of treatment.[48] In addition to lack of μ-agonist effects of opioids during treatment with naltrexone either by remission or effective mu-opioid receptor blockade, up-regulation of μ-opioid receptors in response to receptor blockade with naltrexone occurs in animals.[9]

Based on this data, as well as existing recommendations for providers provided by the manufacturer, all patients starting treatment with naltrexone need to be carefully advised about the use of opioids during and after active dosing. Patients should be told they will be more sensitive to lower doses of opioids after treatment with naltrexone and that administration of large dosages or previously tolerated dosages of heroin or other opioids while or after taking naltrexone my lead to injury, coma or death as a result of overdose. This warning, as well as warnings about reduced effectiveness of all opioids including pain medications like hydrocodone, oxycodone, morphine and codeine as well as antitussives such as codeine and dextromethorphan and antidiarrheals such as loperamide should be delivered before and during treatment with naltrexone.

Conclusion

Naltrexone is a mu-opioid antagonist that has been previously used in remission maintenance of opioid dependence. The efficacy of naltrexone treatment has been limited by complex issues of treatment adherence, which has limited its role in opioid dependence treatment compared to μ-opioid agonist therapy. Long-acting formulations, including implantable and injectable naltrexone may increase compliance by insuring consistent blood levels of naltrexone and μ-opioid receptor blockade, as well as limiting treatment discontinuation during the dosage interval. Although there is preliminary evidence supporting efficacy of long-acting injectable naltrexone for maintaining treatment adherence for opioid dependence, research that has been published to date does not compare it to adherence with oral naltrexone or agonist maintenance in a controlled fashion. While the issue of treatment adherence and naltrexone is a sound issue to explore, more data in support of treatment with long-acting injectable will further characterize the role of antagonist-mediated treatment for opioid dependence.

Long-acting injectable naltrexone has some of the same safety concerns as oral naltrexone, including a small but documented risk of hepatotoxicity and increased risk of overdose with opioids. Patients should be assessed individually in regard to their health status, concomitant medications, hepatitis status and risks and benefits profile when deciding to start treatment with naltrexone. They should also be warned at onset of treatment regarding hepatotoxicity

signs and symptoms, as well as risk of overdose and death with ingestion of opioids during treatment with naltrexone and soon after discontinuation of treatment with naltrexone.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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