REVIEW

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Naltrexone Depot Formulations for Opioid and Alcohol Dependence: A Systematic Review

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SUMMARY

Naltrexone is an opioid receptor antagonist that blocks the reinforcing effects of opioids and reduces alcohol consumption and craving. It has no abuse potential, mild and transient side effects, and thus appears an ideal pharmacotherapy for opioid dependence. Its effectiveness in alcohol dependence is less evident, but compliance with naltrexone combined with psychosocial support has been repeatedly shown to improve drinking outcomes. Limited compliance with oral naltrexone treatment is a known drawback. Several naltrexone implant and injectable depot formulations are being investigated and provide naltrexone release for at least 1 month. Studies among opioid-dependent patients indicate significant reductions in heroin use, but sample sizes are usually small. In alcohol dependence, two large multicenter trials report alcohol and craving reductions for naltrexone and placebo groups, indicating a significant but moderate effect. The pharmacokinetic profile of the injectable formulation indicates reliable naltrexone release over 1 month at therapeutic levels. Implant formulations releasing naltrexone up to 7 months are reported. Findings on safety and tolerability confirm the generally mild adverse effects described for naltrexone tablets. However, further research on therapeutic levels (i.e., opioid blocking) is warranted. The majority of naltrexone implants lacks approval for regular clinical use and larger longitudinal studies are needed. The available naltrexone depot formulations have the potential to significantly improve medication compliance in opioid and alcohol dependence. In certain circumstances, they may constitute a promising new treatment option.

Introduction

The endogenous opioid system has several important regulatory functions. The three main opioid receptor (OR) subtypes (μ, γ, and δ) modulate the transmission of dopaminergic, noradrenergic, and serotonergic neurons. Consequently, endogenous opioids influence the motivational, the stress-regulating, and the mood-regulating systems [1]. The motivational system and the neurotransmitter dopamine have primary importance in substance dependence. Behaviors that increase dopamine levels such as the use of psychoactive substances will be linked to *wanting* and *liking*. Repeated stimulation with psychoactive substances is followed by neuroadaptation that may lead to a decrease in *liking* and an increase in *wanting* [2]. These changes are believed to be maintained by substance induced genetic rearrangements of cell functioning, and appear to take a major part in maintaining addictive behavior, that is, the individual's impaired ability to regulate or limit the use of the psychoactive substance [3].

An ideal pharmacotherapy to prevent and treat substance dependence would lie in blocking the reinforcing, agonistic effects of the substance of abuse. Relapse to substance use would not have a reinforcing effect. Continuously blocking the receptors might even allow reversal of the cellular adaptations and reinstatement of normal functioning. For decades, several antagonist pharmacotherapies for drug dependence have been investigated. The primary focus has been the impaired OR system as hypothesized for opioid dependence and this rationale has resulted in extensive research on OR antagonists [4]. Naltrexone, developed in the 1970s by National Institute on Drug Abuse (NIDA), has been the most widely investigated opioid antagonist and its metabolism is well characterized [5–7]. It is a competitive, nonselective, specific OR antagonist with highest affinity at the μ-receptor [8].

Naltrexone has been shown to effectively block heroin effects in humans [9,10]. Plasma levels of 1–2 ng/mL are suggested to block clinically relevant doses (e.g., 25 mg) of intravenously administered heroin (diacetylmorphine), but this issue needs further

investigation [7,11]. Naltrexone has been found to reduce craving for alcohol in rhesus monkeys [12] and among alcohol-dependent patients [13]. In amphetamine dependence, reduced craving during naltrexone treatment has recently been reported [14,15]. The neurobiological mechanisms by which naltrexone reduces craving are not fully understood, but two main hypotheses have emerged. Since the effects of alcohol and amphetamine in the motivational system are partly mediated through ORs [16,17], the receptor blocking with naltrexone could explain the reduction in craving. In alcohol-dependent subjects, naltrexone has been found to augment plasma cortisol and adrenocorticotropic hormone (ACTH) levels through activation of the hypothalamic–pituitary–adrenal (HPA)-axis, which is found to be related to reduced urge and amount of alcohol drinking [18].

Limited compliance with oral naltrexone in opioid and alcohol-dependent patients is described as the main drawback [19,20]. Two strategies seem promising in order to secure long-term naltrexone treatment [21]. One is contingency management [22] and the other is naltrexone depot formulations [23]. Achieving good tolerability in conjunction with sufficient naltrexone release (above 1–2 ng/mL) over at least 4 weeks has been a major challenge [23,24]. Recently, an injectable, once-a-month depot (Vivitrol®, Alkermes, Waltham Massachusetts, USA) has been Food and Drug Administration (FDA)-approved for the treatment of alcoholism and it is under FDA review to receive approval for opioid dependence. Naltrexone implants with 3–6 months duration are also being investigated for the treatment of opioid dependence.

This article systematically reviews the literature on naltrexone depot or implant treatment for alcohol and opioid dependence. Apart from treatment effect outcomes such as reduction in heroin use and alcohol consumption, data on safety and tolerability were considered. Also, the pharmacokinetic (PK) characteristics of the various formulations are described.

Literature Search

A systematic search of seven electronic databases from their inception to December 2009 was performed: CINAHL, The Cochrane Library, EMBASE, ISI Web of Knowledge, LILACS, MEDLINE, and PsycINFO. The search strategy was developed in cooperation with the Cochrane Drugs and Alcohol Group, and the first search was performed in November 2007. The following terms were used for the MEDLINE and EMBASE search: (1) naltrexone.mp; (2) exp sustained release preparation/; (3) exp sustained drug release/; (4) implant$.ab,ti; (5) depot$.ab,ti; (6) (delay$ adj2 action).ti,ab; (7) 2 or 3 or 4 or 5 or 6; (8) 1 and 7; (9) limit 8 to human. The review including the search strategy in detail for each database is available online [25]. The search was updated in December 2009, and the inclusion criteria were extended to any report on the use of naltrexone depot formulations for opioid or alcohol dependence. Besides randomized controlled trials, longitudinal studies with or without a control condition and case reports were included. Excluded were review articles, comments, letters, editorials, press releases, and abstracts from conference proceedings unless previously unpublished data was reported or a full text report was available. Two authors independently assessed all potentially eligible reports. Disagreement was resolved by discussion, if necessary with a third author. Figure 1 gives an overview on study identification and inclusion process. Table 1 briefly summarizes the included studies. Since several different study designs, types

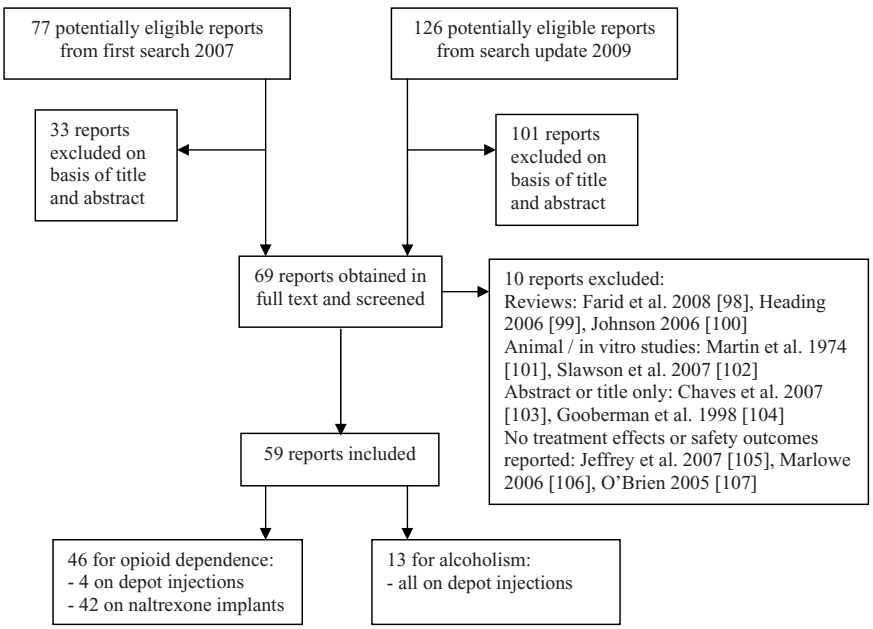

Figure 1 Study identification process from the systematic literature search in November 2007 and the update performed in December 2009.

Table 1 Included reports on treatment effects and tolerability by first author and year of publication

Randomized-controlled trials	Target population (n) and comparison group	Type of naltrexone depot formulation	Main findings for the investigated formulation
Kranzler 2004	Alcohol-dependent (315), placebo-controlled	Monthly injectable during 3 months follow-up	Reduced drinking and greater abstinence rate
Garbutt 2005	Alcohol-dependent (624), placebo-controlled	Monthly injectable during 6 months follow-up	Reduced heavy drinking
Comer 2006	Opioid-dependent (60), placebo-controlled	Monthly injectable during 2 months follow-up	Reduced heroin use and more time spent in treatment
Hulse 2009	Opioid-dependent (70), oral naltrexone	Three months implants	Reduced heroin relapse rates
Kunøe 2009	Opioid-dependent (56), usual-treatment aftercare	Six months implants	Reduced heroin use
Other effect studies	**Condition/intervention**	**Comparison group**	**Main outcomes**
Ciraulo 2008, Lapham 2009, O'Malley 2007, Pettinati 2009	Alcohol dependence/injectable naltrexone	Placebo-controlled trial; same sample as in Garbutt 2005	Quality of life and treatment response
Carreno 2003, Colquhoun 2005	Opioid dependence/naltrexone implants	Oral naltrexone	Opioid use and time spent in treatment
Foster 2003, Gölz 2000, Grusser 2006, Hulse 2003a and b, Reece 2007 and 2009a, Waal 2003 and 2006	Opioid dependence/naltrexone implants	Single group studies; some with a control group of convenience	Opioid use, feasibility in research and primary care settings, naltrexone blood levels
Hulse 2005, Ngo 2007 and 2008, Tait 2008a and b	Opioid dependence/naltrexone implants	Cohorts receiving naltrexone or methadone, database linkage design	Morbidity and mortality
Safety and tolerability	**Condition/Intervention**	**Comparison group**	**Main outcomes**
Lucey 2008	Alcohol dependence/injectable naltrexone	Placebo-controlled trial; same sample as in Garbutt 2005	Hepatic safety
Brewer 2004, Gibson 2007, Hamilton 2002, He 2008 and 2009, Hulse 2008, Lintzeris 2008, Oliver 2005, Reece 2009b	Opioid dependence/naltrexone implants	None	Overdose death and other severe adverse events, hepatic safety, cognitive impairment, biodegradability
Brewer 2002, Fishman 2008, Kruptisky 2007, O'Brien 2006, Sullivan 2006	Opioid dependence/naltrexone implants or injectables	None	Blockade overriding with opioid agonists
Hulse 2002a and b, 2003c, 2004c	Opioid dependence during pregnancy/naltrexone implants	None	Obstetric and neonatal

of depot formulations, and patient populations were included, the methodological heterogeneity among the studies was high. Therefore, meta-analyses of pooled outcome measures across study samples were considered inappropriate and not performed.

Treatment Effects in Alcohol Dependence

Two multicenter, double-blind, placebo-controlled trials were conducted in the US investigating three different dosages of once-a-month injectable naltrexone [26,27]. In both trials participants who received naltrexone or placebo injections reported reductions in alcohol consumption. These reductions were inconsistent in regard of treatment condition indicating a moderate effect size of depot naltrexone.

In the first trial with 315 participants over 3 months, the naltrexone (300 mg) group reported fewer days to the first drink and more abstinent days compared to placebo [26]. However, time to first heavy drinking day showed no difference between the groups. In both groups the γ- glutamyl transferase (GT) values improved throughout the study indicating clinically significant reductions in alcohol consumption. In the subsequent trial 624 alcohol-dependent subjects received up to six monthly injections of naltrexone depot in two dosages (190 or 380 mg) or placebo [27]. The rate of heavy drinking days was found to be 25% lower in the 380-mg group compared to placebo. However, naltrexone treatment did not show a significant advantage in terms of reduction in risky drinking (more than one or two drinks per day) or any drinking. Also, γ-GT values showed no additional improvement

in the naltrexone groups compared to placebo. Attrition rates did not differ across the three groups. Quick treatment response after the first 380-mg naltrexone injection predicted a sustained reduction in alcohol consumption over the 6 months follow-up [28]. In the subgroup that achieved abstinence before treatment start, the 380-mg naltrexone group maintained abstinence significantly longer and reported a greater reduction in alcohol consumption and craving than the placebo group [29,30]. In the full sample, quality of life showed improvement on mental health but not on physical health scores for the 380-mg naltrexone group compared to placebo [31].

The reduction in alcohol drinking and craving that was found in both studies did not unequivocally support the advantages of the naltrexone injections compared to placebo. This finding is in line with inconsistent results from oral naltrexone studies [20,32]. A possible explanation of the mixed results may be performance bias, that is, the participants in double-blinded trials receiving a new, experimental pharmacotherapy may be more likely to report superior outcomes. Another explanation could lie in the psychosocial counseling that was given to placebo and naltrexone participants, which may have made it more difficult to detect a specific effect of the pharmacotherapy. Genetic polymorphism in the μ-OR gene has been related to differential patient response to oral naltrexone treatment and a single transcription factor has been suggested to predict improved drinking outcomes [33,34]. These findings may explain the mixed results and need to be replicated for depot formulations. Further, longitudinal studies of naltrexone depot formulations with or without psychosocial counseling for alcohol-dependent outpatients are warranted and objective markers for alcohol consumption such as ethyl glucoronide should be used. Reasons for nonreturn to treatment should also be investigated considering gender, motivational, and tolerability aspects. Future research on naltrexone depot formulations need to assess the possible impact of reduced blood level variations on drinking outcomes and the possible benefits of receiving monthly (depot) versus daily (oral) medication to compliance, treatment retention, and dropout. Optimal naltrexone blood levels to reduce craving for alcohol need to be established.

Treatment Effects in Opioid Dependence

Findings from three randomized-controlled trials suggest that patients receiving treatment with sustained-release naltrexone use less opioids than patients who receive placebo injections [35], usual-treatment aftercare [36], or oral naltrexone treatment [37]. This is consistent with findings from controlled trials [38,39] and cohort studies or case reports [40–47]. In a pilot study of abstinence 6 months postexpiry of naltrexone release, 8 of 12 naltrexone implant patients had remained abstinent [48].

A reduction in the number of hospital presentations of opioid-dependent patients for physical as well as psychiatric reasons has been shown in several registry-based studies [49–52]. These reductions appear to be greater than those produced by treatment with opioid agonists like methadone or buprenorphine [53–55], although the absence of randomization means these differences could also be due to selection factors.

Retention in treatment is a main concern in the treatment of opioid dependence, as relapse to opioid use following a period of abstinence is associated with greatly elevated risk of overdose and overdose death [56]. Only one study has reported data on retention in naltrexone depot treatment: 32% of the opioid-dependent patients discontinued treatment between the first and the second monthly naltrexone depot injection [35]. The sample receiving therapeutic dosages of naltrexone was small (n = 20), and no data on posttreatment overdoses were provided. One case study has documented that deaths and overdoses do occur following treatment discontinuation [57]. Preclinical literature indicates that naltrexone may cause OR upregulation [58,59]. However, the significance of this finding for human samples is still unclear; longitudinal controlled studies that investigate overdose death rates in former naltrexone patients compared to other abstinent patients at risk of relapse are lacking. Before naltrexone induction, one case of relapse and subsequent fatal overdose has been reported in a patient who discharged himself from detoxification [36]. Autopsy studies have also identified cases of naltrexone implant patients who have died during and after ultra rapid opioid detoxification in outpatient settings [60], or experienced nonfatal adverse events during treatment or induction onto naltrexone [61,62].

Self-testing of the competitive antagonist blockade with heroin or other agonists may occur; two case studies reported patients who challenged the antagonist blockade with very high doses of opioids and experienced an agonist effect [63,64]. As these case reports lack data on plasma levels of naltrexone, opioids, or other substances, it is unclear whether or not these findings are consistent with human laboratory studies reporting the effective blocking provided by naltrexone depot formulations [7,11,65].

For opioid dependence, treatment effect findings give reason for cautious optimism: several small studies, a few of which are randomized-controlled trials (RCTs), suggest that treatment with naltrexone depot formulations leads to significant reductions in opioid use and improved secondary outcomes such as reduced hospital presentations for overdose or psychiatric reasons. Larger controlled trials comparing naltrexone depot formulations with naltrexone tablets or agonist maintenance treatment are needed to confirm these findings and to provide prospective data on safety and tolerability.

Mode of Administration

Naltrexone depot formulations are available as injectables or implants. The implants are surgically inserted into the subcutaneous tissue and release naltrexone for several months. They can be removed surgically upon patient request or if opioid analgesia becomes necessary. Apart from the Russian Federation, no country has approved regular use of naltrexone implants outside of research settings. The injectable formulation Vivitrol is FDA approved for alcohol dependence. It needs to be administered monthly to maintain sufficient naltrexone blood levels. Injectable naltrexone cannot be removed if opioid analgesia becomes necessary. However, the analgesic blockade provided by naltrexone is competitive and during general anesthesia it can be overridden with potent opioid agonists such as fentanyl. The clinical challenge of pain management during treatment with naltrexone depot

formulations has been acknowledged [93]. The systematic search did not retrieve a report that directly compared injectable and implant formulations.

Injectable Depots: Development and PK Properties

Five studies investigated PK and safety outcomes among alcohol-dependent subjects, one among healthy volunteers, and one among an opioid-dependent sample. The injectable naltrexone depots were administered intramuscularly in the gluteal region in dosages ranging from 75 to 400 mg [66–72]. In these studies, three different pharmaceutical companies supplied injectables, which contained naltrexone loaded microspheres of poly-lactide (PLA) or poly-lactide-co-glycolide (PLA-PGA) polymers.

The (PLA-PGA) polymer formulation Vivitrol containing 380 mg of naltrexone has been agreed upon and received FDA approval for treatment of alcohol dependence in April 2006. This formulation releases naltrexone at levels above 1 ng/mL for about 4–5 weeks [71] and findings from alcohol- and opioid-dependent patients suggest that it is not necessary to adjust the dosage to weight, age, gender, or health status [70].

Implants: Development and PK Properties

Although several types of naltrexone implants are commercially available and used in private clinic settings, usually for opioid dependence, our systematic literature search retrieved PK data on only three formulations, with the most extensive data on an Australian-produced implant (O'Neil Implant®, Go Medical Industries, Perth, Australia) [48,73,74]. This formulation consists of 10 pellets containing a poly-lactic-based polymer and naltrexone in dosages ranging from 1.1 to 1.8 g. The single, 10-pellets implant is found to release naltrexone above 1–2 ng/mL for about 3 months. It is surgically inserted, usually in the subcutaneous tissue of the lower abdominal wall. Use of the double implant with 20 pellets extends the period of naltrexone release to approximately 5–6 months. A comparable triple implant containing 3.3 g of naltrexone has been found to provide blood levels above 1–2 ng/mL for up to 7 months.

An implant formulation containing 1 g of naltrexone compounded with magnesium stearate (Wedgewood Implant®; Wedgewood Pharmacy, Sewell, NJ, USA) was found to release naltrexone at levels above 1 ng/mL during 30–80 days, indicating significant interindividual variation [75]. A case report from this type of implant suggests blocking levels at 5 ng/mL about 3 weeks after surgical insertion [65]. Another type of implant containing 1 g of naltrexone (Prodetoxon®, Fidelity Capital, Moscow, Russia) has been approved for the treatment of opioid dependence in the Russian Federation. The PK data suggest naltrexone levels above 20 ng/mL despite considerable interindividual variation [76].

Safety and Tolerability

General adverse effects such as nausea, vomiting, and muscle twitches show a high degree of consistency between depot formulations and oral naltrexone [77,78]. Most adverse affects have been found to be transient and mild to moderate [35,37]. They were more likely in patients receiving depot injections compared to placebo [26,27]. Two Chinese studies reported that naltrexone implants do not negatively affect measures of cognitive functioning [79,80]. The lower plasma concentrations and fewer peaks in the PK profile of naltrexone depot formulations may reduce the intensity of adverse effects, but direct comparisons of safety outcomes between implant or depot formulations and tablets are still lacking. Depressive mood related to oral naltrexone treatment has been hypothesized [81]. However, several subsequent reports did not support depression induced by naltrexone tablets [82,83]. On the contrary, depressive symptoms were found to improve among patients who stayed in treatment [84]. This is in line with the findings from one study among heroin-dependent outpatients that did not report deterioration in depression scores during naltrexone implant treatment [38].

Site-related adverse effects such as pain, induration, infection, and allergic tissue reaction may occur when administering naltrexone depots or implants. In studies of injectable naltrexone, these reactions appear more common among patients receiving naltrexone than placebo injections [26,27,35,67]. In line with these findings, the FDA has issued an alert for Vivitrol concerning increased risk of administration site reactions. Data on site-related adverse effects of naltrexone implants are scarce, but single group studies indicate a low rate of site-related adverse effects [48,85]. The Australian implant formulation was found to biodegrade completely during a period of up to 3.3 years [86] and this implant was well tolerated in a prospective study [37]. In naltrexone implant treatment, attempts at self-removal of naltrexone pellets can cause wounds, infections, and scarring. Although no incident has been reported, attempted self-removal cannot be ruled out as a possible cause of two ruptured implant sites [36].

Hepatic impairment is common among alcohol- and opioid-dependent populations. Excessive alcohol consumption is considered the leading cause of liver cirrhosis in the western world [87]. Up to 35% of heavy drinkers suffer from alcoholic hepatitis and of those about 70% will subsequently develop cirrhosis [88]. Among injecting drug users, high prevalence (up to 94%) of hepatitis C virus (HCV) infection [89] is likely to cause liver cirrhosis in up to 30% of the infected individuals [90]. Since impaired liver functioning is common among the target populations for naltrexone treatment, possibly reduced hepatic capacity to metabolize naltrexone needs to be taken into account. Naltrexone depot has been investigated in patients with alcohol-induced liver impairment [68]. Findings on plasma levels did not show significant deterioration. Liver enzyme tests had improved during follow-up, supposedly due to reduction in alcohol drinking. Adverse effects such as headache were generally rated mild and nonspecific; these occurred more frequently among patients with alcoholic liver disease compared to healthy controls. The same depot injection was found to have good hepatic tolerability in a large alcohol-dependent sample during 6 months of treatment [91]. Another depot injection showed comparable improvements in terms of reduced γ-GT levels in a placebo-controlled trial [26]. A case report from an opioid-dependent patient presenting with acute hepatitis during treatment with a 1-g naltrexone implant suggests that naltrexone did not affect the patient's recovery [92].

Pain management during treatment with sustained-release naltrexone may become a challenge in an outpatient setting, because analgesia with oral opioids such as codeine is not feasible. Patient cases are reported where nonopioid analgesics or a regional nerve blockade were used and provided effective analgesia [93].

Several cases of naltrexone implant treatment among opioid-dependent pregnant women are reported [94–97]. The obstetric and neonatal data were found to be relatively unproblematic despite the rapid detoxification procedures that occasionally were performed during pregnancy. A post hoc comparison between methadone-maintained and naltrexone-implanted women suggests no clinically significant differences in obstetric and neonatal outcomes.

Conclusions

Naltrexone depot formulations have been developed to increase the well-known low compliance with oral naltrexone. Currently available naltrexone injectables and implants have been shown to significantly reduce heroin use and alcohol consumption in patient populations. Several formulations with overall good tolerability release naltrexone above the suggested therapeutic plasma levels for between 1 and 7 months. Further research is required on the level of naltrexone needed to effectively block clinically relevant heroin doses. The duration of naltrexone release at blocking levels from injectable and implant formulations is crucial, because naltrexone promotes abstinence from opioids and the risk of death from opioid overdose is increased upon relapse after prolonged abstinence. Longitudinal multicenter studies that compare naltrexone depot formulations with agonist maintenance treatment or oral naltrexone in opioid dependence are still lacking. In alcohol dependence, the neurobiological mechanisms that reduce craving and alcohol consumption are not fully understood. However, alcohol-dependent patients benefit from treatment with naltrexone injectables whereas longer acting naltrexone implants have not been investigated. An injectable naltrexone formulation is FDA approved for alcohol dependence. The majority of naltrexone implant formulations still lack approval for regular clinical use; more data on safety and tolerability are needed. Naltrexone depot formulations constitute an interesting development in delivering pharmacotherapy to selected opioid- or alcohol-dependent patients.

Conflict of Interest

The authors have no conflict of interest.

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