Long-acting injectable naltrexone for the treatment of alcohol dependence

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Combining pharmacotherapy with psychosocial and behavioral interventions has helped improve the treatment of alcohol dependence. However, the clinical use of effective medications, such as naltrexone, is limited by poor adherence to a daily oral regimen. Recently, a once monthly extended-release injectable formulation of naltrexone (Vivitrol®, Alkermes, Inc.) became the first FDA-approved long-acting formulation of naltrexone for alcohol dependence. Compared with the oral preparation, extended-release naltrexone shows reduced peaks and minimal fluctuations in plasma levels that may possibly lead to a more benign adverse-event profile. The administration of long-acting naltrexone in conjunction with psychosocial support has been associated with significant improvement in drinking outcome measures, especially among patients who are abstinent entering treatment. Additional studies are warranted to increase the knowledge on the clinical applications of long-acting naltrexone in other addictive disorders and to compare extended-release naltrexone with other long-acting formulations that are in development. The clinical availability of extended-release naltrexone has the potential to enhance treatment outcomes for alcohol and other drug dependence disorders.

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Increasing effective treatment options and accessibility is a critical goal in the management of alcohol dependence and related conditions. Nearly 10% of Americans are affected by alcohol abuse or dependence, while an additional 20% will experience problems due to drinking at some point in their life, contributing to $200 billion in medical and social costs associated with alcohol every year [1,2,101]. Unfortunately, effective alcohol screenings are performed inconsistently and less than 10% of individuals presenting with alcohol disorders receive treatment [3,4]. Moreover, while 25% of alcohol patients remain abstinent in the year following treatment, 40–70% resume heavy drinking [4,5]. In this scenario, although abstinence should be a primary goal, in some cases reduced drinking is a reasonable alternative and would contribute to significantly curbing alcohol-related morbidity, as shown in the recently completed National Epidemiologic Survey on Alcohol and Related Condition study [6,7].

Although there are three approved oral medications (disulfiram, naltrexone [NTX] and acamprosate) to treat alcohol dependence, their clinical application has encountered significant difficulties. In particular, NTX has shown efficacy in the treatment of alcohol dependence, but its effectiveness is substantially limited by poor compliance [8–11]. Results from the National Institute on Alcohol Abuse and Alcoholism supported Combining Medications and Behavioral Interventions study (COMBINE) confirm that NTX effects on alcohol consumption are greater when compliance with the drug is above 80% [12]. Reduced NTX efficacy is observed across studies with a lower medication adherence [13–16]. Poor compliance to oral NTX therapy is consistent with clinical cognitive or personality characteristics in heavy drinkers and is partially associated with genetically determined differences in sensitivity of the μ-receptor, while more strongly influenced by adverse events (AEs) such as

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nausea [17–21]. Studies on clinical predictors of compliance confirm that high levels of side effects early in the treatment are responsible for poor compliance [22,23]. On the other hand, a greater belief in the efficacy of the pharmacological intervention and higher alcohol craving may predict better adherence to the medication. Even when efficacy is evident, the risk of patients terminating treatment persists. If NTX significantly alters or diminishes the desirable effects of alcohol, patients may discontinue the medication in preparation for a return to drinking, which is more likely to occur when a daily conscious decision to take the drug on the part of the patient is required [24]. Clinical surveys show that almost half of patients undergoing treatment for alcoholism are not willing to take NTX [11]. From the physicians perspective barriers to widespread use of NTX include concerns for the inconsistent effectiveness and lack of time for patient management [11]. As a consequence, only 3–13% of persons receiving pharmacological treatment for alcohol dependence are being treated with oral NTX and therefore, testing the effectiveness of long-term pharmacological strategies becomes difficult [12,25,26].

In April 2006, the US FDA approved an injectable, extended-release (XR) formulation of NTX (Vivitrol®, Alkermes, Inc.) that expands the pharmacotherapeutic options for alcohol dependence. Evidence gathered in the management of other chronic psychiatric conditions, such as schizophrenia indicates that long-acting medications lead to greater treatment adherence and outcome benefit and are well accepted by patients for long-term treatment [27,28].

This review evaluates the pharmacological properties and therapeutic effects of XR injectable NTX compared with the oral preparation to help clinicians make informed decisions about its appropriate use for the treatment of alcohol disorders. In addition to XR-NTX, another injectable long-acting formulation (Naltrel™, Drug-Abuse Sciences, Inc.), for which there are sufficient published data on the treatment of alcohol dependence, is discussed. Other long-acting preparations that are used for drug dependence, but not among patients with alcohol disorders, are not reviewed here.

Pharmacology

Mechanisms of action

Alcohol (ethanol) affects key neurobiological substrates in the brain, including the mesocorticolimbic dopamine system and the amygdala [29,30]. Several neurotransmitters regulate the reinforcing effects of alcohol in these sites and in a complex fashion, among them GABA, opioid peptides, dopamine, glutamate, neuropeptide Y and glucocorticoids of the hypothalamic–pituitary–adrenal axis [30]. In particular, ethanol modulates the binding properties of μ-, δ- and κ-receptors and also influences opioid peptide synthesis and secretion (e.g., β-endorphin release) [29]. Activation of the endogenous opioid systems in the nucleus accumbens and in the ventral tegmental area, with corresponding increase in mesolimbic dopamine, is believed to contribute to the rewarding properties of ethanol and to participate in the process of acquiring alcohol-related secondary reinforcers and self-administration habits [29,30]. Endogenous opioid activation may also regulate craving and cue-induced elevation of dopamine in alcohol-dependent subjects that are not actively drinking [30]. NTX antagonism at opiate receptors seems a rational means of reducing ethanol reward, by suppressing β-endorphin's stimulation of dopamine neurons, thereby preventing further alcohol drinking in an extinction-like process. At the same time, NTX antagonizes β-endorphins negative control of the tonic GABA blockade of dopamine cells, which is mediated by alcohol [30,31]. Pharmacological opioid blockade by NTX prevents both ethanol and cues' activation of opioid and dopamine systems, thus reducing alcohol craving and helping prevent full-blown relapse if alcohol is consumed.

Naltrexone

NTX is a potent nonselective opiate antagonist with higher affinity for μ-receptors (receptor binding Ki: 0.37 nM), but also affinity for δ- (9.4 nM) and κ-receptors (4.8 nM) [32]. This broad-spectrum effect on opiate receptors may contribute to its effect on alcohol drinking. Using a rat model of drinking, specific antagonists at μ- and δ-receptors were not as effective individually as NTX, which acts on all three types of opiate receptors [33]. NTX also has a long duration of activity at brain receptor sites. Although the plasma half-life of NTX and its active metabolite 6β-naltrexol is only 10–12 h, two studies using C11 carfentanil showed that one 50 mg dose blocks brain μ-receptors for 48–72 h [34,35]. Of course the availability of a long-acting preparation can add inconsistency to the long-term use of NTX.

NTX is extensively metabolized in humans [36]. Production of the primary active metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites without pharmacological activity are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methoxy-naltrexone. NTX and its metabolites are also conjugated to form glucuronide products [37].

Long-acting formulations

Owing to problems with side effects and patient compliance, several long-acting NTX preparations have been explored in the last 30 years, but many remained investigational owing to both technical limitations and low marketing interest [38].

XR-NTX contains NTX embedded into biodegradable polymer microspheres of approximately 100 nm in diameter, fabricated from poly-lactide co-glycolide and produced using Medisorb® Technology [39]. Following injection into the body, polylactide co-glycolide hydrolyzes to lactic and glycolic acids and is further metabolized into carbon dioxide and water. The initial release of NTX on day one is the result of drug diffusion from the surface of the microspheres; the second peak on day 2 is primarily because of polymer hydration [40]. The sustained release (over 30 days) is due to polymer erosion, the rate of which is influenced primarily by polymer composition (i.e., ratio of

lactide to glycolide), polymer molecular weight and drug loading [41]. It is unclear whether body mass and subcutaneous fat influence release of NTX from the microspheres.

There is considerably less published information pertaining to Naltrel as compared with Vivitrol. Nevertheless, it is known that Naltrel comprises naltrexone incorporated into microspheres of the poly-(DL-lactide) polymer. The microspheres are contained in single-dose vials and suspended in a diluent consisting of polysorbate 80, carboxymethylcellulose, mannitol 1 and water for injection. Metabolism of the polylactide polymer yields carbon dioxide and water and NTX is released as the michrospheres degrade [24].

Pharmacokinetic profile

Daily dosing of oral NTX results in fluctuating plasma concentrations of the drug. NTX concentrations peak within the first hour after oral dosing, followed by a steady decline each day during treatment [42]. By contrast, the pharmacokinetic/pharmacodynamic profile of XR-NTX is characterized by a transient, initial peak 2–3 h after dosing, followed by peak concentrations in approximately 2–3 days. From day 14, plasma concentrations slowly decline, with measurable levels for greater than 1 month [40]. NTX concentrations following XR and oral dosing are compared in FIGURE 1.

The potential pharmacokinetic benefits of the XR injection compared with oral dosing includes an absence of high-peak plasma concentrations, a decrease in gastrointestinal exposure and avoidance of first-pass hepatic metabolism [39]. This implies a much lower hepatic exposure and significantly less production of 6β-naltrexol, a major NTX active metabolite. Compared with daily oral dosing with NTX 50 mg over 28 days, total NTX exposure is three- to four-times higher following administration of a single dose of XR-NTX 380 mg, whereas the exposure to 6β-naltrexol is 3.4-fold lower. At the same time, XR-NTX allows for a third lower total monthly dose of NTX than oral administration [40]. As a result, when administered to subjects with mild-to-moderate hepatic impairment, XR-NTX shows a metabolic rate similar to that in healthy controls, indicating no substantial need for dosage adjustment in alcoholics with impaired liver function [43]. Steady state is reached with XR-NTX at the end of the dosing interval following the first injection. There is less than 15% accumulation of NTX or 6β-naltrexol upon repeat injection, with a NTX protein binding of 21% [39,40]. Although the clinical impact of reduced 6β-naltrexol exposure on the safety and efficacy of NTX is not completely clear, it should be noted that there was evidence of a correlation between serum 6β-naltrexol concentrations and increased feelings of sedation independent of the quantity of alcohol ingested [44]. Additionally, peak 6β-naltrexol concentrations were associated with an occurrence of subjective side effects among social drinkers [45].

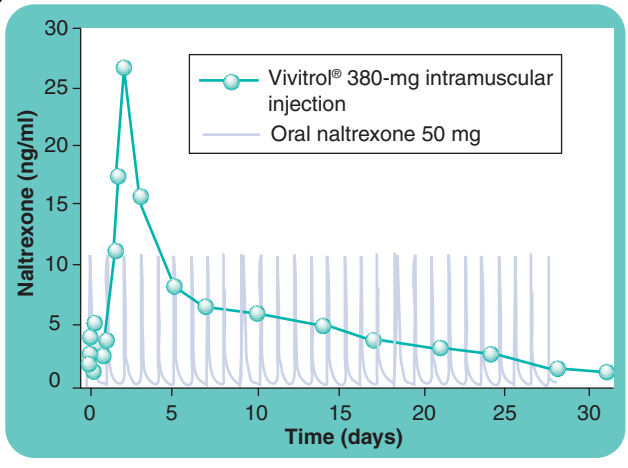

Figure 1. Mean steady-state naltrexone concentration following monthly extended-release naltrexone (Vivitrol®) 380 mg injection compared with naltrexone 50 mg/day. Modified from [38].

The time-action profile of the clinical effects of XR-NTX shows that by day 2 after the first injection patients were able to experience a significant decrease in drinking compared with those injected with placebo, and the effect was sustained and consistent every day of the week, including days of more intense drinking during the weekend [46,47].

Clinical efficacy

The published clinical studies that used long-acting NTX for alcohol dependence are summarized in TABLE 1. We comment on the results of investigations that were designed to include a formal evaluation of efficacy and discuss additional findings of clinical interest.

XR-NTX

Garbutt *et al.* studied 624 alcohol-dependent patients for 24 weeks in a multisite, double-blind, placebo-controlled trial [48]. A total of 415 patients received intramuscular monthly injections of XR-NTX 190 mg (n = 210) or 380 mg (n = 205) and the remaining patients were randomized to matching volumes of placebo. Pharmacological treatment was combined with 12 sessions of psychosocial intervention. Rate of heavy drinking days (defined as five or more drinks per day for men and four drinks per day for women) and total number of drinking days were significantly reduced at the XR-NTX 380 mg dose. The effect did not reach statistical significance in women and was stronger among subjects who had achieved abstinence before receiving the first dose of XR-NTX. With regard to a gender-specific effect, no helpful clinical conclusions can be drawn about its existence in association with XR-NTX use. The study was not designed or powered to investigate this aspect and the difference may be a consequence of different patient characteristics that were not controlled for, such as weight, smoking and use of antidepressants, rather than a function of gender. While gender-related differences in drinking outcomes were hypothesized for oral NTX, single studies did not contain a sufficient number of women to allow for meaningful comparisons [49,50]. On the other hand, the importance of lead-in abstinence to increase treatment effects is supported by an association with higher rate and duration of abstinence in

Table 1. Clinical injectable naltrexone studies in alcohol dependence.

RTC	Population	Treatment/duration	Summary of results with NTX treatment	Ref.
Phase II				
Johnson *et al.* (2004) Multicenter, Vivitrex (Alkermes Inc., MA USA)	n = 30; m = 22; NTX = 25; DSM-IV Alcohol Dependence	400 mg im. injection monthly for 4 months, psychosocial support. Abstinence lead-in	Constant plasma NTX levels; increased abstinent days; decreased heavy drinking days; decreased gamma-glutamyltransferase levels; mild-to-moderate AEs; no SAEs	[31]
Kranzler *et al.* (1998) Naltrexone SRP (BIOTEK Inc., MA, USA)	n = 20 m = 15 NTX = 15 DSM-IV Alcohol Dependence	206 mg sc. injection monthly for 3 months, psychosocial support. Abstinence and oral NTX lead-in	Detectable plasma NTX levels; decreased heavy drinking days; AEs similar to oral NTX	[47]
Phase III				
Garbutt *et al.* (2005) Multicenter, Vivitrol® (Alkermes Inc., MA, USA)	N = 624; m = 490; NTX 415; DSM-IV Alcohol Dependence	380 mg or 190 mg im. injection monthly for 6 months, psychosocial support. No lead-in	Reduced drinking days and heavy drinking days; higher significance in males and subjects abstinent at beginning of the treatment; SAEs comparable in the Vivitrol and placebo groups	[48]
Kranzler *et al.* (2004) Multicenter, Naltrel (Drug Abuse Sciences, CA, USA)	n = 315; m = 205; NTX = 158; DSM-IV Alcohol Dependence	300 mg im. 1st injection and 150 mg monthly for 3 months, psychosocial support. Abstinence and oral NTX lead-in	Decreased heavy drinking and time to first heavy drinking day; greater abstinence rate; no difference with placebo in SAEs, AEs other than injection-site reaction	[24]
Open label				
Gastfriend *et al.* (2005) Vivitrol Extension study (Alkermes Inc., MA, USA)	n = 332; From previous Phase III study	380 mg or 190 mg im. injection monthly for 12 months, psychosocial support	Continued reduction in heavy drinking; significant reduction seen in placebo-treated patients from Phase III study who where switched to Vivitrol, no evidence of hepatotoxicity, no increased discontinuation due to AEs	[52]
Galloway *et al.* (2005) NTX Depot (Drug Abuse Sciences, CA, USA)	n = 16; m = 13; DSM-IV Alcohol Dependence	300 mgim. injection, follow-up for 6 weeks, psychosocial support. Abstinence and oral NTX lead-in	Serum NTX levels detectable throughout the observation period; reduced drinking and heavy drinking days; no SAEs	[53]

AE: Adverse event; DSM: Diagnostic and Statistical Manual of Mental Disorders IV; im.: Intramuscular; m: Male; NTX: Naltrexone; RTC: Randomized controlled trial; SAE: Serious adverse event; sc.: Subcutaneous.

the investigation by Garbutt and colleagues, and has offered the basis for the FDA-indicated use of the formulation [48]. Although the prescribing information (PI) [102] for XR-NTX 380 mg emphasizes the need for a period of abstinence prior to treatment initiation, no specific indication is given concerning the duration of abstinence. A *post hoc* analysis of data on 82 patients treated with XR-NTX suggests that as few as 4 days of previous abstinence may be sufficient to induce a greater treatment effect [51]. A significantly higher proportion of subjects with 4 days or more of voluntary abstinence at baseline maintained abstinence for all 24 weeks of treatment, compared with placebo (32 vs 11%; $p = 0.02$). Patients receiving XR-NTX 380 mg had a significantly increased time to first drink (median durations of 42 vs 12 days; $p = 0.02$) and time to first heavy drinking event (181 vs 20 days; $p = 0.04$) [51]. A period of abstinence of 7 days or longer at the beginning of treatment showed similar positive effects, but no further improvement [51]. Also, in the same patients, the goal of abstinence was associated with a better outcome, as opposed to other treatment goals or the absence of a goal [51]. An analysis of the clinical interactions between motivation to treatment and lead-in abstinence will certainly help optimize treatment delivery. Furthermore, a meta-analytical approach to examine putative gender and lead-in abstinence effects on outcomes across oral NTX studies would help us to understand if there are differences in outcome due to method of NTX delivery and pharmacodynamic factors.

The durability of XR-NTX's effect was investigated by Gastfriend and colleagues [52] among 332 of 377 patients who completed the Garbutt and colleagues [48] trial and elected to enroll in a 12-month, open-label study. Those who continued on XR-NTX maintained improvement in drinking outcomes and patients who switched from placebo injection to active medication experienced a significant reduction in drinking.

The evidence of a physiological improvement secondary to a reduction in alcohol intake is confirmed by a reduction in the serum levels of the hepatic enzyme gamma-glutamyl transferase comparable across condition in both Phase II and III trials. However, XR-NTX-treated patients showed a significant earlier decrease (weeks 4, 8 and 12) of the enzyme compared with placebo [53,54], while no differences were noted in comparison to oral NTX among mixed alcohol/opiate-dependent subjects [55].

In all clinical trials, XR-NTX administration with psychosocial treatment showed positive results. In particular, patients receiving the active medication attended over 90% of study-provided counseling sessions [37,48,56]. The administration of XR-NTX was associated with higher rates of psychosocial support sought outside the trial, and of self-help group attendance than placebo [57,58]. The same patients showed greater improvements in mental health-related quality of life compared with patients receiving placebo injections in conjunction with psychosocial support [58].

Naltrel

Kranzler and colleagues studied the clinical effects of Naltrel intramuscular injection in conjunction with psychosocial treatment among alcohol-dependent individuals in a multisite, 12 week, double-blind, placebo-controlled clinical trial [24]. The first dose of the medication was 300 mg in 158 subjects, with subsequent doses of 150 mg every 4 weeks, while 157 patients received similar volumes of placebo. Subjects who received Naltrel were more likely to have a greater number of total abstinent days, a lengthier time to first drink and a nonsignificant reduction in drinking and heavy drinking days. The medication seemed to be safe and well tolerated and no effects of gender on treatment outcome were explored.

Long-acting & oral efficacy

The comparison of injectable NTX with the oral formulation is made difficult by the unequal number of published investigations and by differences in study design, measures and outcomes. We compared Phase III long-acting NTX trials only with oral NTX investigations of medium duration (6 months) that presented comparable measures of in-treatment abstinence and patients who were abstinent at baseline (TABLE 2) [24,48,59,60]. Comparisons were made for the proportion of abstinent patients using a test of proportions in meta-analysis. XR-NTX was associated with a more favorable difference in the rate of abstinence versus placebo, as compared with Naltrel, or to oral treatment. In general, long-acting NTX seemed to have a more significant impact on abstinence. No comparisons could be performed of other drinking outcomes, owing to a lack of homogeneous measures across studies. Because of this and the selection of oral NTX studies performed, the analysis cannot bear particular clinical salience.

The XR-NTX favors maintenance of abstinence in 63% of the clinical trial patients, as to say that it takes treatment of four patients to demonstrate a significant improvement over placebo (number needed to treat [NNT] analysis), as opposed to 13 patients treated with Naltrel [24] and 20 among those who received oral NTX in the COMBINE study [12]. Even when we limit our attention to short-term treatments (≤3 months), which usually show higher abstinence rates [61], the oral NNT score is 12, and NTX helps only 13% of patients avoid relapse into drinking [62]. Thus, in a hypothetical population of 1000 alcohol-dependent patients, the projected number of abstinent patients attained would be somewhat higher than 200 with XR-NTX and lower than 80 with oral NTX. This XR-NTX effect is comparable to NNT results obtained in the pharmacological treatment of depressive disorders [63].

In some investigations, oral NTX has been associated with reduced drinking in nonabstinent alcoholics [61]. The efficacy of XR-NTX is greater than placebo in reducing heavy drinking (53%; NNT = 14) [48] and it is also better than oral NTX treatment in the COMBINE investigation (50%; NNT = 100) [12]. Of interest, XR-NTX exerts a medium effect size on abstinence, while showing a smaller effect on reducing

Table 2. Oral and injectable depot naltrexone versus placebo: results of the meta-analysis on proportion of abstinent patients by end of study.

Study	Treatment	Duration (weeks)	NTX abstinent rate	Placebo abstinent rate	Effect size*	z-value	t-value	p-value	Ref.
Kranzler *et al.* (2004)	Naltrel™: NTX: n = 158; PL: n = 157	12	0.18	0.10	0.08	1.149	1.149	0.15	[24]
Garbutt *et al.* (2005)	Vivitrol®: NTX: n = 28 ; PL: n = 28	24	0.35	0.14	0.23	1.578	1.579	0.04	[48]
Balldin *et al.* (2003)	Oral NTX: n = 57; PL: n = 62	24	0.05	0.02	0.03	0.327	0.327	ns	[59]
O'Malley *et al.* (2003)	Oral NTX: n = 26; PL: n = 27	24	0.32	0.20	0.12	0.877	0.863	ns	[60]

*Cohen's D effect size was calculated [98].
NTX: Naltrexone; PL: Placebo.
Data from [101].

heavy drinking in premarketing studies [64]. The sample of alcohol-dependent subjects treated with XR-NTX is rather small and more lead-in abstinent and nonabstinent patients need to be studied before full clinical significance can be given to these considerations. Owing to limited published data available and in the absence of head-to-head studies, no real comparison in efficacy can be made between XR-NTX and other long-acting formulations. The results of additional studies on these compounds are eagerly awaited to increase our knowledge of clinical applications of long-acting NTX. Finally, a comparison between injectable and oral NTX should be performed to gain insight into the advantages of using either formulation. In addition to the customary double-blind, double-dummy design, open-label investigations that give patients the choice of NTX formulation, it would be particularly useful to simulate everyday practice and study the relationship between acceptance and compliance with treatment.

Safety profile

As discussed, long-acting formulations are conceived to reduce a number of problems associated with oral NTX through a consistent release and a lower hepatic exposure of the medication. This results in reduced production of NTX metabolites that are potentially related with increased side effects.

General clinical safety

The results of Phase I studies indicated that XR-NTX was well tolerated and demonstrated no serious AEs (SAEs) in healthy volunteers [ALKERMES, INC., DATA ON FILE]. The safety component of the data analysis in the clinical trials that are summarized in TABLE 1 confirms that repeated administration of long-acting NTX is generally safe, with mild-to-moderate side effects that occur both in the placebo and active medication groups and are comparable among different formulations. In particular, more detailed information is available concerning a larger group of subjects treated with XR-NTX in between 4 and 18 months [31,48,52]. In controlled trials of 6 months or less, 9% of patients on active medication discontinued treatment owing to an AE, compared with 7% of the patients treated with placebo [31,48]. AEs in the XR-NTX 380 mg group that led to more dropouts were associated with injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%) and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew owing to injection-site reactions. In patients receiving XR-NTX for up to 18 months, the discontinuation rate owing to AEs did not increase and the side-effect profile was similar [52]. Overall, in the 12-month, open-label study, 273 patients (82%) reported at least one AE, and 92 (27.7%) experienced a drug-related AE. The majority of AEs were mild to moderate in intensity. There was no pattern of AEs or SAEs that emerged in relation to dose or sequence throughout this investigation, and 28 patients (8.4%) discontinued because of AEs. A total of 20 SAEs occurred in 18 patients (5.4%), with the most common SAE being alcohol detoxification. No SAEs were deemed 'probably' or 'definitely' related to the study drug.

Nausea, headache, loss of appetite, nasopharyngitis, upper respiratory tract infections, dizziness, insomnia, depression, anxiety and fatigue were the most frequently reported adverse effects in Phase II and III trials and in extended treatment studies. XR-NTX was discontinued in one patient in the Phase II study owing to angioedema, [31], while two subjects receiving the medication in the Phase III study developed an allergic-type eosinophilic pneumonia and interstitial pneumonia, respectively [48]. The three SAEs resolved following medical treatment. Taking into consideration these cases, the allergic-type reaction rate for XR-NTX would be approximately 1:360, but it is clear that more data are needed to properly appraise the pathophysiological significance of the potential for inducing allergic reaction with XR-NTX and other long-acting formulations.

Hepatotoxicity

The USA product label warns that significant hepatotoxicity may occur with oral NTX [103]. This has been historically observed in obese patients, at doses fivefold or less over the recommended dose. The results of a multicenter investigation by The Naltrexone Usage Study group did not raise new safety concerns [21]. However, recent reports indicate that an interaction between NSAIDs and oral NTX more than 100 mg may lead to hepatotoxicity in alcohol-dependent subjects, but not in other psychiatric patients [65,66].

This indicates that clinicians should be careful in administering high oral doses of NTX in alcohol-use disorders and warn patients of such potentially dangerous drug interaction.

On the other hand, NSAIDs have been administered safely to alcohol-dependent patients in association with XR-NTX [SUMMARY OF CLINICAL SAFETY. ALKERMES, INC., DATA ON FILE]. The administration of XR-NTX 190 or 380 mg to approximately 230 patients for longer than 1 year in controlled or uncontrolled trials has shown no evidence of hepatotoxicity. In particular, only one case of acute hepatitis in a patient with hepatitis C was considered 'possibly' related to the 190 mg dose of the medication in the open-label, 12-month study [52]. Data reviewed by the FDA has led to the conclusion that XR-NTX does not appear to be a hepatotoxin at the recommended doses.

Injectable & oral safety

The spectrum of AEs and SAEs reported for injectable NTX is not dissimilar from the side effects of the oral preparation, with the obvious exception of formulation-related AEs [62,67,68]. Using a number needed to harm analysis approach to compare the Phase III injection NTX trials with the most recent multisite, large-scale oral NTX investigation (COMBINE), the administration of Naltrel was the least likely to be associated with AEs that could lead to discontinuation of the pharmacological treatment (TABLE 3). Moreover, we found no significant difference in the way the incidence of a key symptom such as nausea was affecting patients on XR-NTX, compared with oral NTX. However, it is interesting to note how AEs were more likely to cause treatment discontinuation in the oral NTX COMBINE investigation, which also reported a fairly high adherence to active medication

(>80%). This is consistent with other analyses showing that different groups of AEs can have a significant impact on adherence to oral NTX and on treatment retention, but do not consistently influence both [68]. Overall, the clinical picture of long-acting formulations is that they may display a milder side-effect profile than oral NTX. The safety profile may not need to be considered at the beginning of NTX treatment, if the clinician feels more comfortable with oral induction to the medication, and instead becomes more significant when long-term treatment is planned.

Clinical management

Some of the precautions listed in the XR-NTX PI [102] refer to characteristics of use and clinical conditions that are rather common in alcohol-dependent patients and these precautions require further comment.

Comorbid treatments

Clinical drug interaction studies with long-acting NTX formulations have not been performed. However, antidepressant medications were safely used by 29% of patients in the Garbutt and colleagues study [48] with the most common antidepressant medications used by 5% or more of the subjects including sertraline, citalopram, paroxetine, fluoxetine, trazodone and bupropion hydrochloride [SUMMARY OF CLINICAL PHARMACOLOGY, ALKERMES, INC., DATA ON FILE]. Some commonly prescribed antidepressants are metabolized by the cytochrome P450 hepatic enzymes and there are no data to suggest that these agents induce or inhibit the metabolism of NTX [69], so no pharmacokinetic interaction between the long-acting formulations and antidepressants would be anticipated. Similarly, there are no known reported drug interactions between NTX and other pharmacotherapies for alcohol dependence, such as disulfiram, acamprosate, ondansetron or other agents. In summary, the possibility of combining other medications with long-acting rather than oral NTX would reduce pharmacokinetic interactions and enhance compliance, and the resulting potential increase of clinical response has to be determined in clinical practice. This would be of particular salience, considering that alcohol dependence is frequently associated with comorbid psychiatric disorders and reduced liver function [101].

Use of opiate agonist drugs

A specific drug interaction is represented by the administration of agents that act as an agonist at the opiate receptor in the 30 days following long-acting NTX injection. NTX antagonizes the action of opiates by blocking the receptor, with a resulting absence of clinical effects, or even insurgence of withdrawal symptoms. This can occur either in the case of concomitant alcohol and opioid abuse, or when pain management is needed.

The former condition constitutes a clear contraindication for the use of injectable NTX at the moment, and more research should be conducted before specific indications can be formulated, following the initial studies of long-acting NTX administration to patients with opioid and mixed alcohol and opiod dependence [70–72].

Table 3. Nausea and discontinuation from the study due to adverse events in oral and injectable depot naltrexone investigations: results of a number-needed-to-harm analysis.

Study	AE	NNH*	AUC	Ref.
Kranzler *et al.* (2004) (Naltrel™)	Nausea	25	52%	[24]
	Withdrawal due to AEs	100	50%	
Garbutt *et al.* (2005) (Vivitrol®)	Nausea	5	60%	[48]
	Withdrawal due to AEs	12	54%	
Anton *et al.* (2006) (oral)	Nausea	8	56%	[12]
	Withdrawal due to AEs	3	67%	

*Number of subjects that needed to be treated with the active medication before manifesting the AE, or withdrew from the study due to AEs.
AE: Adverse effect; AUC: Area under the curve; NNH: Number needed to harm.

In the case of analgesic treatment, the most delicate clinical intervention would be the reversal of long-acting NTX blockade in an emergency situation. The suggested approaches are based on the experience accrued with oral NTX and range from regional analgesia and conscious sedation with a benzodiazepine, to using nonopioid analgesics or general anesthesia. Clinical reports confirm that deep sedation may be needed to control discomfort induced by NTX in the presence of opioid medications [73], while conscious sedation or use of weak opiod agonists, such as tramadol, may not be sufficient to induce a safe analgesia [74]. Non-opioid analgesics, may offer a viable treatment alternative. NSAIDs (e.g., ibuprofen 2400 mg/day) seem quite effective [75], and intravenous paracetamol is preferred to oral dosing [76]. Among other drugs that do not interfere with the mechanism of action of NTX, the addition of clonidine to regional anesthesia may improve the efficacy and duration of analgesia [77], while ketamine and other NMDA receptor blockers are effective analgesics and have been shown to minimize the development of dependence during opioid treatment [78]. As with the opioid-based analgesia, interesting preclinical experiences show that high-dose opiate agonists administered in animals pretreated with XR-NTX induce analgesic effects without respiratory depression [79]. More investigation is needed to clarify if these results can become of clinical utility.

Patients should be advised to carry documentation that they are taking long-acting NTX. This will help to ensure adequate emergency medical treatment, if needed.

Dosage & administration

At present, the only FDA-approved long-acting NTX formulation for the treatment of alcohol dependence is XR-NTX. The recommended dose is 380 mg intramuscularly gluteal injection every 4 weeks or once monthly, and must be administered by a healthcare professional. Patients should not be actively drinking

at the time of initial XR-NTX administration and the treatment should be part of a comprehensive management program that includes psychosocial support [102].

Patient acceptability & adherence to medication

To date, there are no available patient satisfaction data regarding long-acting NTX formulations. A relatively limited spectrum and intensity of side effects may have contributed to the rates of compliance with the medication observed in injectable NTX clinical trials. In particular, 78% of patients in the 3-month Naltrel study received all injections [24], four of six doses were administered to 74% of patients in the 6-month XR-NTX trial and 64% of them underwent complete treatment [43]. Considering the 12-month extension study, 39.4% of patients were compliant with the medication for 18 months [50]. Rates of patient drop-out and adherence to medication in selected investigations are reported in TABLE 4. We did not find meaningful differences between injection, placebo and oral adherence rates in these studies, while lower compliance was detected in longer lasting studies, independent of the formulation. The awaited results of an ongoing 3-year XR-NTX extension study (Alkermes, Inc., XR-NTX 006) will provide useful information regarding long-term adherence to the medication. It should be reminded that when a research treatment is translated into clinical practice, adherence to medication has been shown to decrease with the complexity of the regimen [80]. Extensive evidence confirms the existence of an inverse relationship between dose frequency and adherence [81]. One consequence is that long-acting, extended-release compounds help in general to obtain results in clinical practice more closely resembling those observed in clinical trials [82] and the use of long-acting NTX is intended to achieve a similar goal in the treatment of alcohol dependence.

Limitations

Some characteristics of the XR-NTX formulation may potentially limit a widespread clinical use:

- Administration of the injection: Vivitrol does not come in a ready-to-use injectable preparation and has to be reconstituted after mixing and dissolving the michrospheres in the diluent. The dose pack components can be preserved only in a refrigerator. Several physicians, especially psychiatrists, may lack the set up and/or not be comfortable with the administration of the injection.
- Drug delivery and cost: XR-NTX is stocked only at selected pharmacies and not available by routine prescription. A physician has to fax the prescription to the specific pharmacy (or to the marketing company Cephalon, Inc.), in order to get approval from the insurance provider and obtain the drug. Lastly, XR-NTX costs approximately $700 per injection, approximately $23/day, compared with less than $2/day of the oral preparation.

Table 4. Rates of drop out and adherence to active medication in oral and injectable depot naltrexone studies, in order of trial duration.

Study	Duration (weeks)	Drop out (%)	Medication days (%)	Ref.
Kranzler *et al.* (2002) (Naltrel™)	12	22.2	88	[24]
Anton *et al.* (2006) (oral)	16	35	85	[12]
Garbutt *et al.* (2005) (Vivitrol®)	24	39	79	[48]

Expert commentary & five-year review

Alcohol disorders

Long-acting NTX is efficacious and may be more effective than oral NTX for the treatment of alcohol dependence if improved adherence compared with the oral formulation is demonstrated in clinical practice. It remains to be seen if appropriate measures are taken to facilitate access to treatment and if substantial long-term pharmacological effects can be achieved.

The use of XR-NTX should be considered for individuals with alcohol-use disorders who have not responded to other pharmacological and behavioral treatments. In particular, patients who have problems with treatment adherence for social impediments (e.g., homelessness) or poor memory (e.g., cognitive impairment) and patients with low compliance and ineffective response to oral NTX may be eligible. However, the medication can also be considered a first-line therapy. In all this, pharmacogenetic investigations will help determine if genetic variations in the μ-opioid receptor have a significant influence on the response to injected NTX, as it seems to occur with oral NTX treatment [20].

Several questions remain before clear guidelines on the use of XR-NTX can be formulated, concerning effective ways of initiating treatment and its optimal duration. Investigations should be conducted on the nature of the lead-in phase and the efficacy of concomitant psychosocial treatments. In particular, the results of follow-up evaluations after discontinuing the medication will help clinicians understand the utility and limitations of a chronic pharmacologic treatment for alcohol dependence.

In the COMBINE study, patients receiving NTX showed reduced drinking while attending rather limited management interventions focused on medication adherence and abstinence, independent of additional intensive counseling by alcoholism treatment specialist [12]. Similarly, long-acting NTX trials have frequently used the Biopsychosocial Report Empathy Needs Direct Advise and Assessment treatment, a psychosocial program specifically designed to enhance medication and treatment compliance, to be administered by a wide range of healthcare providers, including primary care clinicians [83]. Traditionally, treatment for alcohol dependence has been psychosocial in nature, and physicians have not played an active role. Studies have demonstrated that many psychosocial interventions for alcohol dependence, including Alcoholics Anonymous, can be integrated successfully with pharmacotherapy [3]. The availability of psychosocial treatments brief enough to be

amenable to clinical practice open new possibilities. If the existence of effective treatment approaches, which contain the needed characteristics of accessibility and flexibility, can be promoted in the daily clinical activity, the use of long-acting NTX would contribute to overcoming some of the challenges to the dispersal of pharmacotherapies for alcohol dependence [84].

Opioid disorders

The clinical usefulness of oral NTX in the treatment of opioid dependence is greatly limited by poor compliance [85] and studies on the use of long-acting NTX for opioid dependence show initial positive results on treatment retention and reduction of craving [56,71]. In addition, XR-NTX was safely administered to alcohol-dependent subjects with comorbid opioid disorders [72]. Further investigations should be conducted on the use of injectable NTX in opioid detoxification and for induction to chronic antagonist treatment, after clinical trials have studied the oral formulation in combination or comparison with partial opioid agonists, such as buprenorphine, with variable results [86,87].

Impulsive & compulsive behaviors

The use of opioid antagonist agents for the treatment of the so called 'behavioral addictions', which include repetitive impulsive behaviors without consideration of their potential negative consequences [88], has revealed the importance of a prolonged and sustained exposure to the medication to reach significant clinical effects [89]. The administration of long-acting NTX formulations should be studied in pathologies where oral NTX and other opioid antagonists have demonstrated initial efficacy, such as pathological gambling [90], kleptomania [91] and self-injurious behavior [92,93].

Conclusion

Alcoholism is ruled by a multifactorial etiology and it is possible that the clinical use of long-acting NTX formulations will not offer much better results than the small-to-medium treatment effect size shown on drinking behaviors in premarketing trials. However, there are other limiting factors to the prescription of medications for alcohol dependence that should be recognized. Oral NTX and acamprosate have shown effects comparable to some antidepressants widely used in the treatment of mood disorders [8,94]. Specific to substance dependence, nicotine-replacement therapy has not shown a bigger effect on rates of smoking cessation than oral NTX in the treatment of alcohol dependence and yet it is considered a first-line therapy in treatment guidelines [95,96]. *Ad hoc* analyses confirm that physicians may be hesitant to prescribe medications to treat alcoholism, even if these products have much better characteristics than existing medications in terms of efficacy, side effects and cost [97]. The introduction of XR-NTX and other new effective pharmacological agents may encourage patients to seek treatment and practitioners to intervene appropriately for drug dependence disorders.

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Key issues

- The development of long-acting naltrexone preparations, with the recent US FDA approval of a once monthly 380 mg extended-release injectable naltrexone formulation (Vivitrol®, Alkermes, Inc.), is intended to improve adherence with medication in the treatment of alcohol dependence.
- Compared with the oral formulation, intramuscular extended-release naltrexone shows an absence of high-peak plasma concentrations, a decrease in gastrointestinal exposure and avoidance of first-pass hepatic metabolism.
- Following extended-release administration, the total time of exposure to naltrexone is increased and clinical effects are observed 2 days after administration.
- Long-acting naltrexone use in conjunction with psychosocial support has been associated with significant improvement in abstinent rate or with reduced drinking in clinical trials, especially among patients who are abstinent entering treatment.
- Extended-release naltrexone appears to be safe and well tolerated, with no evidence of hepatotoxicity in subjects treated for 18 months and longer.
- Head-to-head comparisons between extended-release naltrexone and other long-acting formulations, and between long-acting and oral naltrexone, are warranted to increase our knowledge of clinical applications of the treatment.
- Further clinical studies are awaited to establish if management of comorbid disorders may be facilitated in alcohol-dependent patients receiving long-acting naltrexone treatment by reducing the possibility of kinetic interactions and enhancing compliance.
- The clinical availability of long-acting naltrexone has the potential to improve treatment outcomes not only for alcohol-use disorders, but also for other forms of addictions, from opioid dependence to impulse control disorders.

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