Naltrexone long-acting formulation in the treatment of alcohol dependence

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Abstract: While oral naltrexone has a demonstrated ability to decrease alcohol reinforcement, it also has pharmacotherapeutic limitations, such as a small treatment effect size, adverse events, and plasma level fluctuations. The pharmacokinetic profile of naltrexone could be enhanced by intramuscular administration, which would sustain its release over several weeks and keep plasma levels relatively constant, ie, low enough to minimize side effects but high enough to reduce drinking. Vivitrex®/Vivitrol® and Naltrel® are injectable naltrexone depot formulations that have been tested as possible medications for treating alcohol dependence. Their adverse-event profiles appear to be less severe than that of oral naltrexone. Vivitrex®/Vivitrol® has demonstrated efficacy at decreasing heavy drinking among alcohol-dependent males. Naltrel® helped to promote abstinence and decrease the incidence of relapse in two samples of alcohol-dependent subjects. The data on a third formulation, Depotrex®, are still limited. All three formulations require further study of their efficacy.

Keywords: alcohol dependence, depot, Depotrex®, Naltrel®, naltrexone, Vivitrex®, Vivitrol®

Introduction

The reinforcing effects of alcohol associated with its abuse liability are mediated by dopaminergic pathways that originate in the ventral tegmental area, relay to the nucleus accumbens with neuronal inputs from other limbic regions, and progress to the cortex (Wise and Bozarth 1987; Weiss and Porrino 2002; Koob 2003). Naltrexone, a mu-opioid receptor antagonist, decreases alcohol reinforcement via two mechanisms: (1) suppression of alcohol-mediated beta-endorphin stimulation of dopamine neurons directly in the nucleus accumbens, and (2) reduction of beta-endorphin disinhibition of the tonic inhibition of dopamine cells by gamma-aminobutyric acid neurons in the ventral tegmental area (Spanagel and Zieglgansberger 1997; Johnson and Ait-Daoud 2000).

Srisurapanont and Jarusuraisin (2005), in a review of 27 randomized controlled clinical trials, reported that oral naltrexone was efficacious at decreasing relapse and a return to heavy drinking among recently abstinent alcohol-dependent individuals, which is consistent with the above hypothesis. Yet, since the pharmacokinetic properties of oral naltrexone lead to significant fluctuations in plasma levels with oral daily dosing, its general effectiveness has been limited by two consequential factors. First, the low plasma trough level of oral naltrexone diminishes its efficacy, which could explain why medication adherence above 85% is required in order for there to be a therapeutic response (Volpicelli et al 1997). Second, high peak levels are deemed responsible for adverse events (Croop et al 1997; King et al 1997), and up to 15% of oral naltrexone recipients drop out of treatment because of adverse events, especially nausea (Croop et al 1997).

The effectiveness of naltrexone also is limited by its small treatment effect size (Johnson and Ait-Daoud 2000; Feinn and Kranzler 2005), especially in newer

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and multi-site trials; the number needed to treat (ie, to see a difference from placebo) is 7 for decreasing the likelihood of relapse and 12 for decreasing the likelihood of returning to drinking (Srisurapanont and Jarusuraisin 2005). Nevertheless, subjects with the Asp40 allele of the mu-opioid receptor, as opposed to those with the Asn40 allelic type, might derive greater therapeutic benefit than is seen in the averaged response (Oslin et al 2003). Further study is needed to confirm these results.

Optimizing the pharmacokinetic profile of naltrexone by developing a deep intramuscular injection that would release naltrexone over several weeks would, therefore, enhance its overall effectiveness. Consequently, plasma levels would remain relatively constant and low enough to reduce the incidence of adverse events yet high enough for the desired anti-drinking effects (Bartus et al 2003). In other words, while the effect size of naltrexone's long-acting, intramuscular formulation would not be expected to exceed the effect size of oral naltrexone, the overall outcome would probably be enhanced by the increased compliance and longer exposure to a therapeutic dose. This review focuses on the therapeutic effects and pharmacological properties of two long-acting, injectable depot preparations of naltrexone – Vivitrex®, recently renamed Vivitrol® (Alkermes, Inc., Cambridge, MA, USA), and Naltrel® (DrugAbuse Sciences, Inc., Paris, France) – for treating alcohol dependence. Another depot formulation, Depotrex® (Biotek, Inc., Woburn, MA, USA), for which published data are limited, is also mentioned.

Table 1 provides a summary of the advantages and disadvantages of depot naltrexone preparations compared with oral naltrexone in alcohol-dependent individuals.

Currently available preparations

Properly formulated depot preparations can maintain relatively constant plasma levels for days or weeks because of the slow, timed release of the compound. Long-acting naltrexone depot formulations also are designed to minimize the high plasma peaks and exposure of the gastrointestinal tract to naltrexone that occur with the oral formulation. Thus, there is a reduction in nausea, the main adverse event associated with discontinuation of naltrexone treatment. Also, the relatively stable plasma levels of a naltrexone depot formulation help to maintain constant levels of mu-opioid receptor occupancy, and, importantly, this facilitates a linear pharmacodynamic response. Since alcohol-dependent individuals often are relatively non-compliant with regard to medication taking (Rohsenow et al 2000), spacing naltrexone injections at intervals of up to 4 weeks, thereby keeping plasma levels constant, should enhance compliance and promote greater efficacy.

Vivitrex®/Vivitrol® is naltrexone formulated into poly-(lactide-co-glycolide) (Shive and Anderson 1997), small-diameter (<100 μm), injectable microspheres, which contain other proprietary active moieties that lead to its extended-release properties lasting for several weeks (Lewis 1990). In animal studies, these microspheres were suspended in 1 mL of an aqueous solution (3.0% low-viscosity carboxymethylcellulose, 0.9% saline, and 0.1% Tween-20), enabling injection of a 50 mg/kg dose of naltrexone (Bartus et al 2003). The plasma naltrexone level reached its peak at approximately 15 ng/mL by the third day post-injection, was sustained at approximately 12 ng/mL for another 18 days, and then tapered off until it dipped below 1 ng/mL

Table 1 Advantages and disadvantages of depot naltrexone preparations compared with oral naltrexone in alcohol-dependent individuals

Advantages of depot naltrexone preparations compared with oral naltrexone	Disadvantages of depot naltrexone preparations compared with oral naltrexone
• Efficacy is not compromised since there are not significant fluctuations in plasma levels causing low trough levels	• An apparent gender disparity in efficacy (with men receiving the greater benefit) requires further exploration
• Adverse events, particularly nausea, are not increased by high peak levels that would result from the plasma level fluctuations	• Certain adverse events, such as erythema, induration, and injection site reactions, are unique to the depot formulations
• Since injections are spaced 4-weeks apart, problems with compliance are minimized	• Vivitrol® is contraindicated in patients receiving opioid analgesics
• The simplicity of supervision and administration might make the depot formulations suitable for forensic settings	• More health care providers must be involved to ensure proper administration
• Patients who will be in situations where oral naltrexone is unavailable can receive treatment	• Depot formulations could be cost prohibitive for many patients
	• Delivery of psychosocial support might be needed more often than the monthly injections

14 days after that (Bartus et al 2003). Vivitrex® resulted in an approximate 70% reduction, compared with placebo, of morphine-induced analgesia in the hot-plate test for approximately 3 weeks – an effect that disappeared by 4 weeks after injection. The expected rise in mu-receptor density, caused by Vivitrex®-induced antagonist blockade, was evaluated using [D-ala^2, *N*-methyl-phe^4, glycol^5] enkephalin ([^{3}H]DAMGO). This revealed that there was a 110% increase, compared with placebo, in mu-receptor density, from 5 days after the injection until 33 days later, most prominently in the thalamus, nucleus accumbens, dorsal raphe nucleus, and striatum. Vivitrex®, therefore, appears to block effectively the central mu-opioid receptors for a period of approximately 4 weeks after the injection (Bartus et al 2003).

Fewer data on Naltrel® than on Vivitrex®/Vivitrol® exist in the public domain. Naltrel® consists of naltrexone incorporated within microspheres of poly-(DL-lactide) polymer. These microspheres are contained in single-dose vials and suspended in a diluent comprising mannitol, carboxymethylcellulose, polysorbate 80, and water for injection. When metabolized, the polylactide polymer produces water and carbon dioxide. Degradation of the microspheres causes naltrexone to be released (Kranzler et al 2004).

A lesser-known third formulation, Depotrex®, is discussed briefly in the Clinical Results section below.

Pharmacodynamics and pharmacokinetics

The marked analgesic response to morphine in the hot-plate paradigm in rats was blocked by Vivitrex® (50 mg/kg) from the first day of injection until 4 weeks later. An injection of Vivitrex® 5 weeks after the first injection led to suppression of morphine analgesia for another 4 weeks (Bartus et al 2003). When Vivitrex® was injected subcutaneously, plasma naltrexone peaked at approximately 15 ng/mL after approximately 3 days; following intramuscular injection, it peaked at 19 ng/mL, also after approximately 3 days. Mean plasma naltrexone levels were 12 to 14 ng/mL for the next 3 weeks regardless of the route of administration, and they were detectable until 5 weeks after the injection. After the administration of a competitive mu-receptor antagonist, there usually is a neuroadaptive upregulation of these receptors (Lahti and Collins 1978; Zukin et al 1982). This pharmacodynamic response was quantified by measuring the mu-receptor density with [^{3}H]DAMGO radioligand autoradiography following the administration of Vivitrex®. After a single injection, significant increases in mu-receptor density occurred, especially in the midbrain and striatum a week later and in the neocortex a month later; these were sustained for 2–4 weeks. Similar results were seen in immunochemistry studies, but with relatively smaller increases, which ranged from 10% to 40% (Bartus et al 2003). Importantly, the amount of mu-receptor upregulation after injection of Vivitrex® appears similar to the amount after at least 4 weeks of oral naltrexone administration (Giordano et al 1990). In view of the fact that suppression of morphine analgesia also occurred in the hot-plate paradigm for 5 weeks after the administration of a single Vivitrex® injection, it is reasonable to suggest that a pharmacologically relevant dose of Vivitrex®/Vivitrol® continues its pharmacodynamic effect of blocking central mu-receptors for up to 1 month post-injection.

Johnson et al (2004) showed, in a double-blind, placebo-controlled, randomized, multi-site, 16 week study of 30 alcohol-dependent individuals, that the 25 subjects receiving an intramuscular injection of Vivitrex® (400 mg) every 4 weeks for 4 months had a mean plasma 6-beta-naltrexol (naltrexone's major metabolite) trough level of 3.0 ng/mL and a mean naltrexone trough level of 1.3 ng/mL. In contrast, an earlier study found that – 16 hours after administration of oral naltrexone (50 mg) – subjects had a mean serum 6-beta-naltrexol level of 24.9 ng/mL (McCaul et al 2000). The findings of King et al (1997) showed mean urinary concentrations of 29.0 µg/mg for 6-beta-naltrexol and 2.9 µg/mg for naltrexone, 3 hours after oral administration of naltrexone (50 mg) in 24 male moderate-to-heavy social drinkers.

Galloway et al (2005) demonstrated, in an open-label, single-site, 6 week study of 16 alcohol-dependent individuals receiving just one intramuscular injection of Naltrel® (300 mg), that serum naltrexone levels increased to a peak of approximately 2.04 ng/mL at 2 weeks and dissipated slowly to 0.58 ng/mL over the next 4 weeks. Plasma naltrexone and 6-beta-naltrexol levels at week 4 were approximately 0.75 and 2.2 ng/mL, respectively. These levels were proportionately (ie, to dose) less than those found in the Vivitrex® study by Johnson et al (2004).

In humans, the peak plasma concentration of long-acting naltrexone depot formulations is greater than that of oral naltrexone during the days immediately after the injection. The advantage of these formulations with respect to tolerability, therefore, may be that such peaks just occur early in treatment with the depot preparations whereas they occur daily with oral naltrexone. The lack of first-pass metabolism with the long-acting preparations, with diminished 6-beta-naltrexol levels, also might lead to an improved adverse-event profile as increased levels of beta-naltrexol have been associated

with a greater severity and frequency of naltrexone-related adverse events (King et al 1997).

Thus, preclinical and human studies provide a pharmacodynamic and pharmacokinetic basis for the monthly injection of a long-acting naltrexone depot formulation as treatment for alcohol dependence through the blockade of mu-opioid receptors.

Clinical results

Clinical trials involving alcohol-dependent individuals have examined the efficacy, safety, and tolerability of Naltrel® and Vivitrex®/Vivitrol®.

Naltrel®

The first published study on the efficacy, safety, and tolerability of Naltrel® for treating alcohol dependence comprised a multi-site, double-blind, 12 week clinical trial. One hundred fifty-eight alcohol-dependent men and women were assigned to receive Naltrel® and 157 received placebo, both accompanied by motivation enhancement-based psychosocial support, every 4 weeks (Kranzler et al 2004). The first Naltrel® dose consisted of one injection of 150 mg in each buttock, and each dose thereafter was just 150 mg. Placebo was identical in number and volume of injections but did not contain the active compound. Generally, Naltrel® appeared to be well tolerated and safe. Side effects that were reported significantly more frequently in the Naltrel® group than in the placebo group included injection site reactions, chest pain, and upper abdominal pain. Irritability, however, was more common after placebo than after injection of Naltrel®. There were 13 dropouts (8.2%) in the Naltrel® group and only 6 dropouts (3.8%) in the placebo group; the subjects' reasons for discontinuing treatment, however, were similar between the groups. Naltrel® recipients were more likely than placebo recipients to have a higher mean number of cumulative abstinent days (52.8 days, 95% CI 48.5–57.2 days, vs 45.6 days, 95% CI 41.1–50.0 days, respectively; $p = 0.018$) and a longer median time to first drink (5 days, 95% CI 3–9 days, vs 3 days, 95% CI 2–4 days, respectively; $p = 0.003$). The effects of gender on treatment outcome were not examined, probably because of the relatively small sample size (Kranzler et al 2004).

A single-site, 6 week, open-label trial studied 16 alcohol-dependent individuals who were given a single intramuscular dose of Naltrel® (300 mg) (Galloway et al 2005). Of the 198 adverse events that were reported, 17 were rated as severe, including fatigue, gastrointestinal pain, irritability, nausea, somnolence (2 reports), headache (4 reports from 3 subjects), injection site pain, injection site mass, lethargy, depression, increased gamma-glutamyl transferase (GGT) level (an index of heavy drinking) (Conigrave et al 2002), back pain, and flatulence. There were no serious adverse events. Also, the trend was for participants' drinking outcomes to improve between enrollment and the end of the trial (Galloway et al 2005).

Since the Naltrel® formulation has shown promise as an efficacious medication for treating alcohol dependence, it deserves further study. Early findings indicate that Naltrel® is safe and well tolerated, and its adverse-event profile appears to be milder than that reported for oral naltrexone. Additional data are needed regarding the effects of gender on treatment outcome. Future studies also should show whether Naltrel® is likely to cause injection site-related allergic-type reactions.

Vivitrex®/Vivitrol®

The first published study on the initial efficacy, safety, and tolerability of Vivitrex® for treating alcohol dependence was a double-blind, placebo-controlled, randomized, multi-site, 16 week clinical trial (Johnson et al 2004). Twenty-five alcohol-dependent individuals were assigned to receive intramuscular injections of Vivitrex® (400 mg) every 4 weeks, while five participants received placebo via the same route of administration every 4 weeks. Vivitrex® appeared to be relatively safe and well tolerated; the most common adverse events were non-specific abdominal pain, nausea, pain at the injection site, and headaches. Two Vivitrex® recipients and zero placebo recipients discontinued treatment because of side effects. One participant dropped out due to induration at the injection site, and one was discontinued by the research staff because of an allergic reaction that resulted in angioedema, which resolved soon after the participant stopped taking the medication. Even though any conclusions regarding efficacy must take into consideration the study's unbalanced cell design, it did appear that Vivitrex® was more likely than placebo to lead to a lower percentage of heavy drinking days (ie, 11.7% vs 25.3%, respectively). In the exercise of scientific caution, no inferential statistical testing was conducted on these descriptive values. Additionally, participants in both the Vivitrex® and placebo groups demonstrated improved drinking outcomes between enrollment and study end (Johnson et al 2004).

The efficacy, safety, and tolerability of Vivitrex® were later studied in a placebo-controlled, double-blind, randomized, multi-site, 24 week clinical trial (Garbutt et al 2005). Intramuscular injections of high-dose Vivitrex® (380 mg) ($n = 205$), low-dose Vivitrex® (190 mg) ($n = 210$),

or matching placebo (n = 209), along with low-intensity psychosocial support, were administered to alcohol-dependent men and women every 4 weeks. Participants who received high-dose Vivitrex® were significantly more likely than placebo recipients to report the adverse events of decreased appetite, nausea, pain at the injection site, dizziness, and fatigue. The low-dose Vivitrex® and placebo groups experienced adverse events at a similar frequency. Although 14.1% of the high-dose Vivitrex® recipients dropped out of treatment, only 6.7% of the low-dose Vivitrex® and placebo groups did so. Injection site reactions, headaches, and nausea were the most common reasons given for discontinuing treatment. Two high-dose Vivitrex® recipients had serious adverse events caused by an interstitial pneumonia and allergic-type eosinophilic pneumonia, both of which resolved after medical treatment. The high-dose Vivitrex® group, averaged between men and women, had a significantly lower percentage of heavy drinking days than did placebo recipients (hazard ratio [HR] 0.75, 95% CI 0.60–0.94; $p = 0.02$). An analysis by gender, however, demonstrated that the only improvement in drinking outcomes among high-dose Vivitrex® recipients was in men (HR 0.56, 95% CI 0.41–0.77; $p < 0.001$) and not women (HR 1.23, 95% CI 0.85–1.78; $p = 0.28$). These findings demonstrate that although women in the high-dose Vivitrex® group versus the placebo group reported a 23% relative increase in percentage of heavy drinking, men in the high-dose Vivitrex® group reported a relative decrease of 44% in the same variable. High-dose Vivitrex® and placebo recipients did not differ significantly in GGT level, and low-dose Vivitrex® and placebo recipients did not experience a significant difference in GGT level or drinking outcomes (Garbutt et al 2005).

At least four points need to be made concerning the evidence that Vivitrex®/Vivitrol® can decrease heavy drinking in men but not women (Johnson 2006). First, since individuals with alcohol dependence in their family history have reportedly experienced the best results with oral naltrexone (Monterosso et al 2001), it is tempting to speculate that male subjects in the Garbutt et al (2005) trial may have responded to Vivitrex® for the same reason. Comparative rates of family history of alcoholism between men and women, however, were not given. Hence, future studies testing the efficacy of Vivitrex®/Vivitrol® should investigate any potential interaction between familial alcoholism (or related variables including age of alcoholism onset) and treatment outcome.

Second, Vivitrex® injections might have been more likely in women than in men to be delivered subcutaneously instead of intramuscularly, thereby slowing absorption, since women tend to have a relatively higher percentage of body fat (Blaak 2001). Indeed, in a study by Kiefer et al (2005), drinking outcomes appeared to be better for women than for men receiving oral naltrexone. Since Garbutt et al (2005) did not study pharmacokinetic data, a report comparing the kinetic profile of Vivitrex®/Vivitrol® between women and men would be required to exclude this possibility.

Third, alcohol-dependent men and women enrolled in clinical trials perhaps cannot be compared directly as they might differ on non-drinking outcomes, including familial pressure to change, rates of affective disorder, or individual motivation to achieve treatment objectives. There is no evidence, however, to suggest that the women enrolled in this trial were atypical of women participating in pharmacotherapy trials for the treatment of alcohol dependence. Moreover, among the enrolled men, there was probably heterogeneity on these same factors. Attempts to match women and men who are enrolled in pharmacotherapy trials for treating alcohol dependence on multiple non-drinking-related factors would not be practical and would lead to the same conclusion, ie, that the therapeutic effect of Vivitrex®/Vivitrol® to diminish heavy drinking among alcohol-dependent men does not translate to alcohol-dependent women. Subjects who participate in pharmacotherapy trials for treating alcohol dependence are mostly men, and the relatively small sample sizes of single-site studies do not allow meaningful statistical comparisons of drinking outcomes between women and men. Of the two important trials that resulted in US Food and Drug Administration approval of oral naltrexone for treating alcohol dependence (O'Malley et al 1992; Volpicelli et al 1992), only the O'Malley et al (1992) study included women, but not in large enough numbers to permit gender comparisons. Given the multitude of published studies testing oral naltrexone for the treatment of alcohol dependence (Srisurapanont and Jarusuraisin 2005), a meta-analytic approach to examining for a gender effect on treatment outcome would be of scientific interest. If oral naltrexone has demonstrated similar efficacy between women and men, then the absence of an effect for Vivitrex® in women might be a result of the fact that oral naltrexone and Vivitrex®/Vivitrol® are prepared and administered differently. If, on the other hand, meta-analytic studies reveal that oral naltrexone, like Vivitrex®/Vivitrol®, exhibits greater efficacy for men than for women, then it is plausible that such findings would be related to common pharmacodynamic interaction factors. A greater understanding of such factors is necessary for optimization of treatment delivery.

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