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Extended-Release Intramuscular Naltrexone

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Contents

Abstract

▲ An extended-release intramuscular formulation of naltrexone that provides sustained release of the drug over a 28-day period has been developed with the aim of improving treatment adherence in patients treated with naltrexone for alcohol dependence. Biodegradable polylactide-co-glycolide polymer microspheres containing 34% w/w naltrexone are reconstituted in an aqueous suspension just prior to intramuscular administration.

▲ Extended-release intramuscular naltrexone 380mg administered once every 4 weeks, in combination with psychosocial therapy, demonstrated superior efficacy to placebo plus psychosocial therapy in reducing the heavy drinking event rate (primary endpoint) in adult patients with alcohol dependence in a 6-month well controlled trial.

▲ Among the subset of patients who abstained completely from drinking during the 7 days prior to the first dose of medication (n = 53; 8% of the total study population), those treated with extended-release intramuscular naltrexone 380mg had greater reductions in the number of drinking days and the number of heavy drinking days compared with placebo recipients.

▲ Treatment with extended-release intramuscular naltrexone 380mg once every 4 weeks for up to 18 months was generally well tolerated, with infrequent treatment-related serious adverse events. The most common treatment-emergent adverse events leading to treatment discontinuation were nausea, injection site reaction and headache. The proportion of patients with clinically significant plasma transaminase elevations was not different between patients receiving extended-release intramuscular naltrexone and those receiving placebo.

Features and properties of extended-release intramuscular naltrexone (Vivitrol™)	
Featured indication	
For the treatment of alcohol dependence in adult patients in combination with psychosocial therapy	
Mechanism of action	
Opioid antagonist, with mechanism of action thought to involve stabilisation of the role of the endogenous opioid system in alcohol reinforcement	
Dosage and administration	
Dose	380mg
Route of administration	Intramuscular injection
Frequency of administration	Once every 4 weeks or once each month
Multiple-dose pharmacokinetic properties of naltrexone (6β-naltrexol) after extended-release intramuscular naltrexone 380mg every 28d	
Maximum plasma concentration	28 ng/mL (34 ng/mL)
Time to maximum plasma concentration	2d (3d)
Area under the concentration-time curve from 0–28d	160 ng • d/mL (337 ng • d/mL)
Apparent elimination half-life	5d (5d)
Most common treatment-emergent adverse events	
Nausea, headache, fatigue	

Alcohol dependence is a chronic disorder with a devastating impact on the quality of life of individuals and families.[1] The burden of disease relating to alcohol use is considerable and may include cardiovascular disease, cancer or gastrointestinal system diseases, and an increased risk of injury from motor vehicle crashes, sport or recreational activities, or self-inflicted injury.[2] Alcohol use disorders have a considerable economic impact, given their prevalence.[3] In the US in 2004, approximately 18 million individuals aged >12 years abused or were dependent on alcohol.[4] Of these individuals, about 2.7 million received treatment for alcohol use disorders (1.5 million also received treatment for the use of illicit drugs).[4]

Treatment for alcohol dependence usually includes a psychosocial therapy programme, but patients may also receive pharmacotherapy as an adjunctive treatment.[5] Oral naltrexone has shown efficacy in improving some, but not all drinking outcomes (reviewed by Rohsenow[6]). However, the efficacy of oral naltrexone depends on the patients' adherence to their medication,[7] although of the agents available for pharmacotherapy of alcohol dependence, naltrexone is not unique in this respect.[7] Use of an extended-release injectable formulation may improve treatment compliance and, therefore, therapeutic outcomes.[7] With the exception of a long-acting formulation of naltrexone developed by DrugAbuse Sciences (Hayward, CA), which showed efficacy in total abstinence rates achieved by patients with alcohol dependence,[8] most other sustained-release or long-acting formulations of naltrexone that have been previously investigated have had limited success.[9] Limitations included poor tolerability (e.g. significant injection site reactions) and inadequate plasma drug concentrations (reviewed by Dean[9]).

An extended-release intramuscular formulation of naltrexone (Vivitrol™)**1** has been developed using Medisorb® microspheres technology[9] and was approved for use in the treatment of alcohol dependence by the US FDA in April 2006.[10] The extended-release intramuscular formulation of naltrexone is an aqueous suspension of poly(d,l-lactide-co-glycolide) microspheres (Medisorb® naltrexone) reconstituted just prior to administration.[9] Each microsphere is comprised of 34% w/w naltrexone.[11] Following intramuscular injection, the initial release of naltrexone from the microspheres is via diffusion of the naltrexone molecule through the polymer matrix.[9] An initial, transient peak in plasma drug concentrations is achieved approximately 2 hours after injection,[12] and sustained peak drug concentrations are achieved within 2–3 days (see section 3 for further details).[12] Thereafter, the sustained release of naltrexone is via diffusion and biodegradation of the polymer,[9] which is hydrolysed to lactic acid, glycolic acid and monomers that are further metabolised and eliminated from the body as water and carbon dioxide.[9]

This review focuses on the pharmacology, efficacy and tolerability of extended-release intramuscular naltrexone in adult patients with alcohol dependence.

2. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic effects of naltrexone. Pharmacodynamic data are available for the oral formulation;[13-23] there are currently no pharmacodynamic studies of the extended-release intramuscular formulation in humans. Data are available from studies in healthy volunteers (n = 16–51)[14-17,21,22] or patients with alcohol dependence (n = 16–165).[13,18-20,23] Oral naltrexone was administered at a dose of 50mg in single-dose studies,[13-15] and in multiple-dose studies, at a dosage of 50 mg/day[16-22] or 100 mg/day,[16,17] with the exception of one of these latter studies, where patients received oral naltrexone 25mg twice daily.[23] Additional data are available from the prescribing information for oral[24] or extended-release intramuscular[12] naltrexone and a review.[25]

- Naltrexone and its main active metabolite, 6β-naltrexol, are opioid antagonists that competitively bind to opioid receptors, thus blocking the effects of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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endogenous opioids.[24] Although the precise mechanism of action of naltrexone remains unknown, naltrexone is thought to reduce alcohol consumption by reducing the reinforcing attributes of alcohol, which are mediated in part by the endogenous opioid system (reviewed previously).[25] For example, in studies in healthy volunteers, oral naltrexone 50mg (single-dose studies)[14,15] or 50 mg/day (multiple-dose study[22]) reduced the subjective reinforcing effect of alcohol (all $p \leq 0.05$ vs placebo).

- Other potential mechanisms of naltrexone for reducing alcohol consumption include: reducing the urge (all $p < 0.05$ vs placebo)[13,20,23] or craving ($p < 0.05$ vs placebo)[18,19] to drink (studies in patients with alcohol dependence); reducing the subjective liking of alcohol in studies in healthy volunteers ($p < 0.01$ vs placebo),[16,17] although in a small study[21] this effect was not statistically significant; and increasing alcohol-induced aversive responses (e.g. nausea; $p \leq 0.05$ vs placebo).[16]
- In animal studies, the effect of oral naltrexone on alcohol consumption was synergistic with sertraline,[26] but neither additive nor synergistic with fluoxetine[27] or acamprosate.[28]
- Pharmacodynamic drug interaction studies with extended-release intramuscular naltrexone in patients with alcohol dependence have not been conducted. Nevertheless, extended-release intramuscular naltrexone is contraindicated in patients receiving opioid analgesics, because naltrexone blocks the effects of opioids by competitive binding at opioid receptors. For similar reasons, patients may not benefit from opioid-containing medicines (e.g. cold remedies, antidiarrhoeal agents).[12]
- The administration of extended-release intramuscular naltrexone is not associated with the development of tolerance or dependence and it is non-aversive.[12] The efficacy of long-term administration of this formulation of naltrexone in patients with alcohol dependence is reviewed in section 4.

3. Pharmacokinetic Profile

This section focuses on the pharmacokinetic properties of extended-release intramuscular naltrexone; data for oral naltrexone (taken from the manufacturer's prescribing information[24]) are included for comparison and where no data for the extended-release intramuscular formulation exist. The pharmacokinetic properties of naltrexone and its primary active metabolite, 6β-naltrexol (see section 3.2), after administration of the extended-release intramuscular formulation have been evaluated in a randomised, double-blind, placebo-controlled study in healthy adult subjects (n = 42).[11] In the single-dose cohort, subjects received oral naltrexone 50mg on the first day, followed by a 7-day washout period, and then extended-release intramuscular naltrexone 380mg (n = 12) or 190mg (n = 12), or placebo (n = 4).[11] In the multiple-dose cohort (n = 14), oral naltrexone 50 mg/day was given for 5 days before a 7-day washout period. Four doses of extended-release intramuscular naltrexone 380mg (n = 12) or placebo (n = 2) were given, each dose 28 days apart.[11] Additional data are available from the prescribing information for extended-release intramuscular naltrexone.[12]

Absorption and Distribution

- Naltrexone mean plasma concentrations of >1 ng/mL were achieved for at least 35 days following a single 380mg dose of the extended-release intramuscular formulation.[11] No data regarding the minimum effective therapeutic plasma concentration of naltrexone were reported.
- The naltrexone plasma concentration-time profile after administration of extended-release intramuscular naltrexone is characterised by two peaks; one transient peak approximately 2 hours after the injection, and then the peak plasma concentration (C_{max}). Plasma drug concentrations begin to decline slowly approximately 14 days after administration of a dose.[12]
- Naltrexone is well absorbed following multiple-dose administration of extended-release intramuscular naltrexone 380mg (figure 1). The median time to reach C_{max} (t_{max}) was 2 days (range 1.75–3 days) and steady state was reached by the end of the first dose interval (i.e. by 28 days).[11]
- Although patients received a lower total monthly dose of naltrexone over 28 days with extended-

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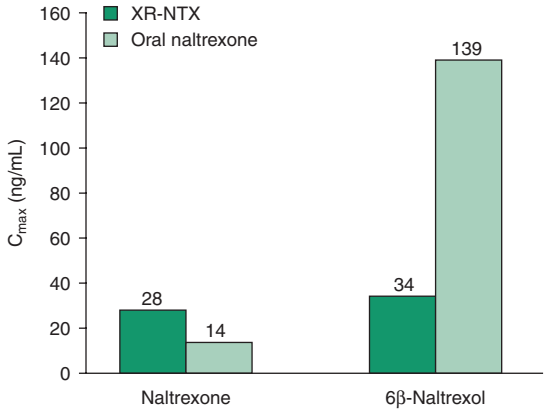

Fig. 1. Absorption of extended-release intramuscular naltrexone (XR-NTX) compared with oral naltrexone. Mean maximum plasma concentrations (C_{max}) of naltrexone and its major active metabolite, 6β-naltrexol, after multiple doses of XR-NTX 380mg once every 28 days for a total of four doses (n = 10) or oral naltrexone 50 mg/day for 5 days (n = 14) in healthy adult subjects. In this randomised, double-blind, placebo-controlled crossover study, there was a 7-day washout period between administration of the oral and extended-release formulations.[11] The numerical value of each C_{max} value is shown above each bar.

release intramuscular naltrexone 380mg than with oral naltrexone 50 mg/day (total monthly dose of 1400mg), systemic exposure to naltrexone at steady state (assessed by mean area under the concentration-time curve from 0 to 28 days [AUC_{28d}]) was approximately 4-fold greater with extended-release intramuscular naltrexone than oral naltrexone (160 vs 41 ng • d/mL).[11] The AUC_{28d} value for oral naltrexone was calculated by multiplying the AUC_{1d} value (1.46 ng • d/mL) by 28 (number of days).[11]

- With repeated doses of extended-release intramuscular naltrexone 380mg once every 28 days, naltrexone pharmacokinetics did not vary with time (the ratio of geometric least squares means of steady-state to single-dose AUC values of naltrexone was 1.12; 90% CI 0.98, 1.29), and there was minimal accumulation of either the parent drug or 6β-naltrexol (13% and 11%).[11]
- Systemic exposure to 6β-naltrexol at steady state was reduced with extended-release intramuscular naltrexone 380mg versus oral naltrexone 50 mg/day because of reduced first-pass metabolism with intramuscular administration. The 6β-naltrexol AUC_{28d} value (337 ng • d/mL) was 2-fold greater than that of naltrexone after multiple doses of extended-release intramuscular naltrexone 380mg compared with a >20-fold difference after multiple doses of oral naltrexone 50 mg/day.[11] The median t_{max} of 6β-naltrexol was 3 days after multiple doses of the extended-release intramuscular formulation.
- Naltrexone AUC from time zero to infinity (AUC_{∞}) values after single doses of extended-release intramuscular naltrexone 190mg or 380mg were dose proportional, and the single-dose pharmacokinetics of the extended-release intramuscular formulation were predictive of multiple-dose pharmacokinetics.[11]
- Naltrexone and 6β-naltrexol mean C_{max} (12.9 and 19.4 ng/mL), and AUC_{∞} (144 and 329 ng • d/mL) and median t_{max} values (2 and 3 days) were reported after a single 380mg dose of extended-release intramuscular naltrexone. Respective values for a single 190mg dose were 10.2 and 14.1 ng/mL for C_{max}, 71.8 and 175 ng • d/mL for AUC_{∞}, and 2 and 3 days for median t_{max}.[11]
- The volume of distribution of naltrexone following intravenous administration is 1350L[24] and naltrexone is 21% bound to plasma proteins.[12]

Metabolism and Elimination

- Naltrexone is metabolised via aldo-keto reductase (previously designated as dihydrodiol dehydrogenase) liver enzymes to the primary active metabolite 6β-naltrexol.[29,30] Minor metabolites are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methyl-naltrexone.[24]
- Excretion of naltrexone and 6β-naltrexol is primarily renal (53–79% of an oral dose). The proportion of an oral dose excreted in the urine as unchanged drug is <2%, and of unchanged drug and conjugated 6β-naltrexol is ≈43%.[24]
- The apparent mean elimination half-life ($t_{½}\beta$) of both naltrexone and 6β-naltrexol was 5 days after multiple-dose administration of extended-release intramuscular naltrexone 380mg and 5–7 days after a single dose of extended-release intramuscular naltrexone 380mg or 190mg.[11] These $t_{½}\beta$ values re-

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flect the extended release of naltrexone from the polymer microspheres.[11]

Special Patient Populations

- There was no clinically significant effect on the pharmacokinetics of extended-release intramuscular naltrexone 190mg in subjects with mild or moderate hepatic impairment (n = 12) compared with healthy subjects (n = 13) in an open-label, single-dose study.[31] Dosage adjustment is not required in these patients.[12]
- Although naltrexone C_{max} values were 86% greater in subjects with mild hepatic impairment (90% CI 1.1, 3.2), and 45% lower in subjects with moderate hepatic impairment (90% CI 0.3, 0.9) than in healthy subjects, naltrexone AUC_{∞} values were not significantly different.[31] The differences in naltrexone C_{max} values were possibly because of high between-group variability.[31]
- The pharmacokinetics of extended-release intramuscular naltrexone are not significantly altered in patients with mild renal impairment (creatinine clearance of 50–80 mL/min), thus no dosage adjustment is required in these patients. However, extended-release intramuscular naltrexone has not been evaluated in patients with moderate or severe renal impairment.[12]
- Extended-release intramuscular naltrexone pharmacokinetic parameters did not differ significantly on the basis of sex in healthy male or female volunteers.[12] The influence of age, race or smoking status on the pharmacokinetics of extended-release intramuscular naltrexone has not been evaluated.

4. Therapeutic Efficacy

The efficacy of extended-release intramuscular naltrexone in combination with a low-intensity psychosocial programme in adult patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[32] criteria for alcohol dependence was evaluated in a 6-month randomised, double-blind, placebo-controlled, multicentre phase III trial[33,34] that also had a 1-year open-label extension phase.[35] In this trial, patients were not excluded if they continued active drinking or if they did not intend to abstain; indeed, patients were required to have had at least two heavy drinking episodes per week within the 30 days prior to screening. Heavy drinking was defined as at least four (for women) or five (for men) drinks per day.[33] Exclusion criteria included evidence of liver failure, certain co-morbid psychiatric disorders or benzodiazepine, opiate or cocaine dependence.[33] Patients were stratified according to sex, whether or not they had a goal of abstinence and self-reported abstinence in the 7-day lead-in period to the trial. Baseline characteristics were broadly similar between treatment groups.[33] Only patients who had received all six injections in the 6-month trial were enrolled in the extension phase.[35]

Patients received extended-release intramuscular naltrexone once every 4 weeks as a 380mg (n = 205) or 190mg (n = 210) dose, or matching volume of placebo (n = 209) [4 or 2mL injections]. During the trial, all patients were provided with 12 sessions of standardised supportive therapy using the Biopsychosocial, Report, Empathy, Needs, Direct advice and Assessment model.[33] In the extension phase,[35] patients from the two active treatment arms remained on the same dosage of extended-release intramuscular naltrexone, while those in the placebo arms were switched to the corresponding dosage of extended-release intramuscular naltrexone. All patients in the extension phase were offered ongoing psychosocial support; however, the proportion of patients who received this therapy was not reported (data available as abstract plus poster).[35] In both the double-blind trial[33] and the extension phase,[35] patients self-reported the number of standard drinks consumed per day by using the timeline follow-back method.[36]

The primary efficacy endpoint was the event rate of heavy drinking days, defined as the number of heavy drinking days divided by the number of days at risk for heavy drinking, which measures both the frequency and pattern of heavy drinking,[33] and thus assesses the effectiveness of treatment in changing the subject's drinking pattern over a defined period of time.[37] This method of assessment captures

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treatment efficacy where abstinence is not the treatment goal.[37] Secondary endpoints included drinking more than the National Institute on Alcohol Abuse and Alcoholism-specified level of risky drinking and the number of nonabstinent days.[33] Analyses were for the intent-to-treat population, unless reported otherwise, and primary endpoint analyses were performed for each of the predefined stratification variables (sex, goal of abstinence, 7-day period of abstinence prior to treatment).

- Extended-release intramuscular naltrexone 380mg once every 4 weeks significantly reduced the heavy drinking event rate in the overall patient group by 25% compared with placebo (primary efficacy endpoint) [figure 2]. There was no significant difference between patients receiving placebo and those receiving extended-release intramuscular naltrexone 190mg once every 4 weeks for this endpoint.[33]

- In the overall patient group, there was no significant difference from placebo in either of the extended-release intramuscular naltrexone treatment groups for secondary efficacy endpoints (risky drinking or nonabstinent days) [figure 2].

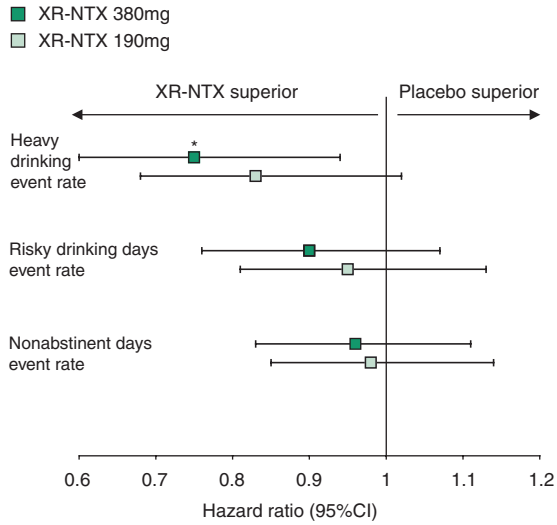

Fig. 2. Efficacy of extended-release intramuscular naltrexone (XR-NTX) in adult patients with alcohol dependence. The heavy drinking event rate (primary efficacy endpoint) was defined as the number of heavy drinking days divided by the number of days at risk for heavy drinking, and risky drinking was defined as more than one (women) or two (men) drinks per day. In this 6-month, randomised, double-blind, placebo-controlled, multicentre phase III trial, patients received, in combination with psychosocial therapy, XR-NTX 380mg (n = 205) or 190mg (n = 210) or placebo (n = 209) once every 4 weeks.[33] Intent-to-treat analysis. * p = 0.03 vs placebo.

- The percentage of heavy drinking days in the 30 days prior to randomisation was 64–66% and overall pretreatment median heavy drinking days per month was 19.[33] During the trial, the median number of heavy drinking days per month was 3.1, 4.5 and 6.0 in patients receiving extended-release intramuscular naltrexone 380mg, 190mg or placebo, respectively (*post hoc* analysis).[33,38]

- In the 7-day lead-in period immediately prior to randomisation, 8.3% of patients were abstinent (i.e. consumed no alcoholic drinks at all), whereas 7% of extended-release intramuscular naltrexone 380mg recipients, 6% of extended-release intramuscular naltrexone 190mg recipients and 5% of placebo recipients remained abstinent during the trial.[33]

- Extended-release intramuscular naltrexone 380mg was associated with continued abstinence in patients abstinent at the time of commencing treatment.[12,33] In the subgroup of patients (n = 53) who were abstinent during the 7-day lead-in period, 41% of extended-release intramuscular naltrexone 380mg recipients (7 of 17 patients), 35% of extended-release intramuscular naltrexone 190mg recipients (6 of 17) and 17% of placebo recipients (3 of 19) remained abstinent throughout treatment.[33]

- *Post hoc* analysis of the subgroup of patients abstinent in the 4 days prior to starting treatment (n = 83) showed that extended-release intramuscular naltrexone 380mg recipients were more likely than placebo recipients to maintain abstinence (p = 0.02; available as an abstract and oral presentation).[34]

- Extended-release intramuscular naltrexone 380mg significantly reduced the number of heavy drinking and drinking days in the subgroup of patients (n = 53) who were abstinent during the 7-day lead-in period.[12,33,34] For instance, the heavy drinking event rate relative to placebo was reduced by 80% in these patients (HR = 0.20; 95% CI 0.07, 0.62; p = 0.005), compared with 21% in those (n = 571) who drank during this time (HR = 0.79, 95% CI 0.62, 1.00; p = 0.05) [results should be

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interpreted with caution due to small patient numbers in certain subgroups].[33]

- Almost two-thirds of patients received all six injections (64%) and most patients received at least four injections (74%). However, fewer than half the patients attended all therapy sessions (43%). Nevertheless, the median number of therapy sessions completed was 11 out of 12 sessions.[33]
- Improvements in health-related quality of life, assessed via changes from baseline in Short Form-36 questionnaire component scores, were significantly greater with extended-release intramuscular naltrexone 380mg once every 4 weeks than with placebo in the mental component scores (+7.9 vs +6.0; $p < 0.05$) [available as an abstract plus poster].[39] Baseline values were 38.7 for the extended-release intramuscular naltrexone group (n = 205) and 40.6 for the placebo group (n = 209), and were significantly lower than US population norms (statistical analyses not reported).[39]
- Although the physical component scores did not alter significantly from baseline in either the extended-release intramuscular naltrexone or placebo treatment groups, baseline values were not different from US population norms (statistical analyses vs US norms not reported).[39]
- Extended-release intramuscular naltrexone 380mg (n = 175) and 190mg (n = 157) once every 4 weeks appeared to improve drinking outcomes over 1.5 years.[35] Although statistical analyses were not reported, the median number of heavy drinking days per month were 2.63–5.23 during the 6-month trial compared with 1.6–2.45 days during the 1-year extension phase.[35] Placebo recipients switched to treatment with extended-release intramuscular naltrexone 380mg in the extension phase (n = 60) experienced a significant ($p < 0.01$) reduction in the percentage heavy drinking days at the end of the extension phase (quantitative data not reported).[35]

5. Tolerability

During the premarketing development of extended-release intramuscular naltrexone, >900 patients with alcohol and/or opioid dependence were treated with the drug in controlled and uncontrolled trials, including 460 patients who received the drug for ≥6 months and 230 who received the drug for at least 1 year.[12] Although the tolerability of extended-release intramuscular naltrexone was initially assessed in a small 4-month, randomised, double-blind, placebo-controlled pilot study in adult patients with alcohol dependence,[40] this section focuses on tolerability data from the 6-month trial[33] and 1-year open-label extension phase[35] discussed in section 4. Additional data are available from a poster presentation (on serum γ-glutamyl transferase [GGT] levels)[41] and from the manufacturer's prescribing information.[12] Analyses are for the intent-to-treat population unless stated otherwise.

- Extended-release intramuscular naltrexone 380mg or 190mg once every 4 weeks was generally well tolerated for treatment periods of up to 18 months' duration in adult patients with alcohol dependence.[33,35]
- Nausea (of mild to moderate severity), headache and fatigue were the most frequent treatment-emergent adverse events with extended-release intramuscular naltrexone (figure 3),[33] and nausea, fatigue, decreased appetite, dizziness and injection site pain occurred significantly more frequently with extended-release intramuscular naltrexone 380mg than with placebo.
- In addition, abdominal pain, injection site induration, injection site pruritus and decreased libido, which all occurred in <10% of patients in any group, occurred significantly more frequently with extended-release intramuscular naltrexone 380mg than with placebo (quantitative data not reported; all $p < 0.05$).[33]
- Tenderness was the most frequent injection site reaction, occurring in 16%, 14%, 18% and 9% of patients receiving extended-release intramuscular naltrexone 380mg or 190mg, or placebo 4mL or 2mL, respectively.[33]
- Serious adverse events that were possibly treatment related occurred in two patients in the extended-release intramuscular naltrexone 380mg group in the double-blind trial[33] (one diagnosed case and one suspected case of eosinophilic pneumonia[12]), and in one patient in the 190mg group in the exten-

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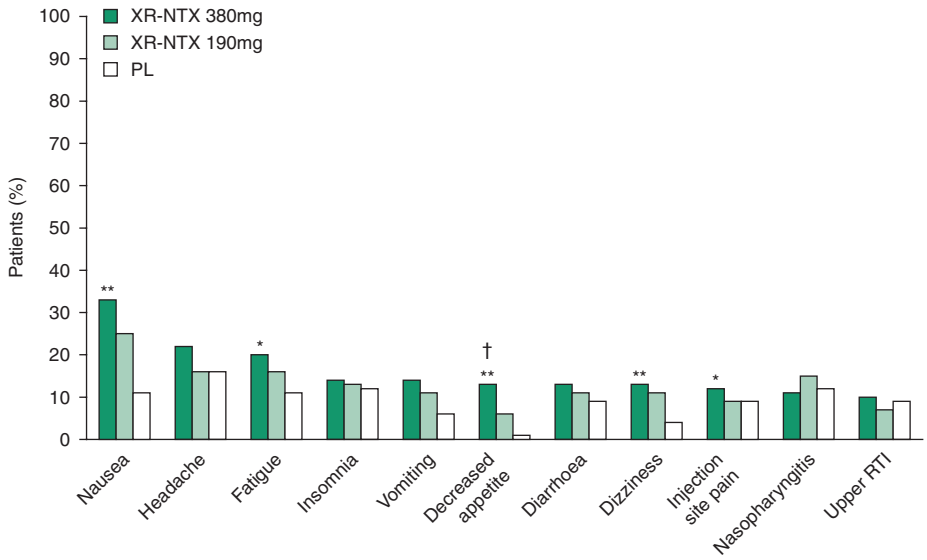

Fig. 3. Tolerability of extended-release intramuscular naltrexone (XR-NTX) in adult patients with alcohol dependence. The incidence of treatment-emergent adverse events occurring in ≥10% of patients in any treatment group in a 6-month, randomised, double-blind, placebo (PL)-controlled, multicentre phase III trial is shown. In combination with psychosocial therapy, patients received XR-NTX 380mg (n = 205) or 190mg (n = 210) or PL (n = 209) every 4 weeks. **RTI** = respiratory tract infection. * $p < 0.05$, ** $p \leq 0.001$ vs PL; † $p < 0.05$ vs XR-NTX 190mg.

sion study (acute hepatitis in a patient with hepatitis C).[35] One death occurred in the extension study, but was not considered to be treatment-related.[35] Otherwise, treatment-related adverse events (of any severity) were reported in 27% of patients receiving 1 year of treatment with extended-release intramuscular naltrexone 380mg or 190mg.[35]

- According to the manufacturer's prescribing information,[12] adverse events of a suicidal nature occurred in 1% of extended-release intramuscular naltrexone recipients (dosage not reported) but did not occur in any patients receiving placebo. Two completed suicides occurred in recipients of extended-release intramuscular naltrexone (whether these were considered treatment-related was not reported).[12]

- Nevertheless, the incidence of serious adverse events with extended-release intramuscular naltrexone (mainly hospitalisation for alcohol detoxification) was infrequent and similar in the 380mg and 190mg dose groups in the 6-month study (both 5% vs 7% with placebo).[33] In contrast, in the extension study,[35] more than twice as many patients in the extended-release intramuscular naltrexone 190mg group than in the 380mg group experienced these events (7.6% vs 3.4%; statistical analysis not reported).

- In addition, significantly more patients in the extended-release intramuscular naltrexone 380mg group than in the 190mg or placebo groups discontinued treatment because of an adverse event (14% vs 7% and 7%; both p = 0.01).[33] Adverse events leading to discontinuation were mainly nausea, injection site reaction and headache.[33] According to a *post hoc* analysis, the time to discontinuation (for any reason) was not significantly different between treatment groups.[33] In the extension study, 8.4% of extended-release intramuscular naltrexone recipients discontinued treatment because of an adverse event.[35]

- Treatment with extended-release intramuscular naltrexone 380mg was associated with a significant decrease in serum GGT levels relative to placebo (least squares means ratio = 0.89; 95% CI 0.82, 0.96; p = 0.003).[41] Extended-release intramuscular

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naltrexone 190mg was not different from placebo in this respect.

- However, the reductions from baseline in GGT levels were significant in both extended-release intramuscular naltrexone groups and the placebo group (reductions of 9–19%; all $p < 0.001$ vs baseline), and in all patients (15%; $p < 0.001$ vs baseline).[41] Baseline serum GGT levels were 58.6, 73.5 and 75.6 U/L in patients receiving extended-release intramuscular naltrexone 380mg or 190mg or placebo.[33]
- Clinically significant effects of extended-release intramuscular naltrexone on aminotransferase levels were not different from those with placebo;[33] the proportion of patients with AST or ALT levels more than than three times the upper limit of normal were not different between treatment groups.[33] In the prescribing information, 1.5% of extended-release intramuscular naltrexone recipients and 0.9% of placebo recipients had elevated AST levels.[12]
- Additionally in clinical trials, extended-release intramuscular naltrexone was associated with a decrease in platelet count of $17.8 \times 10^3/\mu L$ versus $2.6 \times 10^3/\mu L$ in placebo recipients (baseline values not reported), and increases from normal creatinine phosphokinase (CPK) levels at baseline to abnormal (not defined) levels, reported in 11% of extended-release intramuscular naltrexone, 17% of oral naltrexone and 8% of placebo recipients (source of data for oral naltrexone not reported).[12]
- The overall proportion of patients with elevated CPK levels (i.e. levels three times the upper limit of normal) was similar between extended-release intramuscular or oral naltrexone and placebo groups (all data regarding CPK levels are from the manufacturer's prescribing information).[12]

6. Dosage and Administration

In the US, extended-release intramuscular naltrexone is approved for the treatment of alcohol dependence as part of a treatment programme that includes psychosocial therapy.[12] Patients should demonstrate an ability to abstain from drinking in the outpatient setting prior to initiation of treatment, and should not be actively drinking at the initial administration of extended-release intramuscular naltrexone.[12] In addition, patients should be free of opioids for at least 7–10 days prior to treatment with extended-release intramuscular naltrexone to prevent occurrence of an acute abstinence syndrome (withdrawal).[12] The recommended dosage is a single 380mg dose administered as an intramuscular gluteal injection every 4 weeks or once each month.[12] Pretreatment with oral naltrexone is not required, and there are no specific recommendations regarding switching from the oral to intramuscular formulation.

Whilst there is a boxed warning in relation to hepatotoxicity, and naltrexone is contraindicated in acute hepatitis or liver failure and should be used with caution in patients with active liver disease, extended-release intramuscular naltrexone does not appear to be a hepatotoxin at the recommended dosage.[12] Further information regarding warnings, precautions and dosage recommendations in special patient populations are contained in the manufacturer's prescribing information.

7. Extended-Release Intramuscular Naltrexone: Current Status

Extended-release intramuscular naltrexone is approved in the US for the treatment of alcohol dependence in an ambulatory setting in combination with psychosocial therapy, in patients who are able to abstain from drinking and who are not actively drinking at commencement of treatment. The approved dosage is a single intramuscular 380mg dose administered once per month.

In a phase III clinical trial, extended-release intramuscular naltrexone 380mg once every 4 weeks, in combination with psychosocial therapy, reduced heavy drinking over a 6-month period in adult patients with alcohol dependence, most of whom were active drinkers. This reduction in frequency of heavy drinking appeared to be maintained for a further year of treatment. In the subset of patients who were abstinent prior to treatment initiation, extended-release intramuscular naltrexone 380mg reduced the number of drinking days and heavy drinking days relative to placebo and was more

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likely to maintain abstinence. Extended-release intramuscular naltrexone was generally well tolerated.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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