Early Treatment Response in Alcohol Dependence With Extended-Release Naltrexone

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Objective: We sought to determine the time course for onset of effect of intramuscular injectable extended-release naltrexone (XR-NTX), which has demonstrated efficacy for alcohol dependence.

Method: A post hoc analysis of a randomized, double-blind, placebo-controlled, multicenter study was conducted. In the study, actively drinking men and women who met DSM-IV-TR criteria for alcohol dependence were randomly assigned to receive injections of XR-NTX 380 mg (N = 205) or 190 mg (N = 210) or placebo (N = 209) every 4 weeks for 24 weeks. Patients also received 12 sessions of standardized, low-intensity psychosocial intervention. Drinking data were analyzed by month and, during the first month, by day to explore the time course for onset of effect on heavy drinking days in patients receiving XR-NTX versus placebo. The study data were collected between February 2002 and September 2003.

Results: During the first month following injection, patients receiving XR-NTX 380 mg had 37% fewer heavy drinking days versus placebo ($p < .01$). By day 2, a significant reduction in the median number of drinks consumed per day was observed in patients given XR-NTX 380 mg compared with placebo ($p < .05$). By day 3, XR-NTX 380 mg resulted in a significant reduction in the percentage of patients reporting heavy drinking compared with placebo ($p < .05$); this reduction was maintained throughout the study. A dose-response effect was observed, with intermediate results for XR-NTX 190 mg.

Conclusion: XR-NTX 380 mg provided a rapid onset of therapeutic effect in the first 2 days after the first injection that was sustained throughout the 24-week trial. Potential clinical implications of the rapid, early onset of effect of this medication's delivery system for patients who are dependent on alcohol include facilitation of early engagement in treatment, motivation to continue treatment, and focus on the goals established in counseling.

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Alcohol dependence is a common disorder; nearly 19 million people (7.7%) abused or were dependent on alcohol in the United States in 2005.[1] Despite the public health impact of this neurobiological-based disorder, only 1.6 million people report receiving treatment[1] and even fewer receive pharmacotherapy. Although medication for alcohol dependence has been available in the United States for more than 40 years, models for addressing alcohol dependence remain focused almost exclusively on psychosocial- and spiritual-based approaches.[2,3] Indeed, the slow adoption of pharmacotherapy in the treatment of alcohol dependence may be due in part to poor adherence to oral agents.[4–6]

Naltrexone, the first approved agent for treatment of the pathologic reward and reinforcement effected by alcohol, is an opioid receptor antagonist that appears to reduce these responses in alcohol-dependent patients via the endogenous opioid system.[7–11] Oral naltrexone has established efficacy and safety for the treatment of alcohol dependence in controlled trials[12,13]; however, the vast majority of patients in clinical care are unable to adhere to a 6-month course of treatment.[14] To improve adherence, an intramuscular (IM), injectable,

extended-release formulation of naltrexone (XR-NTX, Alkermes, Inc., Cambridge, Mass.) has been developed.[15,16] This formulation uses Medisorb drug-delivery technology (Alkermes, Inc., Cambridge, Mass.), whereby naltrexone is embedded within biodegradable polymer microspheres[16] and released over at least 30 days.[17] The recommended dosage of XR-NTX is 380 mg IM every month.[18]

XR-NTX is approved for the treatment of alcohol dependence in patients who are able to abstain from alcohol upon treatment initiation. Analysis of results from the intent-to-treat (ITT) population (N = 624) of mostly actively drinking patients (92.5%) in a multisite, double-blind, randomized, controlled trial in alcohol-dependent patients demonstrated that XR-NTX 380 mg yielded a median reduction in heavy drinking days from a baseline of 19 days per month to 3.1 days per month for the study duration—a 48% benefit over that observed for placebo injection ($p < .002$).[19] A subsequent analysis of the randomized double-blind study in patients with 4 days of initial abstinence (N = 82) showed that 11% of those undergoing counseling and receiving placebo injection maintained complete abstinence for the 6-month trial duration versus 32% of patients in counseling and receiving XR-NTX 380 mg ($p = .02$). In general, outcomes for the half dose of XR-NTX (190 mg) were intermediate, between those obtained with placebo and XR-NTX 380 mg, i.e., a dose response was observed.[20] XR-NTX 380 mg is the approved dose for use in patients who are alcohol dependent.

Of importance in evaluating the clinical use of any agent is the time course of the therapeutic response. Pharmacokinetic analyses have evaluated the plasma concentration–time profile of naltrexone after administration of XR-NTX.[17] Following a single injection, plasma levels of the drug persist for at least 30 days, with minimal accumulation after subsequent monthly injections. On the first day, plasma concentrations reach levels equal to approximately half of those measured with oral naltrexone 50 mg. Peak plasma levels occur during the first week, and concentrations begin to decline in a linear fashion thereafter. Although the efficacy of XR-NTX has been demonstrated over a 6-month period, recovery from alcohol dependence is highly unstable in the early treatment phase, when most relapses occur.[21,22] Therefore, this article considers the question of when, following initial injection, efficacy may first be detected. Patients may experience acute urges to drink up to 6 months and longer after treatment initiation and, in the case of oral agents, may have difficulty adhering to treatment for several reasons (e.g., denial of the disease and impatience waiting for the drug to work).[5,22]

The objective of this analysis of the randomized study was to determine the time course for the onset of clinical effect of XR-NTX.

METHOD

This was a post hoc analysis of a randomized, double-blind, placebo-controlled study conducted at 24 centers across the United States.[19] A complete description of the study design and findings was reported previously.[19] Eligible patients were outpatient men and women aged 18 years or older with a diagnosis of alcohol dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. For inclusion, patients had to have a minimum of 2 heavy drinking episodes per week during the month prior to screening. Heavy drinking was defined as greater than or equal to 5 standard drinks per day for men and greater than or equal to 4 standard drinks per day for women. Inclusion did not require detoxification, abstinence, or intent to abstain from alcohol; 92.5% of patients were actively drinking at the time of study entry.[19] The protocol for this study was approved by each center's institutional review board, and each patient provided written informed consent. The study data were collected between February 2002 and September 2003.

Patients received, in double-blind fashion, IM (gluteal) injections of XR-NTX 380 or 190 mg or of placebo microspheres every 4 weeks for 24 weeks. In addition, patients received 12 sessions of standardized, low-intensity psychosocial intervention using the Biopsychosocial, Report, Empathy, Needs, Direct Advice, and Assessment model.[19,23] Data on the number of standard drinks consumed per day were collected for each patient via the time line follow-back (TLFB) method. Use of the TLFB method in this study was fully described previously.[19]

Statistical Analysis

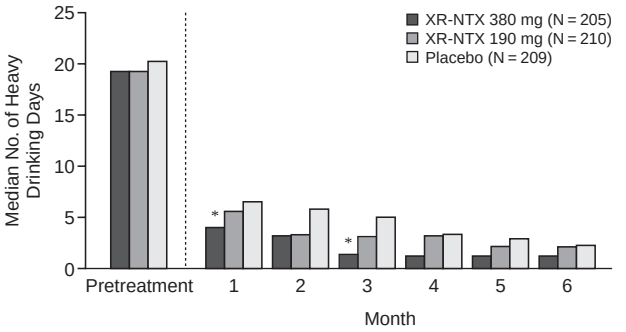
The previous randomized, double-blind, placebo-controlled study reported the treatment effects of XR-NTX injections over a 24-week period.[19] The present analysis specifically focuses on the 30-day period following the first injection of XR-NTX 380 mg and 190 mg. Drinking data were analyzed by month and, during the first month, by day to explore the time course for onset of effect on heavy drinking days in patients receiving XR-NTX versus placebo. The ITT population included all eligible, randomized patients who received at least 1 dose of study drug. The completer population was defined as the subset of the ITT population who received all 6 doses of treatment and provided sufficient TLFB information without any major protocol violations. Between-group differences were analyzed for the number of drinks per day, using the Wilcoxon rank sum test, and for the percentage of patients reporting a heavy drinking day, using the Fisher exact test. Because the mean can be skewed by the large variances inherent in the data, the median is used to report the results.

Table 1. Demographic and Drinking Characteristics at Baseline by Study Group (intent-to-treat population)

Characteristic	XR-NTX 380 mg (N = 205)	XR-NTX 190 mg (N = 210)	Placebo (N = 209)
Age, mean ± SD, y	45.0 ± 10.1	44.6 ± 10.8	44.7 ± 10.8
Male, N (%)	137 (67)	143 (68)	142 (68)
Body mass index, mean ± SD, kg/m^2	27.6 ± 5.6	27.2 ± 5.6	26.8 ± 4.8
White, N (%)	172 (84)	170 (81)	180 (86)
Patients reporting heavy drinking on average in the 30 days prior to random assignment, N (%)	131 (64)	139 (66)	136 (65)

Abbreviation: XR-NTX = intramuscular injectable extended-release naltrexone.

Figure 1. Median Number of Heavy Drinking Days per Month by Study Group (intent-to-treat population)



*p < .01, XR-NTX 380 mg vs. placebo.
Abbreviation: XR-NTX = intramuscular injectable extended-release naltrexone.

RESULTS

In the original study, 899 alcohol-dependent patients were screened, of whom 624 (ITT population) were deemed eligible and were randomly assigned to receive XR-NTX 380 mg (N = 205) or XR-NTX 190 mg (N = 210) or placebo (N = 209). Demographics and characteristics at baseline were similar across the study groups (Table 1). The mean patient age was 45 years (range, 19–74 years), and the predominant race of each group was white (> 80%). Of the 624 patients in the ITT population, 401 (64%) received all 6 injections: 130 (63%) in the XR-NTX 380-mg group, 137 (65%) in the XR-NTX 190-mg group, and 134 (64%) in the placebo group. Of the 401 patients receiving all 6 injections, 23 were excluded from the completer analysis (N = 378) because they did not provide sufficient TLFB data after receiving their last dose.

Early Outcomes by Month

The median patient drank heavily on approximately 19 days during the month prior to random assignment and reported consuming an average of greater than or equal to 6 drinks per day. Reductions in the median number of heavy drinking days from baseline to month 1 were observed in patients receiving XR-NTX 380 mg (19.3 vs. 4.1), XR-NTX 190 mg (19.3 vs. 5.7), and placebo (20.3 vs. 6.5). Month 1 was the first month during which a significantly lower median number of heavy drinking days was observed for patients taking XR-NTX 380 mg compared with those taking placebo ($p < .01$, Figure 1). These reductions continued, indicating a sustained and dose-dependent effect throughout the 24-week study (Figure 1).

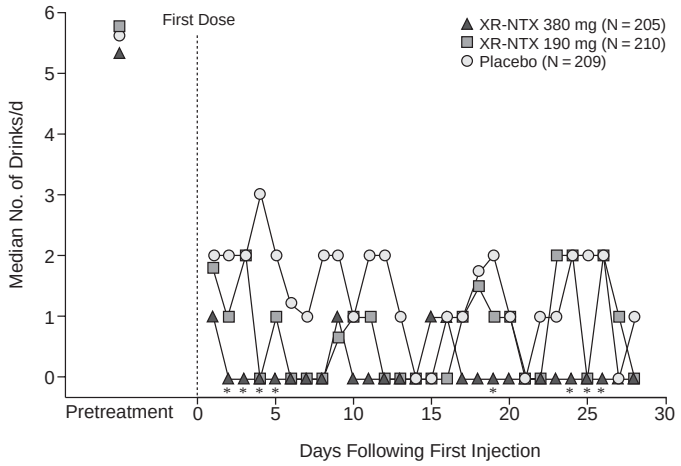
Results of the completer analysis showed that, among patients who completed the study, the number of heavy drinking days per month for both XR-NTX treatment groups (380 and 190 mg) was similar to numbers for the ITT population and the placebo group. In the completers, month 1 was also the first month during which patients treated with XR-NTX 380 mg had significantly fewer heavy drinking days than patients receiving placebo ($p < .01$).

Early Outcomes by Day

Patients receiving XR-NTX consumed fewer drinks per day in the first month following injection compared with the previous month. The median number of drinks consumed per day in the month prior to random assignment was 5.6 for patients taking XR-NTX 380 mg, 5.9 for those taking XR-NTX 190 mg, and 5.6 for those given placebo. Patients receiving XR-NTX 380 mg had 37% fewer heavy drinking days versus placebo (4.1 vs. 6.5, respectively). As early as 1 day after injection, the median number of drinks consumed per day declined in each group to 1.0, 1.8, and 2.0 for XR-NTX 380 mg, XR-NTX 190 mg, and placebo, respectively (Figure 2). Day 2 was the first day following injection on which the XR-NTX 380-mg group reported consuming significantly fewer median drinks per day compared with the placebo group ($p < .05$).

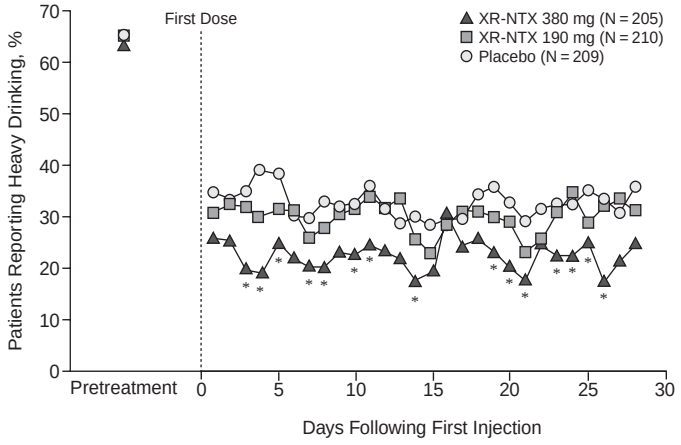
Treatment with XR-NTX (380 or 190 mg) also had an early effect on the proportion of patients reporting heavy drinking days. The median percentage of heavy drinking days in the 30 days before the first dose was 64% for XR-NTX 380 mg, 66% for XR-NTX 190 mg, and 65% for placebo. As shown in Figure 3, the first day after treatment was initiated (day 1), the percentage of patients reporting heavy drinking days had decreased in each group: XR-NTX 380 mg, 26%; XR-NTX 190 mg, 31%; and placebo, 35%. Day 3 was the first day on which the percentage of patients in the XR-NTX 380-mg treatment group reporting a heavy drinking day was significantly lower than that in the placebo group (20% vs. 35%, respectively, $p < .05$, Figure 3).

Figure 2. Median Number of Drinks per Day During the Month Following the First Injection of Intramuscular Injectable Extended-Release Naltrexone (XR-NTX) or Placebo (intent-to-treat population)



*p < .05, XR-NTX 380 mg vs. placebo.

Figure 3. Percentage of Patients Reporting Heavy Drinking on the Days Following the First Injection of Intramuscular Injectable Extended-Release Naltrexone (XR-NTX) or Placebo (intent-to-treat population)



*p < .05, XR-NTX 380 mg vs. placebo.

DISCUSSION

In the treatment of alcohol dependence, beginning 30 years ago, calls for the development of an extended-release pharmacotherapeutic agent to address medication adherence problems were primarily focused on the need to sustain the duration of effect.[24] It is also important, however, to establish benefit soon after treatment initiation.

According to this post hoc analysis of data from a randomized, double-blind, placebo-controlled study, there is an early onset of effect of XR-NTX in alcohol dependence. In conjunction with psychosocial intervention, treatment with XR-NTX significantly reduced heavy drinking in the ITT population over 6 months,[19] with onset of benefit observed during the first month of treatment, particularly within the first 2 days following the initial injection. Treatment with XR-NTX 380 mg resulted in a noticeable reduction in the number of heavy drinking days during the first month of therapy compared with placebo; this effect was maintained throughout the 24-week study in both the ITT and completer analyses. The present analysis demonstrated that as early as day 2 postinjection, patients in the XR-NTX 380-mg treatment arm reported having consumed significantly fewer drinks per day compared with patients in the placebo group ($p < .05$). In addition, by day 3, treatment with XR-NTX 380 mg was associated with statistically significant reductions in the percentage of patients reporting heavy drinking compared with placebo ($p < .05$). The vast majority of patients who showed a good early response tended to be stable over the treatment period; also, a meaningful minority of patients showed improvement during the months subsequent to month 1. Conversely, only a small number of early responders subsequently shifted to less of a response. This early clinical effect was consistent with the release characteristics of the formulation, in which plasma naltrexone levels began to appear on day 1 postinjection.[17]

Patients receiving XR-NTX 190 mg experienced similar reductions in these measures, although the differences compared with placebo were not significant. These intermediate findings indicate the presence of a dose-response effect in the initial postinjection period as well as in the overall 6-month treatment period. This dose-response effect strengthens the robustness of the results and suggests that clinicians and patients in routine practice will be able to anticipate a therapeutic response to XR-NTX 380 mg within the first few days of treatment.

The early onset of effect observed with XR-NTX in this study has important implications for the treatment of patients with alcohol dependence. Analysis of data from pharmacy claims in an insured population (N = 1138) indicates that the majority of insured patients who fill a prescription for oral naltrexone for alcohol dependence do not obtain a refill the following month.[14] It follows that patients who experience benefits soon after treatment initiation may perceive an enhanced sense of self-efficacy[25] and therefore may be encouraged to persist in both pharmacotherapy and counseling sessions. They also may be able to focus on their treatment goals as early as the first month of treatment.

Several limitations of this study have been described previously.[19] In addition to those already reported, it should be noted that patient motivation for change may have affected the response to treatment. That is, patients who enroll in clinical studies may be more motivated to change their behavior than those who are treated in traditional outpatient settings. Indeed, the motivation to change can dramatically influence the success of treatment in patients with alcohol dependence.[26] Motivation for change should be reflected in responsiveness to counseling. For example, the group receiving placebo and counseling showed substantial reductions in heavy drinking and number of drinks consumed. These results were consistent with the positive impact that psychosocial counseling and participation in relapse prevention activities were observed to have in other studies involving alcohol-dependent patients.[27–29] A strong response to counseling, such as occurred in this trial, may be expected to obscure the detection of additional benefit from pharmacotherapy. Therefore, the positive results for XR-NTX observed here, particularly those seen in the early posttreatment period, suggest a clinically meaningful effect. Additionally, this study was not specifically designed to assess the onset of effect of XR-NTX and may have been insufficiently powered for this purpose. Nonetheless, an early treatment effect was observed overall in patients who mostly did not initiate abstinence prior to the trial. Given that an early onset of significant benefits was detected, these results appear meaningful, and clinical experience would be expected to yield similar findings.

CONCLUSIONS

In conclusion, the targeted retrospective analysis we conducted for this article revealed that XR-NTX 380 mg had a rapid onset of therapeutic effects in the first 2 days after the first injection—the period considered most volatile in engaging patients in treatment. Potential clinical implications of the rapid, early onset of effect of this medication's delivery system for patients who are dependent on alcohol include facilitation of early engagement in treatment, motivation to continue treatment, and focus on the goals established in counseling.

Drug name: naltrexone (Vivitrol, Revia, and others).

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