Efficacy of Extended-Release Naltrexone in Patients with Relatively Higher Severity of Alcohol Dependence

Helen M. Pettinati, Bernard L. Silverman, John J. Battisti, Robert Forman, Edward Schweizer, and David R. Gastfriend

Background: Because some literature reviews have suggested that naltrexone’s benefit may be limited to less-severe alcohol dependence, and exclusively to reduction in heavy drinking rather than abstinence, we examined the efficacy of once per month, injectable extended-release naltrexone (XR-NTX 380 mg) in patients with relatively higher severity alcohol dependence.

Methods: Post hoc analyses examined data from a multicenter, placebo-controlled, 24-week randomized trial of XR-NTX for alcohol dependence (N = 624). We analyzed treatment effects in alcohol-dependent patients who had higher baseline severity, as measured by: (i) the Alcohol Dependence Scale (ADS) or (ii) having been medically detoxified in the week before randomization. Efficacy was also examined via the relationship between pretreatment severity indices and reporting at least 4 days of lead-in abstinence prior to treatment—a major predictor of good outcome in the original study.

Results: Higher severity alcohol-dependent patients, defined by the ADS, when receiving XR-NTX 380 mg (n = 50) compared with placebo (n = 47), had significantly fewer heavy-drinking days in-trial (hazard ratio=0.583; p = 0.0049) and showed an average reduction of 37.3% in heavy-drinking days compared with 27.4% for placebo-treated patients (p = 0.039). Among those who had a detoxification just prior to randomization, these reductions were 48.9% (XR-NTX 380 mg; n = 11) and 30.9% (placebo; n = 15) (p = 0.004). Subjects with at least 4 days of pretreatment abstinence (n = 82) versus those without (n = 542) had significantly higher pretreatment ADS scores (p = 0.002) and were more likely to require detoxification prior to randomization (p < 0.001). Patients with lead-in abstinence experienced significantly better maintenance of initial and 6-month abstinence.

Conclusions: These secondary analyses support the efficacy of XR-NTX 380 mg in relatively higher severity alcohol dependence for both reduction in heavy drinking and maintenance of abstinence, with implications for the role of adherence pharmacotherapy.

Key Words: Extended-Release Naltrexone, Alcohol Dependence, Severity, Heavy Drinking, Abstinence.

Alcohol Dependence is a common and debilitating disorder afflicting almost 4% of the adult U.S. population (Grant et al., 2004). While alcohol dependence at any level of severity is a public health concern, individuals with high-severity alcohol dependence are particularly at risk for negative consequences from their alcohol consumption. Compared with alcohol-dependent individuals at low severity levels, those with relatively higher severity have worse symptoms of tolerance and withdrawal, abnormal values on biomarkers of alcohol dependence, higher rates of craving, greater tobacco use, more psychiatric symptoms, and impaired quality of life. Notably, they also are more likely to endorse abstinence as their treatment goal (Berggren et al., 2007; Donovan et al., 2006; Lima et al., 2005; Morgan et al., 2004).

There are multiple aspects of the disorder of alcohol dependence that can be used to define severity levels. Most obviously, severity can be measured in terms of the quantity and frequency of patterns of alcohol consumption (Goldstein et al., 2006; Li et al., 2007). In the widely used Addiction Severity Index (McLellan et al., 1992), severity is defined as the degree of related social, legal, employment, medical, and psychological problems that co-occur with alcohol use, as well as the frequency and quantity of alcohol use per se. Symptom counts have also been used to define severity of alcohol dependence (e.g., Hicks et al., 2004; Rose et al., 2004; Saha et al., 2006; Young et al., 2000). Instruments that have been used to measure severity of alcohol dependence, such as the Alcohol Dependence Scale (ADS; Skinner and Allen, 1982) and the
oral naltrexone. Administered as an intramuscular monthly injection, XR-NTX 380 and 190 mg in combination with psychosocial management found that, among the subgroup of patients with at least 4 days of abstinent prior to initiating treatment, there were about 3 times as many patients treated with XR-NTX 380 mg as compared with placebo who achieved 24 weeks of consecutive abstinence (32 vs. 11%; \( p = 0.02 \)) and had a 3-fold longer median time to their first drink after starting treatment (41 vs. 12 days, \( p = 0.02 \)) (Garbutt et al., 2005; O’Malley et al., 2007). XR-NTX 380 mg was approved by the FDA with an indication for alcohol-dependent patients who are able to abstain from alcohol prior to treatment initiation.

While the Garbutt and colleagues (2005) report documents the efficacy of XR-NTX 380 mg for most alcohol-dependent patients, regardless of their severity of dependence, there are persistent questions about the efficacy of naltrexone for more severely dependent individuals. This report describes a secondary analysis of data from the Garbutt and colleagues (2005) trial that examined the efficacy of XR-NTX 380 mg for both heavy drinking and abstinence outcomes in patients with relatively severe alcohol dependence with respect to the impact of lead-in abstinence prior to treatment.

MATERIALS AND METHODS

Study Design and Patients

The current study is a post hoc analysis of alcohol consumption data from a 6-month, double-blind, randomized controlled trial of XR-NTX versus placebo injection, conducted at 24 U.S. public hospitals, private and Veterans Administration clinics, and tertiary care medical centers (details are given in the primary manuscript; Garbutt et al., 2005).

The study recruited adult patients (men and women aged ≥18 years) with a diagnosis of alcohol dependence, who had at least 2 episodes per week of heavy drinking (≥5 drinks per day for men, ≥4 for women) in the 30 days prior to enrollment. Excluded from the trial were individuals who had any clinically significant medical condition that might adversely affect safety or study participation; major depression with suicidal ideation, psychosis, or bipolar disorder; or dependence on benzodiazepines, opioids, or cocaine within the past year. Patients with more than 7 days of inpatient treatment for substance abuse during the 30 days prior to screening were also excluded.

Patients were randomized to receive treatment with a single intramuscular injection of XR-NTX 380 mg, XR-NTX 190 mg, or placebo every 4 weeks for the 24-week treatment period. All the patients also received 12 sessions of concurrent low-intensity psychosocial counseling (Volpicelli et al., 2001).

Assessments

Alcohol consumption was measured using the timeline follow-back (TLFB) method (Sobell and Sobell, 1992) for the 30 days prior to treatment, during treatment at weekly intervals for the first 4 weeks, and then every 2 weeks for the next 20 weeks or at the final visit. The TLFB assessment used calendars and recall of drinking on specific days to record the frequency and amount of drinking since the previous assessment. This yielded a continuous record of daily drinking, heavy-drinking days, and abstinence rates for the 24-week treatment period.

Pretreatment (baseline) TLFB data were used to identify patients with ≥4 days of voluntary abstinence prior to treatment initiation. Patients in the XR-NTX efficacy trial with at least 4 days of abstinence prior to treatment initiation showed a clinically meaningful and robust treatment effect with XR-NTX 380 mg compared with

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Alcohol Use Disorders Identification Test (Saunders et al., 1993), rely on both alcohol consumption and alcohol-related symptoms and impairments to measure the dimension.

In evaluating treatment options for individuals with alcohol dependence, severity of the disorder is likely to be one of the key considerations. Medical detoxification is often a clinical recommendation for those with more severe dependence. One aspect of severity, the presence of alcohol withdrawal symptoms, is a central element of the American Society of Addiction Medicine (ASAM) Patient Placement Criteria that are used to match patients with levels of care (Mee-Lee et al., 2001).

The role of pharmacological treatments of alcohol dependence within the subgroup of more severely dependent patients is less clear. Available pharmacological treatment studies have rarely reported the impact of severity of alcohol dependence on outcome. There is some evidence, however, that questions the efficacy of certain medications, particularly oral naltrexone, among those with more severe alcohol dependence. Oral naltrexone was not found to be significantly superior to placebo in a large-scale randomized clinical trial conducted with chronic, severe alcohol-dependent veterans (Krystal et al., 2001). In another study comparing oral naltrexone, acamprosate, and placebo, naltrexone was found to be superior to acamprosate only within the subgroup of alcohol-dependent patients who had lower severity. There were no differences among these 3 treatments in the high-severity patients (Morley et al., 2009). Furthermore, a link between severity and medication adherence was recently suggested by a study that reported that high-severity alcohol dependence was associated with drinking distilled spirits (rather than wine or beer), which, in turn, was related to lower adherence to combined psychosocial and medication (oral naltrexone or topiramate) treatments for alcohol dependence (Baltieri et al., 2009). Across 10 studies of oral naltrexone for alcohol dependence, a meta-analytic review found no significant efficacy in regard to abstinence rates and stated that “naltrexone seems more…geared to control consumption,” a conclusion, which suggests that naltrexone is more helpful to less severely dependent individuals (Bouza et al., 2004, p. 825). The perspective that oral naltrexone is potentially ineffective in severely dependent patients has been cited as one of the reasons that this medication is not more widely used to treat alcohol dependence (Thomas et al., 2003).

An extended-release formulation of naltrexone (XR-NTX, VIVITROL®, Alkermes, Inc., Waltham, MA), approved by the U.S. Food and Drug Administration (FDA) in April 2006, has been developed to address adherence issues with oral naltrexone. Administered as an intramuscular monthly injection, XR-NTX 380 mg has been shown to maintain continuous plasma levels of naltrexone for more than 30 days following a single injection (Dunbar et al., 2006). A 6-month, randomized, multicenter, double-blind, placebo-controlled study of XR-NTX 380 and 190 mg in combination with psychosocial management found that, among the subgroup of alcohol-dependent patients who achieved at least 4 days of abstinence prior to initiating treatment, there were about 3 times as many patients treated with XR-NTX 380 mg as compared with placebo who achieved 24 weeks of consecutive abstinence (32 vs. 11%; \( p = 0.02 \)) and had a 3-fold longer median time to their first drink after starting treatment (41 vs. 12 days, \( p = 0.02 \)) (Garbutt et al., 2005; O’Malley et al., 2007). XR-NTX 380 mg was approved by the FDA with an indication for alcohol-dependent patients who are able to abstain from alcohol prior to treatment initiation.

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placebo (O’Malley et al., 2007). A 4-day lead-in abstinent period has been a requirement in many other studies of pharmacotherapies for alcohol dependence, including the large-scale COMBINE Study (Anton et al., 2006). Four days is also the median length in the United States for complete detoxification episodes (Drug and Alcohol Services Information System, 2004).

Severity of alcohol dependence was measured in 2 ways: (i) the ADS (Skinner and Horn, 1984) and (ii) the occurrence of detoxification just prior to randomization to medication treatment.

The ADS is a widely used 25-item self-report scale that quantitatively measures alcohol dependence severity by focusing on alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and salience of drink seeking behavior. A score $\geq 29$ is highly predictive of DSM-IV alcohol dependence (Ross et al., 1990). The ADS is used within the ASAM Patient Placement Criteria for level of care planning for alcohol treatment (American Society of Addiction Medicine, 1996). Because the ADS scale was added to the protocol after the trial had begun, only about half of the patients in the trial received the ADS. A median split on the ADS was used to identify patients with relatively higher severity (ADS $> 16$). There were 97 patients (380 mg: 50; placebo: 47) classified as severely dependent on the ADS.

Medical detoxification in the week before randomization was utilized as a reasonable measure of severity because medical detoxification is typically instituted when there are signs of severe dependence, e.g., symptoms of tolerance and withdrawal. Therefore, a clinician’s decision to have a patient undergo medical detoxification would likely be a good indicator of severe alcohol dependence. There were 26 patients (11 in the XR-NTX 380 mg group; 15 in the placebo group) who were classified with severe alcohol dependence based on receiving a medical detoxification immediately prior to randomization.

Statistical Analyses

The primary statistical analysis paralleled that conducted for the main efficacy report (Garbutt et al., 2005) except the focus in this investigation is on the XR-NTX 380-mg dose versus placebo because the 380-mg dose is the clinically approved and available dose of XR-NTX. Among the subgroup of more severely dependent patients, XR-NTX 380 mg and placebo were compared on the occurrence of heavy-drinking events during the 24-week treatment period. This comparison was performed using a stratified generalized Andersen–Gill recurrent-event Cox model (Andersen and Gill, 1982). To adjust for the impact of patient discontinuation during the study on the occurrence of heavy-drinking events, a pattern mixture-model approach was implemented in the generalized Andersen–Gill recurrent-event Cox model (Hogan et al., 2004). Site was also included in the model.

The analysis included all heavy-drinking events captured during the treatment period, up to 30 days following the last injection (dose) of study medication. All randomized subjects within the defined severely dependent subgroup who received at least 1 dose of study drug were included in this analysis. The primary descriptive statistic from the Andersen–Gill analysis is a hazard ratio that compares the failure rate, where failure here is the occurrence of heavy-drinking events, for the XR-NTX 380 mg and placebo group. A hazard ratio below 1 indicates a slower failure rate (i.e., a longer time to the occurrence of heavy-drinking events for XR-NTX 380 mg compared with placebo).

The Andersen–Gill analysis was conducted for those patients defined as having high severity on the ADS. The sample of patients who had undergone a detoxification prior to randomization was too small to conduct the Andersen–Gill analysis with the pattern mixture addition and site as a covariate. For the detoxification sample, and for the severely dependent sample defined by the ADS, the percent-age of heavy-drinking days in the XR-NTX 380 mg and placebo groups were compared with the baseline. For this comparison, an analysis of covariance was conducted specifying the contrast of the XR-NTX 380 mg group versus placebo and using baseline percentage heavy-drinking days as a covariate. The percentage of respondents to treatment was compared for XR-NTX 380 mg versus placebo using Fisher’s exact test. A clinical response was defined as $\geq 2$ heavy-drinking days in any 28-day period during 6-month treatment phase (O’Malley et al., 2007). This definition of clinical response was selected as representing substantial improvement from the minimum of 8 days of heavy drinking in the month prior to randomization that was required for enrollment. To present a complete understanding of the impact of severity, responder rates in the low severity subgroups (no detox; ADS $\leq 16$) were also examined.

Finally, we used logistic regression to examine all 3 binary variables of higher versus lower severity as predictors of clinical response to XR-NTX 380 mg: (i) ADS score $> 16$ versus $\leq 16$; (ii) detoxification versus no detoxification; and (iii) lead-in abstinence versus no lead-in abstinence.

RESULTS

Baseline Demographic and Clinical Characteristics of Sample

Table 1 provides demographic and clinical information on 3 patient subgroups derived from the total patient sample reported in the Garbutt and colleagues (2005) trial. Each of the subgroups is further subdivided into patients who received either XR-NTX 380 or placebo. The 3 patient subgroups listed in Table 1 are (i) those who were above versus below the median ADS score of 16 for the sample, (ii) those who received versus did not receive a medical detoxification immediately prior to randomization, and (iii) patients who had versus did not have at least 4 days of lead-in abstinence prior to treatment initiation. Within each of the 3 subgroups displayed in Table 1, there were no significant pretreatment (baseline) differences on demographic and clinical characteristics for the patients who had received XR-NTX 380 versus placebo.

For each definition of severity, there were no significant demographic differences between the high and low severity subgroups, but there were some notable clinical characteristic differences (Table 1). Patients with higher (vs. lower) severe alcohol dependence on the ADS were significantly more likely to (i) have had a medical detoxification just prior to randomization ($p = 0.042$), (ii) lead-in abstinence of $\geq 4$ days ($p = 0.038$), and (iii) endorsed abstinence as their treatment goal ($p = 0.035$). Those who had been detoxified just prior to treatment (vs. those who were not) were significantly more likely to endorse abstinence as their treatment goal ($p = 0.004$) and have $\geq 4$ days of lead-in abstinence ($p < 0.001$). Patients with lead-in abstinence of $\geq 4$ days, compared with those who did not have lead-in abstinence of $\geq 4$ days, were significantly more likely to have severe alcohol dependence, as evidenced by significantly higher scores on the ADS ($p = 0.002$), and require detoxification prior to randomization ($p < 0.001$).

A significant overlap between a medical detoxification just prior to randomization and lead-in abstinence of $\geq 4$ days would be anticipated. However, the overlap was limited:
only 28% of the 82 patients with ≥4 days of lead-in abstinence had received a medical detoxification, and only about half (54.8%) of those who had received a medical detoxification also had ≥4 days of lead-in abstinence. Also, Table 1 depicts that those with (vs. without) lead-in abstinence of ≥4 days reported significantly (p < 0.001) fewer heavy-drinking days in the past 30 days. However, we believe this is a temporary artifact of detoxification and voluntary drinking taper just prior to entering the study because when a longer pretreatment time period is examined (90 days, as seen in Fig. 1), the lead-in abstinence group displayed higher levels of pretreatment drinking, with an average of about 1.5 drinks per day more than the no lead-in abstinence group.

Table 1. Demographic and Clinical Characteristics: Baseline Data for XR-NTX 380 mg and Placebo by Potential Severity Indices

<table>
<thead>
<tr>
<th></th>
<th>Alcohol Dependence Scale (ADS) ≤ 16</th>
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<tbody>
<tr>
<td></td>
<td>XR-NTX 380</td>
<td>Placebo</td>
<td>XR-NTX 380</td>
<td>Placebo</td>
<td>XR-NTX 380</td>
<td>Placebo</td>
<td>XR-NTX 380</td>
</tr>
<tr>
<td>Age, years; Mean (±SD)</td>
<td>46.0 (9.6)</td>
<td>47.4 (10.4)</td>
<td>43.5 (10.4)</td>
<td>43.3 (10.7)</td>
<td>44.8 (10.1)</td>
<td>44.5 (11.0)</td>
<td>48.0 (9.8)</td>
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<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (66%)</td>
<td>33 (62.3%)</td>
<td>35 (70%)</td>
<td>33 (70.2%)</td>
<td>130 (67.0%)</td>
<td>131 (67.5%)</td>
<td>8 (72.7%)</td>
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<tr>
<td>Female</td>
<td>18 (34%)</td>
<td>20 (37.7%)</td>
<td>15 (30%)</td>
<td>14 (29.8%)</td>
<td>64 (33.0%)</td>
<td>63 (32.5%)</td>
<td>3 (27.3%)</td>
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<tr>
<td>Race, N (%)</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>44 (83%)</td>
<td>49 (92.5%)</td>
<td>44 (88%)</td>
<td>41 (87.2%)</td>
<td>164 (84.5%)</td>
<td>167 (86.1%)</td>
<td>8 (72.7%)</td>
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<tr>
<td>African American</td>
<td>4 (7.5%)</td>
<td>4 (7.5%)</td>
<td>2 (4%)</td>
<td>3 (6.4%)</td>
<td>15 (7.7%)</td>
<td>16 (8.2%)</td>
<td>1 (9.1%)</td>
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<td>Hispanic</td>
<td>2 (3.8%)</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
<td>2 (4.3%)</td>
<td>8 (4.1%)</td>
<td>6 (3.1%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.1%)</td>
<td>7 (3.6%)</td>
<td>5 (2.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Treatment goal is abstinence, N (%)</td>
<td>20 (37.7%)</td>
<td>19 (35.8%)</td>
<td>23 (46%)</td>
<td>22 (46.8%)</td>
<td>83 (42.8%)</td>
<td>80 (41.2%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>ADS score N (%) with ADS</td>
<td>53 (100%)</td>
<td>53 (100%)</td>
<td>50 (100%)</td>
<td>47 (100%)</td>
<td>97 (50.0%)</td>
<td>92 (47.4%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.9 (3.9)</td>
<td>11.5 (3.4)</td>
<td>23.4 (5.7)</td>
<td>22.3 (5.8)</td>
<td>16.9 (8.0)</td>
<td>16.1 (6.4)</td>
<td>18.3 (5.5)</td>
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<tr>
<td>Detox status, N (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>50 (100%)</td>
<td>47 (100%)</td>
<td>46 (47.4%)</td>
<td>42 (46.7%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Detox</td>
<td>2 (3.8%)</td>
<td>3 (5.7%)</td>
<td>4 (8%)</td>
<td>5 (10.6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>≥4 days of abstinence prior to randomization, N (%)</td>
<td>5 (11.3%)</td>
<td>3 (5.7%)</td>
<td>9 (18%)</td>
<td>8 (17%)</td>
<td>21 (10.8%)</td>
<td>20 (10.3%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>Percentage of days with heavy drinking in month prior to baseline, Mean (SD)</td>
<td>62.2 (27.1)</td>
<td>60.7 (24.5)</td>
<td>60.9 (24.3)</td>
<td>66.1 (23.0)</td>
<td>64.4 (26.3)</td>
<td>66.3 (24.6)</td>
<td>56.1 (15.6)</td>
</tr>
</tbody>
</table>

No significant differences between XR-NTX 380 and placebo. XR-NTX, extended-release naltrexone.
Efficacy of XR-NTX for Patients with Relatively High-Severity Alcohol Dependence

Results of the Andersen–Gill recurrent-event Cox model revealed that the more severely dependent group, as defined by the ADS score, had significantly longer time for the occurrence of heavy-drinking events with XR-NTX 380 mg versus placebo. The overall occurrence of heavy drinking per unit time in the 380 mg group was 42% lower than the placebo group over the course of the 24-week treatment period (hazard ratio = 0.583; \( p = 0.0049 \) [95% CI: 0.400–0.849]).

Patients with higher ADS scores treated with XR-NTX 380 mg also showed a significantly greater reduction from baseline in the percentage heavy-drinking days (37.3%; \( p = 0.039 \)) (see Fig. 2). This effect was even more pronounced when severity was defined by the presence of a detoxification immediately prior to randomization: the XR-NTX 380 mg group showed a 48.9% reduction in heavy-drinking days compared with 30.9% for placebo (\( p = 0.004 \)) (see Fig. 2).

For those with an ADS score > 16, responder rates (clinical response = having ≤2 heavy-drinking days in any 28-day period during 6-month treatment phase) tended to be greater, by 86%, for XR-NTX 380 mg than for placebo (28.3% [13/46] vs. 15.2% [7/46]; \( p = 0.13 \)). Among those with ADS ≤ 16, responder rates were 32.7% (17/52) for XR-NTX 380 mg and 6% (3/50) for placebo (\( p = 0.001 \)). For those who had a detoxification immediately prior to randomization, responder rates tended to be greater, by 122%, for XR-NTX 380 mg (63.6% [7/11] vs. 28.6% [4/14]; \( p = 0.08 \)). Among those who did not have a detoxification prior to randomization, responder rates were 28.6% (53/185) for XR-NTX 380 mg and 17.6% (33/188) for placebo (\( p = 0.014 \)).

Prediction of Clinical Response to XR-NTX 380 mg

Logistic regression analyses indicated that detoxification status and lead-in abstinence status were significant univariate predictors of a clinical response to XR-NTX 380 mg. In a multivariate logistic regression, only lead-in abstinence status remained as a significant predictor of clinical response (see Table 2).

DISCUSSION

These analyses for this paper were derived from one of the largest (\( N = 624 \)) and longest (6 months), multisite, double-blind, randomized clinical trials of alcohol pharmacotherapies yet reported in the literature, and results are placebo controlled. The main finding of this study was that XR-NTX 380 mg combined with a low-intensity psychosocial intervention demonstrated efficacy compared with placebo in patients...
with relatively higher severity alcohol dependence. Efficacy was measured as significant reductions in heavy drinking and longer maintenance of abstinence over the course of 24 weeks of treatment. These results were evident with either of 2 definitions of pretreatment severity—high ADS score or a medical detoxification just prior to randomization. Clinical response to XR-NTX 380 mg versus placebo among those with higher severity was found to be similar to those with lower severity, as measured on the ADS. Neither of the 2 severity measures significantly predicted clinical response to XR-NTX 380 mg once the overlap with lead-in (≥4 days) of abstinence was statistically considered in a multivariate analysis. Nonetheless, the comparison with placebo among the high-severity subgroup indicates that XR-NTX 380 mg is efficacious for alcohol-dependent patients with relatively higher severity.

An additional interesting and important finding of this study was that lead-in abstinence of ≥4 days was associated with a relatively higher severity alcohol dependence. Lead-in abstinence was associated with a higher ADS score, greater probability of receiving a medical detoxification, and more drinks per day prior to randomization (particularly from 20 to 90 days prior to first dose of study medication, i.e., excluding the 3 weeks prior to study initiation during which detoxification or drinking taper may have been under way).

The fact that lead-in abstinence was associated with greater severity of alcohol dependence provides a further understanding of the results of the primary efficacy trial on XR-NTX (Garbutt et al., 2005). In the Garbutt and colleagues (2005) report, and elaborated upon in more depth in a subsequent article (O’Malley et al., 2007), it was found that XR-NTX 380 mg was particularly efficacious among the subgroup of patients with lead-in abstinence. For patients who had at least 4 days of lead-in abstinence, those who received XR-NTX 380 mg, compared with placebo, had a 3-fold longer duration of initial abstinence (41 vs. 12 days, respectively) and almost 3 times as many achieved a full 24 weeks of consecutive abstinence (31% vs. 11%, respectively) (O’Malley et al., 2007). The current report clarifies that these patients who achieve lead-in abstinence (and for whom XR-NTX 380 mg is approved for use by the FDA) are more likely to be the relatively severely dependent individuals.

Some clinicians may perceive that patients who achieve abstinence before treatment is administered are able to do so primarily because their illness is less severe. However, the current data contradict this finding. This clinical perception is likely reinforced by the awareness of individuals who stop alcohol consumption on their own without treatment. However, data on individuals who stop drinking without treatment have focused on problem drinkers rather than those who are dependent on alcohol (e.g., Sobell et al., 1996). Within a sample of treatment-seeking alcohol-dependent patients, the data presented here indicate that, despite consuming more alcohol on a daily basis in the 90 days prior to treatment, the more severe alcohol-dependent patients are more likely to endorse abstinence as a goal of treatment and become initially abstinent (either on their own or through a medical detoxification) prior to beginning treatment. Previous research has also found that those more severely dependent on alcohol are more likely to endorse abstinence as a treatment goal (Donovan et al., 2006).

The finding in this study of efficacy of XR-NTX 380 mg among the more severely alcohol-dependent patients challenges previous findings that have suggested that naltrexone be confined to alcohol-dependent patients with lower severity. Oral naltrexone was used in these previous studies that did not show efficacy compared with placebo in high-severity patient subgroups. The link between reduced efficacy of oral naltrexone and high-severity alcohol dependence may be mediated by poor adherence among patients with more severe dependence. High-severity alcohol dependence has been associated with lower adherence to medication treatments for alcohol dependence (Baltieri et al., 2009). Adherence to oral naltrexone has repeatedly been found to be essential to the efficacy of the medication (Baros et al., 2007; Chick et al., 2000; Krystal et al., 2001; Pettinati et al., 2000). Psychosocial means of managing adherence have been developed and validated, including behavioral couples therapy (OFarrell and Fals-Stewart, 2002) and laboratory monitoring (Cone et al., 1974; Meyer et al., 1984). A pharmacological approach to addressing adherence is the extended-release formulation of naltrexone, because it maintains continuous plasma levels of naltrexone for more than 30 days following a single injection (Dunbar et al., 2006). By addressing adherence pharmacokinetically, XR-NTX 380 mg may be particularly well-suited for the treatment of the severely alcohol-dependent individual. This suggests that, whereas outcomes from medication-assisted treatment employing oral agents may be compromised by nonadherence, an approach that might be termed “adherence pharmacotherapy,” may hold promise, even for patients with severe alcohol dependence.

Severity may occur in other dimensions besides withdrawal or physical dependence. Two recent studies have examined treatment with XR-NTX in another high-severity subpopulation, that is, alcohol-dependent patients with repeat driving-while-intoxicated (DWI) offenses. A 10-patient case series

### Table 2. Logistic Regressions Predicting Responder Rates from Severity Criteria Within XR-NTX 380 mg Group

<table>
<thead>
<tr>
<th></th>
<th>Univariate results</th>
<th>Multivariate Results (N = 98; 17 responders)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio p-value</td>
<td>Odds ratio p-value</td>
</tr>
<tr>
<td>Alcohol Dependence Scale &gt;16 (n = 50) vs. ≤16 (n = 55)</td>
<td>0.811 0.63</td>
<td>0.535 0.234</td>
</tr>
<tr>
<td>Detox (n = 7) vs. no detox (n = 189)</td>
<td>4.36 0.023</td>
<td>6.50 0.136</td>
</tr>
<tr>
<td>Lead-in abstinence status ≥ 4 days (n = 19) vs. not (n = 177)</td>
<td>7.42 &lt;0.001</td>
<td>12.73 0.001</td>
</tr>
</tbody>
</table>

XR-NTX, extended-release naltrexone.
reported significant within-subject decreases from pre-to posttreatment in drinks per day and drinks per drinking day, and significant increases in abstinent days (Lapham and McMillan, 2010). A study of 64 case-matched multiple offenders (averaging approximately 3 prior DWI offenses) found that XR-NTX patients versus patients given treatment-as-usual in the DUI/Drug Court system in Michigan and Missouri had a 62% reduction in the annualized re-arrest rate (8% vs. 26% for treatment-as-usual; p < 0.05) (Finigan et al., 2010). Taken together, these findings suggest that XR-NTX may be a useful treatment for high severity in a variety of severity dimensions.

A limitation of the present report is that the analyses were post hoc and were conducted on a subsample of the original randomized sample and therefore had reduced statistical power relative to the parent study because of the small sample sizes. It would therefore be important to confirm the current results in a larger fully powered prospective study that targets high-severity patients. In addition, as with the parent study, the results reported here may not generalize to all patients with alcohol dependence (the trial excluded patients with unstable major depressive disorder, bipolar disorder, psychosis, or dependence within the past year on benzodiazepines, opiates, or cocaine). Another limitation of this research is that the lack of occurrence of a medical detoxification is not always an indicator of low severity of alcohol dependence. Some individuals with high severity of alcohol dependence might not receive a detoxification because of logistical barriers (i.e., availability of clinicians who can provide this type of treatment and financial constraints). Additional research is also needed to determine the optimal duration of treatment and the causal relationships between severity of alcohol dependence, initial abstinence, attrition from treatment, and drinking outcomes.

In summary, the data from these analyses demonstrated that patients with lead-in abstinence of at least 4 days had more severe alcohol dependence. More severely dependent patients receiving XR-NTX 380 mg over the course of 24 weeks of treatment were found to have a significantly reduced rate of heavy-drinking days, compared with placebo. XR-NTX 380 mg also demonstrated efficacy for maintaining initial and total abstinence in the subset of more severely dependent patients who had lead-in abstinence. The results support the use of XR-NTX 380 mg for maintaining abstinence as well as reduction in heavy drinking among those with relatively more severe alcohol dependence. The implication of these data, in contrast to the conclusions drawn in literature reviews of oral naltrexone trials, is that adherence pharmacotherapy with XR-NTX 380 mg may have an impact in treating alcohol-dependent patients with higher severity.

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REFERENCES


