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Hepatic Safety of Once-Monthly Injectable Extended-Release Naltrexone Administered to Actively Drinking Alcoholics

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Background: Hepatoxicity has been reported with oral naltrexone. Hepatic safety data were examined from a 6-month study evaluating the efficacy and safety of a now available extended-release formulation of naltrexone (XR-NTX) in patients with alcohol dependence.

Methods: In all, 624 patients (68% male; median age of 44 years) were randomly assigned to XR-NTX 380 mg (n = 205), XR-NTX 190 mg (n = 210), or placebo (n = 209).

Results: There were no significant differences in alanine aminotrasferase, aspartate aminotransferase, or bilirubin levels between the study groups at study initiation or at subsequent assessments. Gamma-glutamyltransferase in the XR-NTX 380 mg group was lower compared with placebo at weeks 4, 8, 12, and 20. Both high (>3 times the upper limit of normal) liver chemistry tests (LCTs) and hepatic-related adverse events were infrequent in all study groups. In patients who were drinking heavily throughout the study, obese subjects, or those taking nonsteroidal anti-inflammatory drugs, there was no increase in frequency of high LCTs or hepatic-related adverse events in patients receiving XR-NTX (either dose) compared with placebo.

Conclusion: Extended-release formulation of naltrexone does not appear to be hepatotoxic when taken at the recommended clinical doses in actively drinking alcohol-dependent patients.

Key Words: Alcohol Dependence, Liver Injury, Injectable Naltrexone, Randomized Clinical Study, Liver Chemistry Tests.

ALCOHOL DEPENDENCE IS a chronic, debilitating disease associated with substantial morbidity and mortality, including hepatic-related disorders (Rehm et al., 2003). Approximately 10% to 35% of heavy drinkers develop alcoholic hepatitis, and 10 to 20% develop cirrhosis (National Institute on Alcohol Abuse and Alcoholism, 1998). Pharmacologic options for the treatment of alcohol dependence include oral naltrexone which, when used in combination with psychosocial intervention, has demonstrated modest efficacy in multiple randomized clinical studies (Bouza et al., 2004; Roozen et al., 2006). Concern has been raised regarding administration of excessive doses of oral naltrexone or administration to patients with active liver disease, leading to a boxed warning in relation to hepatotoxicity in the manufacturer's package insert. This warning states that naltrexone has the capacity to cause liver damage when taken in excessive doses, that naltrexone is contraindicated in acute hepatitis or liver failure, and urges caution when it is administered to patients with active liver disease (ReVia, 2006). This was based on reports of hepatotoxicity at high dosages of oral naltrexone (350 mg/d, which is 7 times the recommended dosage) in studies with obese patients and those with senile dementia (Pfohl et al., 1986). However, in contrast to these findings, many studies with oral naltrexone have concluded that it is safe within the recommended dosage range and even at higher dosages, as long as the use of over-the-counter nonsteroidal anti-inflammatory drugs (NSAID) is restricted (Balldin et al., 2003; Croop et al., 1997; Gastpar et al., 2002; Kim et al., 2001a, 2006; Verebey and Mule, 1986; Yen et al., 2006).

Recently, an injectable formulation of naltrexone (XR-NTX; Vivitrol®, Alkermes, Inc., Cambridge, MA, USA) has been developed that provides continuous release of naltrexone for approximately 30 days, with little or no daily fluctuation (Bartus et al., 2003; Dunbar et al., 2006; Turncliff et al., 2005). In a 6-month, randomized, double-blind, study, XR-NTX 380 mg significantly decreased rates of heavy drinking and any drinking (and prolonged abstinence in a subset of patients who were initially abstinent) compared to placebo injection in patients who were receiving counseling for alcohol dependence (Garbutt et al., 2005).

Preliminary analysis of hepatic safety data presented in the primary efficacy report on XR-NTX revealed no evidence for hepatotoxicity (Garbutt et al., 2005). In order to inform the

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clinical use of XR-NTX in alcohol-dependent patients, the current article provides a comprehensive analysis of hepatic safety from the 6-month large scale, multicenter, placebo-controlled study of XR-NTX for alcohol dependence, including subgroups of patients who were drinking heavily, obese, or using NSAIDs during the study.

MATERIALS AND METHODS

Patient Selection

Eligible participants (18 years or older) were required to meet a current diagnosis of alcohol dependence, defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994), and also report a minimum of 2 episodes of heavy drinking (≥5 standard drinks/d for men and ≥4 standard drinks/d for women) per week during the 30 days prior to screening. Patients were excluded if they had any clinically significant medical condition that might adversely affect safety or study participation; major depression with suicidal ideation, psychosis, or bipolar disorder; dependence on benzodiazepines, opiates, or cocaine within the past year; or more than 7 days of inpatient treatment for substance abuse during the 30 days prior to screening. Exclusion criteria also included evidence of liver failure, and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal (> 3×ULN).

Most subjects (48.6%) in the randomized sample were recruited and enrolled at a clinical addiction treatment center; 34.0% enrolled at a research center; and 17.5% enrolled at a setting that was a combination clinical addiction and research center. All patients who participated in the trial provided written, informed consent, and the protocol was approved by the respective institutional review boards at the participating clinical sites.

Treatment

Patients were randomly assigned to 6 months of treatment with XR-NTX 380 mg, XR-NTX 190 mg, or placebo. XR-NTX was given every 4 weeks as an intramuscular gluteal injection, alternating sides with each visit. Patients were not required to be abstinent at the time of initial injection and were not withdrawn if they continued to use alcohol. In addition to receiving study medication, patients were also provided with psychosocial support with the Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment model at study visits (Volpicelli et al., 2001). No specific recommendations were communicated to the patients about NSAID use. The following medications were not permitted during the study unless required to treat an adverse event, when no other alternative was available: acamprosate, buprenorphine, disulfiram, levomethadyl acetate/l-α-acetylmethadol (LAAM), methadone, oral naltrexone, phenelzine, selegiline, and tranylcyprominc.

Assessment of Hepatic Health

Patients were asked about all concomitant medications taken during the study, including but not limited to NSAIDs. Liver health was assessed every 4 weeks for the 6-month treatment period by measuring liver chemistry test (LCT) levels of the following enzymes: ALT, AST, gamma-glutamyl transferase (GGT), and total bilirubin. Safety data collected during the study included adverse events as reported by patients or noted by study staff, physical examination results (including vital signs), and clinical laboratory measurements.

Results of LCTs were classified as normal, elevated (any increase above the ULN but below 3×ULN), or high (> 3×ULN). Examination of study group differences in enzyme levels and adverse events were also conducted within 3 subgroups: (1) those patients continuing to drink alcohol at a high rate throughout the study (greater than 50% of days with ≥5 drinks per day for men or ≥4 drinks per day for women); (2) obese patients (Body Mass Index > 30 kg/m^2); and (3) patients taking NSAIDs. NSAID use during the 6-month treatment period was examined using 2 consumption levels defined post-hoc on the basis of patient reports: (1) continuous NSAID use; and (2) any NSAID use.

RESULTS

Patient Characteristics and Duration of Exposure to Study Drug

In all, 624 patients had at least 1 injection of XR-NTX and comprised the intent-to-treat population. The 3 study groups (XR-NTX 380 mg, n = 205; XR-NTX 190 mg, n = 210; placebo, n = 209) were similar in terms of baseline demographic, clinical characteristics, and baseline LCT levels (Table 1). Similar percentages of patients in the 3 study groups received all 6 injections (63% for XR-NTX 380 mg; 65% for XR-NTX 190 mg; 64% for placebo) during the 6-month treatment period. As specified by the study selection criteria, all patients had either normal (70%) or elevated (30%) levels of ALT and AST. Four patients had elevated baseline levels of total bilirubin; all others had values in the normal range. As for GGT levels at baseline, 64% of patients had normal levels, 28% elevated, and 8% high. The baseline demographic and clinical characteristics of the heavy drinking, obese, and noncontinuous NSAID-taking subgroups (values were similar for the smaller continuously using NSAID group) were also similar for the XR-NTX 380 mg, XR-NTX 190 mg, and placebo groups (Table 2). Postbaseline laboratory assessment of hepatic function was available for 193 (94%) patients who received XR-NTX 380 mg, 193 (92%) patients who received XR-NTX 190 mg, and 198 (95%) patients who received placebo. Only 2 patients withdrew from the study due to hepatic-related adverse events.

Liver Chemistry Test Results

There were no significant differences (by Kruskal–Wallis test) between the study groups at any study visit on median levels of ALT, AST, or total bilirubin. For serum GGT levels, lower values were apparent for the XR-NTX 380 mg group at weeks 4, 8, 12, and 20 ($p < 0.05$) and the XR-NTX 190 mg group at weeks 8 and 12, which reached statistical significance ($p < 0.05$) compared with placebo.

The percentage of patients with any high postbaseline (treatment-emergent) enzyme levels was low and was not significantly different (by Fisher's exact test) for XR-NTX 380 mg (9% [17/193]) and XR-NTX 190 mg [12% (24/193)] compared with placebo [15% (29/198)] (Table 3). Rates for high levels of specific LCTs (ALT, AST, GGT, and total bilirubin) were also low and not significantly different among the study groups. Specifically, the percent of patients with a high (> 3×ULN) ALT value at any time during the 6-month treatment period was 3% for XR-NTX 380 mg, 1% for XR-NTX 190 mg, and 3% for placebo. For AST, the rates of high

Table 1. Baseline Demographic and Clinical Characteristics and Liver Chemistry Test (LCT) Results for the Intent-to-Treat Population

Baseline characteristics	XR-NTX 380 mg (n = 205)	XR-NTX 190 mg (n = 210)	Placebo (n = 209)
Male, n (%)	138 (67%)	142 (67%)	143 (68%)
Age in years, median	45.0	44.0	44.0
Race, n (%)			
White	172 (84%)	169 (80%)	180 (86%)
Black	16 (8%)	17 (8%)	17 (8%)
Hispanic	10 (5%)	15 (7%)	7 (3%)
Number of heavy drinking days within the past 30 days, median	19.0	19.0	20.0
Number of drinking days within the last 30 days, median	25.0	25.0	24.0
Body weight (kg), mean (SD)	84.3 (21)	82.8 (20)	81.9 (17)
LCTs, median			
ALT	27.0	28.0	27.5
AST	26.0	27.0	26.0
GGT	41.0	43.0	42.0
Total bilirubin	0.50	0.50	0.50

Heavy drinking defined as ≥5 drinks/d for men and ≥4 for women.

XR-NTX, extended-release formulation of naltrexone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Table 2. Baseline Demographic and Clinical Characteristics and Liver Chemistry Test (LCT) Results for Subgroup Populations

	Heavy drinking patients			Obese patients			NSAID-taking patients		
Characteristic	XR-NTX 380 mg (n = 33)	XR-NTX 190 mg (n = 47)	Placebo (n = 52)	XR-NTX 380 mg (n = 58)	XR-NTX 190 mg (n = 45)	Placebo (n = 50)	XR-NTX 380 mg (n = 62)	XR-NTX 190 mg (n = 50)	Placebo (n = 52)
Male, n (%)	18 (55%)	33 (70%)	37 (71%)	44 (76%)	35 (78%)	36 (72%)	44 (71%)	29 (58%)	28 (54%)
Age in years, median	47.0	46.0	44.0	45.0	44.0	47.0	47.5	40.5	44.0
Race, n (%)									
White	29 (88%)	43 (92%)	50 (96%)	49 (85%)	32 (71%)	42 (84%)	52 (84%)	36 (72%)	49 (94%)
Black	2 (6%)	2 (4%)	2 (4%)	5 (9%)	5 (11%)	3 (6%)	5 (8%)	6 (12%)	2 (4%)
Other	2 (6%)	2 (4%)	0 (0%)	4 (7%)	4 (9%)	3 (6%)	2 (3%)	5 (10%)	1 (2%)
Number of heavy drinking days within the past 30 days, median	29.0	27.0	27.5	18.5	20.0	20.5	17.5	16.5	14.0
Number of drinking days within the last 30 days, median	30.0	30.0	29.0	21.5	26.0	25.5	27.5	22.0	19.5
Body weight (kg), mean (SD)	87.1 (23)	83.1 (15)	83.6 (16)	106.4 (16)	110.0 (18)	102.0 (13)	86.0 (18)	82.1 (24)	79.7 (16)
LCTs, median									
ALT	27.0	31.0	34.5	32.5	38.0	37.0	30.0	27.5	24.5
AST	28.0	30.0	31.0	27.0	30.0	28.0	30.0	27.5	24.0
GGT	62.0	54.0	63.0	46.0	72.0	59.5	44.0	40.5	32.0
Total bilirubin	0.40	0.60	0.50	0.50	0.50	0.50	0.50	0.50	0.50

Heavy drinking defined as ≥5 drinks/d for men and ≥4 for women. Nonsteroidal anti-inflammatory drugs (NSAID)-taking subgroup includes those patients taking NSAIDs at any time during the treatment period, but not continuously throughout.

XR-NTX, extended-release formulation of naltrexone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

values were 5, 5, and 6% (380 mg, 190 mg, and placebo, respectively). For GGT, the rates of high values were 7, 11, and 11% for the XR-NTX 380 mg, XT-NTX 190 mg, and placebo groups, respectively. For all of the LCTs, the percentage of patients in the placebo group with high or elevated (higher than the ULN but $< 3\times$ULN) hepatic enzyme levels was numerically greater than in the XR-NTX 380 mg group (Table 3).

A similar, albeit small, percentage of patients whose LCT values were elevated (and high for GGT) at baseline moved into normal range during the course of the study: data for the XR-NTX 380 mg, XR-NTX 190 mg, and placebo groups were respectively 5, 2, and 2% (ALT); 7, 6, and 5% (AST); 8, 7, and 7% (GGT) (Table 4). There were no significant differences among the study groups in the cumulative proportion of patients having any specific LCT result classified as high, as determined by log-rank tests of the Kaplan-Meier curves (Table 5). There was no evidence of increased rates of high values of LCTs during the first few weeks of treatment with XR-NTX.

Of the patients who had normal ALT values at baseline, the percentages that had elevated and high values, respectively, at the end of the study were 11% (16/151) and 0% (XR-NTX 380 mg), 10% (15/148) and 0% (XR-NTX 190 mg), and 7% (10/150), 1% (1/150) (placebo). For AST, the percentages with normal values at baseline that had elevated and high values at final visit were 6% (9/147) and 1% (2/147) (XR-NTX 380 mg), 7% (10/144) and 0% (XR-NTX

Table 3. Treatment-Emergent Abnormalities in Liver Chemistry Tests (LCTs) and Hepatic Adverse Events During 6 Months of Treatment

LCT	XR-NTX 380 mg (*n* = 205)	XR-NTX 190 mg (*n* = 210)	Placebo (*n* = 209)
LCTs, total, *n* (%)			
Elevated	69 (36%)	89 (46%)	79 (40%)
High	17 (9%)	24 (12%)	29 (15%)
ALT, *n* (%)			
Elevated	55 (29%)	60 (31%)	64 (32%)
High	5 (3%)	2 (1%)	6 (3%)
AST, *n* (%)			
Elevated	44 (23%)	60 (31%)	70 (35%)
High	9 (5%)	9 (5%)	12 (6%)
GGT, *n* (%)			
Elevated	40 (21%)	61 (32%)	58 (29%)
High	13 (7%)	22 (11%)	22 (11%)
Bilirubin, *n* (%)			
Elevated	7 (4%)	15 (8%)	14 (7%)
High	0	0	0
Hepatic adverse events, *n* (%)			
Hepatomegaly	1 (<1%)	1 (<1%)	0
Cholelithiasis	0	1 (<1%)	0
Hepatitis C	1 (<1%)	1 (<1%)	0

Elevated baseline defined as above upper limit normal range (ULN) but ≤3×ULN; high defined as >3×ULN.

XR-NTX, extended-release formulation of naltrexone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Table 4. Liver Chemistry Test (LCT) Results at Final Visit Among Patients With Elevated Levels at Baseline

LCT	XR-NTX 380 mg	XR-NTX 190 mg	Placebo
ALT, *n* (%)			
Normal	18 (42.9%)	27 (60.0%)	22 (46.8%)
Elevated	22 (52.4%)	17 (37.8%)	24 (51.1%)
High	2 (4.8%)	1 (2.2%)	1 (2.1%)
AST, *n* (%)			
Normal	23 (51.1%)	31 (64.6%)	16 (38.1%)
Elevated	19 (42.2%)	14 (29.2%)	24 (57.1%)
High	3 (6.7%)	3 (6.3%)	2 (4.8%)
GGT, *n* (%)			
Normal	18 (34.0%)	19 (35.2%	22 (38.6%)
Elevated	31 (58.5%)	31 (57.4%)	31 (54.4%)
High	4 (7.5%)	4 (7.4%)	4 (7.0%)
Bilirubin, *n* (%)			
Normal	None elevated	1 (33.3%)	1 (100%)
Elevated		2 (66.7%)	0
High		0	0

Elevated baseline defined as above upper limit normal range (ULN) but ≤3×ULN; high defined as >3×ULN. The denominators for the percentages are the numbers with an elevated baseline value in that study group.

XR-NTX, extended-release formulation of naltrexone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

190 mg), and 12% (18/155), 1% (2/155) (placebo). For GGT, the percentages with normal values at baseline that had elevated and high values at the end of the study were 3% (3/132) and 1% (1/132) (XR-NTX 380 mg), 7% (9/121) and 0% (XR-NTX 190 mg), and 10% (12/124), 0% (placebo). Of the patients with normal levels of total bilirubin at baseline,

Table 5. Time of Onset of Treatment-Emergent Abnormalities in Liver Chemistry Tests (LCTs)

LCT	XR-NTX 380 mg (*n* = 205)	XR-NTX 190 mg (*n* = 210)	Placebo (*n* = 209)
Any LCT, *n* (%) <3×ULN	196 (96%)	190 (91%)	191 (91%)
Cumulative rate of abnormality, *n* (%)			
Week 4	3 (2%)	3 (2%)	5 (3%)
Week 8	3 (2%)	8 (5%)	6 (3%)
Week 12	8 (5%)	9 (6%)	9 (5%)
Week 16	8 (5%)	10 (6%)	12 (8%)
Week 20	8 (5%)	10 (6%)	13 (8%)
Week 24	10 (7%)	10 (6%)	14 (9%)
ALT, *n* (%) <3×ULN	205 (100%)	210 (100%)	208 (100%)
Cumulative rate of abnormality, *n* (%)			
Week 4	1 (<1%)	1 (<1%)	1 (<1%)
Week 8	3 (2%)	1 (<1%)	1 (<1%)
Week 12	5 (3%)	1 (<1%)	3 (2%)
Week 16	5 (3%)	1 (<1%)	5 (3%)
Week 20	5 (3%)	2 (1%)	6 (4%)
Week 24	5 (3%)	2 (1%)	6 (4%)
AST, *n* (%) <3×ULN	205 (100%)	209 (100%)	208 (100%)
Cumulative rate of abnormality, *n* (%)			
Week 4	1 (<1%)	3 (2%)	5 (3%)
Week 8	4 (2%)	8 (4%)	6 (3%)
Week 12	6 (4%)	8 (4%)	9 (5%)
Week 16	6 (4%)	8 (4%)	11 (6%)
Week 20	7 (4%)	9 (5%)	11 (6%)
Week 24	9 (6%)	9 (5%)	12 (7%)
GGT, *n* (%) <3×ULN	196 (96%)	190 (91%)	191 (91%)
Cumulative rate of abnormality, *n* (%)			
Week 4	2 (1%)	3 (2%)	3 (2%)
Week 8	3 (2%)	6 (4%)	3 (2%)
Week 12	5 (3%)	7 (4%)	4 (2%)
Week 16	5 (3%)	8 (5%)	6 (4%)
Week 20	5 (3%)	8 (5%)	6 (4%)
Week 24	6 (4%)	8 (5%)	7 (5%)
Total Bilirubin, *n* (%) <3×ULN	205 (100%)	210 (100%)	208 (100%)
Cumulative rate of abnormality, *n* (%)			
Week 4	0	0	0
Week 8	0	0	0
Week 12	0	0	0
Week 16	0	0	0
Week 20	0	0	0
Week 24	0	0	0

Rates are Kaplan-Meier estimates of cumulative number of patients who had a laboratory value >3xULN on or before the designated week.

XR-NTX, extended-release formulation of naltrexone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

1% (2/193) in the XR-NTX 380 mg group, 4% (7/190) in the XR-NTX 190 mg group, and 3% (5/196) in the placebo group had elevated values at final visit (none had high values).

Reported Hepatic Adverse Events

Overall, all study medications were well tolerated and rates of hepatic-related adverse events were low (Table 3). In the XR-NTX 380 mg group, there was 1 patient with hepatomegaly with an onset 182 days after receipt of the first study injection, and 1 patient diagnosed with hepatitis C infection (71 days after first dose of medication). In the XR-NTX

190 mg group, there was also 1 patient diagnosed with hepatomegaly (onset 168 days after first study injection) and 1 with hepatitis C infection (64 days after first study injection). No patients in the placebo group had any hepatic-related adverse events. One serious adverse event (biliary colic), judged as not related to study drug, was reported during the 6-month treatment period in the XR-NTX 190 group.

Subgroup Analyses: Heavy Drinking, Obese, and NSAID-Using Patients

In all, 126 (20%) patients continued to drink alcohol heavily throughout the study and had postbaseline assessments of LCTs [XR-NTX 380 mg, $n = 33$ of 205 (16%); XR-NTX 190 mg, $n = 44$ of 210 (21%); placebo, $n = 49$ of 209 (23%)]. Comparison of the subgroups in rates of high (> 3×ULN) values of postbaseline LCTs revealed no significant differences overall or for specific LCTs. The percent of patients with high values on any LCT were 12% (4/33), 25% (11/44), and 22% (11/49) for the 380 mg, 190 mg, and placebo groups, respectively. Rates for high individual LCTs were as follows: ALT [380 mg: 0% (0/33); 190 mg: 2% (1/44), placebo: 6% (3/49)], AST [3% (1/33), 11% (5/44), 10% (5/49)], GGT [9% (3/33), 21% (9/44), 20% (10/49)], and total bilirubin [3% (1/33), 0% (0/44), 4% (2/49)].

One hundred and fifty three (25%) obese patients participated in the study and had postbaseline assessments of LCTs. There were no significant differences between the study groups with regard to the percentage of patients with high levels of ALT [3% (2/58), 2% (1/45), and 4% (2/50), for XR-NTX 380 mg, XR-NTX 190 mg, and placebo groups, respectively], AST [3% (2/58), 9% (4/45), and 6% (3/50)], or total bilirubin (0% for all 3 groups).

Among patients taking NSAIDs continuously ($n = 81$; 13%), there was no significant difference between the study groups in the overall rate of any LCT during the 6-month study period, or in the rates of specific LCTs, in the high range. Rates for any high laboratory tests were similar for XR-NTX 380 mg [17% (5/29)], XR-NTX 190 mg [5% (1/20)] and placebo [25% (32/52)]. There were also no significant study group differences in the rates of hepatic-related adverse events within the subgroup of patients using NSAIDs continuously. For patients ($n = 164$; 26%) using NSAIDs at some point during the treatment period, but not continuously, there were also no significant differences between the study groups in rates of LCT results (overall or specific tests) classified as high, or in hepatic-related adverse events.

Few hepatic-related adverse events and serious adverse events were reported by patients in these subgroups. There were 2 cases of hepatitis C infection within the obese subgroup: 1 case in the XR-NTX 380 mg group and 1 case in the XR-NTX 190 mg group (this latter case also was in the heavy drinking subgroup). The only serious adverse event (described above), occurred in an obese woman receiving XR-NTX

DISCUSSION

Alcohol dependence is a chronic and debilitating disease, wherein approximately 10 to 35% of heavy drinkers develop alcoholic hepatitis, and 10 to 20% develop cirrhosis (National Institute on Alcohol Abuse and Alcoholism, 1998). Many factors including alcohol consumption, gender, comorbid diseases and host susceptibility determine whether alcohol-dependent individuals progress to significant liver injury (Tome and Lucey, 2004). Among these factors, there is a dose-response curve linking alcohol dose to incidence of cirrhosis (Bellentani et al., 1997). Consequently, therapies which promote either abstinence from or at least reduced intake of alcohol are urgently needed. Antagonism of opiate receptors by naltrexone has been shown to reduce drinking in alcohol-dependent patients. However, the utility of this oral naltrexone has been compromised by difficulties in maintaining daily dosing, by fluctuating naltrexone blood levels, and by concerns about hepatotoxicity in relation to the "black box warning". Thus, XR-NTX offers potential advantages by alleviating the patient burden of daily dosing, and reduced total dosage which may lead to better medication adherence, reduced risk of toxicity and improved outcomes.

In order to be clinically acceptable, it is necessary to determine whether XR-NTX is safe, particularly in actively drinking alcoholic subjects. A previous publication reported that nausea, fatigue, decreased appetite, dizziness, and injection site pain occurred significantly more frequently in XR-NTX 380 mg-treated patients compared to placebo-treated patients (Garbutt et al., 2005). In regard to hepatotoxicity, there had been some reports that treatment of alcohol dependence with oral naltrexone is associated with liver-related problems (excessive doses in obese patients); more likely, however, tolerability issues arise from the ongoing alcohol use. Pilot studies of injectable naltrexone have been encouraging in regard to hepatic safety. A small ($n = 12$) open-label, nonplacebo-controlled pharmacokinetic study provided preliminary hepatic safety data regarding a single dose of 190 mg of XR-NTX (no clinically meaningful changes in hepatic enzymes were found among subjects with mild or moderate hepatic impairment) (Turncliff et al., 2005). Additional preliminary hepatic safety data on XR-NTX was reported in the context of a safety study in which 25 alcohol-dependent patients received 400 mg of XR-NTX and 5 received placebo in 4 monthly injections (1 severe event of hepatomegaly was determined to be unrelated to the use of study medication) (Johnson et al., 2004). Another placebo-controlled study of a different injectable version of naltrexone reported no difference in GGT levels for extended-release naltrexone compared to placebo over 3 months of treatment (Kranzler et al., 2004).

In the present analysis, the effects of XR-NTX on hepatic function in patients with alcohol dependence were investigated in this 6-month, randomized, double-blind, placebo-controlled study. The LCTs (ALT, AST, GGT, total bilirubin) suggest that there is no evidence of hepatic dysfunc-

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