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Extended-release naltrexone is not linked to hepatotoxicity in adults experiencing homelessness and alcohol use disorder

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Abstract

Objectives: The use of extended-release naltrexone (XR-NTX) as treatment for alcohol use disorder (AUD) has been limited by a prior black box warning for hepatotoxicity. We performed a secondary analysis of data from a randomized clinical trial to compare serum liver enzyme levels for those randomized to XR-NTX versus placebo.

Methods: The parent study aimed to test the efficacy of combined pharmacobehavioral harm-reduction treatment in improving alcohol and quality-of-life outcomes for adults experiencing homelessness and AUD. We compared the two arms that received intramuscular injections of either 380 mg XR-NTX [N=74] or placebo [N=77]. Outcomes included a) liver enzyme levels and b) liver enzyme values categorized as normal (<1x upper-limit-of-normal [ULN]), elevated (1–3xULN), or high (>3xULN). We performed multinomial logistic regression and negative binomial generalized estimating equations modeling to assess the effects of treatment group and the time x treatment group interaction on liver enzyme outcomes.

Results: The mean age was 47.9 ± 9.9 years and the mean baseline alcohol consumption was 23.2 ± 14.0 drinks per day. There were no significant differences in the development of liver enzyme elevations 1–3xULN or >3xULN (all *P*s >0.25) or in the change in liver enzyme values (all *P*s >0.41) between the placebo and the XR-NTX groups over the treatment course.

Conclusions: In our study of adults experiencing homelessness and AUD, receipt of XR-NTX was not associated with hepatotoxicity. These findings support the use of XR-NTX to treat AUD even in patients who are drinking heavily and physiologically dependent on alcohol.

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All authors, PV, NJK, JOM, MHD, GNI, and SC, contributed to the conception of the work. SC performed the data analysis. PV, NJK, and SC interpreted the data. PV, NJK, and SC took the lead in writing this manuscript. All authors, PV, NJK, JOM, MHD, GNI, and SC, provided critical feedback and contributed to the writing of this manuscript.

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Keywords

Alcoholism; chemical and drug induced liver injury; homelessness; liver disease; liver function tests

Introduction

Increasing patient access to effective alcohol use disorder (AUD) treatments can minimize the risk of alcohol-associated liver disease and further liver injury. Intramuscularly injected extended-release naltrexone (XR-NTX, Vivitrol®) is a synthetic opioid antagonist that blunts the reinforcing, euphoric effects of alcohol, reduces cravings, and supports abstinence and drinking reduction. Although multiple studies suggest that XR-NTX is minimally hepatotoxic,[5, 7, 6, 8] the presence of a prior (now removed) black box warning for hepatotoxicity has limited its use in AUD treatment. There is also scant data on the hepatic safety of XR-NTX among people with active AUD with daily use and physiological dependence, as prior studies have only included people with opioid-use disorder or those undergoing alcohol abstinence-based treatment.[5, 7, 6]

We recently studied the efficacy of combined XR-NTX and community-based behavioral Harm-Reduction Treatment for AUD (HaRT-A) in non-treatment-seeking adults experiencing homelessness and AUD.[3] This was a study population impacted by severe AUD (95% physiologically dependent) that maintained a high level of alcohol use throughout the study despite these interventions. This secondary analysis tested changes in liver enzyme levels during the parent study's 3-month course of XR-NTX and harm-reduction treatment for AUD.

Methods

We performed a secondary analysis of data from a randomized clinical trial testing the efficacy of combined pharmacobehavioral harm-reduction treatment in improving alcohol and quality-of-life outcomes for adults experiencing homelessness and AUD. Participants in the parent study[4, 3] were randomized to four treatment arms: a) HaRT-A+XR-NTX [N=74], b) HaRT-A+placebo [N=77], c) HaRT-A only [N=79], and d) supportive services as usual [N=77]. We compared the two arms of the trial that received HaRT-A and intramuscular injections of either 380 mg XR-NTX or placebo at weeks 0, 4, and 8. Both groups received 5 HaRT-A sessions, which also served as medication management sessions. HaRT-A aims to help people reduce alcohol-related harm and improve health-related quality of life without requiring, prescribing, or favoring alcohol abstinence as a treatment goal.

Inclusion and exclusion criteria

Participant inclusion criteria included being ≥21 years of age and fulfilling criteria for current AUD based on Diagnostic and Statistical Manual IV: Text Revision (DSM-IV-TR)[2] criteria and as determined by the Structural Clinical Interview for DSM-IV Axis I Disorders Patient Edition. Symptoms of physiological dependence on alcohol were ascertained by a standardized interview conducted by study providers. Exclusion criteria included known

sensitivity or allergy to naltrexone; current treatment with naltrexone; being pregnant or nursing; ≥1 suicide attempts in the past year; renal insufficiency (serum creatinine level >2); current opioid dependence according to the DSM-IV-TR criteria; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels >5x upper-limit-of-normal (ULN); a clinical diagnosis of decompensated liver disease (i.e. ascites, gastro-esophageal variceal bleeding, or hepatic encephalopathy); or other condition deemed by the Principal Investigator and/or Medical Director to make study participation clinically unsafe. If participants developed an AST or ALT level >5xULN during the study, they were retested a week prior to the next scheduled injection. If AST or ALT elevation persisted, the study medication was discontinued to ensure participant safety.

Study outcomes

Outcomes included a) serum liver enzyme levels (i.e., AST, ALT, and gamma-glutamyl transferase [GGT]) and b) serum liver enzyme values categorized as normal (<1xULN), elevated (1–3xULN), or high (>3xULN) for AST (1x/3x ULN: 38/114 IU/L), ALT (1x/3x ULN: 48/144 IU/L) and GGT (1x/3x ULN: 55/165 IU/L). We performed multinomial logistic regression (with robust standard errors) and negative binomial generalized estimating equations modeling to assess the effects of time, treatment group, and the time x treatment group interaction on liver enzyme outcomes. In all models, we adjusted for typical daily standard alcohol content. Analyses were performed using Stata v. 16.1 (StataCorp, College Station, TX).

Results

Baseline participant characteristics

The mean participant age was 47.9 ± 9.9 years, and 21 (13.8%) reported female sex assigned at birth. Regarding self-reported race, 59 (38.8%) were Black/African American, 44 (28.9%) were White, 19 (12.5%) were American Indian/Alaska Native, 2 (1.3%) were Native Hawaiian/Pacific Islander, 21 (13.8%) were Multiracial, and 7 (4.6%) reported “Other.” The majority of participants (96.7%) were physiologically dependent on alcohol. The mean typical baseline alcohol consumption was 23.2 ± 14.0 drinks per day. The overall baseline AST and ALT values were ≥1xULN in 59 (39.1%) and 32 (21.2%) participants, respectively. The Fibrosis-4 score was ≥3.25 in 22 (14.5%) participants.

Associations between receipt of XR-NTX and liver enzyme elevations

Multinomial logistic regressions showed that higher typical daily alcohol consumption was associated with an overall increased risk of AST and ALT elevations 1–3xULN and an increased risk of AST, ALT and GGT elevations >3xULN. There were, however, no statistically significant differences between the placebo and the XR-NTX groups on the development of liver enzyme elevations 1–3xULN or >3xULN over the treatment course (all *P*s > .25; see Table 1 for descriptive statistics and Table 2 for model parameters).

Associations between receipt of XR-NTX and liver enzyme values

After controlling for typical daily alcohol consumption, which predicted elevated AST and ALT levels overall, generalized estimating equations models likewise indicated no

statistically significant differences between the placebo and the XR-NTX groups on changes in liver enzyme values over the treatment course (all *P*s >0.41, see Supplement eTable for model parameters).

Discussion

In this secondary analysis of a randomized clinical trial that showed the efficacy of combined XR-NTX and harm-reduction counseling, we found no effect of XR-NTX on liver enzyme values or elevations over the three-month treatment course. A strength of our study was that it included participants experiencing active AUD (96.7% physiological dependence with average typical daily alcohol consumption over 5 times the National Institutes of Health definition of "heavy drinking") as well as co-occurring medical and psychiatric disorders that characterize the chronically homeless population. Nonetheless, our findings were consistent with other studies, including another randomized clinical trial by Lucey et al[7], that have also found no indications of hepatotoxicity with XR-NTX use.

Our study capitalizes on the strengths of the parent study. Participants were randomized to treatment arms, thus minimizing the effect of confounding due to differences in baseline characteristics. We analyzed two treatment arms that were identical except for receipt of XR-NTX or placebo, and importantly, we controlled for average daily alcohol consumption.

Our study has limitations. First, we performed post-hoc analyses; thus, the parent study was not specifically powered to detect significant treatment arm differences on liver enzyme values and thus the hepatic safety of XR-NTX. Second, people with baseline liver enzyme values (AST, ALT, or GGT) >5xULN or current decompensated liver disease were excluded from study participation. Thus, our results are not generalizable to these populations. Finally, our findings should not preclude providers from monitoring patients for potential hepatotoxicity during XR-NTX use. Although the risk of hepatotoxicity with XR-NTX use is low at recommended doses, the U.S. Food and Drug Administration recommends that providers counsel their patients about the potential risk of hepatotoxicity and need for clinical monitoring when taking XR-NTX.[1]

Conclusions

In summary, receipt of XR-NTX was not associated with signs of hepatotoxicity in our study of adults experiencing homelessness and alcohol use disorder. These findings corroborate those of prior studies supporting the hepatic safety of XR-NTX, and show it may be used even with patients who are physiologically dependent on alcohol and actively drinking, on average, 23 standard drinks daily.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AUD	Alcohol use disorder
XR-NTX	Extended-release naltrexone
HaRT-A	Harm Reduction Treatment for Alcohol use disorder
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
ULN	Upper limit of normal
GEE	Generalized estimating equations

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Table 1.

Descriptive data on liver transaminases by treatment group

	AST levels			
	Baseline	**Week 4**	**Week 8**	**Week 12**
HaRT-A + XR-NTX (N=74/54/48/53)				
Enzyme value (median, IQR)	30.5	29.5	31	30
<1x ULN (n, %)	49 (66.2%)	37 (68.5%)	36 (75%)	32 (60.4%)
1–3x ULN (n, %)	23 (31.1%)	15 (27.8%)	8 (16.7%)	17 32.1%
>3x ULN (n, %)	2 (2.7%)	2 (3.7%)	4 (8.3%)	4 (7.6%)
HaRT-A + placebo (N= 77/54/47/48)				
Enzyme value (median, IQR)	35	31.5	40	39.5
<1x ULN (n,%)	43 (55.8%)	30 (55.6%)	23 (48.9%)	22 (45.8%)
1–3x ULN (n, %)	26 (33.8%)	18 (33.3%)	20 (42.6%)	20 (41.7%)
>3x ULN (n, %)	8 (10.4%)	6 (11.1%)	4 (8.5%)	6 (12.5%)
	ALT levels			
	Baseline	**Week 4**	**Week 8**	**Week 12**
HaRT-A + XR-NTX (N=74/54/48/53)				
Enzyme value (median, IQR)	24	23	25	22
<1x ULN (n, %)	64 (86.5%)	51 (94.4%)	44 (91.7%)	45 (84.9%)
1–3x ULN (n, %)	8 (10.8%)	2 (3.7%)	4 (8.3%)	6 (11.3%)
>3x ULN (n, %)	2 (2.7%)	1 (1.9%)	0 (0%)	2 (3.8%)
HaRT-A + placebo (N= 77/54/47/48)				
Enzyme value (median, IQR)	26	27.5	32	29
<1x ULN (n,%)	55 (71.4%)	43 (79.6%)	40 (85.1%)	34 (70.8%)
1–3x ULN (n, %)	19 (24.7%)	10 (18.5%)	6 (12.8%)	12 (25%)
>3x ULN (n, %)	3 (3.9%)	1 (1.9%)	1 (2.1%)	2 (4.2%)
	GGT levels			
	Baseline	**Week 4**	**Week 8**	**Week 12**
HaRT-A + XR-NTX (N=74/54/48/53)				
Enzyme value (median, IQR)	38.5	28	27.5	32

	AST levels			
	Baseline	**Week 4**	**Week 8**	**Week 12**
<1x ULN (n, %)	48 (64.9%)	37 (68.5%)	33 (68.8%)	33 (62.3%)
1–3x ULN (n, %)	18 (24.3%)	12 (22.2%)	10 (20.8%)	14 (26.4%)
>3x ULN (n, %)	8 (10.8%)	5 (9.3%)	5 (10.4%)	6 (11.3%)
HaRT-A + placebo (N= 77/54/47/48)				
Enzyme value (median, IQR)	38	37	36	56.5
<1x ULN (n,%)	47 (61%)	34 (63%)	27 (57.5%)	23 (47.9%)
1–3x ULN (n, %)	16 (20.8%)	10 (18.5%)	9 (19.2%)	14 (29.2%)
>3x ULN (n, %)	14 (18.2%)	10 (18.5%)	11 (23.4%)	11 (22.9%)

ALT: alanine aminotransferase. AST: aspartate aminotransferase. GGT: gamma glutamyl-transferase. HaRT-A: behavioral harm reduction treatment sessions. IQR: interquartile range.

XR-NTX: extended-release naltrexone.

Table 2.

Multivariate multinomial logistic regression for estimating the effects of time and treatment group on liver enzyme values[†]

Characteristics	Adjusted[‡] relative risk ratio Elevated: 1–3xULN (95% CI)	*P*-value	Adjusted[‡] relative risk ratio High: >3xULN (95% CI)	*P*-value
AST				
Treatment arm: XR-NTX vs. placebo (referent)	0.74 (0.37 to 1.45)	0.38	0.25 (0.04 to 1.44)	0.12
Time (per month increase)	1.27 (1.01 to 1.6)	0.04	1.38 (0.97 to 1.97)	0.07
Typical daily alcohol consumption (per drink)	1.03 (1.01 to 1.05)	0.006	1.07 (1.04 to 1.09)	< 0.001
TimexTreatment arm	0.83 (0.6 to 1.15)	0.26	1.25 (0.71 to 2.19)	0.44
ALT				
Treatment arm: XR-NTX vs. placebo (referent)	0.32 (0.12 to 0.83)	0.02	0.57 (0.1 to 3.17)	0.52
Time (per month increase)	1.06 (0.8 to 1.41)	0.67	1.15 (0.66 to 2)	0.61
Typical daily alcohol consumption (per drink)	1.04 (1.02 to 1.06)	0.001	1.05 (1.02 to 1.08)	0.001
Time x Treatment arm	1.09 (0.69 to 1.73)	0.7	1 (0.47 to 2.11)	1
GGT				
Treatment arm: XR-NTX vs. placebo (referent)	1.21 (0.53 to 2.72)	0.65	0.56 (0.21 to 1.54)	0.26
Time (per month increase)	1.29 (0.98 to 1.7)	0.07	1.47 (1.17 to 1.83)	0.001
Typical daily alcohol consumption (per drink)	1.03 (1 to 1.06)	0.06	1.07 (1.04 to 1.09)	<0.001
Time x Treatment arm	0.84 (0.61 to 1.16)	0.3	0.84 (0.59 to 1.2)	0.35

ALT: alanine aminotransferase. AST: aspartate aminotransferase. GGT: gamma glutamyl-transferase. XR-NTX: extended release naltrexone. ULN: upper limit of normal.

[†]Liver enzyme value <1xULN (normal) is set as the referent group

[‡]Adjusted for follow-up time, treatment arm, and typical daily alcohol consumption