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Extended-Release Naltrexone and Harm Reduction Counseling for Chronically Homeless People With Alcohol Dependence

Susan E. Collins, PhD,¹ Mark H. Duncan, MD,¹ Brian F. Smart, MD,¹ Andrew J. Saxon, MD,^{1,2}
Daniel K. Malone, MPH,³ T. Ron Jackson, MSW,⁴ and Richard K. Ries, MD¹

ABSTRACT. *Background:* Abstinence-based alcohol interventions are minimally desirable to and effective for chronically homeless individuals with alcohol dependence who have multimorbidity and high publicly funded service utilization and associated costs. Lower-barrier, patient-centered combined pharmacobehavioral interventions may more effectively treat this population. Harm reduction counseling involves a nonjudgmental, empathic style and patient-driven goal setting that requires neither abstinence nor use reduction. Extended-release naltrexone (XR-NTX), a monthly injectable formulation of an opioid receptor antagonist, reduces craving, is safe and effective for active drinkers, and may thereby support harm reduction goal setting. The aims of this 12-week, single-arm pilot were to initially document some aspects of feasibility, acceptability, and alcohol outcomes following XR-NTX administration and harm reduction counseling for chronically homeless individuals with alcohol dependence. *Methods:* Participants were currently/formerly chronically homeless, alcohol-dependent individuals ($N = 31$) from 2 community-based agencies in the US Pacific Northwest. Measures included self-reported alcohol craving, quantity/frequency, problems, and biomarkers (ethyl glucuronide [EtG], liver transaminases). XR-NTX and harm reduction counseling were administered monthly over the 3-month treatment course. *Results:* Of the 45 individuals approached, 43 were interested in participation. The first injection was received by 31 participants, and 24 complied with all study procedures. Participants reported the treatment was acceptable. Participants evinced decreases in alcohol craving (33%), typical (25%) and peak (34%) use, frequency (17%), problems (60%), and EtG from the baseline to the 12-week follow-up ($P_s < .05$). *Conclusions:* XR-NTX and harm reduction counseling are promising means of supporting reductions in alcohol use and alcohol-related harm among chronically homeless, alcohol-dependent individuals.

Keywords: Alcohol dependence, extended-release naltrexone, harm reduction, homelessness

INTRODUCTION

An international meta-analysis showed a mean of 38% of homeless individuals are affected by alcohol dependence as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*,¹ which is 10 times the prevalence of alcohol dependence in the general US population (3.8%).² Alcohol dependence interferes with tasks of daily living, such as attaining and maintaining housing, employment, and social networks.^{3,4} The more severe alcohol dependence that often affects homeless individuals is associated with both acute and chronic alcohol-related harm.^{5,6} Additionally, chronically homeless people (i.e., those who have a disability and have been homeless for at least 1 year or on 4 or more separate occasions in the past 3 years⁷) are often multiply affected by psychiatric,

¹Department of Psychiatry and Behavioral Sciences, University of Washington–Harborview Medical Center, Seattle, Washington, USA

²VA Puget Sound Health Care System, Seattle, Washington, USA

³Downtown Emergency Service Center, Seattle, Washington, USA

⁴Evergreen Treatment Services, Seattle, Washington, USA

Correspondence should be addressed to Susan E. Collins, Department of Psychiatry and Behavioral Sciences, University of Washington–Harborview Medical Center, 325 Ninth Avenue, Box 359911, Seattle, WA 98104, USA. E-mail: collins@uw.edu

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medical, and substance use disorders.^{1,6,8} Taken together, these factors lead to greater risk for alcohol-related mortality^{9–11} as well as increased burden on the health care and criminal justice systems.^{4,12} Considering the extent and cost of negative consequences for both affected individuals and their communities, effective approaches are needed to address the issues facing chronically homeless people with alcohol dependence.

Although abstinence-based approaches have long been assumed to be the *sine qua non* of effective treatment, particularly for more severely affected populations, studies show that few homeless people voluntarily start treatment (15–28%),^{13,14} and even fewer complete it (2.5–33%).¹⁵ A National Institute on Alcohol Abuse and Alcoholism (NIAAA) review showed that treatment engagement in this population decreased as program demands—particularly abstinence—increased.¹⁵ Some individuals, however, do not have a choice about treatment engagement: chronically homeless people with alcohol dependence are often mandated to treatment through drug courts or as a condition of pretrial release, probation, or parole.¹⁶ Nonetheless, abstinence-based treatment does not typically have long-lasting effects in this population. A recent study conducted with chronically homeless people with alcohol dependence indicated a mean of 16 lifetime abstinence-based treatment attempts.¹² Such repeated failed treatment attempts have led to negative evaluations of abstinence-based approaches,^{17,18} which are, in turn, correlated with decreased treatment attendance¹⁹ and poorer outcomes.²⁰ Additionally, inpatient detoxification and treatment—typically a medical necessity for this population—are expensive and can become another spoke in a “revolving door,”^{21,22} in which abstinence-based treatment episodes are regularly alternated with resumed use in a circular pattern. This revolving door effect is a concern in this population because an increasing number of alcohol withdrawals and medical detoxifications can precipitate increasingly severe and potentially fatal alcohol withdrawal symptoms (i.e., kindling effect),²³ which may make abstinence-based treatment a more harmful course of action for more severely affected individuals. Taken together, the current evidence indicates that traditional abstinence-based treatments are neither engaging nor effective for this high-utilizing, multimorbid population.

As an alternative to abstinence-based treatment, lower-barrier approaches have begun to be applied with chronically homeless individuals with alcohol dependence.^{12,24–26} Such approaches are referred to as harm reduction interventions because they focus on improving quality of life and reducing alcohol-related harm without requiring abstinence or use reduction.²⁷ To date, these interventions have primarily included low-barrier shelter programs paired with medically supervised alcohol administration^{24,25} and Housing First programs, which entail provision of immediate, permanent, low-barrier, non-abstinence-based supportive housing.^{12,28} Although they do not require abstinence or use reduction, these interventions have been shown to be effective in reducing alcohol use and alcohol-related harm.^{12,24–26}

Whereas harm reduction-oriented housing and service provision are finding increased application in this population, no behavioral or pharmacological treatment counterparts have been tested to further support these efforts. Harm reduction behavioral interventions have been applied with other types of substance use (e.g., opioid/injection drug use^{29–31}) as well as alcohol use in nonclinical populations (e.g., college drinkers^{32,33}). With more severely affected populations, however, alcohol abstinence has been widely

endorsed as the most desirable goal.^{34–37} Because abstinence-based or use reduction approaches (i.e., drinking moderation or controlled drinking goals^{38–41}) have been the focus of the research to date,^{42–48} there are currently no evidence-based harm reduction behavioral interventions for individuals with alcohol dependence.

On the other hand, harm reduction psychotherapy and counseling have begun to be conceptualized and clinically applied.^{27,49,50} As applied to alcohol use, harm reduction refers to compassionate and pragmatic strategies that minimize alcohol-related harm for affected individuals and society at large.²⁷ Harm reduction counseling focuses on “accepting people where they’re at” and deemphasizes pathologizing or placing moral value on alcohol use.⁴⁹ Harm reduction counseling supports the realization of patient-driven goals and recognizes any movement towards reducing harm and improving quality of life as steps in the right direction.⁵¹ There has been some disagreement about what differentiates harm reduction counseling from other approaches that involve an empathic, patient-centered style.⁵² However, the focus on patient-driven harm reduction goals versus provider-driven abstinence or use reduction goals provides the clearest point of differentiation.²⁷ This shift in intervention priorities requires focus on whatever compassionate and pragmatic means can result in harm reduction, which, depending on patients’ own goals, may or may not involve alcohol use reduction or abstinence. Given the unmet treatment needs of chronically homeless people with alcohol dependence as well as the rising importance of harm reduction interventions, research is needed to understand the outcomes of such approaches in this population.

As in behavioral treatment, there are currently no pharmacological counterparts to support alcohol harm reduction in severely affected populations. One medication that could address this treatment gap is naltrexone, an opioid receptor antagonist. Naltrexone’s putative clinical actions include reductions in alcohol craving and urges to drink, blunting of the stimulatory effects of alcohol, potentiation of alcohol’s depressant effects, and improved executive functioning and impulse control.⁵³ Indeed, studies have shown that oral-dose naltrexone is associated with significant reductions in alcohol craving, use, dependence, and problems.^{54–62} Despite its efficacy, however, low medication adherence has been a barrier to its consistent use.^{63–66}

Extended-release naltrexone (XR-NTX; marketed as Vivitrol) was introduced to overcome the challenge of medication nonadherence. XR-NTX is a 30-day, extended-release formulation of naltrexone and is administered monthly via gluteal intramuscular injection, delivering 380 mg of medication. Large-scale randomized controlled trials (RCTs) have shown that XR-NTX is efficacious in the treatment of alcohol dependence.^{67,68} In the first, large-scale RCT testing the current Food and Drug Administration (FDA)-approved dose ($N = 626$), the 380 mg formulation resulted in a statistically significant 25% reduction in heavy drinking compared with matching placebo.⁶⁸ In recent open-label trials, XR-NTX was deemed acceptable and feasible for delivery in a health care setting.^{69,70}

Unlike other pharmacotherapies for alcohol dependence (e.g., disulfiram), naltrexone is safe and effective among both individuals who are abstinent^{57,71} and actively drinking,⁶⁸ which makes it compatible with this population’s chronic relapsing drinking pattern. Further, in accordance with harm reduction principles,²⁷ XR-NTX has been shown to be associated with improved alcohol outcomes without requiring abstinence from alcohol prior to

administration.⁶⁸ Because it is a monthly injectable versus a daily oral medication, XR-NTX may also support medication adherence and greater follow-up with health care professionals, which often poses a challenge for homeless individuals.^{72–74} Finally, recent utilization studies have shown that XR-NTX precipitates reductions in health care utilization and associated costs that can offset the cost of the drug itself.^{75,76} Because chronically homeless people with alcohol dependence are often high utilizers of health care services,¹² XR-NTX is well situated to address this population's burden on the health care system. Taken together, these features make XR-NTX compatible with the needs and goals of this population.

It deserves mention that a recent randomized, open-label study explored the feasibility of oral naltrexone and XR-NTX in supporting alcohol use reduction among homeless individuals with alcohol dependence.⁷⁷ This study found very low rates of acceptability for both formulations: only 3% (7/215) of participants approached were willing to participate and be randomized, and only 1 participant who received XR-NTX returned after the first injection. Although the primary reason for participation refusal was “fear of needles,” the study authors suggest that reluctance may have been due to “ambivalence toward recovery.”^{77(p96)} In the latter case, this study's findings suggest that a shift from provider- to patient-driven goals may help reach a population that otherwise does not present for, successfully complete, or maximally benefit from existing treatment.^{13–15,78} Specifically, a focus on patient-elicited harm reduction goals versus predetermined use reduction or abstinence-based goals may be a more inclusive approach, which could thereby increase the future reach and population impact of alcohol treatment for homeless individuals.

This study's aims were thereby to initially assess some aspects of feasibility, acceptability, and alcohol outcomes following administration of XR-NTX and a newly developed harm reduction counseling component in 2 community-based settings providing low-barrier supportive services to chronically homeless individuals with alcohol dependence. It was hypothesized that this treatment would be (a) feasible (i.e., participants would be interested in, present for, and be retained in the study intervention, which represents one aspect of feasibility⁷⁹); (b) acceptable (i.e., participants would report that XR-NTX was acceptable and effective and that they would be likely to continue it); and (c) followed by reductions in alcohol craving, use, and problems.

METHODS

Participants

Participants were currently or formerly (i.e., now living in permanent supportive housing) chronically homeless individuals (i.e., those who have a disability and have been homeless for at least 1 year or on 4 or more separate occasions in the past 3 years⁷) with alcohol dependence. Inclusion criteria included receiving services from 1 of the 2 partnering agencies, being 21–65 years old, agreeing to use an adequate form of birth control (if female and in child-bearing years), and fulfilling criteria for current alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR). Exclusion criteria included refusal or inability to consent to participation in research, constituting a risk to safety/security of other

patients/staff, known sensitivity or allergy to naltrexone/XR-NTX, current treatment with naltrexone/XR-NTX, being pregnant/nursing, suicide attempts within the past year, renal insufficiency/serum creatinine level >1.5 mg/dl, current opioid dependence according to the DSM-IV-TR criteria, liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) >5 times the upper limit of normal (ULN), and a clinical diagnosis of decompensated liver disease.

Settings

Settings included 2 community-based agencies on the forefront of harm reduction housing and service provision to chronically homeless people in a large city in the US Pacific Northwest. Both agencies serve the same population, have highly overlapping client bases, and use a harm reduction approach. Formerly homeless participants were recruited at one of the agencies' Housing First programs, which provide immediate, permanent, low-barrier, non-abstinence-based housing to chronically homeless people with severe alcohol problems. In this model, individuals are not required to be abstinent from substances, are allowed to drink in their units, and are not required to attend treatment.^{17,26,80} Currently homeless participants were recruited through an agency that provides outreach, nursing care, and case management to chronically homeless people on the street and in various facilities serving homeless people throughout the city. Likewise, individuals are not required to be abstinent from substances to receive services.

Measures

Measures to establish study inclusion

The *UCSD Brief Assessment of Capacity to Consent* (UBACC) is a 10-item, 3-point Likert-scale measure.⁸¹ It was used during the informed consent process to ensure participants understood the study protocol, potential risks/benefits, and their rights as participants prior to enrollment. The alcohol dependence portion of the DSM-IV-TR Structured Clinical Interview (SCID)⁸² was used to document fulfillment of that inclusion criterion in the past 30 days.

Measures for baseline sample description

The *Personal Information Form*¹² comprises single items that were created for use with a similar population. This measure assessed age, gender, race, ethnicity, education level, and employment status. The *Housing Timeline Followback*^{83,84} is a set of monthly calendars used to record where participants resided/spent the night each day over the past 30 days.

Measures for acceptability and tolerability outcomes

The *Acceptability Ruler* was adapted from a measure reported on in a previous study⁸⁵ and includes 3 items prompting participants to rate how acceptable and effective they believe XR-NTX to be as well as how likely they are to continue it in the future. Ratings are made on a 10-point Likert-type scale, where 1 = not at all acceptable/effective/likely and 10 = totally acceptable/effective/likely. The *Systematic Assessment for Treatment Emergent Effects* (SAFTEE) interview includes open-ended, categorical, and Likert-scale questions assessing symptoms that correspond to potential adverse events associated with XR-NTX.^{86,87} The summary

score of the number of endorsed items reached adequate internal consistency (Kuder-Richardson coefficient [K-R] = .84).

Measures for alcohol outcome analyses

The *Alcohol and Substance Use Frequency Assessment* questions were adapted from the Addiction Severity Index (ASI)⁸⁸ and were used to assess frequency of alcohol and other drug use over the past 30 days. The *Alcohol Quantity of Use Assessment* (AQUA) was created in the context of a previous study with this population and assessed alcohol quantity consumed on peak and typical drinking days in the past 30 days.¹² Alcohol craving was measured for the past week using the 5-item, Likert-type *Penn Alcohol Craving Scale* (PACS).⁸⁹ Internal consistency was adequate ($\alpha = .91$). The *Short Inventory of Problems* (SIP-2R) is a 15-item, Likert-scale questionnaire that measured social, occupational, and psychological alcohol problems over the past 30 days.⁹⁰ Internal consistency was adequate ($\alpha = .91$).

Materials and Tests

Blood tests were conducted at baseline and weeks 4, 8, and 12 and included a complete blood count (CBC), basic metabolic panel (CHEM 7), liver panel (AST, ALT, γ -glutamyltranspeptidase [GGT], alkaline phosphatase, albumin, bilirubin total and direct), and human chorionic gonadotropin (hCG) testing (for women in childbearing years). These tests were conducted to assess hepatic and renal functioning and to detect other medical conditions that contraindicated the use of XR-NTX (e.g., pregnancy) or were important to monitor during its administration.

Urine tests included (a) complete urinalysis, which was used to detect contraindicating conditions (e.g., renal damage); (b) urine toxicology tests, which were used to screen for the presence of opioids; and (c) ethyl glucuronide (EtG) tests,⁹¹ which were used to corroborate self-reported alcohol use. The concentration of EtG, which is a metabolite of ethyl alcohol formed in the body by glucuronidation after ethanol exposure, was used as a quantitative measure (EtG/creatinine). Previous studies have shown that EtG is positively associated with self-reported alcohol quantity.^{92,93}

Study Treatment

Study physicians administered XR-NTX, harm reduction counseling and medication management at monthly sessions. Although it was developed for the current study, the structure of the medication management sessions was informed by procedures from the COMBINE Study and other naltrexone medication management manuals.^{94,95} A harm reduction style, which is similar to motivational interviewing, was utilized. This style involves a compassionate, nonjudgmental, and empathic stance; unconditional positive regard; and acceptance of patients wherever they fall on the spectrum of readiness to change.^{49,96} Study physicians provided integrated medication management and harm reduction counseling, including (a) offering personalized feedback about alcohol assessments/laboratory tests; (b) assessing vital signs and (c) concomitant medications; (d) obtaining medical history (baseline only); (e) assessing for adverse events using the Systematic Assessment for Treatment Emergent Events (SAFTEE);

(e) conducting a brief physical examination (baseline and as clinically indicated); (f) providing medication management (discussing the medication, side effects and ways to manage them; ensuring participants have medication bracelets/ID tags; providing emergency contact information); (g) eliciting participants' own harm reduction goals and progress made towards them; (h) discussing safer drinking using the Safer Drinking Steps worksheet (see Figure 1); and (i) administering XR-NTX. Sessions were manualized, and study physicians received training on the manual prior to participant recruitment (i.e., demonstrations, role playing, feedback). Sessions were audiorecorded to facilitate in-person, weekly group supervision by the first author and medical director (R.K.R.).

Harm reduction goals were entirely participant driven. Study staff and physicians told participants that these goals did not require a focus on alcohol, and neither use reduction nor abstinence-based goals were recommended or encouraged unless they were volunteered by the participant. During the study, goals ranged from improving quality of life (e.g., "going to the library," "doing my drawings again," "visiting my son") to reducing harm (e.g., "not having blackouts," "avoiding withdrawal") to safer drinking (e.g., "switching from whiskey to beer," "drinking in a safe place") to engaging in recovery (e.g., "getting a sponsor") to use reduction (e.g., "drinking 8 beers [versus previous 12 a day]," "making 3 beers last all day") to abstinence. XR-NTX was introduced to participants as a medication that had been shown to help reduce alcohol craving, heavy use, and problems. It was discussed as a means of supporting participants' own goal achievement.

Study physicians ($N = 2$) were trained in both family medicine and psychiatry and were completing an additional 1-year subspecialty training in addiction psychiatry while serving on the study team. Both were male with white/European American ($n = 1$) and multiracial ($n = 1$; white/European American and American Indian/Alaska Native) backgrounds. Neither identified as Hispanic/Latino.

Procedures

This research complied with the Declaration of Helsinki, and all procedures were reviewed and approved by the institutional review board at the home institution. Agency and research staff notified agency clients of the opportunity to participate in a study involving counseling and a medication, which aimed to reduce alcohol craving and alcohol-related harm but did not require abstinence and did not require participants to change their drinking in any particular way. Soon thereafter, research staff were onsite to conduct information sessions with interested agency clients. During information sessions, research staff explained study procedures, participants' rights, and informed consent materials. Next, the UBACC was administered to assess capacity to provide informed consent. Potential participants received \$5 for attending the information session, regardless of their decision, ability, or qualification to participate.

Written informed consent was obtained, and participants completed the baseline assessment with research staff, which included all measures listed above except the SAFTEE. Next, participants met with study physicians, who collected a medical history, conducted a brief physical examination, administered the SAFTEE, and collected blood and urine samples for laboratory testing. Participants were compensated \$20 for their time and were scheduled for the following week (Week 0). During the interim week, the



FIGURE 1 Safer drinking strategies handout.

research team discussed laboratory results and determined inclusion and exclusion criteria fulfillment.

All participants attended Week 0 with the study physician and were told whether they qualified for the study. Those who did not qualify received feedback about their laboratory tests and alcohol use, were told why they did not qualify, and were provided with a handout and brief counseling on safer drinking strategies (see Figure 1). Study qualifiers received the treatment content as described above and were scheduled for the Week 1 safety meeting. At Week 1, study physicians administered the SAFTEE and checked in with participants regarding progress towards their harm reduction goals and use of safer drinking strategies. Participants were paid \$20 for each appointment they attended. Participants attended additional sessions with both research assessment staff and study physicians at Weeks 4, 8, and 12, during which they repeated the

assessment, harm reduction counseling, and medication management (see Figure 2). It should be noted that research and agency staff communicated throughout the study to track and locate participants. Special agreements were put into place for researchers to communicate with agency staff in case of a potentially life-threatening medical emergency.

RESULTS

Study Sample Description

Participants ($N = 31$; 12.9% women) were currently ($n = 14$) or formerly chronically homeless ($n = 17$) individuals with alcohol dependence (see Table 1 for baseline demographic data).

Feasibility and Participant Retention

Of the 45 individuals approached by researchers for recruitment, 43 (96%) expressed interest in participation, and 42 provided written informed consent. (One individual was deemed incapable of providing written informed consent due to cognitive deficits.) As shown in Figure 2, 31 individuals qualified for participation and received the initial injection. At Weeks 4 and 8, 84% (26/31) and 77% (24/31) of participants received injections, respectively. Complete data were collected from 100%, 94% (29/31), 77% (24/31), and 77% (24/31) of participants at Weeks 1, 4, 8, and 12, respectively.

Acceptability and Tolerability of XR-NTX

Although their acceptability ratings significantly decreased over time, participants reported XR-NTX was both acceptable and effective for them, and they would be likely to continue to come to appointments to receive XR-NTX in the future (see Table 2). At the end of the study, 63% (15/24) of participants were interested in off-study continuation of either oral naltrexone or XR-NTX. XR-NTX was well tolerated in this sample according to symptom experience as measured by the SAFTEE (see Table 3). Aside from injection site irritation, which precipitated discontinuation of the study medication for 3

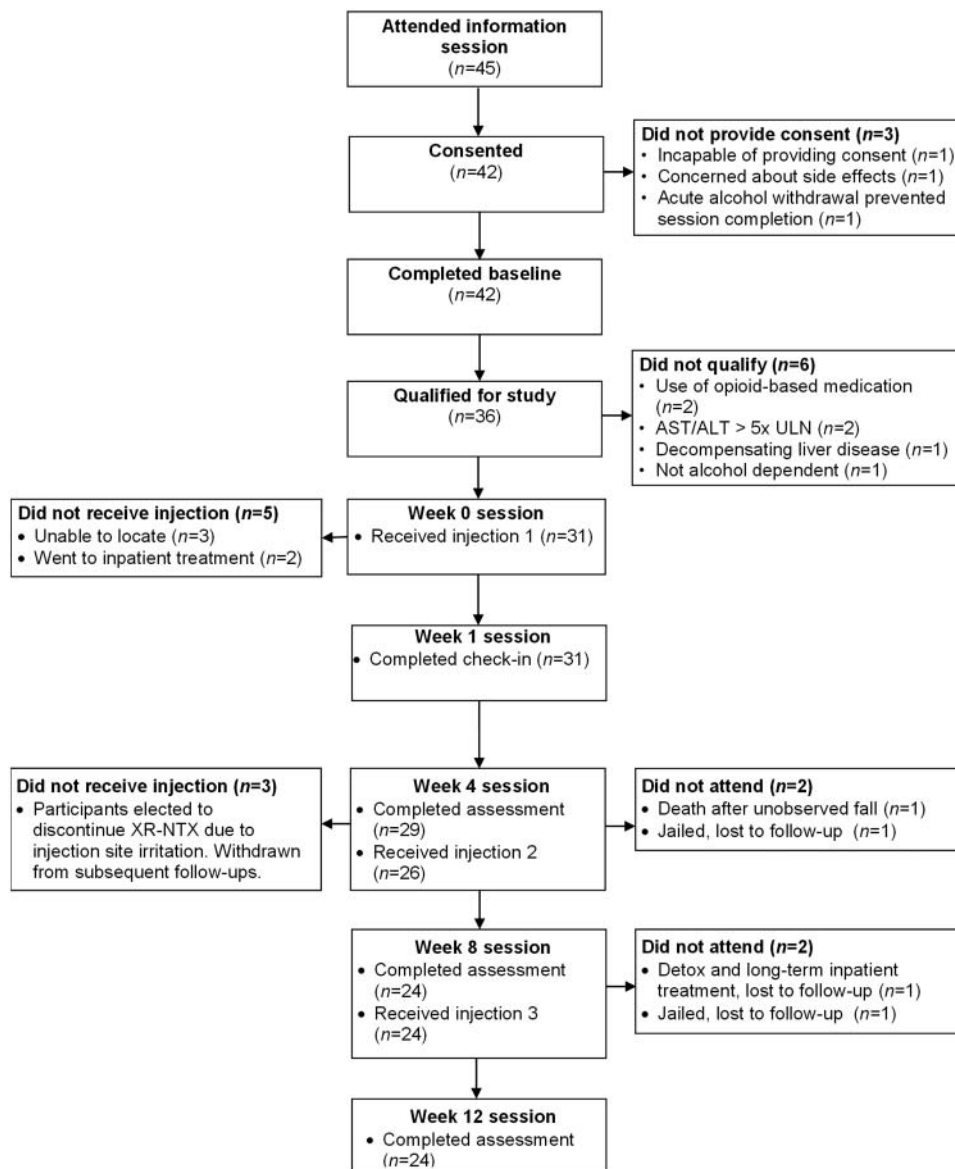


FIGURE 2 Participant flowchart.

TABLE 1
Baseline Descriptive Statistics for the Study Sample (N = 31)

Variable	M (SD) /%
Age	50.16 (6.35) ^a
Housing status 1 week prior to baseline assessment	54.8% Housing First ^b residents 45.2% Currently homeless 29% Sleep-off facility 6.5% Emergency shelter 3.2% Outside 3.2% Friend's house 3.2% Other
Ethnicity	3.3% Hispanic/Latino/a
Race	
American Indian/Alaska Native/First Nation ^c	35.5%
Asian	0%
Black/African American	9.7%
Native Hawaiian/Pacific Islander	3.2%
White/European American	38.7%
"More than 1 race"	12.9%
Highest education level	
No high school degree	29.0%
HS graduate/GED	29.0%
Vocational school	16.1%
Some college	16.1%
College graduate	3.2%
Some graduate school/advanced degree	6.4%
Employment status	
Full time	0%
Part time	3.2%
Unemployed (no assistance)	9.7%
Unemployed (Aged, Blind, Disabled Cash Assistance Program) ^d	38.7%
Disability (SSI/SSDI)	45.2%
Other	3.2%

Note. Percentages may not total 100% due to rounding.

^aAges ranged from 35 to 63.

^bHousing First is an innovative model of housing that entails the provision of immediate, permanent, low-barrier, non-abstinence-based supportive housing to chronically homeless people who often have co-occurring psychiatric, medical, and substance use disorders.

^cNative American/Alaska Native/First Nation tribal affiliations included Pacheedaht (1), Salish (1), Lummi (1), Yup'ik (1), Menominee (1), Sioux (2), Makah (1), Haida (1), and Cherokee (1).

^dThe Aged, Blind, Disabled Cash Assistance Program is a state program that provides cash grants to people who (a) are 65 or older, blind, or have a long-term medical condition that is likely to meet federal disability criteria; (b) meet income and resource requirements; (c) meet citizenship/alien status requirements; and (d) reside in-state. This program is applied until individuals qualify for federal disability income.

individuals, experience of adverse events decreased over the course of the study (see Table 3). As shown in Table 3, although the study sample experienced numerous emergency room (ER) visits, hospitalizations, and 1 death, only 1 serious adverse event was found to be related to the study medication (i.e., vomiting that precipitated dehydration requiring an ER visit).

Alcohol Outcome Analyses

As shown in Table 4, Wilcoxon signed-rank tests indicated that participants' median alcohol craving, use, and problems decreased significantly from baseline to Week 12. Specifically, alcohol craving decreased by 33%, typical quantity by 25%, peak quantity by 34%, frequency of alcohol use (drinking days) by 17%, and alcohol problems by 60%. EtG/creatinine ratios significantly decreased from baseline to Week 12, which corresponded to self-reported decreases in alcohol use. Mean AST, ALT, and GGT levels did not change significantly over the course of treatment.

DISCUSSION

Monthly administration of XR-NTX and harm reduction counseling was feasible in this sample. Of those approached by researchers, 96% were interested in participation, 86% of those who consented were found eligible, and 77% of participants who started on XR-NTX completed all procedures. This finding stands in contrast to that of a recent study of XR-NTX in a similar population, in which 97% of individuals approached refused participation, and only a single XR-NTX participant returned after the initial injection.⁷⁷ Many different explanations for this discrepancy could exist: differences in the research setting (medically supervised withdrawal at a VA [Veterans Administration] hospital versus community-based centers serving active drinkers), recruitment procedures, and cultural differences among homeless populations in different geographical areas. In that study, however, 1 of the top 3 reasons for refusal was "not wanting to change drinking habits."^{77(p95)} Thus, it is possible that providers' potentially implicit expectation that participants want to change their drinking in a certain way—in this case to maintain abstinence or reduce drinking—may have created a barrier to participation. The current study removed this barrier by not asking participants to endorse abstinence-based, use reduction, or specific alcohol-related goals. Instead, we asked whether participants had a goal. What that goal was and whether it directly involved changes in alcohol use was entirely up to them.

The study medication was tolerable in this sample. Only 3 participants decided to discontinue XR-NTX over the course of the study, all due to perceived injection site irritation. This 9.7% dropout rate due to side effects is lower than the 14.1% dropout rate shown in the original, large-scale XR-NTX RCT.⁶⁸ Aside from injection site irritation, all adverse event experiences decreased over the course of the study. Only 1 study-related serious adverse event, vomiting that precipitated dehydration requiring ER attention, was observed. That said, the multimorbid nature of this population's medical conditions led to multiple ER visits and hospitalizations over the course of the study and also to 1 death. Although these were not determined to be associated with the study medication, they do highlight the well-documented medical frailty and high-utilizing nature of the population as well as the need for acceptable and effective interventions to address alcohol-related harm.^{6,11,12,97}

Participants rated XR-NTX as relatively acceptable and effective (i.e., consistently above the midpoint of the range across time points). Acceptability ratings, however, significantly decreased over the course of the 12-week study. This corroborates clinical observations during the baseline interviews, during which

TABLE 2
Within-Subjects Analyses of Acceptability Outcomes

Variable	Baseline Median (IQR)	12-week follow-up Median (IQR)	Wilcoxon signed-rank statistic (z)	Significance level (P)
Acceptability	9.5 (7, 10)	6 (4, 10)	-3.23	.001
Perceived effectiveness	9 (6, 10)	6 (5, 9.75)	-1.95	.05
Likelihood to continue XR-NTX	10 (10, 10)	9 (3, 10)	-2.92	.003

Note. IQR = interquartile range. Medians and IQRs are presented because data were non-normal and were analyzed using nonparametric statistics. All items were on a 10-point Likert-type scale ranging from 1 (*not at all acceptable/effective/likely*) to 10 (*totally acceptable/effective/likely*).

participants often effusively endorsed XR-NTX prior to their initial injection. It is possible that later ratings reflected participants' more realistic appraisal of XR-NTX. For example, at the end of the study, one participant noted, "I just thought it was going to be a magic cure. And that's not true . . . but it will slow you down, and that's very positive." On the other hand, participants' median rating of the likelihood they would continue to come to appointments to receive XR-NTX injections decreased only 1 point on

the 10-point Likert scale. Further, 63% of participants were interested in continuing with naltrexone after the study ended. Thus, many participants accepted increasingly realistic expectations about the medication's side effects and effectiveness. For some, the pros outweighed the cons. For example, reflecting back on his lack of appetite after the first injection, one participant noted, "I wouldn't eat for days . . . [but] after the initial [dose] my appetite was back. I don't desire to drink as much. And I have little projects

TABLE 3
Adverse and Serious Adverse Events

Event	3 Months prior to baseline (N = 31)	Week 1 (N = 31)	Week 4 (N = 29)	Week 8 (N = 24)	Week 12 (N = 24)
Deaths	0	0	1 ^a	0	0
Hospitalizations	6	2	3	0	2
ER visits	37	4 ^b	1	6	6
Acute serious illness	24	5	4	3	7
SAFETEE, Median (IQR)	6 (4, 11)	7 (3, 9)	6 (3, 9)	5 (2.25, 7.75)	5.5 (2, 7.75)
SAFETEE symptoms (%)					
1. Nausea	21 (70)	23 (76.7)	15 (50)	13 (43.3)	9 (30)
2. Vomiting	18 (60)	14 (46.7)	15 (50)	10 (33.3)	10 (33.3)
3. Diarrhea	19 (63.3)	11 (36.7)	14 (46.7)	8 (26.7)	7 (23.3)
4. Abdominal pain	10 (33.3)	9 (30)	11 (36.7)	7 (23.3)	7 (23.3)
5. Decreased appetite	13 (43.3)	11 (36.7)	6 (20)	4 (13.3)	7 (23.3)
6. Increased appetite	4 (13.3)	8 (26.7)	10 (33.3)	5 (16.7)	4 (13.3)
7. Headache	10 (33.3)	8 (26.7)	9 (30)	6 (20)	5 (16.7)
8. Dizziness	14 (46.7)	11 (36.7)	8 (26.7)	8 (26.7)	8 (26.7)
9. Fatigue	14 (46.7)	18 (60)	14 (46.7)	7 (23.3)	8 (26.7)
10. Nervousness/anxiety	19 (63.3)	15 (50)	16 (53.3)	11 (36.7)	9 (30)
11. Insomnia	17 (56.7)	11 (36.7)	11 (36.7)	9 (30)	6 (20)
12. Somnolence	6 (20)	3 (10)	5 (16.7)	2 (6.7)	4 (13.3)
13. Depression	21 (70)	14 (46.7)	17 (56.7)	11 (36.7)	7 (23.3)
14. Suicidal ideation	6 (20)	3 (10)	3 (10)	2 (6.7)	0 (0)
15. Itching	14 (46.7)	9 (30)	10 (33.3)	6 (20)	6 (20)
16. Rash	5 (16.7)	6 (20)	6 (20)	4 (13)	2 (6.7)
17. Injection site irritation	0 (0)	10 (33.3)	6 (20)	4 (13.3)	5 (16.7)
18. Decreased libido	1 (3.3)	3 (10)	1 (3.3)	2 (6.7)	1 (3.3)
19. Increased libido	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	0 (0)
20. Missed menses ^c	0 (0)	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)
21. Other	8 (26.7)	12 (40)	9 (30)	5 (16.7)	4 (13.3)

Note. IQR = interquartile range. Medians and IQRs are presented because data were non-normal and were analyzed using nonparametric statistics.

^aCause of death was determined to be a subdural hematoma sustained subsequent to an unobserved fall. This SAE was determined to not be related to the study medication and procedures.

^bOnly 1 SAE was determined to be likely due to study medication: 1 individual was taken to the ER for dehydration that resulted from vomiting after the initial injection. Vomiting is an expected adverse event that is known to be associated with the study medication. We worked with the individual to manage this side effect after the initial injection, and the participant had no subsequent problems.

^cAsked of female participants only.

TABLE 4
Within-Subjects Analyses of Alcohol Outcomes ($N = 24$)

Variable	Baseline Median (IQR)	Week 12 Median (IQR)	Wilcoxon signed-rank statistic (z)	Significance level (P)	Effect size (r)
Self-report outcomes					
Typical quantity	19.07 (11.95, 25.33)	14.38 (9.05, 9.62)	-2.87	.004	.41
Peak quantity	29.17 (23.65, 44.46)	19.17 (12.22, 29.03)	-3.00	.003	.43
Frequency	30 (27.25, 30)	25 (18.5, 30)	-2.07	.04	.30
Craving	21 (14, 28.75)	14 (5.5, 24.5)	-3.31	.001	.48
Alcohol problems	21.5 (14.25, 34)	8.5 (4.25, 16.75)	-3.87	<.001	.56
Biological outcomes					
AST	64.5 (34.5, 95.5)	60 (29.25, 90.5)	-.77	.44	.11
ALT	40.5 (30.25, 51.5)	32 (21.5, 56.75)	-.70	.48	.10
GGT	94 (49, 206)	99 (42, 337)	-.61	.54	.09
EtG/creatinine	315,279.45 (10,435.38, 494,656.48)	27,626.15 (1102.00, 283,265.8)	-2.22	.03	.32

Note. AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ -glutamyltranspeptidase; EtG = ethyl glucuronide; IQR = interquartile range.

Alcohol variables were based on self-report in the past 30 days. Typical and peak quantity referred to the number of standard drinks consumed on a typical/the heaviest drinking day in the past 30 days, respectively. Standard drinks were calculated using a blood alcohol level calculator.¹⁰¹ Frequency referred to the number of drinking days in the past 30 days. Craving was measured using the PACS,⁸⁸ and alcohol problems were measured using the SIP-2R.⁸⁹

Medians and IQRs are presented because data were non-normal and were analyzed using nonparametric statistics. Effect size $r = \frac{z}{\sqrt{N}}$, where .1 = small effect, .3 = medium effect, and .5 = large effect.

that I do. I keep my room clean, wash my clothes, do my dishes, and go for long walks.”

Finally, although participants were not asked to change their drinking in any way, they showed significant reductions in alcohol craving, use, and problems. These reductions were corroborated by EtG tests showing statistically significant decreases in the alcohol metabolite in participants’ urine from baseline to the 12-week follow-up. These findings further support the growing literature suggesting that homeless people with alcohol dependence are motivated^{80,98} and, within the context of low-barrier approaches, are capable of setting realistic goals and working towards positive health behavior change.^{26,99}

Limitations

This study did not include a randomized design or control group. The within-subjects design therefore precludes our ability to make causal interpretations regarding study findings. It is possible that other factors besides the intervention accounted for the observed decreases on alcohol outcomes. For example, the Housing First program, from which a portion of the participants were recruited, was previously shown to be associated with reductions in alcohol use and related harm.²⁶ Further, these decreases could reflect statistical artifacts, including the ceiling effect (i.e., participants may not be physically able to increase drinking beyond current levels) or regression to the mean.¹⁰⁰ RCTs that include a control group are necessary to provide a rigorous causal test of the efficacy of XR-NTX and harm reduction counseling in reducing alcohol-related harm among homeless individuals with alcohol dependence.

Second, this study had a small sample size, which can produce false-positive results or overestimate the effect size of an intervention.¹⁰¹ On the other hand, small studies are often underpowered to find statistically significant differences where they exist. In

either case, the current findings are promising but require a stronger confirmatory test in a larger, adequately powered sample.

Given the small sample size as well as the unique demographic features of the sample (e.g., predominantly Native American/Alaska Native/First Nations and white/European American individuals) and the settings (i.e., community-based harm reduction service providers), it remains to be seen whether these findings are generalizable to other settings and to the larger population of homeless people with alcohol dependence. Further, because it is unclear how many participants may have heard about the study via word of mouth, our sample may be subject to self-selection bias. Future, larger studies will be better positioned to determine how generalizable and representative these findings are.

Finally, although it is a key aspect of harm reduction, this study did not include a measure of quality of life. Thus, interpretation of the study findings is limited to a discussion of participants’ reduction in alcohol use and alcohol-related harm. Future studies should include a more comprehensive assessment of harm reduction outcomes.

Conclusions and Future Directions

Larger-scale RCTs have tested the efficacy of XR-NTX combined with use reduction counseling in the general alcohol-dependent population^{67,68} and have tested the feasibility of use reduction supported by XR-NTX among homeless patients.⁷⁷ In contrast, the current study is the first study examining initial aspects of feasibility, acceptability, and alcohol outcomes for XR-NTX as a support for patient-driven harm reduction goals versus provider-driven use reduction or abstinence-based goals. Findings indicated that combined XR-NTX and harm reduction counseling were feasible and acceptable. Additionally, participants evinced significant reductions in alcohol craving, use, and problems from baseline to the 12-week follow-up.

Although promising, these findings should not be overinterpreted. This study was a small, single-arm, open-label study, and larger-scale, well-controlled studies are needed to test treatment efficacy. To this end, an RCT is necessary to provide a more rigorous test of XR-NTX and harm reduction counseling to support reductions in alcohol-related harm as well as reductions in high-cost, publicly funded emergency service utilization among homeless individuals with alcohol dependence. Such research is increasingly important, given current health care reform mandates for inclusion of underserved, high-cost, multimorbid populations and the need to address both these populations' needs and their cost to society.

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AUTHOR CONTRIBUTIONS

Dr. Collins codeveloped the study idea. She led the study and intervention design, conducted the primary statistical analyses, and served as the lead author. She has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Duncan and Smart served as study physicians on the study and contributed to intervention design and interpretation of the findings. Dr. Saxon, Mr. Malone, and Mr. Jackson contributed to study design and interpretation of the findings. Dr. Ries codeveloped the study idea and contributed to study and intervention design as well as interpretation of the findings. All authors critically reviewed, provided edits for, and approved the final article. There is no one else who fulfills these criteria but has not been included as an author.

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