Combining behavioral harm-reduction treatment and extended-release naltrexone for people experiencing homelessness and alcohol use disorder in the USA: a randomised clinical trial

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Summary

Background The rate of alcohol-related mortality in people experiencing homelessness and alcohol use disorder is high and necessitates accessible and effective treatment for alcohol use disorder. However, typical abstinence-based treatments do not optimally engage this population. Recent studies have shown that harm-reduction treatment, which does not require abstinence, but instead aims to incrementally reduce alcohol-related harm and improve health-related quality of life, is acceptable to and effective for this population. The aim of this study was to test the efficacy of combined pharmacological and behavioural harm-reduction treatment for alcohol use disorder (HaRT-A) in people experiencing homelessness and alcohol use disorder.

Methods This randomised clinical trial was done at three community-based service sites (low-barrier shelters and housing programmes) in Seattle (WA, USA). Eligible participants were adults (aged 21–65 years) who met the DSM-IV-TR criteria for alcohol use disorder and who experienced homelessness in the past year. Participants were randomly assigned (1:1:1:1) by permuted block randomisation, stratified by site, to receive either HaRT-A plus intramuscular injections of 380 mg extended-release naltrexone (XR-NTX; HaRT-A plus XR-NTX group); HaRT-A plus placebo injection (HaRT-A plus placebo group); HaRT-A alone (HaRT-A alone group); or community-based supportive services as usual (services-as-usual control group). Patients assigned to receive HaRT-A attended sessions at baseline (week 0) and in weeks 1, 4, 8, and 12. XR-NTX and placebo injections were administered in weeks 0, 4, and 8. During the study, participants, interventionists, and investigators were masked to group assignment in the two injection arms. All participants were invited to follow-up assessments at weeks 4, 8, 12, 24, and 36. The primary outcomes were self-reported alcohol use quantity (ie, alcohol quantity consumed on peak drinking occasion, as measured with the Alcohol Quantity Use Assessment questionnaire) and frequency (measured with the Addiction Severity Index), alcohol-related harm (measured with the Short Inventory of Problems-2R questionnaire), and physical and mental health-related quality of life (measured with the Short Form-12 survey). Using piecewise growth modelling and an intention-to-treat model, we compared the effects of the three active treatment groups with the services-as-usual control group, and the HaRT-A plus XR-NTX group with the HaRT-A plus placebo group, over the 12-week treatment course and during the 24 weeks following treatment withdrawal. Safety analyses were done on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, NCT01932801.

Findings Between Oct 14, 2013, and Nov 30, 2017, 417 individuals experiencing homelessness and alcohol use disorder were screened, of whom 308 were eligible and randomly assigned to the HaRT-A plus XR-NTX group (n=74), the HaRT-A plus placebo group (n=78), the HaRT-A alone group (n=79), or the services-as-usual control group (n=77). Compared with the services-as-usual control group, the HaRT-A plus XR-NTX group showed significant improvements from baseline to 12 weeks post-treatment across four of the five primary outcomes: peak alcohol quantity (linear B –0·48 [95% CI –0·79 to –0·18] p=0·010; full model Cohen's d=–0·68), alcohol frequency (linear B –4·42 [–8·09 to –0·76], p=0·047; full model Cohen's d=–0·16), alcohol-related harm (linear B –2·22 [–3·39 to –1·06], p=0·002; full model Cohen's d=–0·56), and physical health-related quality of life (linear B 0·66 [0·23 to 1·10], p=0·012; full model Cohen's d=0·43). Compared with the services-as-usual control group, the HaRT-A plus placebo group showed significant improvements in three of the five primary outcomes: peak alcohol quantity (linear B –0·41 [95% CI –0·67 to –0·15] p=0·010; full model Cohen's d=–0·23), alcohol frequency (linear B –5·95 [–9·72 to –2·19], p=0·009; full model Cohen's d=–0·13), and physical health-related quality of life (linear B 0·53 [0·09 to 0·98], p=0·050; full model Cohen's d=0·35). Compared with the services-as-usual control group, the HaRT-A alone group showed significant improvements in two of the five primary outcomes: alcohol-related harm (linear B –1·58 [95% CI –2·73 to –0·42] p=0·025; full model Cohen's d=–0·40) and physical health-related quality of life (linear B 0·63 [0·18 to 1·07], p=0·020; full model Cohen's d=0·41). After treatment discontinuation at 12 weeks, the active treatment groups plateaued, whereas the services-as-usual group showed improvements. Thus, during the post-treatment period (weeks 12 to 36), the services-as-usual control group showed greater reductions in alcohol-related harm compared with both the

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HaRT-A plus XR-NTX group (linear B 0·96 [0·24 to 1·67], p=0·028; full model Cohen's d=0·24) and the HaRT-A alone group (linear B 1·02 [0·35 to 1·70], p=0·013; full model Cohen's d=0·26). During the post-treatment period, the services-as-usual control group significantly improved on mental health-related quality of life compared with the HaRT-A alone group (linear B –0·46 [–0·79 to –0·12], p=0·024; full model Cohen's d=–0·28), and on physical health-related quality of life compared with the HaRT-A plus XR-NTX group (linear B –0·42 [–0·67 to –0·17], p=0·006; full model Cohen's d=–0·27), the HaRT-A plus placebo group (linear B –0·42 [–0·69 to –0·15], p=0·009; full model Cohen's d=–0·27), and the HaRT-A alone group (linear B –0·47 [–0·72 to –0·22], p=0·002; full model Cohen's d=–0·31). For all other primary outcomes, there were no significant linear differences between the services-as-usual and active treatment groups. When comparing the HaRT-A plus placebo group with the HaRT-A plus XR-NTX group, there were no significant differences for any of the primary outcomes. Missing data analysis indicated that participants were more likely to drop out in the services-as-usual control group than in the active treatment groups; however, primary outcome findings were found to be robust to attrition. Participants in the HaRT-A plus XR-NTX, HaRT-A plus placebo, and HaRT-A alone groups were not more likely to experience adverse events than those in the services-as-usual control group.

Interpretation **Compared with existing services, combined pharmacological and behavioural harm-reduction treatment resulted in decreased alcohol use and alcohol-related harm and improved physical health-related quality of life during the 12-week treatment period for people experiencing homelessness and alcohol use disorder. Although not as consistent, there were also positive findings for behavioural harm-reduction treatment alone. Considering the non-significant differences between participants receiving HaRT-A plus placebo and HaRT-A plus XR-NTX, the combined pharmacological and behavioural treatment effect cannot be attributed to XR-NTX alone. Future studies are needed to further investigate the relative contributions of the pharmacological and behavioural components of harm-reduction treatment for alcohol use disorder, and to ascertain whether a maintenance treatment approach could extend these positive outcome trajectories.**

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Introduction

Alcohol use disorder is ten times more prevalent in people experiencing homelessness than in the general population,[1–3] and people experiencing homelessness are six to ten times more likely to die of alcohol-attributable causes than the general population.[4,5] Given the disproportionate prevalence of alcohol use disorder and alcohol-related mortality in people experiencing homelessness, it is important to ensure that this population has access to effective treatment. However, currently available treatments are not highly engaging or effective for this population,[6–11] and the typical requirements of high-intensity, often inpatient, treatment, combined with the expectation of achieving alcohol abstinence, pose the most formidable barriers.[12–14] Our previous studies in this population showed that few participants (5–11%) experiencing homelessness and alcohol use disorder in community-based service settings (ie, shelters, supportive housing, neighbourhood clinics, and drop-in centres) aspired to achieve abstinence.[15,16] Instead, participants preferred lower intensity approaches that do not require abstinence, with patient-driven goal-setting and a focus on health-related quality of life.[12,14,17]

Accordingly, our team, in collaboration with community-based agencies, has developed a behavioural harm-reduction treatment for alcohol use disorder (HaRT-A), consisting of low-intensity counselling that does not require abstinence, and that supports patient-driven goals for reducing alcohol-related harm and improving health-related quality of life.[18–20] In a previous 3-month randomised controlled trial, this approach was associated with high engagement, and a reduction in alcohol use and alcohol-related harm was observed when compared with a services-as-usual control condition.[18] However, additional studies are needed to investigate the longer term effects of this behavioural treatment approach, and whether its effects could be enhanced with pharmacotherapy.

One medication that is well positioned to support alcohol-related harm reduction is extended-release naltrexone (XR-NTX; Vivitrol; Alkermes, Waltham, MA, USA), a long-acting opioid receptor antagonist that is safe for use in active drinkers with alcohol use disorder.[21] In previous studies, XR-NTX has shown efficacy in reducing alcohol craving and use, and alcohol-related harm,[22–25] and has engendered higher treatment adherence than daily oral medication.[26] More recently (2015), our single-arm pilot study involving 31 people experiencing homelessness and alcohol use disorder showed that XR-NTX combined with HaRT-A was feasible and acceptable in this population, and participants showed significant decreases in alcohol craving, alcohol use, and alcohol-related harm.[19]

The present, four-arm, parallel-group, randomised controlled trial comprised a 12-week active treatment phase, during which we tested the efficacy of combining

Research in context

Evidence before this study

Abstinence-based treatment for alcohol use disorder is not a highly engaging or an effective strategy for people experiencing homelessness. By contrast, harm-reduction approaches are more patient centred and forgo an absolute focus on alcohol abstinence to instead support decreased alcohol-related harm and an improved quality of life.

We searched PubMed and Google Scholar on Jan 5, 2020, using the search terms "harm reduction treatment", "homelessness", and "alcohol use disorder". We searched for clinical trials published between Jan 1, 2000, and Jan 5, 2020, with no language restrictions. We found two relevant clinical trials. One previous randomised clinical trial involving 168 people experiencing homelessness showed significant improvements in outcomes at 3 months in those treated with behavioural harm-reduction treatment for alcohol use disorder (HaRT-A) compared with those who received community-based services as usual. A single-arm pilot study involving 31 people experiencing homelessness indicated that combining HaRT-A and extended-release naltrexone (XR-NTX) was promising in reducing alcohol use and alcohol-related harm.

Added value of the study

Our results support the positive treatment effects of HaRT-A for alcohol use disorder that were shown in the previous randomised controlled trial. This study adds to the existing research by showing that combining pharmacological and behavioural harm-reduction treatment can synergistically strengthen the effects of these treatments on both alcohol-related outcomes and physical health-related quality of life. However, the findings from double-blind comparisons showed no significant differences between participants who received XR-NTX versus placebo injections. Therefore, the positive outcomes associated with the combined treatment cannot be ascribed to the pharmacological intervention alone.

Implications of all the available evidence

Over the past two decades, harm-reduction approaches have emerged as important means of engaging people experiencing homelessness and alcohol use disorder, who are often marginalised by or excluded from alcohol use disorder treatment settings that aim for complete abstinence. The present study showed that removing typical barriers to alcohol use disorder treatment, by providing treatment in community-based settings, respecting patient autonomy, and not requiring abstinence, engenders strong study engagement and retention in a population long considered by medical professionals to be difficult to treat. Additionally, our findings indicated that combined pharmacological and behavioural harm-reduction treatment is efficacious and that, even alone, behavioural harm-reduction treatment confers benefits. These positive treatment effects plateaued after treatment withdrawal, which suggests the need for a maintenance approach in this population rather than a short-term brief intervention approach. However, when harm-reduction treatment is integrated into community-based settings, where other services are provided, visits can be brief and distributed up to a month apart. Future larger-scale studies are needed to investigate whether this combined pharmacological and behavioural harm-reduction treatment approach can save on cost and effort while increasing treatment reach.

HaRT-A and XR-NTX in people experiencing homelessness and alcohol use disorder, and a 24-week follow-up period, during which we tested for delayed treatment effects or decay after withdrawal.[20] HaRT-A plus XR-NTX, HaRT-A plus placebo, and HaRT-A alone were compared with a community-based services-as-usual control group on peak alcohol quantity (ie, number of standard alcoholic drinks consumed on the heaviest drinking day in the past month), alcohol frequency, alcohol-related harm, and physical and mental health-related quality of life. We hypothesised that the three active treatment groups would show greater decreases in alcohol frequency, peak alcohol quantity, and alcohol-related harm, and increases in physical and mental health-related quality of life, when compared with the services-as-usual control group. In the double-blinded groups, we expected that the HaRT-A plus XR-NTX group would show greater decreases in alcohol frequency, peak alcohol quantity, and alcohol-related harm, and increases in physical and mental health-related quality of life than the HaRT-A plus placebo group.

Methods

Study design and participants

Details on the study rationale, design, and methods are available elsewhere,[20] and the pretrial protocol is in the appendix (p 2).

See Online for appendix

This randomised clinical trial was done at three community-based service sites (shelters and housing programmes) in Seattle (WA, USA), which serve people experiencing homelessness and alcohol use disorder. Participants (aged 21–65 years) were included in the study if they fulfilled at least three DSM-IV-TR criteria for alcohol use disorder (ie, alcohol dependence), according to the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition; had experienced homelessness in the past year; were receiving services as usual at the three community-based service sites; and agreed to use an adequate form of birth control (if female and of childbearing age).[27] Exclusion criteria were refusal or inability to consent (established by use of the University of California, San Diego Brief Assessment of Capacity to Consent);[28] presenting a risk to the safety and security of other service-site clients or staff; a known

sensitivity or allergy to NTX or XR-NTX; concurrent participation in a clinical study involving an unapproved, experimental drug; concurrent participation in other harm-reduction treatment studies done by the same team (this exclusion criterion was added after two similar counselling studies were initiated in overlapping service settings); concurrent treatment with NTX or XR-NTX; being pregnant or nursing; a suicide attempt in the past year; renal insufficiency (ie, a serum creatinine concentration of >2 mg/dL); a current opioid use disorder (ie, opioid dependence according to DSM-IV-TR criteria); aspartate aminotransferase and alanine aminotransferase concentrations that were more than five times the upper limit of normal; a clinical diagnosis of decompensated liver disease; or any other condition that was deemed by the medical director of the trial to make participation clinically unsafe.

Procedures were approved by the institutional review board at the University of Washington (Seattle, WA, USA). All participants provided written informed consent before baseline assessments and any treatments were administered.[20]

Randomisation and masking

Eligible participants were randomly assigned (1:1:1:1) by use of a computer-generated, permuted block randomisation schema, stratified by site, to either the HaRT-A plus XR-NTX group, HaRT-A plus placebo group, HaRT-A alone group, or supportive services-as-usual control group. Randomisation was done by the Harborview Medical Center Investigational Drug Program independently from research staff, who were masked to the HaRT-A plus XR-NTX and HaRT-A plus placebo groups until all participant procedures had been completed. At the baseline appointment (week 0), research staff informed participants of their allocated treatment group (HaRT-A plus blinded injection groups, HaRT-A alone group, or services-as-usual control group).

Procedures

Research staff typically recruited participants in the early morning (ie, between 0700 h and 1000 h) before they left their community-based sites for the day. Trust-building was paramount. Research staff offered participant-preferred, non-alcoholic refreshments, used a community-aligned and compassionate approach, and indicated that the study treatment was participant driven and did not require abstinence or alcohol use reduction. Service staff often introduced researchers to potential participants, and recruitment later on in the trial was augmented by the participants' own independent endorsement of the project to their social networks.

Potential participants were screened using the aforementioned criteria. Those who met initial criteria were provided with detailed study information and offered the opportunity to ask questions. Participants provided written, informed consent, and baseline measures were administered.[20]

Participants in the three active treatment groups (HaRT-A plus XR-NTX, HaRT-A plus placebo, and HaRT-A alone groups) attended five, manualised HaRT-A sessions, delivered by study physicians or nurses (see manual in appendix p 39 and the published protocol[20]) in weeks 0, 1, 4, 8, and 12. The aim of HaRT-A is to help people reduce alcohol-related harm and improve health-related quality of life without requiring, prescribing, or favouring alcohol abstinence as a treatment goal. Study physicians or nurses used a compassionate, pragmatic, and participant-driven approach when delivering the following treatment components: (1) feedback on results of physical exams and laboratory tests, and their implications for physiological alcohol-related harm; (2) collaborative tracking of participant-preferred alcohol-related outcomes; (3) elicitation of harm-reduction and health-related quality of life goals; and (4) discussion of safer drinking strategies. Participants in the HaRT-A plus XR-NTX group and HaRT-A plus placebo group also received information about the medication and the injections in weeks 0, 4, and 8.[20] The XR-NTX (380 mg) and placebo doses were provided by Alkermes, and were administered intramuscularly by study nurses and physicians.

Participants in the services-as-usual control group received the community-based sites' supportive services, including emergency shelter or permanent supportive housing; intensive case management; basic nursing or medical care; referral to external service providers; and assistance with basic needs.

Participants in the active treatment groups attended abbreviated safety and goals check-ins at weeks 0 and 1. All participants attended follow-up assessments at weeks 4, 8, 12, 24, and 36. Only data collected at the baseline and weeks 4, 8, 12, 24, and 36 were used for primary analyses. Participants were paid US$20 for each assessment they attended. Research staff provided appointment reminders in person at the community-based sites where participants regularly received services; via detailed tracking information (eg, addresses, mobile phone or telephone numbers, email addresses, social network handles, contacts for service providers, or through friends and family members); and during community walk-throughs (ie, parks, particular street corners, or other service settings).

Outcomes

The primary outcomes were self-reported peak alcohol quantity, alcohol frequency, alcohol-related harm, and physical and mental health-related quality of life.

The Alcohol Quantity Use Assessment is a standard alcohol quantity questionnaire assessing alcohol use on a peak drinking day in the past month.[29] This tool was developed in a previous study involving people experiencing homelessness and alcohol use disorder,[30] and was refined in a pilot study[19] to better capture alcohol use that does not conform to typical standard drink

measures (eg, sharing bottles and consuming beverages from large-volume containers, such as 16 ounce, 24 ounce, and 40 ounce bottles and cans) or beverage type (eg, high-gravity malt liquor, and non-beverage alcohol). The "Alcohol and Drugs" section of the Addiction Severity Index[31] was used to assess frequency of alcohol use and other substance use over the past 30 days. The Short Inventory of Problems-2R is a 15-item Likert-type questionnaire that was used to measure social, occupational, and psychological alcohol-related harm over the past 30 days.[32] The Short Form-12 survey[33] was used to document physical health-related quality of life (ie, evaluation of general health, physical functioning, bodily pain, and ability to fulfil daily tasks or roles in light of physical limitations) and mental health-related quality of life (ie, sense of vitality, social functioning, ability to fulfil daily tasks or roles given emotional problems, and mental health), with higher scores indicating greater health-related quality of life.[34]

Secondary outcomes included an alcohol use biomarker, ethyl glucuronide[35] (ie, urinary ethyl glucoronide-to-creatinine ratio), and treatment manual adherence and competence. Treatment manual adherence and competence was assessed with an adapted version of the COMBINE study Medical Management Adherence Checklist and coding schema.[36,37] The measure comprised a count of required components for adherence and six dimensions of competence (ie, informativeness, direction, warmth, authoritativeness, avoidance of non-manualised components, and overall competence), on which a score of 0 indicates an "absence of this characteristic" and a score of 6 indicates "very high levels of this characteristic, top 10% of providers".

Study interventionists used the Systematic Assessment for Treatment Emergent Effects interview[38,39] to assess adverse events known to be associated with XR-NTX (eg, nausea, vomiting, diarrhoea, abdominal pain, decreased or increased appetite, headache, dizziness, fatigue, nervousness or anxiety, insomnia or somnolence, depressive symptoms, suicidal ideation, itching, rash, injection site irritation, missed menses, or increased or decreased libido). Adverse events and serious adverse events (ie, emergency department visits, admissions to hospital, or suicide attempts) were self reported and recorded in participant records. Also planned in the protocol are analyses of potential mediators of the hypothesized treatment effects and treatment effects on publicly funded service costs (see protocol in appendix [p 29] for the additional analysis plan). These findings will be presented elsewhere.

Statistical analysis

Assuming sample size of 300 participants, an α level of 0·05, and 20% loss to follow-up, a priori analyses indicated power (β–1) of 0·99 to detect a medium effect (γ=0·2; approximately corresponding to a Cohen's d of 0·63[40]) of HaRT-A plus XR-NTX when compared with the services-as-usual control group, and 0·92 to detect small-to-medium effects (γ=0·15) of HaRT-A plus placebo and HaRT-A alone compared with the services-as-usual control group. With a sample size of 150 participants, power was adequate (β–1=0·83) to detect a medium effect of HaRT-A plus XR-NTX compared with HaRT-A plus placebo.

In preliminary data analyses, descriptive analyses documented completion, attrition, and baseline characteristics of participants. Initially, logistic generalised estimating equations with robust standard errors were used to test potential associations of missingness with treatment group assignment, sociodemographic factors, and baseline outcomes. Sensitivity analyses were used to ascertain the robustness of treatment effects to plausible non-ignorable missingness mechanisms that could cause bias.[41–43] The use of direct maximum likelihood estimation in the primary analyses also served to minimise bias that would otherwise have been introduced if simple imputation or methods that result in listwise data deletion had been used.[44,45]

There were two parts to the treatment efficacy analysis. First, we tested the efficacy of the three active treatment groups compared with the services-as-usual control group. Second, we compared primary outcomes between the HaRT-A plus XR-NTX group and HaRT-A plus placebo group. This two-part design allowed us to dismantle active treatment components and thereby detect potential placebo effects of both the administration of an injection and attention from a medical professional, which have been observed in previous studies.[46,47]

Piecewise growth modelling with Mplus 8.3 was used to test the effects of treatment on primary outcome trajectories over time.[48] Piecewise growth models are latent growth curve models that allow for varying sequential stage-based growth profiles[49] to characterise different phases of development in a trajectory and thus detect potential treatment delays or decay.[50] Primary alcohol-related outcomes (peak alcohol quantity, alcohol frequency, and alcohol-related harm) and health-related quality of life (physical and mental health) outcomes measured at each timepoint were indicators of the intercept (ie, baseline), the linear, and, as needed, quadratic slopes (ie, change in outcomes over time). Treatment group was the primary predictor of the slope.

Regression coefficients for growth models that include quadratic functions are not easily interpretable. Therefore, we also calculated Cohen's d measures of effect size, which consider both linear and quadratic effects to help interpret the unstandardised coefficient effects.[51] Although such effect sizes should always be interpreted with caution, we refer to the conventional definitions of small (Cohen's d=0·2), medium (Cohen's d=0·5), and large (Cohen's d=0·8) effect sizes in the reporting of the results.[52]

As the ethyl glucuronide-to-creatinine ratio was zero-inflated and overdispersed, it did not conform to distributional assumptions for growth modelling. Therefore, we used the cross-sectional, negative

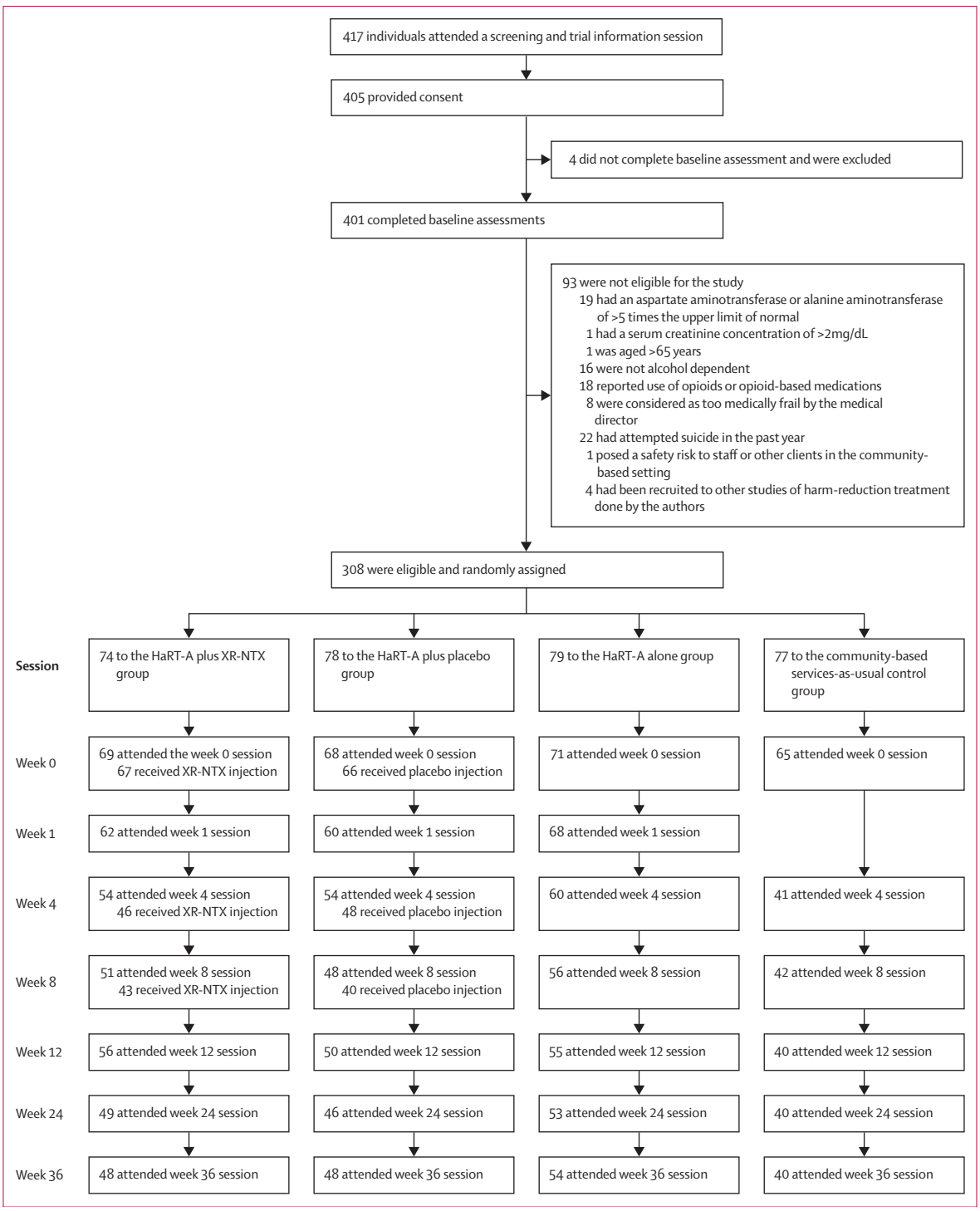

Figure 1: **Trial profile**
On weeks 0, 4, and 8 in the groups eligible to receive injections of either XR-NTX or placebo, some individuals attended the assessment sessions but not the treatment sessions, and others attended both sessions but chose not to receive injections. HaRT-A=behavioural harm-reduction treatment for alcohol use disorder. XR-NTX=extended-release naltrexone.

binomial logit hurdle model to test treatment effects on the ethyl glucuronide-to-creatinine ratio at weeks 12 and 36, while controlling for baseline ethyl glucuronide-to-creatinine ratios. Descriptive analyses documented the degree of treatment manual adherence and competence.

Descriptive analyses, robust logistic generalised estimating equations, and χ^2 analyses probed potential differences in adverse and serious adverse events between the active treatment groups and the services-as-usual control group during the treatment period. We did not adjust for multiple comparisons.

A data safety monitoring board met on a biannual basis to monitor study progress and patient safety. Patient safety was reviewed in sessions closed to investigators. The board permitted additional recruitment within the study period, given that attrition was greater than accounted for in power analyses. We recruited eight additional people.

We used Mplus version 8.3 and Stata SE version 16.1 to analyse the data.

This trial is registered with ClinicalTrials.gov, NCT01932801.

Role of the funding source

Neither the funder of the study (the National Institute on Alcohol Abuse and Alcoholism) nor the company that donated the placebo and NTX doses (Alkermes) had any role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 14, 2013, and Nov 30, 2017, 417 individuals experiencing homelessness attended an initial trial information session, of whom 405 (97%) consented to participate in the trial. Of those who consented, 308 (76%) individuals were eligible and randomly assigned to the HaRT-A plus XR-NTX group (n=74), the HaRT-A plus placebo group (n=78), the HaRT-A alone group (n=79), or the services-as-usual control group (n=77; figure 1). Data collection was completed on Oct 11, 2018. The characteristics of participants by treatment group are shown in table 1. On average, 161 (70%) of 231 participants in the three active treatment groups completed their assigned 12-week treatment course, including 56 (76%) of 74 participants in the HaRT-A plus XR-NTX group. By contrast, only 40 (52%) of 77 participants in the services-as-usual control group attended the week 12 assessment.

Participants in the services-as-usual control group were more likely to have missing data subsequent to baseline than participants in the HaRT-A plus XR-NTX group and the HaRT-A alone group (p<0·014). Neither sociodemographic factors (p>0·052) nor baseline outcomes (p>0·18) were associated with a greater likelihood of missing data. As treatment group was the predictor in the primary analyses, the missing at random assumption could plausibly be satisfied.[44] Sensitivity analyses also indicated robustness of primary analyses to the data missingness mechanisms tested, as evidenced by the low variation in associated effect size (see appendix p 83).

	HaRT-A plus XR-NTX (n=74)	HaRT-A plus placebo (n=78)	HaRT-A alone (n=79)	Services-as-usual control (n=77)
Age, years	49·27 (9·11)	46·55 (10·46)	49·38 (7·35)	47·51 (9·50)
Sex assigned at birth				
Female	11 (15%)	10 (13%)	13 (16%)	16 (21%)
Male	63 (85%)	68 (87%)	66 (84%)	61 (79%)
Hispanic or Latinx ethnicity	6 (8%)	7 (9%)	11 (14%)	10 (13%)
Race				
American Indian or Alaska Native	11 (15%)	8 (10%)	12 (15%)	18 (23%)
Black or African American	32 (43%)	27 (35%)	22 (28%)	14 (18%)
Native Hawaiian or Pacific Islander	1 (1%)	1 (1%)	0	1 (1%)
White or European American	20 (27%)	24 (31%)	24 (30%)	28 (36%)
More than one race*	8 (11%)	13 (17%)	10 (13%)	14 (18%)
Other	2 (3%)	5 (6%)	11 (14%)	2 (3%)
Cigarette smoking	61 (82%)	68 (87%)	60 (76%)	66 (86%)
Polysubstance use in the past month†	59 (80%)	63 (81%)	57 (73%)	60 (78%)
Concurrent substance-use treatment attendance	4 (6%)	2 (3%)	6 (8%)	1 (1%)

Data are mean (SD) or n (%). 295 (96%) of 308 participants met criteria for alcohol dependence with physiological dependence. Totals might not add up to 100% due to rounding error. HaRT-A=behavioural harm-reduction treatment for alcohol use disorder. XR-NTX=extended-release naltrexone. *Of 45 participants who identified with "more than one race", 31 (69%) reported American Indian or Alaska Native heritage; thus, 81 (26%) of the overall sample reported some American Indian or Alaska Native heritage, representing 30 American Indian, Alaska Native, or First Nations tribes and communities. †In the whole study sample, polysubstance use in the past month included cannabis (206 [67%]), crack cocaine or powder cocaine (89 [29%]), methamphetamine or amphetamine (47 [15%]), non-heroin opioids (30 [10%]), benzodiazepine (ten [3%]), and heroin (seven [2%]), and nine (3%) of the study sample reported using inhalants, barbiturates, 3,4-methylenedioxymethamphetamine, or psychedelics.

Table 1: **Baseline characteristics of participants by treatment group**

Compared with the services-as-usual control group, participants in the HaRT-A plus XR-NTX group showed significant improvements in four of the five primary outcomes during the 12-week treatment period (see figure 2 for model-estimated values, table 2 for raw values, and appendix p 86 for full model statistics, including intercept and quadratic parameters as applicable). Compared with the services-as-usual control group, the HaRT-A plus XR-NTX group showed a medium-to-large effect for reductions in peak alcohol quantity (linear B –0·48 [95% CI –0·79 to –0·18], p=0·010; full model Cohen's d=–0·68), medium effects for alcohol-related harm reduction (linear B –2·22 [–3·39 to –1·06], p=0·002; full model Cohen's d=–0·56), and physical health-related quality of life improvement (linear B 0·66 [0·23 to 1·10], p=0·012; full model Cohen's d=0·43), and a small effect for reduction in alcohol frequency (linear B –4·42 [–8·09 to –0·76], p=0·047; full model Cohen's d=–0·16). There was no significant effect for the HaRT-A plus XR-NTX group in mental health-related quality of life (linear B 1·69 [0·12 to 3·27], p=0·076; full model Cohen's d=0·45).

Compared with the services-as-usual control group, there were significant treatment effects for three of the five primary outcomes for the HaRT-A plus placebo group (figure 2; see appendix pp 85–89 for full model statistics).

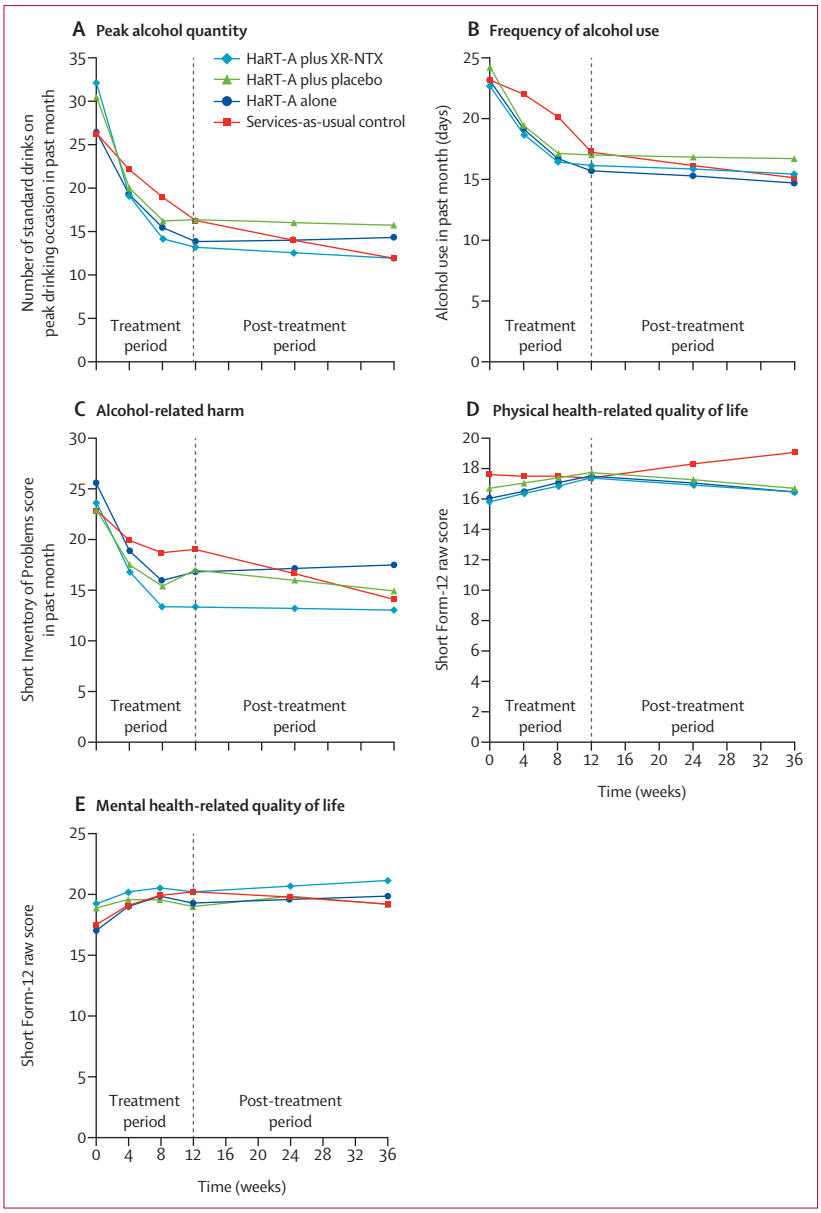

Figure 2: **Estimated marginal means for outcome variables over the 36-week follow-up period**
(A) Peak alcohol quantity (defined as the number of standard alcoholic drinks consumed on the heaviest drinking day in the past month), measured by use of the Alcohol Quantity Use Assessment questionnaire. (B) Frequency of alcohol use measured by use of the Addiction Severity Index. (C) Alcohol-related harm in the past month, measured by use of the Short Inventory of Problems questionnaire. (D) Physical health-related quality of life score, and (E) mental health-related quality of life score, measured by use of the Short Form-12 survey. HaRT-A=behavioural harm-reduction treatment for alcohol use disorder. XR-NTX=extended-release naltrexone.

Participants in the HaRT-A plus placebo group showed small-to-medium effects for physical health-related quality of life improvement at the end of treatment compared with the services-as-usual control group (linear B 0·53 [95% CI 0·09 to 0·98], p=0·050; Cohen's d=0·35). The HaRT-A plus placebo group also showed a small effect for reduction in peak alcohol quantity (linear B –0·41 [–0·67 to –0·15], p=0·010; Cohen's d=–0·23), and alcohol frequency (linear B –5·95 [–9·72 to –2·19], p=0·009; Cohen's d=–0·13) compared with the services-as-usual control group. There were no significant effects for the HaRT-A plus placebo group in alcohol-related harm (linear B –0·82 [–1·89 to 0·25], p=0·21; full model Cohen's d=–0·21), or mental health-related quality of life (linear B 0·47 [95% CI –1·17 to 2·10], p=0·64; full model Cohen's d=0·19).

When comparing the HaRT-A alone group to the services-as-usual control group, there were small-to-medium effects for a reduction in alcohol-related harm (linear B –1·58 [95% CI –2·73 to –0·42], p=0·025; Cohen's d=–0·40) and an improvement in physical health-related quality of life (linear B 0·63 [0·18 to 1·07], p=0·020; Cohen's d=0·41). There were no significant effects for the HaRT-A alone group in peak alcohol quantity (linear B –0·23 [–0·52 to 0·06], p=0·19; full model Cohen's d=–0·25), alcohol frequency (linear B –4·12 [–7·88 to –0·36], p=0·072; full model Cohen's d=–0·18), or mental health-related quality of life (linear B 0·92 [–0·77 to 2·62], p=0·37; full model Cohen's d=0·53).

After treatment discontinuation at 12 weeks, the active treatment groups plateaued, whereas the services-as-usual group showed improvements. Thus, during the post-treatment period (weeks 12–36), the services-as-usual control group showed greater reductions in alcohol-related harm compared with both the HaRT-A plus XR-NTX group (linear B 0·96 [95% CI 0·24 to 1·67], p=0·028; full model Cohen's d=0·24) and the HaRT-A alone group (linear B 1·02 [0·35 to 1·70], p=0·013; full model Cohen's d=0·26). During the post-treatment period, the services-as-usual control group significantly improved on mental health-related quality of life compared with the HaRT-A alone group (linear B –0·46 [–0·79 to –0·12], p=0·024; full model Cohen's d=–0·28), and on physical health-related quality of life compared with the HaRT-A plus XR-NTX group (linear B –0·42 [–0·67 to –0·17], p=0·006; full model Cohen's d=–0·27), the HaRT-A plus placebo group (linear B –0·42 [–0·69 to –0·15], p=0·009; full model Cohen's d=–0·27), and the HaRT-A alone group (linear B –0·47 [–0·72 to –0·22], p=0·002, full model Cohen's d=–0·31).

In a dismantling design feature, we isolated the effect of XR-NTX alone by comparing alcohol and quality-of-life outcomes in the double-blinded HaRT-A plus XR-NTX group and the HaRT-A plus placebo group. The models showed no significant group differences in any of the five primary outcomes (see appendix p 91 for model and parameter statistics).

Considering secondary outcomes, participants in the HaRT-A plus XR-NTX group were nearly three times more likely to have undetectable ethyl glucuronide concentrations at the 12-week follow-up visit than those in the services-as-usual control group (odds ratio [OR] 2·77 [95% CI 1·01–7·58], p=0·048). The odds of having detectable ethyl glucuronide concentrations did not differ significantly between the HaRT-A plus XR-NTX group and services-as-usual control group at week 36 (1·60 [0·57–4·49], p=0·37; table 2).

	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36
Peak alcohol quantity*						
HaRT-A plus XR-NTX	32·02 (1·70)	18·18 (2·41)	13·56 (3·15)	12·81 (3·30)	13·14 (3·91)	12·46 (3·36)
HaRT-A plus placebo	32·15 (1·74)	21·33 (2·32)	17·21 (2·44)	19·09 (2·28)	18·01 (3·04)	16·30 (2·73)
HaRT-A alone	25·95 (1·79)	18·97 (2·76)	15·85 (2·56)	12·92 (3·18)	13·43 (3·78)	14·31 (3·46)
Services-as-usual control	27·37 (1·98)	22·40 (2·23)	20·45 (2·41)	16·80 (3·16)	16·77 (3·36)	13·94 (3·42)
Alcohol use frequency, days per month†						
HaRT-A plus XR-NTX	23·08 (7·55)	17·87 (10·85)	17·18 (11·83)	15·15 (11·33)	16·20 (11·82)	15·65 (11·58)
HaRT-A plus placebo	24·63 (8·02)	18·81 (11·45)	18·67 (11·22)	18·68 (11·45)	18·94 (11·68)	16·88 (11·12)
HaRT-A alone	23·42 (8·63)	17·43 (10·91)	18·00 (11·80)	15·32 (11·97)	13·04 (11·66)	15·02 (11·75)
Services-as-usual control	23·35 (8·66)	22·37 (10·46)	20·83 (10·51)	17·15 (10·98)	17·93 (11·91)	14·59 (11·51)
Alcohol-related harm score‡						
HaRT-A plus XR-NTX	23·70 (12·03)	15·33 (11·59)	13·98 (12·48)	12·15 (11·25)	12·76 (12·97)	13·35 (12·50)
HaRT-A plus placebo	23·00 (12·05)	17·00 (11·43)	15·52 (12·85)	16·08 (13·20)	15·89 (13·88)	13·19 (13·40)
HaRT-A alone	25·69 (10·25)	17·98 (12·51)	17·15 (11·97)	15·50 (13·03)	17·90 (16·19)	16·87 (14·54)
Services-as-usual control	22·70 (12·05)	21·39 (13·67)	18·31 (14·15)	21·00 (14·06)	16·15 (11·99)	16·36 (13·62)
Mental health-related quality of life score§						
HaRT-A plus XR-NTX	17·21 (4·63)	18·90 (5·77)	20·10 (5·32)	19·63 (4·09)	19·29 (4·98)	20·10 (4·87)
HaRT-A plus placebo	18·95 (4·80)	20·38 (4·92)	19·80 (4·88)	20·60 (5·81)	20·04 (5·30)	21·88 (5·30)
HaRT-A alone	17·45 (4·75)	19·44 (5·20)	19·11 (5·64)	20·55 (5·80)	19·47 (5·31)	19·41 (5·64)
Services-as-usual control	18·86 (5·50)	19·37 (5·93)	18·77 (7·08)	18·10 (6·17)	19·77 (4·52)	19·51 (5·42)
Physical health-related quality of life score§						
HaRT-A plus XR-NTX	15·64 (4·52)	17·10 (4·66)	17·31 (4·64)	17·63 (4·73)	17·15 (5·01)	16·75 (5·31)
HaRT-A plus placebo	16·78 (4·32)	17·16 (4·58)	17·74 (4·99)	17·96 (5·02)	16·94 (4·92)	17·46 (5·31)
HaRT-A alone	15·91 (4·67)	16·17 (4·92)	16·11 (4·83)	16·86 (5·20)	17·09 (5·23)	15·98 (5·35)
Services-as-usual control	17·25 (4·80)	17·66 (5·91)	17·23 (6·17)	16·73 (5·67)	17·26 (5·40)	18·23 (4·57)
Number of negative ethyl glucuronide tests						
HaRT-A plus XR-NTX	19/74 (25·7%)	18/54 (33·3%)	20/50 (40·0%)	21/55 (38·2%)	13/48 (27·1%)	16/47 (34·0%)
HaRT-A plus placebo	20/78 (25·6%)	10/53 (18·9%)	10/47 (21·3%)	7/50 (14·0)%	10/47 (21·3%)	10/48 (20·8%)
HaRT-A alone	24/78 (30·8%)	15/58 (25·9%)	15/55 (27·3%)	24/56 (42·9%)	14/52 (26·9%)	13/52 (25·0%)
Services-as-usual control	12/77 (15·6%)	7/39 (18·0%)	10/41 (24·4%)	7/39 (18·0%)	11/40 (27·5%)	8/38 (21·1%)

Data are mean (SD) or n/N (%). HaRT-A=behavioural harm-reduction treatment for alcohol use disorder. XR-NTX=extended-release naltrexone. *Measured with the Alcohol Quantity Use Assessment questionnaire, and defined by the number of standard (11·671 g) alcoholic drinks consumed on the heaviest drinking day in the past month; means and SDs were exponentiated back to their original scale following the log transformation applied for primary analyses. †Measured with the Addiction Severity Index. ‡Measured with the Short Inventory of Problems-2R questionnaire. §Measured with the Short Form-12 survey.

Table 2: **Raw descriptive statistics for outcome variables by time and treatment group**

Participants in the HaRT-A alone group were over four times more likely to have undetectable levels of ethyl glucuronide at the 12-week follow-up visit than those in the services-as-usual control group (OR 4·02 [95% CI 1·46–11·11], p=0·0072). The odds of having detectable ethyl glucuronide concentrations did not differ significantly between the HaRT-A alone group and services-as-usual control group at week 36 (1·16 [0·40–3·34], p=0·783).

There were no significant differences in the odds of having detectable ethyl glucuronide concentrations between the HaRT-A plus placebo group and the services-as-usual control group at the 12-week (OR 0·91 [95% CI 0·28–2·95], p=0·88) or 36-week (1·09 [0·36–3·33], p=0·87) follow-up visits.

On average, study physicians or nurses delivered 93% (SD 0·11) of expected treatment components per session, and were scored as showing between "acceptable" and "high competence" (mean scores ranged from 4·28 to 4·85) across competence dimensions.

There were no significant differences in the likelihood of adverse events and potential side-effects of XR-NTX between the HaRT-A plus XR-NTX group and the HaRT-A plus placebo group, apart from for itching, which was reported by a significantly lower proportion of patients in the HaRT-A plus XR-NTX group than the HaRT-A plus placebo group (OR 0·35 [95% CI 0·17–0·72], p=0·004) after treatment exposure.

As expected in a population experiencing chronic homelessness and alcohol dependence, participants had serious adverse events during the study period, including 66 participants reporting a hospital admission, three participants reporting a suicide attempt, and three participant deaths (table 3). Only one hospital admission was associated with the study procedures. Difficulties ambulating due to an injection site haematoma

	HaRT-A plus XR-NTX (n=68)	HaRT-A plus placebo (n=66)	HaRT-A alone (n=71)	Services as usual (n=64)
Death*	0	0	0	3 (5%)
Hospital admission†	17 (25%)	19 (29%)	17 (24%)	13 (20%)
Emergency department visit*†	42 (62%)	44 (67%)	44 (62%)	38 (59%)
Suicide attempt*†	1 (1%)	1 (2%)	1 (1%)	0

Data are n (%). HaRT-A=behavioural harm-reduction treatment for alcohol use disorder. XR-NTX=extended-release naltrexone. *Considered to be unrelated to the study procedures. †Self-report data were available for 269 participants.

Table 3: **Serious adverse events recorded during the trial**

led to an emergency department visit, which precipitated alcohol withdrawal and subsequent hospital admission. This participant had a full recovery and completed all follow-up assessments. χ^2 tests of independence indicated that there were no significant differences between active treatment groups and the services-as-usual control group in terms of the number of hospital admissions (χ^2 [three degrees of freedom]=1·28, p=0·73) and emergency department visits (χ^2 [three degrees of freedom]=0·78, p=0·85). Given the low cell size (ie, the low numbers of participants in each group who had serious adverse events), we were unable to test for differences in the number of suicide attempts and deaths between the active treatment groups and the services-as-usual control group.

Discussion

The results of our study indicate that combining HaRT-A with XR-NTX is engaging and efficacious for people experiencing homelessness and alcohol use disorder. Consistent with our hypotheses, participants who received HaRT-A plus XR-NTX had the most consistent positive outcomes when compared with those who received only community-based services as usual, with improvements in five of six primary and secondary alcohol-related outcomes and health-related quality of life outcomes over the 12-week treatment period. Participants in the HaRT-A plus placebo and HaRT-A alone groups showed significant improvements in three of the six primary and secondary outcomes when compared with the services-as-usual control group. In the active treatment groups, treatment effects plateaued but were maintained over the 24-week post-treatment period. Contrary to our hypotheses, however, there was no significant difference in outcomes between the HaRT-A plus XR-NTX group and the HaRT-A plus placebo group. Therefore the positive and significant effects observed in the HaRT-A plus XR-NTX group are not attributable to the medication effect alone.

The results of our study indicated strong engagement. Of those approached, 405 (97%) of 417 individuals were interested in participating in the trial. Retention was particularly high in the HaRT-A plus XR-NTX group (56 [76%] of 74 participants attended the final week 12 treatment session). By contrast, just over half of participants (40 [52%] of 77) in the services-as-usual control group attended the week 12 assessment session. This strong engagement is in direct contrast to that observed in the only other previous randomised controlled trial of XR-NTX in this population, in which 200 (93%) of 215 individuals who were approached refused participation, and only one participant returned for follow-up visits after the initial injection.[53] The authors explained that a key reason for this lack of engagement was the unwillingness of participants to change their drinking habits. The present study removed this barrier by supporting participants to develop their own treatment goals.

The results of our study provide additional support for the efficacy of XR-NTX in alcohol use disorder treatment. Therefore, the findings of previous studies showing positive outcomes with XR-NTX[22–25] can be extrapolated to a population severely affected by homelessness and alcohol use disorder, one in which all had experienced homelessness in the past year and 96% had symptoms of physiological dependence. Our results also indicated some positive but less consistent effects for the HaRT-A plus placebo and HaRT-A alone groups compared with the services-as-usual control group. Therefore, it appears that treatment effects of both elements of the combined pharmacological and behavioural approach are cumulative, but not strictly additive.

Following treatment withdrawal at week 12, the outcome trajectories of the active treatment groups plateaued and were maintained through the 36-week follow-up period. Given the observed plateau in post-treatment effects, applying HaRT-A plus XR-NTX as a maintenance treatment might better facilitate continued treatment gains instead of the briefer treatment course featured in this study.

Of note, services-as-usual participants appeared to rebound with improved outcomes during the post-treatment period. Missing data analyses shed some light on this phenomenon. Attrition in the services-as-usual control group was higher than the active treatment groups and started immediately after treatment assignment, perhaps due to participants in this group feeling demoralised after realising that they had not been assigned to an active treatment group. Aside from treatment group, we found no other significant baseline predictors of missing data. As study staff noted anecdotally, it is possible that participants in the services-as-usual control group who were able to return for follow-up assessments were simply those who were on a higher-functioning trajectory.

Our results did not support all hypothesised effects. We found no significant differences in outcomes between the HaRT-A plus XR-NTX group and HaRT-A plus placebo group. Of note, this study was powered to detect

a medium effect of comparing the XR-NTX and placebo treatment groups, therefore, a smaller effect might not have been detectable with the given sample size. Further, there was absence of clear one-to-one additive effects of HaRT-A and XR-NTX when compared with services-as-usual control. Therefore, it appears that the effects of XR-NTX alone do not explain the study findings. Instead, both XR-NTX and HaRT-A appear to build on one another in a more subtle way. Future, large-scale studies are needed to better understand the underlying mechanisms of the combined pharmacological and behavioural treatment effects.

Notably, there were no significant effects of treatment on mental health-related quality of life in any of the groups, and the clinical significance of treatment effects on physical health-related quality of life is not entirely clear. Some insights could be provided by a previous systematic review, which showed that common health-related quality of life measures rarely reflect significant treatment effects in trials involving people with alcohol use disorder,[54] potentially due to the generic nature of such questionnaires. Fortunately, alcohol researchers developed and validated a participant-driven, alcohol-specific, health-related quality of life measure in 2016 that shows promise for future trials.[55]

This study has several limitations. First, treatment was brief; participants in the three active treatment arms had five HaRT-A treatment sessions, and participants in the HaRT-A plus XR-NTX group additionally received three doses of XR-NTX. Although the active treatments had significant effects on the outcome trajectories of a highly physiologically dependent, multi-morbid, and non-treatment-seeking population, the relative brevity of treatment does not mirror typically longer-term clinical contacts this population often has for their chronic conditions. Future studies are needed to test whether HaRT-A plus XR-NTX, as a longer-term maintenance treatment approach versus a brief treatment, can facilitate even greater reductions in alcohol use and alcohol-related harm, and improvements in health-related quality of life. An additional limitation of the current findings is that we did not correct p values for multiple comparisons. Fortunately, the consistently positive findings across outcomes point to the robustness of the support for combined HaRT-A plus XR-NTX in this population.

Even though the two groups in which participants received XR-NTX or placebo injections were double-blinded, there was no feasible way to mask study staff to the behavioural interventions because our aim was to keep staffing across the groups consistent to minimise differences between treatment groups. We therefore cannot preclude experimenter bias or expectancy effects for the unmasked treatment groups.

Considering the necessary focus of the study population on day-to-day survival and the resulting itinerance and displacement, the proportion of participants who completed treatment was relatively high (161 [70%] of 231 participants). This proportion was consistent with that observed in a meta-analysis of 151 studies of substance use treatment published in 2020, which showed a treatment completion rate of 70%.[56] This meta-analysis largely included studies involving participants with greater incomes, more housing stability, greater treatment readiness, and fewer risk factors than those included in our study. Follow-up completion in the present study (190 [62%] of 308) was slightly better than that of the flagship study of XR-NTX for the treatment of people with alcohol use disorder (378 [60%] of 627).[22] However, missing data can lead to reduced power and biased estimates. Therefore, we used various methods of minimising and addressing attrition and the effects of the resulting missing data.[41] We built trust over many years with the three community-based agency sites involved in the study, which resulted in strong partnerships and community-inspired and integrated engagement and retention strategies.[57] We used analyses and estimation methods that utilised all available data and thus avoided problematic listwise deletion or simple imputation methods that could have introduced bias.[45] Finally, we modelled potential missing data patterns to test the overall robustness of our models.[43] These analyses indicated that most of the dropout occurred in the services-as-usual control group and was related to treatment assignment, but that our treatment effects were largely robust to data missingness. These measures do not fully preclude concerns about estimate bias, and future developments of strategies that account for missing data are needed to refine our methodological strategies.

The generalisability of our findings could be limited by geographical location, as well as sociodemographic factors and substance-use patterns that are specific to homeless populations in this particular region. Specifically, this study was done in low-barrier settings serving a non-treatment-seeking homeless population in a large resource-rich city in the US Pacific Northwest. Additionally, we did not exclude polysubstance users, in order to provide a real-world assessment of treatment efficacy and represent the inclusive and low-barrier approach of harm reduction. Therefore, our findings might not be generalisable to other communities in which abstinence-based service settings or populations who only use alcohol are the norm. Finally, our sample population was representative of the larger US homeless population in terms of race and age,[58] and of the local community of people experiencing homelessness and alcohol use disorder. However, the results of our study might not be generalisable to young (ie, aged <18 years) people experiencing homelessness, communities with greater Latinx representation, and housed individuals.

In conclusion, this study is the first randomised clinical trial to show the efficacy of XR-NTX as a pharmacological support for patient-driven harm reduction and

health-related quality of life improvements in people experiencing homelessness and alcohol use disorder. Compared with the services-as-usual control group, HaRT-A plus XR-NTX showed consistent and significant improvements across five of six primary and secondary alcohol-related outcomes and health-related quality of life outcomes. Outcome trajectories plateaued but were maintained after treatment withdrawal. Our findings indicated some positive, but weaker and less consistent effects of HaRT-A plus placebo and HaRT-A alone when compared with services as usual. Given the observed plateau in post-treatment effects, applying HaRT-A plus XR-NTX as a maintenance treatment approach might better facilitate continued treatment gains than a brief treatment approach. Further research is needed to investigate whether this approach could help to reduce health-care service utilisation and the associated costs, and to establish the optimal length of harm-reduction treatment for alcohol use disorder.

Contributors

SEC and RKR conceptualised the project, study, and treatment design. SEC took primary responsibility for primary analyses and manuscript writing. MHD helped to co-develop the treatment manual and protocols, reviewed the manuscript, and provided detailed edits for and rewrites of the draft. Additionally, MHD drafted portions of the discussion. AJS contributed to the study and treatment design, and contributed to the writing and editing of all sections of the manuscript. EMT and GEH helped to develop the analysis strategy, did the preliminary analyses, generated the figures, and contributed to the tables. NM helped to refine various protocols, and reviewed multiple drafts of the manuscript and provided feedback. SEC, RKR, JOM, SLC, and AJS all contributed to the development of the treatment, and reviewed and provided key edits of the manuscript.

Declaration of interests

AJS reports serving on a Scientific Advisory Board for Alkermes and Indivior; receiving consulting fees from Alkermes and Indivior; receiving travel support from Alkermes; and receiving royalties from UpToDate. SEC reports funding from the National Institutes of Health to conduct the study, and was provided with donated injections from Alkermes to conduct the study but no financial support. All other authors declare no competing interests.

Data sharing

This study involved the collection of highly sensitive data, including data on illegal behaviours, health-care data, and suicide attempts, from people who were severely affected by chronic homelessness and by multiple psychiatric, medical, and substance use disorders. Participants were engaged and often well known in community-based and criminal justice settings within a tight-knit urban community. Participating agencies are likewise well known for their approaches and are regularly part of the national conversation about interventions for chronic homelessness. Therefore, even with the removal of all identifiers, we believe that it could become difficult to fully protect the identities of participants, their data, and the involved agencies. Additionally, the planning and commencement of this study pre-dated the regular inclusion of data sharing plans in National Institute of Health-funded studies, thus agreements with the participating agencies and discussions about consent with study participants did not mention data sharing. For these reasons, we do not plan to share the study data.

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