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RESEARCH REPORT

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Secondary analysis of a combined harm-reduction treatment and extended-release naltrexone randomized clinical trial for alcohol use disorder: Differences across race, ethnicity and sex assigned at birth

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Abstract

Background and Aims: In a prior randomized clinical trial (RCT), combined pharmacobehavioral harm-reduction treatment improved alcohol outcomes and physical health-related quality of life (PH-QoL). In this secondary analysis, we tested race, ethnicity and sex assigned at birth as predictors and moderators of these effects.

Design: Secondary study of a four-arm RCT.

Setting: Community settings serving people experiencing homelessness in the US Pacific Northwest.

Participants: Adults aged 21–65 (N = 308) with alcohol use disorder (AUD) who experienced past-year homelessness.

Intervention: In the parent RCT, participants were randomized to brief behavioral harm-reduction treatment for AUD + extended-release naltrexone (HaRT-A + XR-NTX); HaRT-A + placebo; HaRT-A alone, or services-as-usual control.

Measurement: We tested whether baseline outcomes, trial inclusion, data missingness, treatment adherence, side effects, and treatment effects on alcohol frequency, quantity, alcohol-related harm, urinary ethyl glucuronide, and PH-QoL differed by race, ethnicity, and sex assigned at birth.

Findings: Race, ethnicity and sex assigned at birth were not associated with differential trial inclusion, missingness, treatment adherence or side effects with one exception: the Multiracial/other people of color (POC) group attended fewer HaRT-A sessions than the white group (odds ratio [*OR*] = 0.49, $p = 0.03$, 95% confidence interval [CI] [0.25, 0.95]). There were no statistically significant moderators of the behavioral HaRT-A effect; however, Multiracial/other POC race ($B = -3.34$, $p = 0.03$, 95% CI [−6.35, −0.34]) and sex assigned at birth ($B = 2.43$, $p = 0.04$, 95% CI [0.14, 4.73]) moderated the XR-NTX versus placebo effect on one variable: PH-QoL. Simple slope analysis indicated the Multiracial/other POC group who received placebo showed improvement on PH-QoL ($dy/dx = 2.61$, $p = 0.003$, 95% CI [0.91, 4.31]); the XR-NTX group did not ($dy/dx = -0.22$, $p = 0.79$, 95%

CI [−1.90, 1.45]). Among XR-NTX recipients, the female group (dy/dx = 2.89, p < 0.001, 95% CI [1.53, 4.25]) showed faster improvement rates than the male group (dy/dx = 1.19, p = 0.02, 95% CI [0.23, 2.16]) on PH-QoL.

Conclusion: Race, ethnicity and sex assigned at birth were largely not associated with trial inclusion, data missingness, treatment adherence, side effects, or outcomes in a combined harm-reduction treatment and extended-release naltrexone randomised clinical trial for alcohol use disorder (AUD). Although Multiracial/other people of color (POC) participants attended fewer brief behavioral harm-reduction treatment for AUD sessions, they did not differ from white participants on alcohol and physical health-related quality of life outcomes. Among participants receiving extended-release naltrexone (XR-NTX), women showed greater improvement than men on physical health-related quality of life. Compared with white participants, Multiracial/other POC participants who received XR-NTX showed less improvement than those who received placebo. Given their post hoc nature and limited power, findings are hypothesis-generating. They suggest the equitable utility of behavioral harm-reduction treatment and the importance of assessing sociodemographic differences in AUD treatment response.

KEYWORDS

alcohol, alcohol use disorder, ethnicity, extended-release naltrexone, harm reduction, homelessness, race, sex assigned at birth

INTRODUCTION

Harm-reduction treatment for alcohol (HaRT-A) was co-created with people with lived experience of homelessness and alcohol use disorder (AUD) to address the needs of people who are not ready, willing or able to attain abstinence or engage with the abstinence-based treatment system [1]. The resulting HaRT-A aims to help people reduce alcohol-related harm and improve their quality of life, without requiring abstinence or use reduction [1]. It entails pragmatic and compassionate means of: (i) collaborative assessment and tracking of self-reported alcohol-related harm alongside client-preferred metrics; (ii) the elicitation of client-driven, harm-reduction and quality-of-life goals [2]; and (iii) the discussion of community crowdsourced safer-drinking strategies [3].

Recent randomized controlled trials (RCTs) have shown HaRT-A to be efficacious in reducing alcohol and other drug use, attenuating alcohol-related harm and improving physical health-related quality of life (PH-QoL), both as stand-alone counseling [1] and as a combined pharmacobehavioral approach, with the integration of extended-release naltrexone (XR-NTX; 4). In the most recent RCT, findings indicated that this low-barrier approach yielded relatively high engagement (97%) and retention in both behavioral (Mdn = 5/5 sessions attended) and pharmacological (Mdn = 3/3 doses received) components. Primarily medium treatment effect sizes were observed across alcohol outcomes and PH-QoL when comparing the three active treatment groups (i.e. HaRT-A + XR-NTX, HaRT-A + placebo and HaRT-A alone) with a services-as-usual control condition. Despite differential follow-up rates at the assessments (70% in active treatment groups vs 52% in the control group), the treatment differences were robust to missingness [4].

Initial findings signal that it is possible—via community-based, low-barrier, patient-led and non-abstinence-based harm-reduction treatment provision—to engage and treat people with AUD more equitably. Indeed, the research described above involved a more marginalized population (i.e. people experiencing homelessness) and a more racially and ethnically diverse sample than is typically found in the general population in the recruitment locations and in most alcohol treatment trials [4].

It is, however, important to acknowledge that the prior research literature has shown inequities in AUD treatment across race, ethnicity and sex assigned at birth. Regarding behavioral treatments for AUD, studies have shown differences in treatment efficacy across race and ethnicity, reflecting inequities for people from minoritized racial and ethnic populations in the USA [5–7], who are also less likely to access, receive, engage and complete AUD treatment [8–13], compared with individuals from dominant groups. Findings for sex assigned at birth are more mixed: with some research finding differential treatment outcomes for women people compared with men [14, 15, 16, 17].

Regarding pharmacotherapy treatments for alcohol, XR-NTX is one of three US Food and Drug Administration (FDA)-approved and effective medications for AUD that is well positioned to support the reduction of alcohol-related harm [18, 19]. However, XR-NTX for AUD is understudied among people from minoritized and marginalized race, ethnic and sex assigned at birth groups [20]. One study assessed NTX across racial or ethnic groups, finding similar benefits [21]. However, most studies assessing NTX among racial and ethnic groups in the USA are focused on race-specific samples, finding differences between groups [22] and poorer treatment response [23–26].

Although a handful of studies have conducted *post hoc* moderation analysis of NTX efficacy by sex assigned at birth, the findings are mixed [16, 27–31]. Some studies have found women experience poorer treatment outcomes [32, 33]. These findings highlight the need for further study of XR-NTX as a treatment for AUD across race, ethnicity and sex assigned at birth.

To fill these important gaps in the literature, we conducted secondary, *post hoc* tests to assess potential socio-demographic differences on baseline outcomes, trial inclusion, data missingness, treatment adherence and side effects, and whether the behavioral (HaRT-A) and pharmacological (XR-NTX) effects observed in the parent study were moderated by race, ethnicity and sex assigned at birth. Based on the balance of findings in the literature to date, we hypothesized that participants from minoritized and marginalized races [i.e. Black, North American Indigenous (NAI) and multi-racial/other people of color (POC)], ethnicity (i.e. Hispanic/Latine) and sex at birth (i.e. female) groups would show significantly less improvement in alcohol use, alcohol-related harm and PH-QoL during the treatment course than white, non-Hispanic/Latine and male participants.

METHODS

Parent study design and context

This secondary study drew on data from a four-arm RCT (n = 308) testing the relative efficacy of: (i) HaRT-A + XR-NTX; (ii) HaRT-A + placebo; and (iii) HaRT-A alone; compared with (iv) a services-as-usual control condition in reducing alcohol use, attenuating alcohol-related harm and improving PH-QoL [34]. Participants were adults who met the criteria for current AUD, had experienced homelessness in the past year and were receiving services as usual at three community-based service sites in a large city in the Pacific Northwest. Those who qualified for participation attended assessments at baseline and weeks 4, 8, 12, 24 and 36 (see the protocol and parent studies for more information; 4, 34).

The services-as-usual control group received supportive services at community-based sites for the duration of the study. These services included: 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 three active treatment arms (HaRT-A + XR-NTX, HaRT-A + placebo and HaRT-A alone groups) additionally attended five, manualized HaRT-A sessions, delivered by study physicians or nurses [see published protocol (34)] in weeks 0, 1, 4, 8 and 12. HaRT-A aims to help people reduce alcohol-related harm and improve health-related quality of life without requiring, prescribing or favoring alcohol abstinence as a treatment goal. Study interventionists used a compassionate, pragmatic and patient-driven style in administering the following treatment components: (i) feedback on results of self-reported alcohol outcomes, physical exam findings, lab testing and their implications for physiological alcohol-related harm; (ii) collaborative tracking of participant-preferred alcohol-related outcomes; (iii) elicitation of harm-reduction and health-related quality-of-life goals; and (iv) discussion of safer-drinking strategies. The HaRT-A + XR-NTX and HaRT-A + placebo conditions additionally received information about the medication and injections at weeks 0, 4 and 8. For greater description, please see the parent study protocol [34], the parent article and supplement, which includes the full treatment protocol [4], and the subsequently published long-form treatment manual [35].

Current study design

In this secondary study, we conducted *post hoc* analyses to test race, ethnicity and sex assigned at birth as moderators of both the HaRT-A effect (compared with the services-as-usual control arm; n = 308) and the XR-NTX effect (compared with the placebo arm; n = 152) from the baseline through the 12-week active treatment period. We additionally tested socio-demographic differences on baseline outcomes, trial inclusion, data missingness, treatment adherence and side effects. Given that the data were derived from a parent RCT, the present secondary study was not specifically powered to detect the proposed moderation effects or perform the additional analyses on engagement with and experience of treatment. Additionally, the analyses were not pre-registered and therefore the results should be considered exploratory.

Participants

All participants (n = 308) in the parent study described above were included in this secondary analysis, and the sample description is in Table 1.

Measures

Personal Information Questionnaire (PIQ)

Socio-demographic questions assessed participants' self-reported race, ethnicity, sex assigned at birth, age, highest education level and past-year homelessness.

Addiction Severity Index (ASI)

The 'Alcohol and Drugs' section of the fifth edition of the ASI was used to assess frequency of alcohol use over the past 30 days [36]. The ASI has demonstrated good reliability and validity [37].

Alcohol Quantity Use Assessment (AQUA)

The AQUA is an alcohol quantity questionnaire, developed and administered in prior studies with this population [38]. It was used to assess alcohol use on the peak drinking day in the past month [39].

TABLE 1 Baseline descriptive statistics for the study sample (N = 308).

Socio-demographic variables	M (SD)/*n* (%)	*Mdn*
Age	48.17 (9.21)	
Race		
Black/African American	95 (30.8%)	
North American Indigenous	49 (15.9%)	
White/European American	96 (31.2%)	
Native Hawaiian/Pacific Islander	3 (1.0%)	
Asian	0 (0%)	
'More than one race'	45 (14.6%)	
Self-reported 'Other'	20 (6.5%)	
Ethnicity		
Hispanic/Latine	34 (11.1%)	
Non-Hispanic/Latine	273 (88.9%)	
Sex assigned at birth		
Female	50 (16.2%)	
Male	258 (83.8%)	
Intersex	0 (0.0%)	
Gender identity		
Woman	42 (13.6%)	
Man	223 (72.4%)	
Prefer not to respond	43 (86.0%)	
Highest education level		
Some high school	77 (25.0%)	
High school graduate/GED diploma	128 (41.6%)	
Vocational school	10 (3.2%)	
Some college	73 (23.7%)	
College graduate	16 (5.2%)	
Some graduate school/advanced degree	4 (1.2%)	
Outcome variables		
Frequency of alcohol use	23.63 (8.22)	29
Peak alcohol use	33.70 (21.55)	28.8
Alcohol-related harm	23.78 (11.62)	24
PH-QoL	16.40 (4.60)	16

Abbreviations: GED, General Education Development; *Mdn*, median; PH-QoL, physical health-related quality of life.

Short Inventory of Problems (SIP-2R)

The SIP-2R is a 15-item Likert-type questionnaire that measures social, occupational and psychological alcohol-related harm over the past 30 days, with higher scores indicating greater alcohol-related harm [40, 41].

Short Form-12®v2 (SF-12®v2)

The SF-12®v2 is a 12-item Likert-type questionnaire used to evaluate physical (i.e. general health, physical functioning, bodily pain and ability to fulfil daily tasks or roles in light of physical limitations) and mental (sense of vitality, social functioning, ability to fulfill daily tasks/roles given emotional problems, mental health) health-related quality of life, where higher scores indicate greater health-related quality of life [42, 43]. Only PH-QoL was used because it reflected positive treatment effects in the parent study.

Systematic Assessment for Treatment Emergent Effects (SAFTEE)

The SAFTEE interview [44] was administered by study interventionists to assess self-reported symptoms that correspond to potential adverse events associated with XR-NTX. The number of side effects was summed for this secondary analysis.

Ethyl glucuronide (EtG)/creatinine ratio

The urinary EtG/creatinine ratio served as an alcohol-use biomarker [45].

Data analytic plan

Socio-demographic coding

We dummy-coded the socio-demographic groups with minoritized and marginalized groups as the indicator group (coded 1) and dominant groups (i.e. white, non-Hispanic/Latine, male) as the referent group (coded 0). Informing the coding, the primary racial groups were Black (30.8%; *n* = 95), NAI (15.9%; *n* = 49) and white (31.2%; *n* = 96). People who identified as multi-racial or any other racial group made up an additional and sizeable minority of participants (22.1%; *n* = 68). They were grouped into the multi-racial/other POC category owing to the low representation of specific groups in this diverse sample (e.g. participants who were Native Hawaiian and Pacific Islander), belonging to a group not typically included in US federally defined racial categories (e.g. 'North African') and/or to honor participants' preferred self-reported multi-racial identity.[1] Calls in the literature emphasize the importance of studying AUD among people who identify as multi-racial [46]. Given that a multi-racial identity is theorized to develop in the social context of feeling 'othered' among larger, monoracial groups [47], it is plausible that the multi-racial/other POC group has meaningful similarities as a socially minoritized and marginalized group.

[1]Of the 45 individuals who identified as 'more than one race', 69.0% reported NAI heritage; thus, 26.0% of the overall sample reported some NAI heritage, representing 30 NAI tribes and communities. The statistical decision to collapse across groups is imperfect and may contribute to the historical oppression of NAI culture. It can reflect an erasure of NAI identity and an oversimplification of racial and ethnic identities more generally through the limitations of US federally defined categories and our statistical methods. Throughout these challenges, we also sought to preserve how people self-identified racially, and most in the multi-racial/other POC group preferred acknowledgment of their multi-racial identity or identities that did not readily fit into current US federally defined categories (e.g. 'North African'). The authors recognize that the methodological and statistical practices in racial categorization within our field are deeply flawed.

Approximately one in 10 participants reported Hispanic/Latine ethnicity (11.1%; *n* = 34), and 88.9% reported non-Hispanic/Latine ethnicity (*n* = 273). In terms of sex assigned at birth, 16.2% of participants (*n* = 50) reported that they were female and 83.8% (*n* = 258) reported that they were male. No participants reported intersex as their sex assigned at birth. Among participants who responded to the gender identity question, sex assigned at birth and gender identity were aligned; however, 43 participants chose not to respond to the gender identity item. Given the latter point and the fact that sex assigned at birth can be a relevant factor in alcohol metabolism and outcomes, we used this variable in the analyses.

Tests of socio-demographic differences on trial inclusion, data missingness, treatment adherence and experience of side effects

One-way analyses of variance (ANOVAs) were used to examine baseline differences in alcohol and PH-QoL outcomes by race, ethnicity and sex assigned at birth. There was an exception: negative binomial hurdle models were used to accommodate zero-inflation in the urinary EtG/creatinine outcome.

Logistic regression was used to test whether inclusion in the parent RCT was differentially predicted by race, ethnicity or sex assigned at birth. To test whether socio-demographic variables predicted behavioral HaRT-A and medication adherence, we modeled session attendance (0–5) and medication adherence (0–3) using binomial regression with a logit link. We treated the number of sessions or injections as the number of 'successes' out of a fixed number of 'trials'.

Generalized estimating equation models were used to explore the association of socio-demographic variables (i.e. race, ethnicity or sex assigned at birth) with data missingness and experience of side effects during the 12-week treatment period. Such models were used because they could account for correlation across time.

Tests of moderation of treatment effects by sociodemographic variables

We used generalized estimating equation models to test time × treatment arm × socio-demographic variable interaction effects on alcohol and PH-QoL outcomes. Reduced models included time (0 = baseline, 1 = treatment period, which encompassed months 4, 8 and 12), treatment arm (0 = control, 1 = active treatment) and the time × treatment arm interaction. In the parent study, all three HaRT-A arms showed statistically significant improvements on outcomes compared with the services-as-usual control group but did not significantly differ from one another [34]. We thus collapsed them into a single group for behavioral analyses to isolate the shared intervention component (*n* = 308; HaRT-A, *n* = 231; services-as-usual control, *n* = 77). For pharmacologic analyses, we compared only the HaRT-A + XR-NTX (*n* = 74) and HaRT-A + placebo (*n* = 78) groups, excluding those who received HaRT-A alone or services as usual. As noted above, socio-demographic variables were included with minoritized and marginalized groups as the indicator (1) and dominant groups as the reference group (0). Full models included time × treatment arm × socio-demographic interactions and their subordinate main effects and interactions.

Generalized estimating equation (GEE) models were used for moderation analyses because they accommodate correlated data (repeated measures), make use of all available data, are robust to model misspecification and provide population-averaged estimates. The last point was deemed constructive in testing treatment effects on groups (i.e. race, ethnicity, sex assigned at birth) versus people individually. We assumed exchangeable correlations to accommodate repeated measures over time collected on the same participant, which served as the sole clustering variable. We assumed Gaussian distributions with the identity link for normally distributed variables, negative binomial distributions with a log link for count and over-dispersed variables, and binomial distributions with logit link for dichotomous variables. Owing to its skewness, peak alcohol use was subject to a natural log transformation prior to analysis. Alpha values were set to $P = 0.05$. Confidence intervals were set to 95%. We reported marginal effects using unstandardized coefficients from primary analyses and dy/dx values from simple slope analyses, indicating the estimated change in the outcome per unit change in the predictor. These values serve as effect size estimates in the context of interaction models and are reported in the natural units of the outcomes.

We used a different analytic strategy to accommodate the zero-inflated data we encountered for the EtG/creatinine outcome: a two-part negative binomial hurdle model. Predictors were baseline EtG/creatinine ratio, treatment group, socio-demographic group and the treatment group × socio-demographic group interaction. The outcome was the EtG/creatinine ratio at the 12-week follow-up. We used an additional model for NAI participants, whose cell size limitations precluded inclusion in the treatment × race interaction of the larger model.

RESULTS

Sample description

Descriptive statistics on participant demographics and key outcome variables at baseline are reported in Table 1.

Primary findings

Baseline differences on alcohol outcomes and PH-QoL across race, ethnicity and sex assigned at birth

As shown in Table 2, statistical tests indicated predominantly no significant differences on outcome variables at baseline across race, ethnicity and sex assigned at birth. However, male participants had

TABLE 2 Analyses of variance (ANOVAs) for race, ethnicity, and sex assigned at birth across study outcome variables at baseline.

Outcome variable	Sum of squares	d.f.	Mean square	*F*	*P*
Race					
Alcohol frequency Black (M = 24.45, SD = 7.82) NAI (M = 24.69, SD = 8.15) Multi-racial/other POC (M = 22.47, SD = 8.79) White (M = 23.08, SD = 8.19)	239.842	3	79.95	1.19	0.32
Peak alcohol quantity Black (M = 34.65, SD = 21.44) NAI (M = 37.95, SD = 26.88) Multi-racial/other POC (M = 31.30, SD = 19.76) White (M = 32.28, SD = 19.71)	1548.36	3	516.12	1.11	0.34
Alcohol-related harm Black (M = 23.11, SD = 11.98) NAI (M = 25.27, SD = 12.21) Multi-racial/other POC (M = 23.51, SD = 11.33) White (M = 23.86, SD = 11.25)	155.63	3	51.88	0.38	0.77
PH-QoL Black (M = 16.62, SD = 4.42) NAI (M = 16.02, SD = 4.59) Multi-racial/other POC (M = 16.58, SD = 4.80) White (M = 16.20, SD = 4.71)	15.99	3	5.33	0.25	0.86
Ethnicity					
Alcohol frequency Hispanic/Latine (M = 22.00, SD = 9.37) Non-Hispanic/Latine (M = 23.81, SD = 8.06)	98.60	1	98.60	1.46	0.228
Peak alcohol quantity Hispanic/Latine (M = 31.15, SD = 20.98) Non-Hispanic/Latine (M = 34.02, SD = 21.68)	248.99	1	248.99	0.53	0.47
Alcohol-related harm Hispanic/Latine (M = 25.32, SD = 10.71) Non-Hispanic/Latine (M = 23.57, SD = 11.75)	92.68	1	92.68	0.68	0.41
PH-QoL Hispanic/Latine (M = 16.00, SD = 4.07) Non-Hispanic/Latine (M = 16.44, SD = 4.67)	5.62	1	5.62	0.26	0.61
Sex assigned at birth					
Alcohol frequency Female (M = 23.40, SD = 9.47) Male (M = 23.67, SD = 7.97)	3.07	1	3.07	0.05	0.83
Peak alcohol quantity Female (M = 29.57, SD = 18.93) Male (M = 34.51, SD = 21.97)	1022.48	1	1022.48	2.21	0.14
Alcohol-related harm Female (M = 25.62, SD = 11.90) Male (M = 23.42, SD = 11.55)	202.11	1	202.11	1.50	0.22
PH-QoL Female (M = 15.00, SD = 4.14) Male (M = 16.67, SD = 4.65)	**111.89**	**1**	**111.89**	**5.36**	**0.02**

Note: Bold = $P < 0.05$. To accommodate zero-inflation, we analyzed the association of race, ethnicity and sex assigned at birth with EtG/creatinine ratio at baseline using hurdle models. Omnibus models were not significant for race [$\chi^2(3) = 5.60$, $P = 0.11$] or ethnicity [$\chi^2(1) = 0.66$, $P = 0.42$]. However, individual parameters in the negative binomial model were statistically significant, showing white participants had higher EtG/creatinine ratios than Black participants (IRR = −0.67, $P = 0.007$) and lower EtG/creatinine ratios than NAI participants (IRR = 0.65, $P = 0.01$). Additionally, the omnibus model was likewise not significant for sex assigned at birth [$\chi^2(1) = 0.01$, $P = 0.94$], but the individual parameter was (IRR = 0.63, $P = 0.03$), indicating men (M = 192410.4, SD = 347741.8) had lower EtG/creatinine ratios than women (M = 364482.1, SD = 710771.9).

Abbreviations: ANOVA, analysis of variance; NAI, North American Indigenous; PH-QoL, physical health-related quality of life; POC, people of color.

significantly higher mean PH-QoL and significantly lower EtG/creatinine ratio compared with female participants (Table 2). Further, within the negative binomial model only, white participants had higher and lower EtG/creatinine ratios than Black participants and NAI participants, respectively.

Prediction of trial inclusion, data missingness, treatment adherence and experience of side effects by race, ethnicity and sex assigned at birth

As shown in Table 3, logistic regression analyses indicated that race, ethnicity and sex assigned at birth did not significantly predict trial inclusion (all $P > 0.17$). Second, generalized estimating equation modeling showed no statistically significant predictors of data missingness across race, ethnicity or sex assigned at birth (all $P > 0.20$). The overall effect of race on HaRT-A attendance was not statistically significant [Wald's $\chi^2(3) = 5.16$, $P = 0.16$]; however, participants in the multi-racial/other POC group attended fewer HaRT-A sessions on average than white participants (OR = 0.49, SE = 0.16, $P = 0.034$, 95% CI = 0.25–0.95). Sex assigned at birth and ethnicity were not significant predictors of HaRT-A attendance (both $P > 0.05$), and none of the socio-demographic variables were significantly associated with medication adherence (all $P > 0.20$). Among those who received injections (XR-NTX and placebo), generalized estimating equations showed no statistically significant differences in self-reported number of side effects in treatment arm × socio-demographic interaction effects (all $P > 0.14$).

Moderation of treatment effects by race, ethnicity and sex assigned at birth

Replication of the primary study findings indicated the same pattern for the overall study sample. There were statistically significant treatment effects for the behavioral HaRT-A arms compared with the control arm on alcohol and PH-QoL outcomes, but none for the XR-NTX versus placebo arms. Regarding moderation analyses, there were no statistically significant moderators of the behavioral HaRT-A treatment effects (all $P > 0.11$; Tables S1 and S2).

However, as shown in Table 4, the medication (XR-NTX) effect on PH-QoL was significantly moderated by race and sex assigned at birth. Regarding the moderation of the XR-NTX effect on PH-QoL by race, there was a significant effect for the time × XR-NTX × multi-racial/other POC interaction (for parameters, see Figure 1 and Table 4). No other racial groups showed statistically

TABLE 3 Descriptive data on trial inclusion, data missingness, treatment adherence and experience of side effects by race, ethnicity and sex assigned at birth.

Demographic group	Trial inclusion (*n* = 401)	Data missingness during treatment period (*n* = 308)	Behavioral HaRT-A adherence (*n* = 231)	Medication adherence (*n* = 152)	Experience of side effects during treatment period (*n* = 152)
Race					
Black	95/121 79%	155/380 41%	3.69(1.78) 5	1.93(1.17) 2	5.93(3.47) 6
NAI	49/61 80%	77/189 41%	3.97(1.62) 5	1.95(1.13) 2	7(3.31) 8
Multi-racial/ other POC	68/87 78%	102/245 42%	3.45(1.93) 4	1.93(1.17) 2	5.97(3.77) 6
White	96/132 73%	162/392 41%	4.07(1.47) 5	2.23(1.01) 3	6.96(3.24) 7
Ethnicity					
Hispanic/Latine	34/47 72%	48/119 40%	3.46(2.11) 5	1.92(1.32) 3	8.38(4.15) 9
Non-Hispanic/ Latine	273/352 78%	446/1082 41%	3.85(1.64) 5	2.04(1.10) 3	6.29(3.38) 7
Sex assigned at birth					
Female	50/69 72%	87/218 40%	4.38(1.48) 5	2.33(1.06) 3	8.44(3.24) 8.5
Male	258/331 78%	409/988 41%	3.72(1.71) 5	1.98(1.12) 2	6.32(3.36) 6
'Other'	0/1 0%	–	–	–	–

Note: Descriptive statistics are proportions/% for dichotomous outcomes and M (SD)/*Mdn* for count outcomes.
Abbreviations: HaRT-A, harm-reduction treatment for alcohol use disorder; NAI, North American Indigenous; POC, people of color.

TABLE 4 Model statistics and parameters showing socio-demographic moderation of the XR-NTX (n = 152) treatment effects on PH-QoL.

PH-QoL				
Predictors	**Simple treatment effects model[a]**	**Race model[b]**	**Ethnicity model[c]**	**Sex assigned at birth model[d]**
Time	**1.25(0.43)**** **(0.40, 2.09)**	0.58(0.64) (−0.68, 1.84)	**1.23(0.47)**** **(0.32, 2.15)**	**1.36(0.49)**** **(0.40, 2.33)**
Treatment	−1.31(0.73) (−2.73, 0.12)	−1.54(1.48) (−4.44, 1.36)	−1.37(0.78) (−2.90, 0.16)	−0.95(0.80) (−2.52, 0.61)
Time × treatment	0.22(0.61) (−0.97, 1.42)	0.51(0.93) (−1.31, 2.33)	0.24(0.66) (−1.06, 1.53)	−0.17(0.70) (−1.54, 1.19)
Black		0.60(1.24) (−1.83, 3.04)		
NAI		0.71(1.25) (−1.74, 3.17)		
Multi-racial/other POC		−0.18(1.43) (−2.99, 2.62)		
Time × Black		0.43(1.04) (−1.61, 2.47)		
Time × NAI		0.66(1.10) (−1.49, 2.82)		
Time × multi-racial/other POC		2.03(1.08) (−0.09, 4.15)		
Treatment × Black		−0.00(1.82) (−3.58, 3.57)		
Treatment × NAI		−1.19(2.39) (−5.89, 3.50)		
Treatment × multi-racial/other POC		1.83(2.20) (−2.49, 6.15)		
Time × treatment × Black		0.88(1.45) (−1.97, 3.73)		
Time × treatment × NAI		−0.32(1.49) (−3.24, 2.60)		
Time × treatment × multi-racial/other POC		**−3.34(1.53)*** **(−6.35, −0.34)**		
Hispanic/Latine			−1.66(1.33) (−4.25, 0.94)	
Time × Hispanic/Latine			0.04(0.65) (−1.23, 1.32)	
Treatment × Hispanic/Latine			0.61(1.77) (−2.85, 4.08)	
Time × treatment × Hispanic/Latine			−0.03(1.14) (−2.26, 2.20)	
Female				−1.28(1.23) (−3.68, 1.12)
Time × female				−0.73(0.81) (−2.31, 0.85)
Treatment × female				−2.04(1.61) (−5.20, 1.11)
Time × treatment × female				**2.43(1.17)*** **(0.14, 4.73)**
Constant	**16.93(0.50)***** **(0.40, 2.09)**	**16.71(0.94)***** **(14.87, 18.55)**	**17.09(0.53)***** **(16.04, 18.13)**	**17.09(0.55)***** **(16.03, 18.16)**

Note: The reference group for race = white, ethnicity = non-Hispanic white and sex assigned at birth = males. The statistics presented are unstandardized coefficients and robust standard errors in the following format: B (SE) (95% CI).

Abbreviations: NAI, North American Indigenous; PH-QoL, physical health-related quality of life; POC, people of color; XR-NTX, extended-release naltrexone.

Wald chi-square statistics:

[a]$\chi^2(3) = 80.62$, $P < 0.0001$;

[b]$\chi^2(15) = 33.67$, $p < 0.001$;

[c]$\chi^2(7) = 44.62$, $P < 0.0001$;

[d]$\chi^2(7) = 58.51$, $P < 0.0001$.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

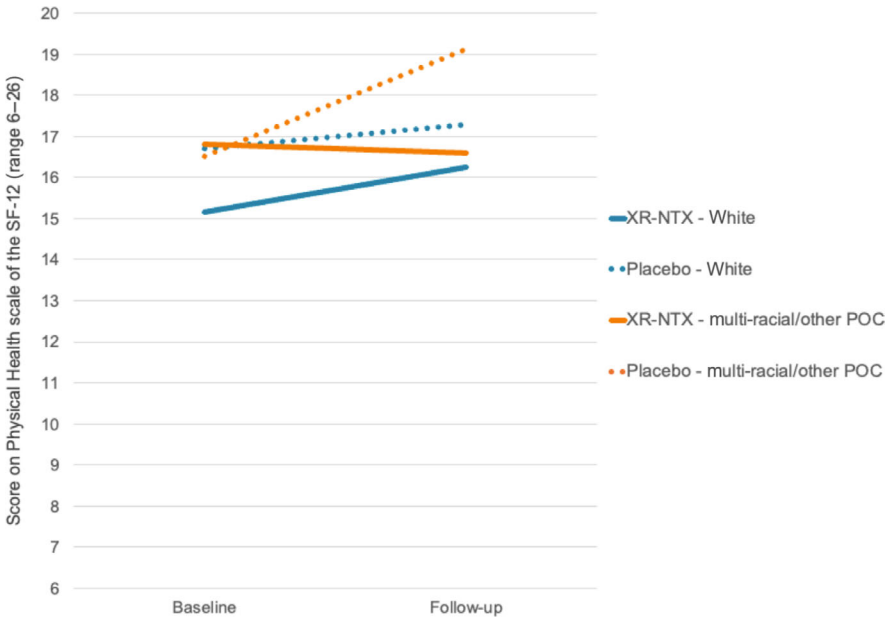

FIGURE 1 Marginal means showing the moderation of the XR-NTX treatment effect by race on physical health-related quality of life. XR-NTX = extended-release naltrexone; POC = People of Color.

significant differences to white participants in their rate of PH-QOL improvement (all $P > 0.54$). Subsequent *post hoc* tests were conducted, and a significant two-way interaction between time and XR-NTX was observed in this group ($B = -2.80$, SE = 1.24, $P = 0.02$, 95% CI = −5.23 to −0.37). Simple slope analysis indicated that among multi-racial/other POC, participants treated with placebo showed significant improvement over time ($dy/dx = 2.61$, SE = 0.87, $P = 0.003$, 95% CI = 0.91 to 4.31), while participants treated with XR-NTX did not ($dy/dx = -0.22$, SE = 0.85, $P = 0.79$, 95% CI = −1.90 to 1.45).

There was also a significant effect observed for the time × XR-NTX × sex assigned at birth interaction (for parameters, see Figure 2 and Table 4). *Post hoc* analyses indicated that a significant two-way interaction between time and treatment was observed for female ($B = 2.25$, SE = 0.96, $P = 0.02$, 95% CI = 0.36–4.14), but not for male ($B = -0.18$, SE = 0.70, $P = 0.79$, 95% CI = −1.55 to 1.18), participants. Simple slope analysis indicated that, although both male ($dy/dx = 1.19$, SE = 0.49, $P = 0.02$, 95% CI = 0.23–2.16) and female ($dy/dx = 2.89$, SE = 0.69, $P < 0.001$, 95% CI = 1.53–4.25) participants in the XR-NTX group showed improvements in PH-QoL, female participants showed a faster rate of improvement in PH-QoL when treated with XR-NTX ($dy/dx = 2.89$, SE = 0.69, $P < 0.001$, 95% CI = 1.53–4.25) versus placebo ($dy/dx = 0.63$, SE = 0.64, $P = 0.32$, 95% CI = −0.62 to 1.88).

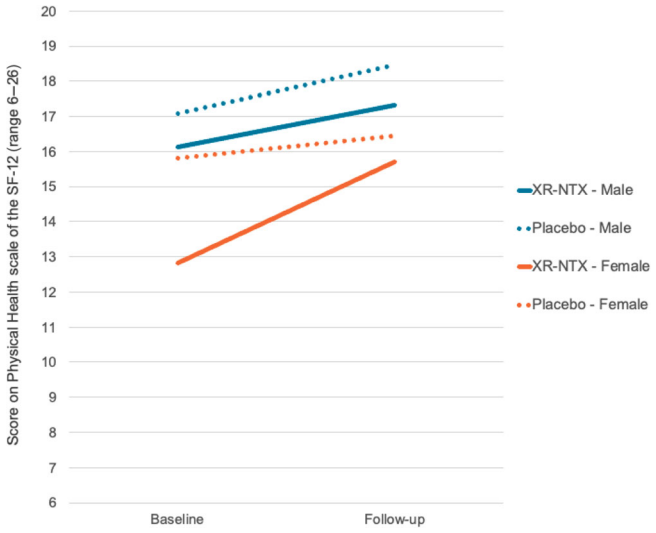

FIGURE 2 Marginal means showing the moderation of the XR-NTX treatment effect by sex assigned at birth on physical health-related quality of life. XR-NTX = extended-release naltrexone.

DISCUSSION

This *post hoc*, secondary analysis examined the association of race, ethnicity and sex assigned at birth on baseline outcomes, trial inclusion, data missingness, treatment adherence, experience of side effects, and potential moderation of behavioral and pharmacological effects of a harm-reduction treatment across these socio-demographic groups. This study represents one of the few to date that assesses differential efficacy of either harm-reduction treatment or pharmacotherapy for AUD across race, ethnicity and sex assigned at birth.

There were few baseline differences on alcohol outcomes or PH-QoL across socio-demographic groups

These findings contrast with large epidemiologic studies that find such differences in the general population. Specifically, prior research has

indicated that Black, NAI and Hispanic/Latine adults experience disproportionate alcohol-related harm [31, 48, 49]. These null findings could be associated with the more leveling impact of chronic homelessness, which is defined by the presence of co-occurring medical, psychiatric and substance use disorders, and is exacerbated by inequities across various systems of care.

We did, however, observe differences for EtG/creatinine ratios across race and sex assigned at birth, such that white participants had lower urinary EtG/creatinine ratios than NAI participants but higher EtG/creatinine ratios than Black participants at baseline, and male participants had lower EtG concentration compared to female participants. Interestingly, these differences were not reflected in self-reported alcohol outcomes, which reflect longer-term (30-day) and potentially more stable patterns in alcohol use than EtG/creatinine ratios. The statistically significant difference for sex assigned at birth on PH-QoL, indicating lower baseline PH-QoL for female participants compared with male participants, tracks with prior research [50].

Socio-demographic variables did not significantly predict trial inclusion, assessment completion, treatment adherence or the reporting of side effects, with one exception

Race, ethnicity and sex assigned at birth were largely not correlated with study or treatment engagement. The one exception was that participants in the multi-racial/other POC group were less likely to attend behavioral HaRT-A sessions compared with white participants. It is possible that this result is spurious and should be interpreted with caution for various methodological reasons (e.g. multiple comparisons, heterogeneity of participants in the multi-racial/other POC category). Nonetheless, this finding serves as an important reminder to continue fostering a strong sense of belonging and cultural relevance in AUD treatment. The broader pattern of results also suggests that this pharmacobehavioral harm-reduction treatment was inclusive of and accessible to a wide range of socio-demographic groups, reinforcing its potential for promoting equity in AUD treatment engagement.

There was no significant moderation of the behavioral HaRT-A effects on alcohol or PH-QoL outcomes by race, ethnicity or sex assigned at birth

These findings were in contrast with the study hypotheses and were somewhat surprising: established literature has indicated that AUD treatment engagement and outcomes can differ across race, ethnicity and sex assigned at birth [5–15, 23–26, 32, 33]. Indeed, individuals from minoritized and marginalized racial and ethnic groups face unique treatment obstacles [51], and the literature has shown these groups may be less likely to access and engage with existing interventions that are not culturally responsive [52]. In line with recommendations from scholars on developing culturally responsive interventions [53, 54], HaRT-A was developed, created and implemented within the community. Results might thus suggest that community-based and patient-led treatment can be more engaging and effective than provider-driven, high-intensity, abstinence-only behavioral treatment approaches that often pose formidable barriers for this population [55, 56]. Alternatively, the homogenously low socio-economic status of the sample may account for this result, given that lower socio-economic status has been shown to relate to greater alcohol treatment engagement, even when controlling for clinical severity [11, 49].

There was no significant moderation for XR-NTX effects on alcohol outcomes across race, ethnicity and sex assigned at birth; however, XR-NTX effects on PH-QoL were moderated by sex assigned at birth and by race

Male participants receiving XR-NTX showed improvement on PH-QoL, but at a slower rate than female participants. Importantly, women in our study had significantly lower mean PH-QoL at baseline compared with men and thus had less of a ceiling effect to overcome. As XR-NTX for AUD is understudied among women [31, 32], this finding is an important addition to the literature. Prior research has signaled that NTX, more broadly, is equally effective for men and women [31], and the present study provides additional support for its use in women.

The effects of XR-NTX on PH-QoL were also moderated by race. Specifically, participants in the multi-racial/other POC group who received XR-NTX showed no statistically significant improvement in PH-QoL, whereas participants who identified as multi-racial/other POC who received placebo injections did. Of note, the multi-racial/other POC group was heterogeneous, no other racial groups showed such effects, and the moderation analyses are subject both to multiple testing issues and to limited power. PH-QoL is also less central to AUD treatment than alcohol outcomes, and there were no differential effects of race, ethnicity or sex assigned at birth on medication treatment adherence, experience of side effects or the primary alcohol outcomes. We thus interpreted the observed moderation effects of race and sex assigned at birth and race on PH-QoL with caution, and view them primarily as 'hypothesis generating' and not conclusive [57].

Limitations

Findings from this study should be interpreted in the context of important limitations. First, there are some statistical and methodological limitations. Data were derived from a larger RCT that was not specifically powered to detect moderation effects. Therefore, it is possible that the lack of significant moderation of the behavioral HaRT-A effects by race, ethnicity and sex assigned at birth may have resulted from insufficient statistical power rather than true null effects. Further, the fact that we did not find significant differences

across these groups is not definitive evidence of equitable treatment effects because the parent study was not designed as a non-inferiority trial. Future studies with larger sample sizes are needed to specifically test whether harm-reduction treatments are equally efficacious across race, ethnicity and sex assigned at birth.

Of note, the parent study did not feature intentional recruitment by race, ethnicity and sex assigned at birth; thus, several socio-demographic groups were not equally represented in the present study. Considering the above, we collapsed groups with low representation (i.e. three Native Hawaiian/Pacific Islander participants) and people who identified with ethnic groups not currently recognized by federal designations (e.g. 'North African') and as multi-racial into the multi-racial/other POC category. The authors recognize that collapsing racial and ethnic groups can blur or erase the vast heterogeneity that exists within each racial and ethnic group [58].

Regarding measurement issues, it is widely known that alcohol can be subject to self-report bias for various reasons (e.g. intoxication level, cultural factors, stigma, social desirability [59–61]). Fortunately, this concern can be mitigated when time frames are relatively short, the target behavior is not stigmatized, negative consequences are not tied to disclosure and biochemical data are collected, which was the case in the parent study [60, 62, 63].

The generalizability of the present findings is also important to consider. Although the parent study team used inclusive gender measures and included non-binary staff in prominent roles, 43 participants did not respond to the gender identity question, and none identified as gender diverse. This likely reflects the structural barriers that gender-diverse individuals faced in accessing traditional service settings in the 2010s, which were organized around binary sex assigned at birth. As such, the findings may not generalize to gender-diverse populations and highlight the need for more inclusive systems of care and research engagement.

This study was also conducted in a large resource-rich city in the US Pacific Northwest with participants recruited from low-barrier community settings serving people experiencing homelessness who were not seeking AUD treatment. Therefore, the generalizability of our findings may be limited by socio-demographic and healthcare factors specific to the homeless population, the era and the geographical region where the study took place. Finally, given the low-barrier, inclusive nature of this approach, participants were not excluded for co-occurring psychiatric or substance use disorders. In fact, 80% of the sample engaged in polysubstance use [34]. Although the generalizability of this study may be limited to similar populations, the present findings are also potentially more expansive than in tightly controlled efficacy trials that have historically excluded people who engage in polysubstance use, despite its high prevalence in the general population (estimated at 40% [64]).

As we acknowledge the limitations of the present study, we also acknowledge these limitations reflect bigger challenges in the field of substance use treatment. Despite longstanding and ongoing mandates in the USA (e.g. 1993 Revitalization Act, National Institutes of Health policy NOT-OD-15-102) and repeated calls from researchers for equity-focused research, few AUD treatment trials conduct or report subgroup analyses by race, ethnicity or sex assigned at birth. Structural barriers—including funding caps and recruitment challenges for clinical trials—understandably impede this critical work. These larger systemic limitations may continue to hinder our collective ability to identify equitable and effective AUD treatments across minoritized and marginalized groups.

CONCLUSION

This secondary study is the first of its kind to assess the differential efficacy of a community-based, harm-reduction oriented and combined pharmacobehavioral treatment for AUD across race, ethnicity and sex assigned at birth in a population experiencing homelessness. Initial analyses indicated no associations of race, ethnicity or sex assigned at birth with trial inclusion, data missingness, medication adherence or the experience of side effects. Although participants from the multi-racial/other POC group attended fewer sessions than white participants, moderation analyses showed no differential effects of behavioral HaRT-A—on alcohol or PH-QoL outcomes—by race, ethnicity or sex assigned at birth. Similarly, XR-NTX effects on alcohol-related outcomes were not significantly moderated by these socio-demographic variables. However, XR-NTX effects on PH-QoL were moderated by both race and sex assigned at birth, with flat or slower improvement observed among multi-racial/other POC and male participants who received XR-NTX relative to their white and female counterparts, respectively. These results should be interpreted with caution given the *post hoc* nature of the analyses and the potential for Type 1 error owing to multiple comparisons.

Although these *post hoc* findings are not conclusive enough to inform clinical or policy decisions, they underscore the promise of harm-reduction treatment as a more equitable approach for minoritized populations and the importance of testing differential efficacy across socio-demographic groups, particularly on broader outcomes like PH-QoL. Future studies should be adequately powered to assess subgroup differences *a priori*. Such work—and the systemic support needed to conduct it—is essential to developing more equitable and effective AUD treatment strategies across diverse populations.

AUTHOR CONTRIBUTIONS

Silvi C. Goldstein: Conceptualization (lead); formal analysis (lead); methodology (lead); writing—original draft (lead). **Nicole H. Weiss:** Writing—review and editing (equal). **Manshu Yang:** Formal analysis (supporting); methodology (supporting); writing—review and editing (supporting). **Sarah W. Feldstein Ewing:** Writing—review and editing (supporting). **Susan E. Collins:** Formal analysis (supporting); funding acquisition (lead); investigation (lead); methodology (supporting); writing—review and editing (equal).

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DECLARATION OF INTERESTS

S.E.C. co-owns a social purpose corporation that provides trainings and consultation in harm-reduction treatment. The authors have no other competing interests to report.

DATA AVAILABILITY STATEMENT

Code and materials are available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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