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Intermittent theta burst to the left dorsolateral prefrontal cortex promoted decreased alcohol consumption and improved outcomes in those with alcohol use disorder: A randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Background: Over 60 % of individuals with alcohol use disorder (AUD) resume hazardous drinking within 6 months post-treatment, necessitating the development of more efficacious interventions. Accumulating evidence suggests transcranial magnetic stimulation (TMS) is a promising intervention for AUD. This randomized, double-blind, placebo-controlled trial assessed the efficacy of intermittent theta burst (iTBS), a form of TMS, as an adjunct treatment for AUD.

Methods: Forty-nine Veterans with AUD (48 males, 1 female) were recruited from residential AUD and substance use disorder treatment. Participants were randomized to 20 sessions of Active (n = 25) or Sham (n = 24) iTBS (1200 pulses/session), targeting the left dorsolateral prefrontal cortex (DLPFC) administered over 14 days or less. Five participants were withdrawn unrelated to iTBS procedure adverse events. Participant alcohol/substance use was monitored for 6-months following final iTBS session.

Results: Relative to participants who received Sham iTBS, those who received Active iTBS showed a significantly greater reduction in percent heavy drinking days and a trend for higher rate of continuous abstinence over 6-months. Among participants who resumed alcohol consumption, those in the Active group demonstrated significantly lower quantity and duration of alcohol consumption than Sham. Pre-study alcohol consumption variables were not related to post-iTBS treatment outcomes.

Conclusions: Findings indicated that Active left DLPFC iTBS, delivered over approximately 2-weeks, was a safe and efficient intervention for AUD that promoted significantly reduced heavy drinking and improved clinical outcomes compared to Sham over 6-months post-iTBS. This study provides novel data to inform and power future larger-scale, multi-site clinical trials employing iTBS for AUD.

1. Introduction

At least 60 % of those treated for alcohol use disorder (AUD) return to hazardous levels of alcohol consumption within 6-months (Durazzo and Meyerhoff, 2017; Maisto et al., 2006). Current evidence-based pharmacological (Bahji et al., 2022; Kotake et al., 2024) and psychosocial interventions (Magill et al., 2019) for AUD, at best, demonstrate moderate efficacy in promoting lower risk alcohol consumption or extended abstinence. The chronic resumption-remit cycle that affects many individuals with AUD necessitates the development of more efficacious primary or adjunct interventions.

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation intervention, has shown promise as a potential adjunct treatment for AUD. Results from TMS studies employing 10 or more sessions that delivered 10 or 20 Hz, intermittent theta burst stimulation (iTBS) or continuous theta burst to the dorsolateral prefrontal cortex (DLPFC), medial anterior frontal cortex, or anterior cingulate cortex, showed reduced post-intervention alcohol craving and consumption

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[see (Cole et al., 2024; Mehta et al., 2024; Padula et al., 2022) for comprehensive reviews]. However, not all studies reporting improved clinical outcomes were randomized, double-blind, placebo-controlled clinical trials (RCT) and most had limited follow-up periods to assess the durability of TMS-related clinical outcomes. Recently, we reported on the clinical efficacy of a pilot RCT that delivered 20 sessions of left DLPFC iTBS (600 pulses per session, two-to-three sessions/day, over approximately 14 days) to US Armed Services Veterans (designated as Veterans in remainder of this manuscript) in residential treatment for AUD (Padula et al., 2024). Among those who resumed alcohol consumption, individuals who received active iTBS, compared to sham, showed reduced rates of hazardous alcohol consumption for 3 months following treatment. Individuals who received active iTBS also demonstrated larger reductions in anhedonic depressive symptoms than those who received sham. fMRI-based alcohol cue-reactivity was reduced following active iTBS, and sham participants showed increased cue-reactivity, within multiple regions of the incentive salience network. These reductions are clinically significant given greater anhedonic symptoms and alcohol cue-reactivity were independently associated with poorer clinical outcomes in those with AUD (Nguyen et al., 2020; Padula et al., 2024).

The present RCT delivered 20 sessions of left DLPFC iTBS to 44 Veterans in residential AUD treatment. In this study, we administered 1200 iTBS pulses/session, compared to 600 pulses/session in our pilot study; all other study procedures were identical. We predicted that participants that received Active (n = 22), versus Sham (n = 22) iTBS, demonstrate: (1) greater reduction in percent heavy drinking days from pre-iTBS to 6-months post-iTBS; (2) higher rates of continuous abstinence 6-months post-iTBS; (3) in those who resumed alcohol consumption, significantly longer abstinence duration before first use over 6-months post-iTBS; (4) significantly lower odds of meeting Project MATCH criteria for poor treatment outcome and higher frequency of World Health Organization defined low risk alcohol consumption, among those who resumed alcohol use.

2. Materials and methods

2.1. Participants

Veterans with AUD (n = 49, 48 males and 1 female) were recruited from a residential substance use treatment program at the VA Palo Alto Health Care System (VAPAHCS) and randomized to active or sham iTBS conditions. Participants had approximately three weeks of abstinence prior to initiation of study procedures (see Table 1). Residential treatment typically ranged from 28 to 35 days. Four participants self-withdrew from the project: three withdrew because they did not wish to complete the multiple daily iTBS sessions and one participant left residential treatment against medical advice. The Principal Investigator (TCD) withdrew one participant before initiation of iTBS sessions, due to a large space occupying cerebral lesion apparent on structural MRI. No participant was withdrawn due to an adverse event (see Fig. 1 CONSORT diagram and Supplementary Information for recruitment details). Prior to the initiation of study procedures, participants signed an informed consent approved by the VAPAHCS and Stanford University, which adhered to the ethical standards of the Declaration of Helsinki. See Table 1 for participant demographic and clinical characteristics. This RCT (NCT03191266) was registered at https://www.clinicaltrials.gov/search?id=NCT03191266. See Supplemental Material Fig. 1 for study experimental timeline. Study recruitment began 2018–04–15 and the final 6-month follow-up was completed on 2024–03–06.

2.2. Group randomization and breaking the blind

Participants were randomly assigned (0.5 probability) to receive 20 sessions of Active or Sham iTBS; group study randomization codes were provided by a biostatistician not directly associated with study

Table 1
Baseline demographic and clinical variables.

Measure	Active (n = 22)	Sham (n = 22)	Group comparisons[a]
Age	50.6 (14.1)	51.3 (14.1)	$p = .89$
Education (years)	14.5 (2.2)	14.0 (2.2)	$p = .37$
Male (%)	22 (100)	21 (95)	$p = .99$
Race (%			All $p > .20$
Asian	1 (5)	1 (5)	
Black	2 (9)	5 (23)	
Native American	3 (14)	0 (0)	
Native Hawaiian/Pacific Islander	0 (0)	1 (5)	
White	16 (72)	15 (67)	
Ethnicity (%)			$p = .99$
Latino	5 (23)	4 (18)	
Days abstinent at study procedure initiation	22 (12)	21 (12)	$p = .76$
Days in residential treatment (median)	29	29	$p = .99$
Number of previous formal AUD inpatient or outpatient treatment programs (median)	2 Min = 0 Max = 10	2 Min = 0 Max = 14	$p = .99$
Lifetime Major Depressive Disorder (%)	14 (62)	13 (59)	$p = .99$
PTSD, past month (%)	15 (68)	12 (50)	$p = .56$
Substance use disorder, past month (%)	5 (23)	6 (27)	$p = .89$
Panic disorder, past month (%)	0 (0)	4 (18)	$p = .70$
Obsessive-compulsive disorder, past month (%)	0 (0)	1 (5)	$p = .99$
Beck Anxiety Inventory	10 (2)	12 (2)	$p = .37$
Beck Depression Inventory-II	17 (2)	21 (2)	$p = .24$
PTSD Checklist−5	53 (4)	58 (4)	$p = .40$
Smoking status (%)			All $p > .27$
Never	5 (23)	6 (28)	
Former	13 (59)	8 (36)	
Current	4 (18)	8 (36)	
Number alcohol drinking days 3-months prior to study	52 (24)	61 (23)	$p = .19$
Total number alcohol drinks 3-months prior to study (median)	602 Min = 12 Max = 1769	1102 Min = 172 Max = 1616	Sham > Active ($p = .039$)
Alcohol drinks per drinking day 3-months prior to study (median)	12 Min = 4 Max = 24	17 Min = 6 Max = 34	Sham > Active ($p = .018$)
Percent heavy drinking days over 3-months prior to study (natural log transformed)	3.7 (.99)	4.1 (.61)	$p = .11$
Alcohol Use Disorder Identification Test	27 Min = 13 Max = 37	30 Min = 17 Max = 35	$p = .99$
Number of DSM−5 alcohol use disorder criteria met	10 Min = 4 Max = 11	11 Min = 6 Max = 11	$p = .90$
Cannabis Use Disorder Identification Test (median)	12.5 Min = 4 Max = 28	7 Min = 4 Max = 18	$p = .24$
Anti-craving/anti-consumption			All $p > .80$
Disulfiram (%)	0 (0)	1 (5)	
Acamprosate (%)	1 (5)	2 (9)	
Topiramate (%)	2 (9)	0 (0)	
Naltrexone (%)	10 (41)	9 (46)	
Gabapentin (%)	7 (32)	8 (36)	
Antidepressants			All > .49
Selective serotonin reuptake inhibitor (%)	8 (36)	7 (32)	
Serotonin-norepinephrine reuptake inhibitor (%)	4 (18)	4 (18)	
Mirtazapine (%)	3 (14)	1 (5)	
Bupropion (%)	2 (9)	1 (5)	
Trazodone (%)	8 (36)	7 (32)	$p = .99$
Nicotine replacement (%)	8 (36)	4 (18)	$p = .31$
Varenicline (%)	2 (9)	1 (5)	$p = .99$

(continued on next page)

Table 1 (*continued*)

Measure	Active (n = 22)	Sham (n = 22)	Group comparisons[a]
Baseline to post-assessment interval (days)	15 (5)	14 (3)	$p = .25$
iTBS interval (days)	13 (4)	12 (2)	$p = .21$
iTBS sessions per day (median and mode)	2	2	$p = .99$
Percent participants predicted they received active iTBS after final session	86	82	$p = .63$
Confidence in rating of treatment assignment (1–10 Likert scale)	7.1 (1.6)	7.4 (1.7)	$p = .68$
Active motor threshold (median)	43 Min = 34 Max = 55	43 Min = 31 Max = 73	$p = .98$
Resting motor threshold (median)	53 Min = 37 Max = 65	50 Min = 36 Max = 88	$p = .62$
Percent of iTBS pulses delivered at target treatment level (median)	83 Min = 30 Max = 99	94 Min = 61 Max = 99	$p = .07$
Follow-up interval (median)	184 Min = 180 Max = 210	184 Min = 183 Max = 200	$p = .99$

Note. Mean (standard deviation) unless otherwise noted. [a]$p < 0.05$ considered statistically
significant; iTBS: intermittent theta burst; PTSD: post-traumatic stress disorder.

procedures. Twenty-five participants were assigned to Active and 24 were assigned to Sham iTBS. All study personnel and participants were blinded to group assignment during the baseline, post-iTBS and follow-up phases (see *2.6. Participant follow-up and Treatment Outcomes*). After the final contact during the 6-month follow-up with the last participant, a biostatistician, not associated with any aspect of the study, provided the PI with participant group assignments corresponding to their randomization code.

2.3. Inclusion/exclusion criteria

Primary inclusion criteria were 18 years of age or older, fluency and literacy in English, and in residential treatment for AUD. Exclusion criteria were: (1) current suicidal ideations representing imminent risk; (2) medical conditions/diseases or neurological disorders known to compromise brain neurobiology or contraindicated for TMS and/or brain magnetic resonance imaging; (3) previous history of clinical or research TMS; (4) documented history of traumatic brain injury with loss of consciousness > 10 minutes; (5) clinically documented impairment of visual and/or auditory acuity or motor skills that would compromise neurocognitive testing; (6) history of bipolar, schizophrenia spectrum or other psychotic disorder. See Supplemental Material for detailed inclusion/exclusion criteria and alcohol/substance use monitoring.

2.4. Psychiatric, substance, and drinking history assessment

At baseline (pre-iTBS), psychiatric diagnoses were assessed using the Mini-International Neuropsychiatric Interview for DSM-5 (MINI). Participants also completed the Clinical Interview for DSM-5 Alcohol Use Disorder and self-report questionnaires assessing demographics, medical history and other substance use. The Timeline Follow-back (TLFB) obtained alcohol consumption over the 3-months prior to study participation as well as monitored alcohol consumption during the 6-month post-treatment follow-up period. Percent heavy drinking days (pHDD; heavy drinking day was ≥4 alcohol units for females and ≥5 for males within 1 day) was calculated from the TLFB for 3-months prior to study and the 6-month follow-up interval and was the primary repeated measure longitudinal outcome index. See Supplemental Materials Treatment Outcome Measures and Cross-Sectional and Longitudinal Analyses for further details. Baseline depressive symptomatology and anxiety symptomatology were measured with the Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) respectively. Post-traumatic stress disorder (PTSD) symptomatology was assessed with the PTSD Checklist for DSM-5 (PCL-5) See (Nguyen et al., 2020) for corresponding references for the above measures.

2.5. iTBS session execution

Motor threshold, clinical assessment, and neuroimaging were conducted at the initial visit (baseline), typically 1 day prior to the first iTBS session, and 1 day following completion of iTBS sessions (post-assessment). iTBS sessions were executed over approximately 14 days (two-to-three sessions/day, five-to-six days/week. iTBS sessions were typically completed in the morning before the beginning of treatment program daily activities, during lunch break (all participants were allotted time to eat lunch) and/or after conclusion of daily program activities; this schedule allowed all participants to fully engage in treatment as usual provided by the VAPAHCS residential program. The median and mode number of iTBS sessions/day was two.

2.6. iTBS parameters

Active and passive motor thresholds (MT) were obtained using a MagVenture C-B60 coil and calculated with the Parameter Estimation by Sequential Training program (Borckardt et al., 2006). iTBS was delivered via a MagVenture MagPro X100 with MagOption, using a figure-of-eight Cool B-65 A/P (active/placebo-sham) coil. The Cool B-65 A/P coil was positioned for participants at each session at the left DLPFC (F3), using the standard electroencephalography 10–20 landmark location via the Beam-F3 method (Beam et al., 2009). The left DLPFC treatment location, determined via the Beam-F3 procedure, was marked on a MagVenture proprietary cap for each participant, which allowed consistent placement of the treatment coil for each session. iTBS was administered at 100 % (participants 1–10) or 110 % (participants 11–49) of each participant's active MT. iTBS was increased to 110 % of active MT after the tenth participant due to research in the depressive disorder treatment literature indicating iTBS delivered at 120 % of resting MT showed equivalent efficacy to 10 Hz TMS (Blumberger et al., 2018). Specifically, the increase of treatment level from 100 % to 110 % of MT was guided by the foregoing study and emerging research from the iTBS depression literature indicating treatment level above 100 % of MT may result in better outcomes (Cole et al., 2024).

In both the active and sham conditions, two electrodes (Pro-Patch, 2 ×2 in., were placed on the left forehead of participants, and a low amperage (2–20 mA, <100 V) current was delivered, to both groups, in a time-synchronized manner to the iTBS pulses to provide cutaneous stimulation that mimicked the sensation of active iTBS. All participants wore soft insert hearing protection, which also assisted with maintaining the participant blind. The above procedure was highly effective in maintaining left DLPFC sham integrity in our pilot study (Padula et al., 2024) and RCTs targeting the left DLPFC for treatment of depression (Cole et al., 2022; Yesavage et al., 2018) and mild cognitive impairment (Cheng et al., 2022).

iTBS pulses were delivered in a biphasic burst pattern (three pulse burst, 50 Hz; 5 pulses/s, 20 ms interpulse interval; 10 pulses/train, 8 s intertrain interval, 40 total trains, stimulation duration 376 s). Data regarding the percentage of total pulses (24,000) delivered at target treatment level was recorded for each participant to assess tolerability (see Table 1 and Supplemental Material Fig. 3). There were no adverse events during the iTBS phase of this study.

Following the last iTBS session, participants completed a questionnaire asking them to indicate if they believed they received active or sham treatment and their level of confidence in this assignment (Likert

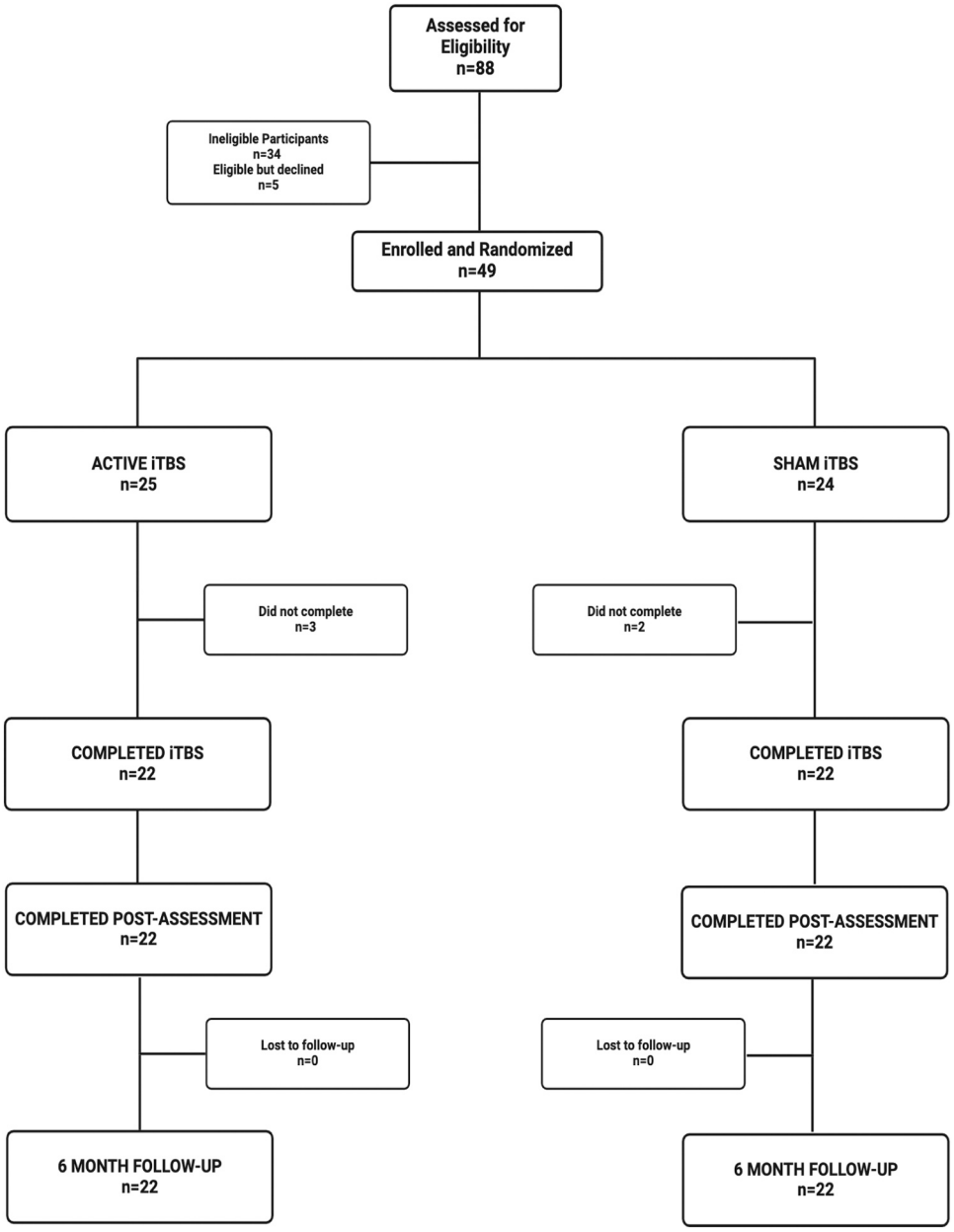

Fig. 1. CONSORT diagram. Four participants self-withdrew from the project; three withdrew because they did not wish to complete multiple daily iTBS sessions (one before and two after initiation of iTBS sessions); one participant left residential treatment against medical advice. The Principal Investigator (TCD) withdrew one participant before initiation of iTBS sessions, due to a large space occupying cerebral lesion apparent on the study structural MRI. No participant was withdrawn due to an adverse event.

scale, 1–10).

2.7. Participant follow-up and treatment outcomes

Participants were contacted monthly, via telephone, over approximately 6 months post-assessment to monitor alcohol and other substance use; if any alcohol or substance use was reported (no participant reported consumption of substances other than tobacco products during follow-up), the TLFB was administered. Participants also provided collateral contact sources (typically family or friends) that would be knowledgeable about their alcohol and/or substance use post-treatment. For all participants, VA electronic medical records were reviewed to corroborate self-reported alcohol and other substance use at each monthly follow-up; VA electronic medical records were also reviewed for participants who were unable to be contacted at a specific monthly follow-up to assist in determining alcohol and/or substance use (date, quantity and frequency). See Supplemental Material for details on post-iTBS 6-month follow-up.

There is currently no universally accepted definition or criteria for poor or successful AUD treatment outcomes (Sliedrecht et al., 2022; Witkiewitz et al., 2020b). The registered primary outcome for this study was frequency of abstinence at 6-month post iTBS. However, since the inception of this study, the AUD field has continued to evolve with respect to treatment outcome definitions for RCTs for AUD. Specifically, any alcohol use versus abstinence is increasingly viewed as having limited biopsychosocial relevance (May et al., 2023; Meyerhoff and Durazzo, 2020; Witkiewitz et al., 2020b; Witkiewitz and Tucker, 2020). Accordingly, in addition to comparing Active and Sham groups on frequency of abstinence, two additional definitions of treatment outcome were employed: Project MATCH and World Health Organization Risk

Drinking Levels (WHO-RDLs). Project MATCH criteria (Project Match Research Group, 1997) has been widely used as an operational definition of poor treatment outcome and meeting criteria was associated with poorer psychosocial functioning in Veterans (Durazzo et al., 2008). WHO-RDLs have been increasingly used as a non-binary definition of AUD treatment outcome that relates to psychosocial functioning, physical health, and quality of life (Knox et al., 2019a, 2018, 2019b; Witkiewitz et al., 2020a). Finally, we employed change in pHDD from pre-study to 6-month follow-up for Active and Sham groups as an additional indicator of iTBS efficacy. See Supplemental Material for operational definitions of Project MATCH poor treatment outcome, WHO-RDLs and pHDD.

2.8. Structural neuroimaging and electrical field modeling

Structural magnetic resonance imaging data were obtained on a 3 T GE system with a 32-channel head coil. High-resolution anatomical images were used to model TMS-induced electrical fields (See Supplemental Material for neuroimaging details and electrical field models).

2.9. Statistical analyses

The five withdrawn participants were not included in statistical analyses. Intention-to-treat analyses were not possible because data for the primary treatment outcome measures could not be retrieved from these participants (unable to contact) or medical records. Given the nature of the treatment outcome measures employed in this study, procedures to address missing data, such last observation carried forward was not possible, and multiple imputation was not conducted, given the modest study sample size.

2.9.1. Cross sectional analyses

Active and Sham groups were compared on baseline demographic and clinical variables via Fisher's Exact Test, Mann-Whitney Test or univariate analysis of variance, as appropriate. Comparisons of Active and Sham groups on pHDD, at baseline and post-assessment, were completed with generalized linear modeling and corresponding pairwise *t*-tests. Comparisons of alcohol consumption variables at 6-month follow-up in the Active and Sham groups were completed with Mann-Whitney Test due to the highly skewed distributions of these variables. $P < .05$ was considered statistically significant for all cross-sectional analyses. See Supplementary Material for analysis details.

2.9.2. Survival and logistic regression analyses

Thirteen Active and nine Sham participants remained continuously abstinent over the 6-month follow-up interval. Cox regression tested the prediction that the number of days until resumption of alcohol use over the 6-month follow-up period was significantly longer in the Active (n = 9) versus Sham (n = 13) participants who resumed drinking. Logistic regression tested the hypothesis that the odds of continuous abstinence was greater, and odds of meeting Project MATCH criteria was lower, at 6 months following post-assessment in the Active (n = 22) versus the Sham (n = 22) group. $P < .05$ was considered statistically significant for these analyses. All cross sectional, survival and logistic regression analyses were completed with SPSS v29.

2.9.3. Longitudinal analysis

Longitudinal comparisons of Active (n = 22) and Sham (n = 22) groups on change in pHDD between 3-months prior to study and 6-month follow-up were completed with R (v4.4.1) linear mixed modeling (package nlme 3.1–164). See Supplementary Information for analysis details.

2.9.4. Covariates

In survival, logistic regression and longitudinal analyses, total number of alcohol-containing drinks 3 months prior to study or average number of drinks per drinking day 3-months prior to study served as covariates, given the significant baseline difference between groups on these measures. In secondary analyses, antidepressant and anti-craving/anti-consumption medication use (see Table 1) were considered as binary covariates (yes, no) in final models of all analyses. These medications were first entered as a class (i.e., antidepressant or anti-craving/anti-consumption); medications from each class with a frequency of at least five participants in both the Active and Sham groups were then individually considered as binary covariates. Potential effect of participants whose treatment level was based on 100 % vs.110 % of active MT was considered as a covariate (binary coding) in all survival, logistic regression and longitudinal analyses. Given the modest sample size, the above covariates were individually entered into models to avoid data overfiting.

2.9.5. Exploratory analyses

The associations between total number of alcohol-containing drinks 3-months prior to study and average number of drinks per drinking day 3-months prior to study and consumption variables obtained over the 6-month follow-up period (total number of drinks, drinks per drinking day, average drinks per day over follow-up and number of days of alcohol consumption) were evaluated in the individual and combined Active and Sham groups via Spearman correlations. Active and Sham groups were compared on the frequency of WHO-RDL low, medium, high and very high-risk categories, based on reported alcohol consumption during the post-iTBS follow-up monitoring period, via Fisher's Exact Test. The association between number of pulses received at target treatment level and continuous abstinence (binary: yes, no) in Active participants was also examined with Spearman correlations and Kendall tau-b. $P < .05$ was considered statistically significant for these exploratory analyses.

3. Results

3.1. Baseline demographics and clinical measures

Active and Sham groups were not significantly different on any baseline demographic characteristics, medication use, psychiatric diagnosis frequency or on the BDI-II, BAI or PCL-5. The number of baseline DSM-5 criteria met in both groups indicated severe AUD. Five Active and six Sham participants met criteria for a substance use disorder (SUD) and the most common SUD in both groups was cannabis use disorder. The Sham group consumed a significantly higher total number of alcohol-containing drinks and average drinks per drinking day than the Active group over the 3-months prior to study participation. There were no reported changes in medication type over the iTBS phase for Active or Sham groups. After the final session, 86 % of Active and 82 % of Sham participants indicated they received active iTBS (overall classification accuracy 52 %) and rated their confidence in this belief as 7.1 ± 1.6 and 7.4 ± 1.7, respectively (see Table 1).

3.2. Longitudinal comparison of active and sham on pHDD

Group x time (baseline-to-6 month post-assessment interval) interaction ($b = -0.006$, standard error of the estimate (SE) = 0.002, t_{42} = -2.04, $p = .048$), time ($b = -0.011$, SE = 0.002, $t_{42} = -5.28$, $p < .001$) and age (b = 0.025, SE = 0.009, $t_{41} = 2.04$, $p = .008$), were significant predictors. Simple effect tests indicated pHDD decreased in both Active ($b = -0.016$, SE = 0.002, $t_{21} = -9.81$, $p < .001$) and Sham ($b = -0.011$, SE = 0.002, $t_{21} = -4.64$, p = .001), but the group x time interaction indicated a greater decrease in pHDD in Active compared to Sham participants (see Fig. 2).

3.3. Survival and logistic regression analyses

For those who resumed alcohol consumption following iTBS, Active

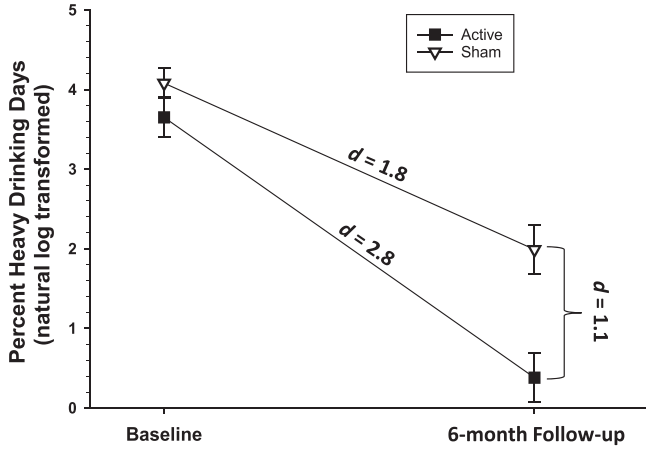

Fig. 2. Percent Heavy Drinking Days (pHDD) over 3-months (Baseline) prior to study and 6-month follow-up in Active (n = 22) and Sham (n = 22) participants. Effect sizes (ES) were calculated with Cohen's *d*.

participants had a significantly greater length of continuous abstinence than Sham [β = 1.04, p = .049, Exp (β) = 2.82 (95 % confidence interval (C.I.) = 1.01–7.92) see Fig. 3]. Active participants demonstrated a trend for 4.4 times greater odds of continuous abstinence over 6-months, [β = 1.47, p = .050, Exp (β) = 4.36 (95 % C.I. = 1.01–18.9)]; this best fitting model included group (Active vs. Sham) and average drinks per day 3-months prior to study, and, overall, correctly classified 71 % of Active and Sham participants into their respective groups. The odds of meeting Project MATCH criteria were 26 times greater in Sham compared to Active participants [β = -3.27, p = .007, Exp (β) = 0.038 (95 % C.I. = 0.004–0.410)]; this best fitting model included group (Active vs. Sham) and number of drinks over 3-months prior to study, and overall, correctly classified 80 % of Active and Sham participants into their respective groups.

In the above longitudinal, survival and logistic regression analyses, drinks per day 3-months prior to study or number of drinks over 3-months prior to study, anti-craving and antidepressant medications and iTBS treatment level (i.e., 100 % vs. 110 % of MT) were not significant predictors (all p > .29) and their inclusion did not improve model fit in any analysis.

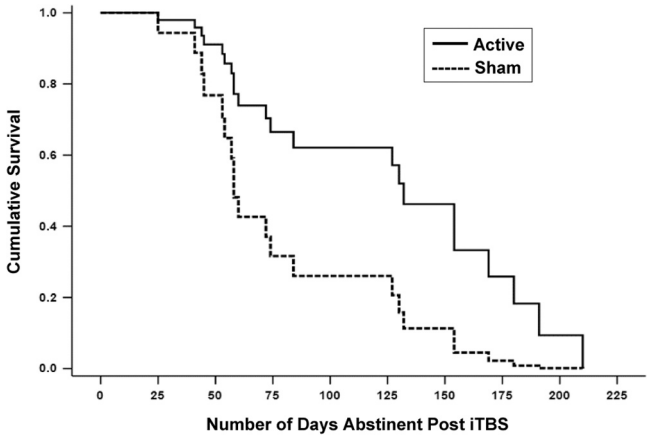

Fig. 3. Cumulative survival estimates for duration of abstinence in Active (n = 9) and Sham (n = 13) participants that resumed alcohol consumption post iTBS over the 6-month follow-up interval.

3.4. Comparison of active and sham groups on alcohol consumption variables at 6-month follow-up

Among participants who resumed alcohol consumption following treatment, Sham participants had a significantly greater number of days of alcohol consumption (z = -2.48, p = .013), number of alcohol-containing drinks consumed (z = -2.91, p = .004), average alcohol-containing drinks per day over entire follow-up interval (z = -2.91, p = .004) and alcohol-containing drinks per drinking day (z = -3.09, p = .002; see Fig. 4A-D). Sham participants showed a higher pHDD than Active participants at 6-month follow-up (p = .002; see Fig. 2)

3.5. TMS electrical field models

There were no significant differences between estimated average electric field model level between Active (55.9 ± 12.2 V/m) and Sham (59.3 ± 12.6 V/m) groups (see Supplementary Material Fig. 4).

3.6. Exploratory analyses

In participants that resumed alcohol consumption, there was a significantly higher frequency of WHO-RDL low risk consumption in the Active, compared to Sham group [χ^2 (3) = 9.23, p = .023; see Table 2]. In the Active group, a higher percent of pulses delivered at target treatment level showed a trend association with continuous abstinence over the 6-month follow-up period (Spearman r = 0.41, p = 0.059; Kendall tau-b, r = 0.36, p = 0.061; see Supplemental Material Fig. 6). There were no significant associations between pre-study alcohol consumption variables and post-treatment alcohol consumption over the 6-month follow-up interval in the combined or individual Active and Sham groups (all p > .07).

4. Discussion

The main findings from this study with primarily male Veterans in residential treatment for AUD were as follows: (1) The Active group demonstrated a significantly greater reduction than Sham in pHDD from 3-months prior to study to 6-months post-iTBS treatment. (2) Active participants demonstrated a trend for a greater frequency and likelihood of continuous abstinence than Sham over the 6-month follow-up period. (3) Among those who resumed alcohol consumption during the 6-month follow-up, the Active group showed a significantly longer duration of post-iTBS abstinence, lower alcohol consumption, and better treatment outcomes (i.e., fewer meeting Project MATCH criteria and higher frequency of WHO-RDL low risk alcohol consumption). (4) Alcohol consumption variables over the 3-months prior to study were not related to alcohol consumption over the 6-month follow-up interval.

The primary goal of this RCT was to present the clinical outcomes associated with 24,000 iTBS pulses in Veterans with AUD, which is double the dose our pilot trial (Padula et al., 2024). The addition of pHDD and non-binary definition of treatment outcome (i.e., WHO RDLs) increases the clinical relevance of this RCT's findings well beyond the registered primary outcome measure of abstinence versus any alcohol consumption over 6-months. The greater reduction in pHDD in Active versus Sham participants is congruent with a recent RCT (Harel et al., 2022) employing 10 Hz stimulation, via an H-coil, to target the medial prefrontal and anterior cingulate cortex. While both Active and Sham groups in our study showed a significant reduction in pHDD, the magnitude of change was considerably larger in Active participants. Additionally, the pHDD at 6-months in Active participants was markedly lower than Sham, reinforcing the importance of the greater longitudinal decrease in pHDD seen in the Active group. Importantly, active iTBS in this study produced a greater rate of continuous abstinence, longer duration of abstinence (in those who resumed drinking), and lower drinking severity over 6-months than our pilot (Padula et al., 2024) and other TMS RCTs that delivered at least 10 sessions [e.g., (Addolorato

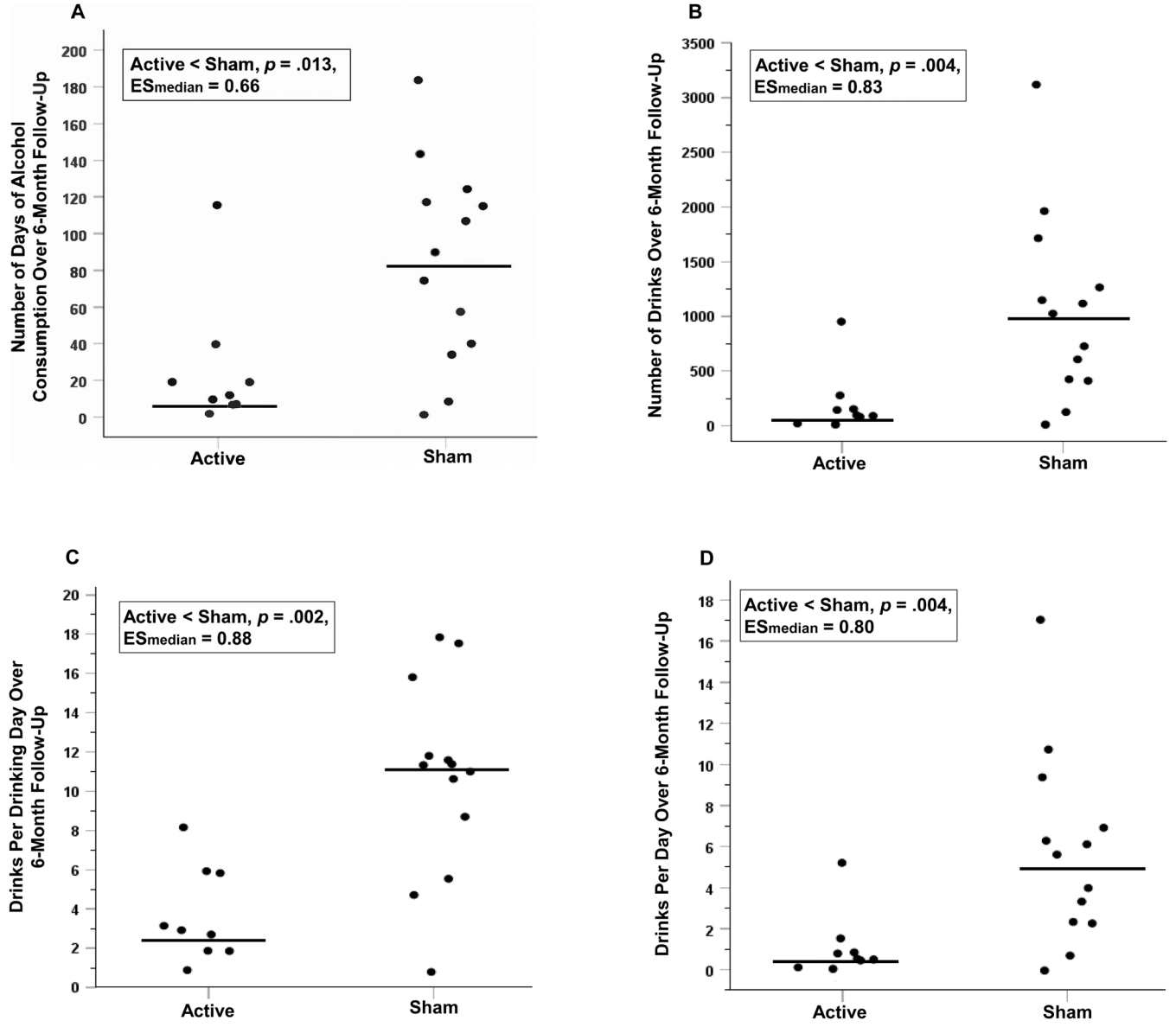

Fig. 4. A. Number of days of alcohol consumption for Active (n = 9) and Sham (n = 13) participants over 6-month follow-up interval. Horizontal bars designate group medians. Effect sizes were calculated for group median differences (ES_{median}) and values of = 0.10, 0.30, and 0.50 correspond to small, medium, and large effect sizes, respectively. B. Number of alcohol-containing drinks for Active (n = 9) and Sham (n = 13) participants over 6-month follow-up interval. Horizontal bars designate group medians. Effect sizes were calculated for group median differences (ES_{median}) and values of = 0.10, 0.30, and 0.50 correspond to small, medium, and large effect sizes, respectively. C. Number of alcohol-containing drinks per drinking day for Active (n = 9) and Sham (n = 13) participants over 6-month follow-up interval. Horizontal bars designate group medians. Effect sizes were calculated for group median differences (ES_{median}) and values of = 0.10, 0.30, and 0.50 correspond to small, medium, and large effect sizes, respectively. D. Number of alcohol-containing drinks per day (averaged across 6-month follow-up) for Active (n = 9) and Sham (n = 13) participants over 6-month follow-up interval. Horizontal bars designate group medians. Effect sizes were calculated for group median differences (ES_{median}) and values of = 0.10, 0.30, and 0.50 correspond to small, medium, and large effect sizes, respectively.

et al., 2017; Harel et al., 2022; Hoven et al., 2023; McCalley et al., 2023; Perini et al., 2020; Zhang et al., 2022)]. Over the 6-month follow-up period, all alcohol consumption variables were markedly lower in Active participants and the effect sizes for differences between Active and Sham were large in magnitude. Additionally, only one Active participant met Project MATCH criteria compared to 10 in Sham participants; in those who resumed alcohol consumption, eight of nine (89 %) in the Active group engaged in WHO-RDL low risk drinking, while only three of 13 (8 %) in the Sham group engaged in WHO-RDL low risk drinking during the 6-month follow-up period. Sustained abstinence from alcohol over 6 or more months was associated with improved psychosocial outcomes in Veterans in our previous work (Durazzo et al., 2008) and post-treatment WHO-RDL low risk drinking was related to decreased regional brain atrophy and better neurocognition than higher risk drinking [see (May et al., 2023) and references therein]. The above clinical outcomes for the Active group indicate the iTBS protocol employed in this study led to adaptive behavioral changes during the follow-up period that are associated with improved quality of life during AUD recovery (Durazzo et al., 2008; Witkiewitz et al., 2020b, 2019).

There was a considerable range in the number of pulses delivered at target treatment level across groups (see Table 1 and Supplemental Material Fig. 3), indicating not all participants were able to fully tolerate their target treatment level at the initiation of each session, consistent with the pattern observed in our pilot. However, all Active participants received at least five trains at target treatment level by session seven. In

Table 2
Six-month follow-up alcohol consumption and outcome variables.

Measure	Active (n = 22)	Sham (n = 22)	Group comparisons[a]
Follow-up interval (median)	184 Min = 180 Max = 210	184 Min = 183 Max = 200	$p = .99$
Number of days abstinent (in participants that resumed alcohol consumption; median)	154 Min = 53 Max = 210	83 Min = 25 Max = 191	Active > Sham ($p = .049$)
Project MATCH criteria (%)	1 (5)	10 (46)	Active < Sham ($p = .004$)
WHO Risk Drinking Level (%)			
Abstinent	13 (59)	9 (41)	Active > Sham ($p = .023$)
Low	8 (36)	3 (14)	
Medium	0	2 (9)	
High	1 (5)	5 (23)	
Very High	0	3 (13)	

Note. [a] $p < 0.05$ considered statistically significant.

Active participants, higher active MT was related to a lower percent of iTBS pulses delivered at target treatment level (see Supplemental Material Fig. 5). Given the positive association between number of pulses administered at target treatment level and abstinence across the 6-month follow-up interval in the Active group, adding trains during each session at the target treatment level to compensate for any delivered at sub-target level should be considered.

Notably, longitudinal change in pHDD, post-treatment alcohol consumption over the 6-month follow-up interval, and duration of abstinence in Active than Sham participants (in those who resumed alcohol consumption) were not related to pre-study alcohol consumption variables. This indicates pre-study alcohol consumption did not account for the differential outcomes apparent in the Active and Sham participants. Despite the greater pre-study alcohol consumption in the Sham participants, study groups were equivalent on Alcohol Use Disorder Identification Test and number of DSM-5 alcohol use disorder criteria met. Additionally, Active and Sham groups were not significantly different on baseline depressive, anxiety and PTSD symptomatology or on frequency of psychiatric diagnoses and prescribed medications (see Table 1); therefore, the greater pre-study alcohol consumption in the Sham group was not related to more severe baseline AUD or common comorbid psychiatric symptomatology than Active participants. Commonly prescribed medications to reduce alcohol consumption and/or treat common psychiatric comorbidities in AUD were not significant predictors in any analysis. Of note, most previous TMS studies for AUD or substance use disorders either excluded participants for medications allowed in this study or did not specifically consider medications in the analytic strategy (Cole et al., 2024; Mehta et al., 2023). However, the sample size of this study precluded definitive assessment of potential medication mediation/moderation effects on iTBS treatment outcomes.

TMS, across coils and pulse types, is indicated to promote adaptive behavioral change via neuroplastic modifications of cortical-subcortical circuits associated with the neocortical or paralimbic node stimulated (Antonelli et al., 2021; George, 2007; Philip et al., 2020); however, the actual neurobiological mechanisms promoting the improved clinical outcomes, as well as the durability of the improvements associated with TMS for AUD, are not fully understood (Cole et al., 2024; Kirkovski et al., 2023; Mehta et al., 2023; Padula et al., 2024). In our pilot RCT (Padula et al., 2024), alcohol cue-reactivity was decreased following active iTBS, and increased following sham, in the left insula, left thalamus, right insula, and right thalamus. The neurobiological mechanism(s) associated with the significantly improved clinical outcomes in Active participants will be examined in a future report, with an emphasis on the neuroimaging-based measures employed in our pilot study (Padula et al., 2024), and related work in AUD (Durazzo et al., 2023, 2024; Zou et al., 2017).

This study has limitations that may affect the generalizability of the findings. Due to the extended halt of human subject recruitment during the COVID-19 pandemic, and the Principal Investigator's (TCD) 1.5 year active duty Army National Guard activationduring the study recruitment phase, the sample size was lower than the 80 used to power the current study. The sample was comprised of predominately male Veterans. Future iTBS studies should incorporate a larger proportion of females considering large-scale TMS RCTs indicated sex may influence clinical outcomes in depressive disorders (Kedzior et al., 2014; Sackeim et al., 2020). There was a large, but equivalent, placebo effect in both groups (i.e., most participant believed they received active iTBS), which is common in TMS and other RCTs for AUD (Cole et al., 2024; Harel et al., 2022; Mehta et al., 2024; Padula et al., 2022). This study primarily relied on self-report of post-treatment drinking history, substance use history, and did not employ biochemical confirmation [e.g., ethyl glucuronide (Junghanns et al., 2009)] to corroborate treatment outcomes. Alcohol consumption variables were not related to the dependent measures in the cross-sectional or longitudinal analyses of this study; however, the greater alcohol consumption in the Sham group, at study entry, may have influenced brain neurobiology and performance on the primary measures that were not directly considered in this report. Premorbid factors (e.g., genetic risk/resiliency factors) and comorbid factors (e.g., diet/nutrition, exercise, and subclinical hepatic, cardiac, or cerebrovascular dysfunction) that were not assessed in this study may have influenced the reported findings.

5. Conclusions

The 24,000 active iTBS pulses delivered in this study is novel and associated with significantly improved clinical outcomes relative to sham. Additionally, the overall clinical outcomes in the current study are more robust that those observed in our pilot RCT (Padula et al., 2024). The use of non-binary definitions of treatment outcomes in this study increases the clinical relevance and generalizability of the findings. Consistent with our pilot RCT, there were no adverse events during the iTBS phase of the study and participant self-discontinuations from the project were unrelated to iTBS procedure tolerability. The overall improved outcomes in the Active group in this study, relative to our pilot, may be related to the doubled number of iTBS pulses; further research on number and delivery interval of iTBS pulses is required to determine the optimal treatment protocol for AUD. This study provides novel data to power future larger-scale RCTs to evaluate the efficacy of iTBS for AUD. Results indicate the left DLPFC iTBS protocol of this study is a promising adjunct intervention for AUD that can be safely and efficiently administered over 2-weeks or less.

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The study sponsor (Department of Veterans Affairs) had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

CRediT authorship contribution statement

Durazzo, Timothy C.: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kraybill, Eric P.:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Stephens, Lauren H.:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Humphreys, Keith:** Writing – review & editing, Writing – original draft, Conceptualization. **McCalley, Daniel M.:** Writing – review & editing, Writing –

original draft, Methodology, Formal analysis. **May, April C.:** Writing – review & editing, Writing – original draft, Conceptualization. **Padula, Claudia B.:** Writing – review & editing, Writing – original draft, Resources, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Appendix A. Supporting information

Supplementary materialassociated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112641.

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