Drug and Alcohol Dependence 275 (2025) 112837

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

World Health Organization risk drinking level reductions as treatment outcomes in PTSD and substance use disorder trials

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ARTICLE INFO

Keywords:
PTSD
Alcohol use disorder
Treatment
Abstinence
Harm reduction
Integrated data analysis

ABSTRACT

Objective: Alcohol use disorder (AUD) clinical trials have traditionally prioritized abstinence, and more recently, heavy drinking cessation as primary treatment endpoints. Reductions in World Health Organization (WHO) risk drinking levels may offer a viable harm reduction-aligned alternative. Despite evidence supporting WHO risk level reductions as meaningful indicators of AUD treatment response, their utility in individuals with co-occurring posttraumatic stress disorder (PTSD) remains unknown. The present study compared 1- and 2-level WHO risk drinking reductions with abstinence and heavy drinking (HD) outcomes, and assessed their sensitivity across PTSD and substance use disorder (SUD) interventions, including behavioral and pharmacological treatments.

Methods: We conducted an integrative data analysis of 10 trials for adults with comorbid PTSD and SUD (PTSD+SUD). The proportion of participants achieving each of the four alcohol outcomes was calculated. Logistic regression models assessed treatment effects relative to treatment as usual (TAU).

Results: Across the 10 trials (N = 433; mean [SD] age, 39.7 [11.6] years; 359 [73.0 %] men), the most frequently achieved drinking outcome at end-of-treatment was a 1 + level WHO risk reduction (82.8 %), followed by a 2 + level reduction (72.2 %), HD cessation (65.6 %) and, least frequently, abstinence (53.0 %). Pharmacological interventions significantly outperformed TAU across all drinking outcomes.

Conclusions: Findings provide initial support for WHO risk drinking levels as viable endpoints in PTSD+SUD trials. Given their attainability, WHO risk levels may provide clinically relevant outcome metrics for these interventions. Future research should assess whether such reductions correspond to improvements in alcohol-related harms and broader functional outcomes.

An estimated 43 % of the global population 15 years or older currently drink alcohol (World Health Organization, 2018). Nearly 11 % of individuals who drink develop alcohol use disorder (AUD). Alcohol use and AUD carry significant public health implications, with

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https://doi.org/10.1016/j.drugalcdep.2025.112837
Received 26 June 2025; Received in revised form 29 July 2025; Accepted 2 August 2025
Available online 9 August 2025

documented negative impacts on physical health (Hendriks, 2020), social relationships (Marshal, 2003) and the economy (Bouchery et al., 2011; Manthey et al., 2021). Alcohol is also a leading cause of morbidity and mortality, associated with more than 50 different causes of death (Esser et al., 2022), and the global prevalence of alcohol use and heavy drinking (HD; for men consuming 5 or more drinks on any day and for women 4 or more drinks on any day) are both expected to increase throughout the decade (Manthey et al., 2019). However, few individuals affected by AUD seek formal treatment and many that do terminate treatment prematurely (Hasin and Grant, 2015).

Traditional benchmarks for AUD treatment "success" have been complete cessation of alcohol use (abstinence), which has servedas the *de facto* primary outcome in many AUD clinical trials. As AUD diagnostic and recovery conceptualizations evolve with the recognition that alcohol use and related harms exist on a continuum (Substance Abuse and Mental Health Services Administration, 2016; Witkiewitz et al., 2020b), the field of AUD treatment research has begun the expansion of treatment efficacy endpoints beyond abstinence. Beginning with the study of controlled drinking (Sobell and Sobell, 1973) and marked by the 2015 Food and Drug Administration (FDA) endorsement of no HD days as an acceptable outcome for clinical trials (U.S. Food and Drug Administration, 2020), non-abstinence endpoints have garnered considerable empirical support as viable trial endpoints. Most recently, in February 2025, the FDA added a 2-level reduction in the World Health Organization's (WHO) risk drinking categorization so that AUD clinical trials now have two non-abstinence endpoints (U.S. Food and Drug Administration, n.d). Unlike the other FDA-endorsed endpoints (abstinence and no HD days), WHOrisk level reductions account for the relative starting point of the individual and thus may provide an alternative, more personalized treatment goal for those with AUD.

The evidence base for the utility of WHO risk level reductions is robust. When applied to populations with AUD, research on WHO risk drinking levels have shown that reductions are achievable and even 1-level reductions are associated with significant health benefits including decreased risk of alcohol dependence at 3-year follow up among those drinking at the very-high and high-risk levels (Hasin et al., 2017). For those in the very-high risk category, any reductions in WHO risk drinking levels were associated with significantly lower odds of anxiety or depression at 3-year follow up, indicative of clinically meaningful improvements in affect and functioning (Knox et al., 2019). In pharmacotherapy trials for AUD (Witkiewitz et al., 2017), WHO risk level reductions have predicted reductions in alcohol-related consequences and improved mental health outcomes and these improvements have been demonstrated to be sustainable, irrespective of AUD severity. A secondary data analysis of multi-site clinical trials of AUD pharmacotherapies and behavioral interventions showed 1- and 2-level risk reductions were maintained at the one-year follow up and associated with fewer alcohol-related consequences, improved mental health, and better liver functioning, even in the context of severe AUD (Witkiewitz et al., 2020a).

Despite growing support for non-abstinence AUD treatment outcomes, an important gap remains in understanding how WHO risk drinking level metrics perform in clinical populations with complex comorbidities. In clinical trials of AUD, comorbid psychiatric and drug use disorders are often excluded (Falk et al., 2019; Witkiewitz et al., 2020a, 2018, 2017), limiting their generalization to real-world treatment settings where concurrent conditions are common. For example, the co-occurrence of posttraumatic stress disorder (PTSD) with alcohol and other substance use disorders (SUD) is prevalent (e.g., one third of individuals with lifetime PTSD have lifetime AUD; [Blanco et al., 2013]) and presents unique challenges for treatment and recovery including more psychiatric impairment, social instability, suicidality, and a greater number of SUDs (Grant et al., 2016; Simpson et al., 2019). The high rates of comorbidity between PTSD and SUD (PTSD+SUD) underscore the need to examine if WHO risk drinking levels may serve as a viable marker of treatment outcomes for those with PTSD+SUD and whether viability differs across PTSD+SUD interventions. In a recent individual participant level meta-analysis of 36 PTSD+SUD treatment studies (Hien et al., 2023) nine treatment classes—defined by treatment focus (PTSD, SUD or both) and intervention type (behavioral, pharmacological, or combination)—were compared. Trauma-focused therapies, either integrated with SUD intervention or on their own, were more effective for treating PTSD—and sometimes SUD—than treatment as usual (TAU). Still, while integrated treatments that address both PTSD and SUD symptoms have demonstrated improved outcomes, the increased complexity of PTSD+SUD may require additional treatment targets, such as WHO risk levels, to achieve clinically meaningful changes (Lyons et al., 2021; Straus et al., 2018).

To this end, we conducted a secondary data analysis of 10 clinical trials for PTSD+SUD. First, we sought to assess the proportion of individuals who achieved reductions in WHO risk drinking levels by the end of treatment. Secondly, we compared the proportion of individuals who achieved 1- or 2-level reductions in WHO risk levels to the proportion of those who achieved two commonly employed metrics of AUD treatment outcomes: abstinence and absence of HD. Third, we assessed the odds of achieving each of the four AUD treatment outcomes by treatment class compared to TAU. Together, these three aims are foundational in systematically evaluating whether WHO risk levels are viable endpoints in PTSD+SUD trials.

1. Methods

1.1. Study and participant selection

Data were drawn from *Project Harmony* (PH; Hien et al., 2023), a compilation of individual patient data from randomized controlled trials (RCTs) of treatments for PTSD and SUDs (Saavedra et al., 2021). The present study included a subset of 10 RCTs that measured alcohol use prior to intervention and at end-of-treatment as a count variable (e.g., drinks per day; see S1 for included studies). Integrative data analysis (IDA) was used to harmonize participant-level data from the included studies and limit bias due to study characteristics (Morgan-López et al., 2022; Saavedra et al., 2021). Given our interest in examining changes in alcohol use outcomes, analyses included participants whose drinking was considered moderate risk (level 2) or greater as defined by the WHO risk levels (see Table 1 for WHO classifications). Of the studies included, four (Brady et al., 2005; Norman et al., 2019; Petrakis et al., 2015; Petrakis et al., 2020) specifically targeted AUD.

1.2. Interventions

There were 13 unique interventions across the 10 included studies. Interventions were organized into four treatment classes in alignment with the original PH configuration (Hien et al., 2023): TAU (n = 49), trauma-focused behavioral interventions (n = 77), non-trauma-focused behavioral interventions (n = 121), and pharmacological interventions (n = 183). Pharmacological interventions included two SUD-targeting medications (N-acetylcysteine [n = 5] and zonisamide + Cognitive Processing Therapy [n = 13]), three PTSD-targeting medications (sertraline [n = 38], prazosin [n = 37], and Paxil [n = 3]), and placebo

Table 1
World Health Organization (WHO) Drinks per Day Alcohol Risk Levels.

Sex	No Risk (0)	Low Risk (1)	Moderate Risk (2)	High Risk (3)	Very High Risk (4)
Female	0.0	> 0.0 – 1.4	> 1.4 – 2.8	> 2.8 – 4.3	> 4.3
Male	0.0	> 0.0 – 2.9	> 2.9 – 4.3	> 4.3 – 7.1	> 7.1

Note. The WHO alcohol risk levels were used to create a 4-level categorical variable corresponding to the risk levels.

(placebo only [n = 82], placebo + Cognitive Processing Therapy [n = 5]). The combined medication and behavioral therapy and the placebo medications were included in the pharmacological class as previous research from PH found that these treatment types resulted in similar effect sizes as medication-only interventions (Morgan-López et al., 2022).

1.3. Measures

1.3.1. Covariates

Baseline covariates included age, sex, race and ethnicity, education, marital status, veteran status, and use of psychotropic medications. The proportion of attendance at available sessions (range: 0–1) was harmonized across studies to create a dose variable. Baseline PTSD severity scores were derived from clinical interviews and self-report measures using IDA and Moderated Nonlinear Factor Analysis (MNLFA). The 42 indicators of PTSD from self-report and clinician-administered assessments were converted into binary items consistent with the Diagnostic and Statistical Manual for Mental Disorders versions IV-Text Revision and 5 (American Psychiatric Association, 2000; American Psychiatric Association, 2013) criteria for PTSD. Severity scores were scaled to N(0,1). See (Hien et al., 2023) for additional detail.

Following the IDA/MNLFA framework, a latent variable for baseline alcohol use severity was derived from two items: (1) number of days of alcohol use in the past 30 days and (2) any alcohol use to intoxication in the past 30 days. A baseline drug use severity item was created using six binary indicators corresponding to any past-month use of cocaine, heroin, other opioids, sedatives, other psychostimulants, and hallucinogens. Measures assessing alcohol and drug use included the Timeline Followback (TLFB; Sobell and Sobell, 1992); Addiction Severity Index (ASI; McLellan et al., 1980), and the Substance Use Inventory (SUI; Weiss et al., 1995).

To adjust for within-study randomization and potential correlations between randomization, treatment type, baseline covariates, and baseline severity of PTSD symptoms, alcohol use, and other drug use, propensity score weighting was used to balance classes and minimize bias due to study characteristics. Separate weights were created for each outcome as the HD models included baseline HD as a binary (no/yes) covariate and the WHO risk level models included baseline WHO level as an ordered categorical (0−4) covariate.

1.3.2. Primary Outcomes

1.3.2.1. Abstinence. Presence of any alcohol use was assessed via the TLFB. At baseline, the TLFB was assessed in 30–60- or 90-day increments. At end-of-treatment, the TLFB assessed the past 7 days. Several studies also employed the ASI which includes an item asking for the number of drinks consumed over the past 30 days. Abstinence at end-of-treatment was coded as 1 (any alcohol use days) or 0 (no use or abstinence).

1.3.2.2. Heavy Drinking (HD) Days. The TLFB and ASI were also used to assess HD, defined as any days in which the individual consumed four/five or more drinks on a single occasion for women and men, respectively; TLFB) or any days in which the individual reported drinking to intoxication (ASI). HD was coded as 1 (one or more HD days) or 0 (no HD days).

1.3.2.3. WHO Risk Levels. The WHO risk drinking levels correspond to the average number of drinks consumed per day in a given timeframe. At baseline and end-of-treatment, we determined the average number of drinks per day (DPD) by dividing the total drinks by the number of days assessed. At baseline and end-of-treatment, a categorical WHO risk level variable was created corresponding to the WHO categorization from 0 (low risk) to 4 (very high risk; see Table 1). Next, binary variables (1 =yes, 2 =no) were created corresponding to a reduction of 1 + and 2 + WHO risk levels from baseline to end-of-treatment. These variables were not mutually exclusive (i.e., those coded as "yes" for WHO risk reduction of 2 + were also coded as "yes" for a WHO risk reduction of 1 +).

1.4. Data analytic plan

Analyses were performed in SAS version 9.4, Mplus, and SPSS. First, classes were compared on baseline characteristics using ANOVAs and chi-square tests. Next, inverse probability of treatment weights were created using multinomial logistic regression to balance the classes on baseline characteristics (Saavedra et al., 2021). In this model GROUP (treatment class) was the criterion and the covariates were the predictors. Descriptive percentages of individuals meeting each of the four alcohol outcomes (i.e., abstinence, no HD, 1-level WHO risk reduction, 2-level WHO risk reduction) were calculated.

To determine if the proportion of individuals achieving each alcohol outcome differed, Cochran's Q test was conducted for each treatment class. Significant Cochran's Q tests were followed up with paired samples *t*-tests. Logistic regression was used to assess the odds of achieving each outcome by treatment class compared to TAU. Lastly, four multilevel logistic regression models were conducted, one for each outcome: abstinence, no HD days, a 1 + level WHO risk reduction, and a 2 + level WHO risk reduction. Parent study was specified as the clustering variable to account for between-study differences; all other covariates and predictors were specified as within-person. To account for missingness in data with multilevel structure and both categorical and continuous variables, regression models were conducted using 20 multiply imputed datasets in Mplus. All models employed their respective propensity weight.

2. Results

A total of 433 participants were included in the analyses (*M*age = 39.68 years, *SD* = 11.58; 72.98 % male; 75.75 % White). Per the inclusion criteria, all participants reported alcohol use at baseline and 84.03 % reported at least one HD day at baseline. Regarding WHO risk levels, 18.71 % (n = 81) were moderate risk, 23.56 % (n = 102) were high risk, and 57.74 % (n = 250) were very high risk at baseline. Treatment classes significantly differed at baseline on most characteristics (see Table 2) which was addressed using propensity score weighting. Presence or absence of AUD at baseline was available for 399 of the 433 participants. Of those, the majority (87.47 %) met criteria for AUD at baseline. At end-of-treatment, a WHO risk reduction of 1 + levels (82.82 %) was the most commonly achieved outcome followed by a WHO risk reduction of 2 + levels (72.16 %), no HD days (65.63 %), and abstinence (53.02 %). The pharmacological treatment class yielded the highest percentage of individuals achieving all outcomes whereas the trauma-focused behavioral class had the lowest percentages for all outcomes except abstinence (non-trauma-focused behavioral). See Table 3 for descriptive changes for the full sample and by treatment class.

2.1. Comparison of treatment outcomes

Comparison of the four treatment outcomes by treatment class yielded significant Cochran's Q tests for all treatment classes. As such, a series of paired-sample t-tests were conducted within each of the treatment classes comparing the four outcomes at end-of-treatment (see Table 4). For those in the TAU and trauma-focused behavioral classes, there was a higher proportion of individuals achieving a WHO risk reduction of 1 or more levels compared to both abstinence and no HD days (*ps* <.001 −.024). Further, in these two classes, more individuals achieved a WHO risk reduction of 2 or more levels compared to abstinence (*ps* <.001 −.007) but not compared to no HD days (*ps* = .422

Table 2
Baseline Demographic Characteristics and Symptom Severity for the Full Sample and by Intervention Class.

	Full Sample (N = 433)	TAU (n = 49)	Trauma-Focused Behavioral (n = 77)	Non-Trauma-Focused Behavioral (n = 121)	Pharmacological (n = 183)
Age	39.68 (11.58)	32.82 (10.10)	42.74 (10.86)	39.91 (12.22)	40.08 (11.13)
Race and ethnicity					
White	75.75 % (328)	97.96 % (48)	61.04 % (47)	77.52 % (100)	74.72 % (133)
Black	17.55 % (76)	0.00 % (0)	27.27 % (21)	11.63 % (15)	22.47 % (40)
Hispanic	8.78 % (38)	2.04 % (1)	11.69 % (9)	17.05 % (22)	3.37 % (6)
Sex (male)	72.98 % (316)	53.06 % (26)	88.31 % (68)	72.09 % (93)	72.47 % (129)
College (yes)	23.09 % (100)	16.33 % (8)	29.87 % (23)	20.93 % (27)	23.60 % (42)
Married (yes)	24.02 % (104)	12.24 % (6)	53.25 % (41)	12.18 % (17)	22.47 % (40)
Veteran (yes)	57.51 % (249)	2.04 % (1)	84.42 % (65)	67.44 % (87)	53.93 % (96)
Dose (mean %)	60.19 %	18.96 %	70.48 %	60.23 %	67.06 %
Medication (yes)	62.36 % (270)	75.51 % (37)	67.53 % (52)	62.79 % (81)	56.18 % (100)
Depression (yes)	53.35 % (231)	87.76 % (43)	41.56 % (32)	54.26 % (70)	48.32 % (86)
Baseline latent alcohol severity	0.65 (0.77)	−0.38 (0.54)	0.99 (0.57)	0.62 (0.80)	0.81 (0.61)
Baseline latent drug severity	−0.13 (0.65)	0.05 (0.78)	−0.31 (0.54)	−0.25 (0.61)	−0.02 (0.66)
Baseline latent PTSD severity	0.36 (0.90)	0.64 (0.70)	0.55 (0.81)	0.59 (0.79)	0.03 (0.97)
Baseline heavy drinking (yes)	83.83 % (363)	40.82 % (20)	92.21 % (71)	81.40 % (105)	93.82 % (167)
Baseline WHO level	3.39 (0.78)	3.49 (0.79)	3.17 (0.82)	3.33 (0.80)	3.51 (0.73)

Note. Bold indicates significant differences between treatment classes prior to propensity score weighting (PSW). Numbers presented refer to the data prior to PSW. Dose is presented as the average percentage of sessions attended.
Trauma-focused behavioral intervention class included Concurrent Treatment of PTSD and Substance Use Disorder using Prolonged Exposure (COPE, n = 65) and Cognitive Behavioral Therapy (CBT) for SUD + Structured Writing Therapy (n = 12). The non-trauma-focused behavioral intervention class includes Seeking Safety (n = 74), Integrated CBT for SUD (n = 48), and Relapse Prevention (n = 10). The pharmacological class included one medication targeting substance use (N-Acetylcysteine [n = 5]), three medications targeting PTSD (Sertraline [n = 38], Prazosin [n = 37], Paxil [n = 3])), one intervention combining Cognitive Processing Therapy (CPT) and Zonisamide (n = 13), one intervention combining CPT + placebo medication (n = 5), and placebo medication (n = 82).

Table 3
Rates of Alcohol Use, No Heavy Drinking Days, and WHO Risk Level at Baseline and End-Of-Treatment by Intervention Class.

	Full Sample		Treatment as Usual		Trauma-Focused Behavioral		Non-Trauma-Focused Behavioral		Pharmacological	
	Baseline	EOT	Baseline	EOT	Baseline	EOT	Baseline	EOT	Baseline	EOT
Abstinent (n)	0.00 % (0)	53.02 % (158)	0.00 % (0)	60.53 % (23)	0.00 % (0)	37.25 % (19)	0.00 % (0)	36.71 % (29)	0.00 % (0)	66.92 % (87)
No heavy drinking (n)	15.97 % (69)	65.63 % (212)	59.18 % (29)	69.23 % (27)	6.58 % (5)	47.06 % (24)	18.60 % (24)	50.00 % (40)	6.18 % (11)	79.08 % (121)
No heavy drinking among those with BL heavy drinking	0.00 % (0)	61.90 % (273)	0.00 % (0)	58.82 % (10)	0.00 % (0)	44.90 % (22)	0.00 % (0)	40.00 % (26)	0.00 % (0)	78.17 % (111)
WHO no risk	0 % (0)	52.23 % (152)	0 % (0)	60.53 % (23)	0 % (0)	37.25 % (19)	0 % (0)	37.97 % (30)	0 % (0)	65.04 % (80)
WHO low risk	0 % (0)	23.37 % (68)	0 % (0)	23.68 % (9)	0 % (0)	15.69 % (8)	0 % (0)	32.91 % (26)	0 % (0)	20.33 % (25)
WHO 2 moderate risk	18.71 % (81)	7.22 % (21)	18.37 % (9)	2.63 % (1)	25.97 % (20)	9.80 % (5)	20.93 % (27)	11.39 % (9)	14.04 % (25)	4.88 % (6)
WHO high risk	23.56 % (102)	5.84 % (17)	14.29 % (7)	2.63 % (1)	31.17 % (24)	9.80 % (5)	25.58 % (33)	10.13 % (8)	21.34 % (38)	2.44 % (3)
WHO very high risk	57.74 % (250)	11.34 % (33)	67.35 % (33)	10.53 % (4)	42.86 % (33)	27.45 % (14)	53.49 % (69)	7.59 % (6)	64.61 % (115)	7.32 % (9)
1 + WHO risk level change (n)		82.82 % (241)		89.47 % (34)		66.67 % (34)		72.22 % (61)		91.06 % (112)
2 + WHO risk level change (n)		72.16 % (201)		73.68 % (28)		50.98 % (26)		62.03 % (49)		86.99 % (107)

Note. EOT = end-of-treatment. BL = baseline WHO = World Health Organization risk drinking levels.

−.598). There was not a significant difference in the number of individuals achieving abstinence compared to no HD days (*ps* =.058 to .083) among those in TAU or the trauma-focused behavioral class. For those in the non-trauma-focused behavioral and pharmacological classes, a greater number of individuals achieved reductions of both 1 and 2 or more WHO risk levels compared to both abstinence and no HD days (*ps* <.001 to .011). More individuals achieved no HD days compared to abstinence (*ps* =.001 to .002).

2.2. Comparison of treatment classes

Compared to TAU, individuals in the pharmacological class had greater odds of abstinence (OR=5.20 [95 % CI 1.97, 13.74]), no HD days (OR=7.34 [95 % CI 2.11, 25.53]), a 1-level WHO risk reduction (OR=22.51 [95 % CI 1.31, 39.97]), and a 2-level WHO risk reduction (OR = 10.71 [95 % CI 1.72, 66.90]; see Table 5). There were no significant differences in odds of achieving the four alcohol outcomes for either the trauma-focused behavioral or the non-trauma-focused behavioral classes compared to TAU (see Table 5).

Greater baseline alcohol use severity was associated with decreased odds of abstinence, a 1-level WHO risk reduction, and a 2-level WHO risk reduction at end-of-treatment (ORs=0.15–0.40). Conversely, greater baseline drug use severity was associated with increased odds of HD cessation (OR=1.69 [95 %CI 1.10, 2.59]) and a 2-level WHO risk reduction (OR=1.87 [95 %CI 1.04, 3.36]). Lastly, being White was associated with decreased odds of achieving a 2-level WHO risk reduction (OR=0.19 [95 % CI 0.06, 0.62]). No other covariates were associated with the alcohol outcomes (see Table 5).

Table 4
Paired Samples t-tests Comparing Alcohol Outcome Achievement within Treatment Classes.

Treatment Class	Outcome	*t*-statistic (df)
Treatment as Usual	Abstinence v. Heavy Drinking	−1.78 (37), $p = .083$
	Abstinence v. 1-Level WHO risk reduction	−3.88 (37), $p < .001$
	Abstinence v. 2-Level WHO risk reduction	−2.37 (37), $p = .023$
	No heavy drinking v. 1-Level WHO risk reduction	−3.14 (37), $p = .003$
	No heavy drinking v. 2-Level WHO risk reduction	−0.81 (37), $p = .422$
Trauma-focused behavioral	Abstinence v. Heavy Drinking	−1.940 (50), $p = .058$
	Abstinence v. 1-Level WHO risk reduction	−4.56 (50), $p < .001$
	Abstinence v. 2-Level WHO risk reduction	−2.820 (5), $p = .007$
	No heavy drinking v. 1-Level WHO risk reduction	−2.33 (50), $p = .024$
	No heavy drinking v. 2-Level WHO risk reduction	−0.53 (50), $p = .598$
Non-trauma-focused behavioral	Abstinence v. Heavy Drinking	−3.36 (78), $p = .001$
	Abstinence v. 1-Level WHO risk reduction	−7.29 (78), $p < .001$
	Abstinence v. 2-Level WHO risk eduction	−5.14 (78), $p < .001$
	No heavy drinking v. 1-Level WHO risk reduction	−5.17 (78), $p < .001$
	No heavy drinking v. 2-Level WHO risk reduction	−2.59 (78), $p = .011$
Pharmacological	Abstinence v. Heavy Drinking	−3.15 (129), $p = .002$
	Abstinence v. 1-Level WHO risk reduction	−6.42 (121), $p < .001$
	Abstinence v. 2-Level WHO risk reduction	−5.86 (121), $p < .001$
	No heavy drinking v. 1-Level WHO risk reduction	−4.87 (122), $p < .001$
	No heavy drinking v. 2-Level WHO risk reduction	−3.61 (122), $p < .001$

Note. WHO = World Health Organization alcohol risk levels.

3. Discussion

This integrative analysis of 10 clinical trials ($N = 433$) examined the viability of WHO risk drinking level reductions as a treatment outcome for individuals with PTSD+SUD through the evaluation of: (1) rates of 1- and 2-level WHO risk reduction compared to traditional treatment endpoints (i.e., abstinence, HD) and (2) differences in outcome achievement by treatment type compared to TAU. To begin to understand potential differences in outcome sensitivity across PTSD +SUD intervention types, we compared the proportion of four outcomes – WHO risk level reductions, abstinence, and no HD days – across four broad PTSD+SUD treatment classes. WHO risk reductions were highly achievable in these samples with more than four out of five individuals demonstrating a 1- or more level reduction and nearly three-quarters attaining a 2-level reduction. Notably, these reductions were observed across all PTSD+SUD treatment classes. Compared to the traditional outcomes of abstinence and no HD days, WHO risk level reductions were achieved by a greater proportion of participants across all treatment classes, suggestive of the importance of considering non-abstinence endpoints in PTSD+SUD clinical research and practice.

These findings build upon research in AUD-only samples, where WHO risk drinking level reductions have been validated as meaningful indicators of treatment response (Witkiewitz et al., 2020a). Prior studies have shown that 1- and 2-level WHO risk reductions corresponded with decreases in alcohol-related consequences, psychiatric symptoms, and medical complications (Hasin et al., 2017; Knox et al., 2020, 2019). This study's findings extend this evidence base by demonstrating that WHO risk level reductions were achievable in individuals with PTSD+SUD, a sizeable subpopulation often excluded from alcohol treatment trials. Notably, WHO risk level reductions were more frequently attained than abstinence or no HD, reinforcing the potential utility of this endpoint as a harm reduction-aligned treatment outcome for individuals with PTSD+SUD.

The expansion of treatment success beyond binary outcomes such as

Table 5
Logistic Regression Models Predicting Odds of Alcohol Outcome Achievement.

	Abstinence aOR (95 % CI)	No Heavy Drinking aOR (95 % CI)	1 + level WHO Risk Reduction aOR (95 % CI)	2 + level WHO Risk Reduction aOR (95 % CI)
Treatment Class (ref = TAU)				
Trauma-Focused Behavioral	1.48 (0.51, 4.27)	2.37 (0.79, 7.15)	6.22 (0.88, 43.98)	2.86 (0.66, 12.34)
Non-Trauma-Focused Behavioral	0.92 (0.39, 2.16)	2.20 (0.67, 7.24)	2.16 (0.31, 14.98)	2.85 (0.65, 12.61)
Pharmacological	**5.20 (1.97, 13.74)**	**7.34 (2.11, 25.53)**	**22.51 (1.31, 39.97)**	**10.71 (1.72, 66.90)**
Age	0.98 (0.96, 1.01)	0.98 (0.95, 1.00)	1.01 (0.98, 1.05)	1.00 (0.96, 1.03)
Race and ethnicity				
White	0.75 (0.26, 2.14)	0.85 (0.33, 2.20)	0.69 (0.23, 2.09)	**0.19 (0.06, 0.62)**
Black	1.04 (0.30, 3.54)	1.17 (0.37, 3.67)	1.60 (0.26, 9.98)	0.21 (0.04, 1.04)
Hispanic	0.73 (0.30, 1.79)	0.84 (0.34, 2.08)	0.78 (0.34, 1.83)	0.98 (0.34, 2.85)
Sex (ref = male)	0.86 (0.46, 1.61)	0.80 (0.38, 1.66)	1.24 (0.45, 3.40)	1.10 (0.41, 2.95)
College (ref = no)	0.48 (0.29, 0.78)	0.67 (0.38, 1.18)	0.83 (0.40, 1.74)	0.96 (0.47, 1.94)
Married (ref = no)	1.62 (0.72, 3.62)	1.05 (0.50, 2.19)	2.03 (0.69, 6.00)	1.56 (0.65, 3.76)
Veteran (ref = no)	1.21 (0.48, 3.05)	0.50 (0.03, 7.95)	1.83 (0.17, 19.47)	0.96 (0.11, 8.12)
Dose	0.97 (0.40, 2.36)	1.24 (0.45, 3.93)	3.48 (0.66, 19.49)	2.04 (0.76, 5.46)
Medication (ref = no)	1.22 (0.75, 1.97)	1.35 (0.84, 2.18)	1.58 (0.68, 3.67)	1.96 (0.95, 4.04)
Depression (ref = no)	1.28 (0.76, 2.15)	0.96 (0.47, 1.98)	1.08 (0.57, 2.05)	1.37 (0.80, 2.35)
Baseline latent alcohol severity	**0.40 (0.23, 0.68)**	0.63 (0.36, 1.12)	**0.15 (0.05, 0.46)**	**0.21 (0.07, 0.67)**
Baseline latent drug severity	1.14 (0.70, 1.84)	**1.69 (1.10, 2.59)**	1.58 (0.89, 2.78)	**1.87 (1.04, 3.36)**
Baseline latent PTSD severity	1.03 (0.74, 1.43)	0.96 (0.72, 1.27)	0.76 (0.45, 1.28)	0.77 (0.52, 1.13)
Baseline heavy drinking (ref = no)	-	0.36 (0.13, 1.00)	-	-
Baseline WHO level	-	-	1.77 (0.95, 3.29)	1.00 (0.83, 1.20)

Note. TAU = treatment as usual. WHO = World Health Organization risk drinking level

abstinence or the absence of HD days is particularly relevant for PTSD+SUD. Abstinence presumes a single, uniform treatment goal that may not align with the preferences or needs of individuals with PTSD+SUDs and cannot account for more gradual reductions in alcohol use that potentially yield significant improvements in health. Individuals with PTSD+SUD face specific recovery challenges stemming from the bidirectional interplay between PTSD symptoms and alcohol use where PTSD symptoms may trigger drinking, and alcohol use exacerbates PTSD symptoms (Tripp et al., 2020). The dynamic relationship between alcohol use and PTSD suggests that any reduction in alcohol use—even if it does not meet the threshold for abstinence or eliminating HD—could potentially contribute to improved functioning in PTSD+SUD. Our results suggest that limiting alcohol outcomes to abstinence and no HD days may obscure the full range of treatment response occurring in PTSD+SUD trials as many individuals in the present study demonstrated substantial reductions in alcohol use that were not captured by these traditional PTSD+SUD trial outcomes.

Comparison of treatment classes to TAU found strong support for pharmacological treatments in reducing alcohol use across the four alcohol metrics, supporting the inclusion of medications as a worthwhile treatment approach for individuals with PTSD+SUD. There were no differences in rates of the various alcohol outcome achievements for either behavioral class compared to TAU. It may be that TAU is predominantly focused on addressing substance use (e.g., drug and alcohol counseling) and thus, may have content overlap with other behavioral interventions.

At higher levels of baseline alcohol use severity, the odds of achieving abstinence and a 1-level WHO risk reduction at end-of-treatment was lower. However, baseline alcohol severity was not associated with HD or 2-level WHO risk reduction outcomes. This suggests that individuals with greater alcohol severity may be less able or interested in relatively minor alcohol changes (i.e., a 1-level reduction) and are able to achieve greater improvements (i.e., no HD days, 2-level reductions). This finding underscores the importance of personalizing interventions to the client's preferred goals and specific level of use. Inversely, greater drug use severity at baseline was associated with greater odds of achieving no HD days and WHO risk reductions of two or more levels. It is possible that targeting other drug use during treatment has a positive effect on decreasing alcohol use; however, more research is needed to understand this link. There were no significant associations between demographic variables, baseline PTSD symptom severity, or other treatment variables (e.g., attendance) and odds of outcome achievement. This finding is encouraging as it indicates that these outcomes may be generalizable to many individuals including those with co-occurring mental health conditions or that terminate treatment prematurely.

This study marks a crucial step toward evaluating WHO risk levels as a viable marker for treatment progress among patients at risk for alcohol harms and living with comorbidities such as PTSD. However, although this analysis was drawn from an original pool of studies containing more than 30 datasets (Hien et al., 2023), WHO risk drinking level metrics were only derivable from a subset of studies that allowed for calculation of drinks per day. As such, we could not compare all PTSD+SUD treatment classes to TAU. Most notably, we were unable to compare TAU to the combination of pharmacology and behavioral interventions, which was found to be the most effective for PTSD+SUD in the PH meta-analysis (Hien et al., 2023). Additionally, due to high rates of treatment dropout, missingness was accounted for with multiple imputation. Lastly, only end-of-treatment outcomes were analyzed, leaving as a future research direction closer examination of within-session changes in WHO risk drinking levels among individuals receiving PTSD+SUD treatment.

Because the stability of clinical improvements is equally critical, repeated measures designs are needed to evaluate in-treatment changes in alcohol use to determine if and how WHO risk level reductions are maintained beyond treatment's end. Importantly, future work is tasked with assessing if WHO risk drinking level reductions are associated with improvements across other metrics such as PTSD, other psychiatric symptoms, and quality of life. Clinically, understanding whether WHO risk level reductions, as a treatment goal, increase patient buy-in to engage with treatment and enhance motivation to continue treatment following lapses could serve as an important step in reaching those who would benefit from substance use treatment but are deterred by the requirement or expectation of abstinence as the treatment goal. Lastly, selection of non-abstinence-based endpoints is a new area of inquiry with several directions for future research. These include developing treatment endpoints for other substances such as cocaine (Votaw et al., 2024), methamphetamine (Amin-Esmaeili et al., 2024), opioids (Bailey et al., 2025), and cannabis (McClure et al., 2024). Such endpoints could include reductions in use, decreased substance-related consequences, neuroimaging and biological endpoints, or other patient-identified endpoints. Although several endpoints could be meaningful, WHO risk levels provide a standardized method for measuring treatment efficacy. For example, WHO risk drinking levels could serve as a readily available screening approach in primary care and medical settings where other health improvement markers associated with reduction levels can be monitored. Over the course of treatment, this metric also allows for examination of incremental progress in alcohol-related risk reduction.

In conclusion, this study represents a fundamental step in evaluating WHO risk drinking levels as treatment endpoints for PTSD+SUD interventions, particularly within a harm reduction framework that prioritizes patient-centered goals and overall well-being. Notably, a greater proportion of individuals achieved WHO risk level reductions than abstinence, and prior research has shown that even a 1-level reduction is associated with meaningful improvements in alcohol-related harms and quality of life. Moreover, the finding that four out of five participants achieved a 1-level WHO risk reduction, and nearly three-quarters achieved a 2-level reduction, highlights the effectiveness of PTSD+SUD interventions in promoting substantial change in harmful drinking behavior.

CRediT authorship contribution statement

Teresa López-Castro: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jordan Gette:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Sudie Back:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Funding acquisition. **Shannon M. Blakey:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Therese K. Killeen:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Antonio A. Morgan-Lopez:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sonya B. Norman:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Lissette M. Saavedra:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Lesia M. Ruglass:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Mark P. McGovern:** Writing – review & editing, Supervision, Investigation. **Ismene Petrakis:** Writing – review & editing, Supervision, Investigation. **Susan Sonne:** Writing – review & editing, Supervision, Investigation. **Thomas Ehring:** Writing – review & editing, Supervision, Investigation. **Kathleen T. Brady:** Writing – review & editing, Supervision, Investigation. **Denise A. Hien:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition.

Funding sources

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (R01AA025853; PI: Hien and Morgan-López). The sponsor was not involved in the study design, collection, analysis and interpretation of data, writing of the report, or decision to submit this article for publication.

Disclosures

Drs. Back and Killeen receive book royalties from Oxford University Press. Dr. Blakey receives book royalties from the American Psychological Association. Dr. Ruglass receives book royalties from Springer Publishing Company and Taylor and Francis. Dr. Norman receives book royalties from Elsevier Press. Dr. Petrakis has received in kind (medications) support for research studies from Alkermes and BioXcel Therapeutics and textbook royalties from MacGraw/Hill. Dr. Petrakis has provided consultation to Eli Lilly and Company. Dr. Petrakis also reports the following patents and inventions: (1) Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no.61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research. (2) Yoon G, Petrakis I, Krystal JH – Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U.S. Provisional Patent Application No. 62/444,552, filed on January 10, 2017 by Yale University Office Cooperative Research OCR 7088 US. Dr. Hien receives book royalties from Guilford Press. The other authors report no financial relationships with commercial interests.

Declaration of Competing Interest

Drs. Brady and Sonne are Editorial Board Members for this journal and were not involved in the editorial review or the decision to publish this article.

Acknowledgments

This research was supported by the National Institute on Alcohol Abuse and Alcoholism (R01AA025853; PI: Hien and Morgan-López). The sponsor did not have any involvement in the study design, collection, analysis and interpretation of data, writing of the report and decision to submit the manuscript for publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112837.

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