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Are non-abstinent reductions in World Health Organization drinking risk level a valid treatment target for alcohol use disorders in adolescents with ADHD?

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ABSTRACT

Introduction: Abstinence from drinking represents the primary treatment target for alcohol use disorders (AUD) in youth, but few adolescents who engage in problematic drinking seek treatment. A reduction in World Health Organization (WHO) drinking risk level has been established as valid and reliable non-abstinent treatment target for AUD in adults but remains unstudied in youth.
Methods: The present study used data from the NIDA-CTN-0028 trial to examine associations between reductions in WHO drinking risk level and changes in global functioning and attention-deficit hyperactivity disorder (ADHD) symptoms during treatment in a sample of adolescents (ages 13–18 years) with ADHD and comorbid substance use disorder (SUD) (n = 297, 61% with AUD) receiving a 16-week intervention that combined ADHD pharmacotherapy (OROS-methylphenidate vs. placebo) and drug-focused cognitive-behavioral therapy.
Results: Shifts in drinking risk level during treatment were highly variable in adolescents treated for ADHD/SUD, and influenced by AUD diagnostic status. In the total sample, 15% of participants had a 2-level or greater reduction in WHO drinking risk level, with 59% and 24% showing no change or an increase in risk-level during treatment respectively. Achieving at least a 2-level change in WHO drinking risk level during treatment was associated with greater reduction in ADHD symptoms and better functional outcomes.
Conclusions: These findings parallel the adult AUD literature and provide preliminary support for the use 2-level reductions in WHO risk levels for alcohol use as a clinically valid non-abstinent treatment outcome for youth with ADHD and comorbid AUD.

1. Introduction

Alcohol use during adolescence is common and represents a major public health concern. Nearly 60% of U.S. high school students report lifetime alcohol use with 21% reporting a history of binge drinking, and 29% reporting drinking in the past 30 days (Johnston, et al., 2019). Despite significant reductions in the prevalence of underage drinking in the U.S. over the past decade, alcohol-related costs to society remain high. Alcohol has continued to be the most commonly used substance by adolescents and the second most commonly used substance for which adolescents seek substance use treatment (Hammond, Kaufman, & Perepletchikova, 2016). Heavy episodic drinking (HED) and alcohol use disorders (AUD) during adolescence are associated with serious psychosocial problems and poorer health and functioning in adulthood (CDC, 2012). Problematically, fewer than 10% of U.S. adolescent 12-to-17-year-olds who would benefit from AUD treatment receive it (SAMHSA, 2016). As such there is a growing need for expanded prevention, early intervention, and treatment efforts to target youth who are at-risk for and who engage in problematic drinking across the continuum of alcohol use frequencies and related problems (Hammond, Kaufman, & Perepletchikova, 2016). One approach with growing traction in adult AUD treatment has been to expand the focus of treatment goals to include non-abstinent reductions in drinking as a way to engage more individuals in AUD treatment (Witkiewitz & Alan Marlatt, 2006).

Abstinence from alcohol is the most widely accepted target of treatment for AUD, and non-abstinence treatment targets are

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controversial in adolescent AUD treatment (Hammond, Kaufman, & Perepletchikova, 2016). The central focus on abstinence from alcohol during AUD treatment in youth makes sense, given strong evidence indicating the increased risk for alcohol-related negative sequelae and disruptions in developmental trajectories related to adolescent as compared to adult alcohol use (Lisdahl et al., 2013). At the same time, only focusing on abstinence-based treatments limits treatment options and likely turns youth who may be experiencing alcohol-related problems but who prefer to reduce their drinking away from seeking treatment (Witkiewitz & Alan Marlatt, 2006). Non-abstinence alcohol reduction endpoints have gained acceptance as a treatment target for adult AUD over the past decade (Hasin et al., 2017), building on the foundation of earlier harm reduction models (Witkiewitz & Alan Marlatt, 2006). This acceptance has emerged in the context of growing empirical evidence supporting that non-abstinent reductions in alcohol consumption are associated with reductions in alcohol-related psychosocial and medical consequences (Knox et al., 2018; Roerecke et al., 2013) and improved mental health functioning in adults with and without AUD diagnoses (Hasin, et al., 2017; Witkiewitz, et al., 2017). This harm-reduction approach has been studied in adolescents, to a lesser extent (Shope et al., 1994; Harm reduction, 2008; Monti et al., 1999). A reduction in World Health Organization (WHO) risk level for alcohol consumption has been established as valid and reliable non-abstinent treatment target for AUD in adult populations (Hasin et al., 2017; Witkiewitz et al., 2017; World Health Organization, 2000). A categorical shift in WHO drinking risk levels of 2 levels or more (e.g., from "very high risk" to "medium risk" or "low risk") has recently been accepted by the European Medicines Agency (EMA) as an alternative endpoint for AUD medication development in adults (EMA, 2010). No published studies to date have evaluated the sensitivity of reductions in WHO drinking risk levels in a sample of adolescent AUD patients.

Alcohol and drug use, and substance use disorders (SUD) (including AUD) are higher among individuals with attention-deficit hyperactivity disorder (ADHD) compared to controls (Adisetiyo & Gray, 2017; Ameringer & Leventhal, 2013; Charach, Yeung, Climans, & Lillie, 2011; Kessler, 1994; Wilens et al., 2011). Furthermore, individuals with SUD and co-occurring ADHD appear to have increased addiction severity, longer SUD course, and poorer substance use treatment outcomes (King, Brooner, Kidorf, Stoller, & Mirsky, 1999; Schubiner, 2005; Wilens, Biederman, & Mick, 1998; Young et al., 2015). Improved understanding of how changes in ADHD symptom severity relate to shifts in alcohol consumption during treatment of youth with ADHD and comorbid AUD is warranted. Additionally, since AUD and ADHD have a high comorbidity rate, an understanding of the course of AUD in youth with ADHD provides results that are applicable to a significant proportion of the adolescent population.

In the present study, we sought to validate shifts in WHO drinking levels as a putative non-abstinent drinking outcome in adolescents with ADHD and comorbid AUD, by using large-scale clinical trial data to examine how shifts in drinking level relate to functioning and mental health outcomes. The analysis used data from 297 adolescents who participated in a multisite clinical trial evaluating treatment of ADHD and comorbid SUD that comprehensively characterized alcohol and other drug use, ADHD symptoms, and global functioning across multiple time points. The aims of this secondary analysis were twofold: (1) to determine if reductions in WHO drinking risk level were a predictor of improved global functioning and (2) to identify whether reductions in WHO drinking risk level were related to reductions in ADHD symptoms during and following treatment in adolescents with ADHD and comorbid SUD.

2. Methods

2.1. Study design and participants

Secondary analyses were performed on data from the NIDA Clinical Trials Network (CTN) multi-site CTN-0028 study (NIDA-CTN-0028) (Riggs, et al., 2011), a 16-week U.S. multisite randomized double-blind clinical trial that evaluated the combination of ADHD-medications (osmotic-release methylphenidate (OROS-MPH) vs. placebo (PBO)) and abstinence-focused weekly cognitive behavioral therapy (CBT) in the treatment of ADHD and comorbid SUD in adolescents. The use of CBT was intended to standardize the participants' treatments across the multiple sites. Therapy sessions were conducted at outpatient facilities and focused on abstinence from all substances implicated in problematic use. NIDA-CTN-0028 study participants were adolescents ages 13–18 years meeting DSM-IV criteria for current ADHD and a non-tobacco SUD (n = 297 total, 181 (61%) with AUD diagnosis). Demographic information of participants is presented in Table 1.

2.2. Measures

2.2.1. Alcohol and drug use

Alcohol and non-tobacco drug use were assessed via calendar method using standardized timeline follow back (TLFB) procedures (Sobell and Sobell, 1992).

2.2.2. Global functioning

Changes in global functioning were assessed using Children's Global Assessment Form (CGAS) (Schaffer, Gould, & Brasic, 1983). The CGAS is a clinician-rated 100-point numeric scale used to rate general global functioning in youth under the age of 18, with higher scores relating to better functioning. The CGAS was administered at baseline, week 7, and week 16.

2.2.3. ADHD symptom severity

ADHD symptoms were assessed via the clinician-administered DSM-IV ADHD rating scale (ADHD-RS; adolescent informant) administered on a weekly basis to adolescent informants (primary ADHD outcome from Riggs et al., 2011) and the Clinical Global Impression – Improvement scale (CGI-I), assessed by a trained clinician on a monthly basis during the study (secondary ADHD outcome). The ADHD-RS is an 18-item checklist assessing the severity of different DSM-IV ADHD symptoms along a 4-point Likert scale (0 = never/rarely; 1 = sometimes; 2 = often; 3 = very often). It is a valid and reliable measure of ADHD symptom severity (Bostic, et al., 2000; Prince, et al., 2000). The CGI-I evaluates overall improvement in ADHD symptoms since treatment initiation in comparison to the participant's baseline, ranging from 1 (very much improved) to 7 (very much worse) (Busner, Targum, & Miller, 2009). ADHD treatment response was defined in the main study as a final CGI-I score of 1 (very much improved) or 2 (much improved) with respect to the participant's baseline ADHD symptom severity.

Table 1
Demographics of sample stratified by AUD diagnostic status.

	ADHD adolescents w/ comorbid AUD (n = 181)	ADHD adolescents w/ o comorbid AUD (n = 116)	Total Sample (n = 297)
Age (SD)	16.6 (1.2)	16.4 (1.3)	16.5 (1.3)
Male/Female	141/40	93/23	234/63
Race			
White (%)	123 (69%)	60 (50%)	183 (61%)
Black (%)	23 (13%)	45 (38%)	68 (23%)
Other (%)	20 (11%)	5 (4%)	25 (8%)
Multiple (%)	13 (7%)	9 (8%)	22 (7%)
InitialWHO AlcoholRisk Level			
None (%)	35 (19%)	60 (52%)	95 (32%)
Low (%)	0 (0%)	0 (0%)	0 (0%)
Moderate (%)	2 (1%)	13 (11%)	15 (5%)
High (%)	3 (2%)	8 (7%)	11 (4%)
Very High (%)	141 (78%)	35 (30%)	176 (59%)

2.3. WHO drinking risk levels

Consistent with studies in adult AUD patient samples, we calculated WHO drinking risk levels based upon patient self-report of the number of standard drinks (defined as approximately 14 g of 100% ethanol) consumed, following established cutoffs (see Table 2). Mean daily ethanol consumption was stratified into five risk levels: abstinent (0), low-risk (1), medium-risk (2), high-risk (3), and very-high-risk (4) (Witkiewitz, et al., 2017). Prior studies have examined WHO risk level changes in adult AUD participants with and without abstinence included as a fifth risk level. Given this, we conducted analyses both ways. Excluding abstinence as a fifth risk level from the analyses did not alter the results (data not shown). Given the abstinence-focus of the CBT intervention used in NIDA-CTN-0028, all analyses presented below were modeled using a 5-level risk stratification including abstinence as a fifth risk level. For the baseline period, drinking risk level was calculated using mean alcohol consumption for the 4 weeks leading up to the beginning of the study. For the end-of-study, drinking risk level was calculated using mean alcohol consumption for the last 4 weeks of the study (weeks 13–16). A change in WHO risk level was computed by subtracting the end-of-study WHO risk level from the baseline-period WHO risk level, resulting in 9 binary risk reduction variables: no change in risk level, a 1-level increase or decrease, a 2-level increase or decrease, a 3-level increase or decrease, and a 4-level increase or decrease. For the primary analyses, we computed a binary variable that reflected at least a 2-level reduction in WHO drinking risk level based upon the reduction ("shift") from baseline to the last month of treatment (Witkiewitz et al., 2017). The reference group for the 2-level reduction was the 1-level reduction, no change, or an increase in WHO drinking risk level from baseline to the last month of treatment. This reference group was selected to be consistent with EMA guidelines that define a responder as achieving at least a 2-level reduction (EMA, 2010), and, in comparison, a non-responder being someone who did not achieve that reduction. Based upon heterogeneity in the change in WHO risk level seen in the sample that included a greater proportion of youth than expected showing a 2-level or more increase in risk level and few youth showing 1-level changes, we performed supplementary analyses comparing at least a 2-level reduction in WHO drinking risk level with no change or at least a 2-level increase in WHO drinking risk level as reference groups (excluding individuals with a 1-level change from the reference group). This analytic approach is consistent with prior studies conducted to validate the WHO risk levels in adults (Witkiewitz et al., 2017).

2.4. Data analysis

Analyses were conducted using R-version 4.0.0 and RStudio-version 1.2.5042. Descriptive analyses investigated the frequency of adolescent participants categorized by each of the WHO risk levels at baseline and end-of-treatment, along with changes in WHO risk drinking level from baseline to end-of-treatment for the total sample. Subgroup analyses were conducted to characterize group level differences in baseline, end of treatment, and change in WHO risk level between participants stratified by AUD diagnostic status. To examine how changes in WHO risk level related to changes in global functioning and ADHD symptoms over the course of treatment, we took a two-part analytic approach. Linear regressions were first used to examine relationships between change in WHO risk level and change in outcome measures following treatment. Then, we used general estimating equation (GEE) models to examine relationships between change in risk level and change in variables of interest (global functioning and ADHD symptoms) during treatment across weeks of active study intervention. For global function, we focused on CGAS scores as our outcome variable. Towards this we performed linear regressions using the least-squares method with changes in CGAS score from baseline to week-16 used as the dependent variable (DV) and group stratification of participants based upon their change in WHO drinking risk level used as the independent variable (IV). This was followed by GEE analyses using CGAS scores and time (baseline, week 7, and week 16) as the DVs and change in WHO drinking risk level as the IV. For ADHD symptoms, we used ADHD-RS and CGI-I scores. First we conducted separate linear regression models using change in ADHD-RS from baseline to week-16 and end-of-treatment CGI-I score as DVs and changes in WHO risk level as the IV to examine relationships with these outcome variables following treatment. Then we conducted GEE analyses with ADHD-RS scores and time (study week) as DVs and WHO risk level change groups as the IV to examine week-by-week relationships during treatment. As noted above, all models were first conducted using a binary 2-level risk reduction grouping variable comparing participants who had a 2-level or greater reduction in WHO drinking level to all others change levels (primary analysis, termed "binary 2-level" throughout this paper), and then using a 3 group stratification comparing participants with a 2-level reduction to those whose risk level did not change and those whose risk level increased by 2 or more levels from baseline to the last month of treatment (supplementary analysis, termed "ordinal 3-level" throughout this paper). Exploratory analyses were also performed using the above described approach but with a binary 1-level risk reduction grouping variable (at least a 1-level reduction in risk vs. all other groups [no change, increase in risk level]) and using all nine WHO risk level reduction categories (4-, 3-, 2-, and 1-level decreases, no change, and 1-, 2-, 3-, and 4-level increases in risk level) with no change in risk serving as the reference group.

Table 2
World Health Organization (WHO) risk levels for alcohol use, stratified by sex.

Unit	Sex	Low Risk	Medium Risk	High Risk	Very High Risk
Grams	Male	1 to 40 g	41 to 60 g	61 to 100 g	> 100 g
	Female	1 to 20 g	21 to 40 g	41 to 60 g	> 60 g

3. Results

3.1. WHO drinking risk levels in adolescents with comorbid ADHD and SUD

Descriptive statistics on the number and proportion of participants categorized at each WHO drinking risk level at baseline and in the last month of treatment, and their change in risk level following treatment are shown for the total sample and stratified by AUD diagnostic status in Table 1 and Fig. 1. AUD diagnostic subgroup differences were observed in WHO drinking risk levels at baseline and in the direction and magnitude of change in risk level following treatment. The majority (59%) of participants were in the "very high risk" category" at baseline with the second most common risk level being the "abstainer" category (32%). AUD diagnostic subgroup differences were observed in WHO drinking risk levels at baseline ($\chi^2 = 195.56$, $p < 0.001$) and in the direction and magnitude of change in risk level following treatment ($\chi^2 = 17.86$, $p < 0.001$).

At baseline, participants with AUD diagnoses were more likely to be in the "very high risk" category (78% vs. 30%) and less likely to be in the "abstainer" category (19% vs. 52%) compared to those without AUD diagnoses. The vast majority of participants in the sample showed either no change or a large change in their alcohol consumption following treatment with few participants showing minor/incremental change in risk levels. No change (59% of total sample), a 4-level increase (20%), and a 4-level decrease (10%) in WHO drinking levels from baseline to the last month of treatment were the three most common change categories reported. In both AUD and non-AUD groups, most participants showed no change in their WHO drinking risk level from baseline to the last month of treatment (AUD: 66%, non-AUD: 49%). In the AUD group, the majority started and remained in the "very high risk" category. Participants with AUD who did show a change in WHO risk level during treatment were most likely to either significantly decrease their alcohol

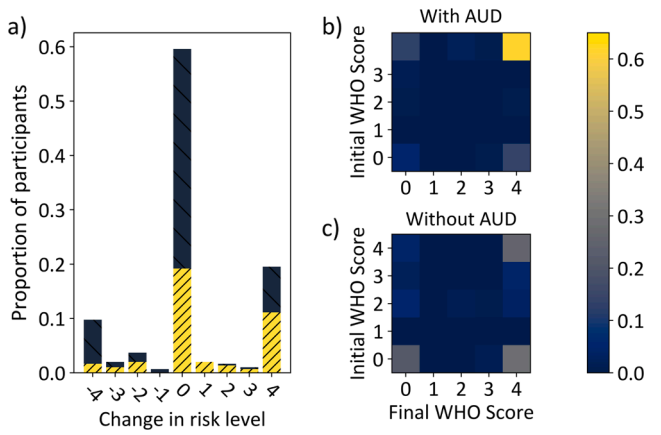

Fig. 1. Distribution of WHO drinking risk level change, level at baseline, and level at end-of-treatment, by proportion of participants. a) Distributions of WHO risk level changes, by proportion of participants. The participants were categorized by their change in drinking risk level (e.g., a change from high-risk to low-risk corresponds to a change of −2), and their AUD diagnostic status. Bar heights represent the proportion of overall participants who presented with a given risk level change. Participants with an AUD make up the blue portion of the bar, and participants without an AUD make up the yellow portion of the bar. b) Starting and final WHO drinking risk levels for ADHD/SUD participants with an AUD diagnosis. The heatmap can be read similarly to a numerical table. The rows correspond to initial WHO drinking risk levels, the columns correspond to final WHO drinking risk levels, and the colors correspond to the proportion of participants in each category. c) Starting and final WHO drinking risk levels for ADHD/SUD participants without an AUD diagnosis. This can be read in the same way as Fig. 1b. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

consumption (13% of participants with AUD showed a 4-level decrease) or significantly increase their alcohol consumption (14% of participants with AUD showed a 4-level increase). In contrast, the majority of participants in the non-AUD group started and remained in the "abstainer" category, indicating that they did not drink in the month prior to and last month of treatment. Participants without an AUD diagnosis who showed a change in WHO risk level were most likely to significantly increase their alcohol consumption (28% of participants without AUD showed a 4-level increase) with few participants showing other changes. By the end of active treatment, 15% of participants (AUD: 18%, non-AUD: 12%) showed at least a 2-level reduction in WHO risk level and 21% of participants (AUD: 14%, non-AUD: 30%) showed at least a 2-level increase.

Given the high proportion of participants in both groups reporting 2-level or more increases in WHO risk level, exploratory post-hoc analyses were conducted to test for possible drug-for-alcohol substitution effects during treatment (Peters and Hughes, 2010). A negative relationship between change in WHO alcohol risk level during treatment with non-alcohol drug use would be consistent with a substitution effect, whereas a positive relationship would be consistent with a complementary effect (Subbaraman, 2016). Our exploratory regression analyses identified a negative correlation between change in WHO risk level and change in marijuana use days from baseline to end of treatment that approached significance ($r^2 = 0.0143$, $p = 0.062$).

3.2. WHO risk level relationships with global functioning and ADHD symptom severity

For global function analyses: regression analyses using the binary 2-level reduction approach identified a significant association between change in WHO risk level and change in CGAS score following treatment ($r^2 = 0.025$, $p < 0.001$). At least a 2-level reduction was associated with a greater baseline to week-16 increase in CGAS scores compared to those with a 1-level reduction, no change, or an increase in WHO drinking risk level (9.5 vs. 4.4, $t = 2.96$, $p = 0.003$). In the GEE analysis using the binary 2-level reduction, a significant effect of time on change in CGAS scores during treatment was observed ($\beta = 0.35$, SE = 0.05, $p < 0.001$), but the change in WHO risk level was unrelated to change in CGAS score during treatment (β = -0.49, SE = 1.44, $p = 0.732$). Results from our supplementary analyses paralleled the main findings (see Fig. 2). Using the 3-level ordinal group stratification (2-level reduction, no change, 2-level increase), regression models identified a significant association between WHO risk level reduction and baseline to week 16 change in CGAS scores ($r^2 = 0.028$, $p < 0.001$). Changes in WHO risk level were unrelated to CGAS scores in GEE models ($\beta = -0.62$, SE = 0.92, $p = 0.498$). In post-hoc comparisons (see Fig. 2A), at least a 2-level reduction was associated with greater baseline to week 16 increase in CGAS scores compared to no change or a 2-level increase in WHO drinking risk level (9.5 vs. 3.9 vs. 4.8, $F = 4.94$, $p = 0.008$).

For ADHD analyses: linear regression models using the binary 2-level reduction approach showed a significant association between reduction in WHO risk level and baseline to week 16 change in ADHD-RS scores ($r^2 = 0.002$, $p = 0.011$), with the association between reduction in WHO risk level and end of treatment CGI-I score approaching significance ($r^2 = 0.016$, $p = 0.090$). Our binary 2-level GEE analyses examining changes in ADHD checklist scores over time, grouped by change in WHO drinking risk level, yielded a significant effect for time (β = -0.43, SE = 0.06, $p < 0.001$), but no group effect on week-by-week change in ADHD-RS scores based upon change in WHO drinking risk level ($\beta = 1.46$, SE = 1.76, $p = 0.410$). Supplementary regression analyses using the ordinal 3-level stratification showed significant associations between change in WHO risk level and reduction in ADHD symptoms measured using baseline to week 16 change in ADHD-RS scores ($r^2 = 0.010$, $p < 0.001$) and end-of-treatment CGI-I scores ($r^2 = 0.035$, $p = 0.011$). At least a 2-level reduction was associated with greater baseline to week 16 reduction in ADHD-RS scores (see Fig. 2B) (8.2 vs. 7.1 vs. 5.1, $F = 3.197$, $p = 0.043$) and lower week-16 CGI-I scores (indexing greater during treatment improvement) (2.89 vs. 3.24 vs. 3.45, $F = 3.20$, $p = 0.043$) compared to no change or a 2-level increase in WHO drinking risk level. GEE analyses using the ordinal 3-level approach showed no effect of risk-level change group on during treatment week-by-week change in ADHD-RS scores ($\beta = -0.76$, SE = 1.13, $p = 0.503$).

For exploratory analyses: Exploratory regression analyses using the binary 1-level reduction groups, identified significant change in WHO risk level relationships with baseline to week 16 CGAS scores ($r^2 = 0.052$, $p < 0.001$) and ADHD-RS scores ($r^2 = 0.019$, $p < 0.001$). In post-hoc comparisons, compared to no change or an increase in WHO drinking risk level, at least a 1-level reduction was associated with greater baseline to week-16 improvements in CGAS scores (9.3 vs. 4.4, $t = 2.90$, $p = 0.004$) but was unrelated to reductions in ADHD-RS scores (8.6 vs. 6.6, $t = 1.16$, $p = 0.245$). No significant relationships were observed between change in WHO risk level, global functioning, and ADHD symptoms in binary 1-level reduction GEE analyses and in ordinal regression and GEE analyses using nine WHO risk level change categories (data not shown, all p's > 0.05).

4. Discussion

The present study used data from a large multisite clinical trial of adolescents with ADHD and comorbid SUD who received a combination of ADHD pharmacotherapy and CBT to investigate the validity of reduction in WHO drinking risk level as a predictor of health and functional outcomes in adolescents diagnosed with ADHD and comorbid SUD with and without AUD diagnoses. We found evidence for significant heterogeneity in risky drinking behaviors among youth receiving treatment for ADHD and comorbid SUD. Despite this, achieving at least a 2-level categorical reduction in WHO drinking risk level following treatment was associated with significant improvements in functioning and ADHD symptom severity. Implications are discussed below.

Our findings showed significant heterogeneity in the WHO drinking

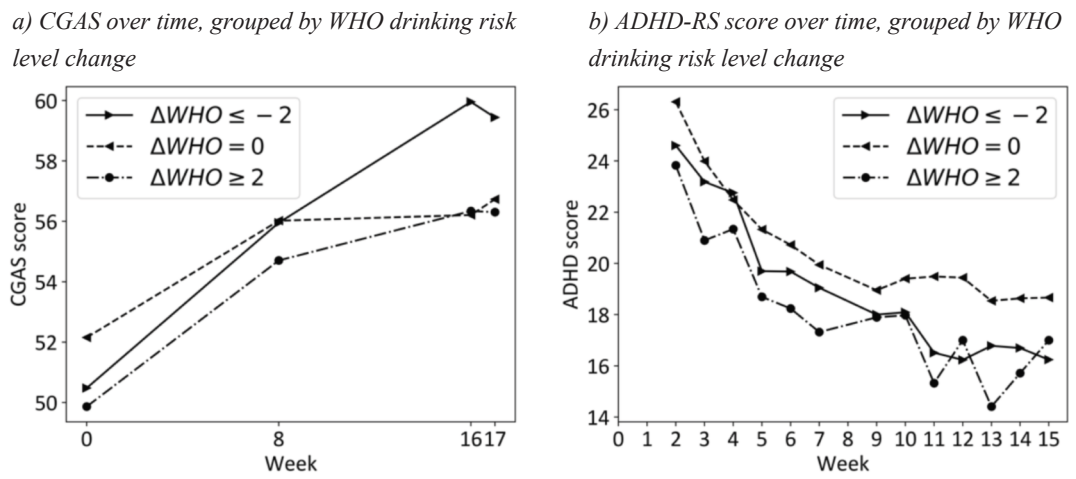

Fig. 2. Average Global functioning and ADHD symptom severity, pre- and post-treatment, by change in WHO risk level a) Mean CGAS score from baseline (solid line) to week 16 (dashed line). b) Mean ADHD-RS score from week 2 (solid line) to week 15 (dashed line). Since participants were given the ADHD checklist every visit, values were highly autocorrelated for each participant.

risk levels at baseline and end-of-treatment among adolescents with ADHD and comorbid SUD, with AUD diagnostic status influencing starting risk-level, ending risk-level, and change in risk-level during treatment. In the total sample, 15% of adolescents with ADHD and a comorbid SUD showed a 2-level or greater reduction in WHO drinking risk level, while 59% and 24% of participants showed no change or an increase in risk-level during treatment respectively. The proportion of adolescent participants showing no change or increasing WHO alcohol risk level contrasts with studies in adult drinkers with and without AUD (Hasin, et al., 2017; Witkiewitz, et al., 2017). For example, Witkiewitz and colleagues found that 71% of adult AUD participants from the COMBINE study showed a 2-level or greater reduction in risk-level during treatment, with only 12% and 1% showing no change and increased risk respectively (Witkiewitz et al., 2017). These differences could reflect variation due to differences in study design, baseline AUD severity of participants, and method of calculating risk levels. Alternatively, differences could be related to comorbidity or polydrug use effects which differed between our sample and prior studies. That 21% of our sample showed at least a 2-level increase in WHO drinking risk level during treatment was surprising, and could reflect a drug substitution effect given the degree of polydrug use and the fact that the primary study found evidence for a reduction in non-tobacco substance use (Peters and Hughes, 2010). Exploratory post-hoc regression analyses provided some support for this explanation showing a trend-level negative correlation between WHO risk level and marijuana use days. Another possibility is that the divergent results compared to adult studies could be due to developmental differences in the pattern of alcohol consumption in youth vs. adults. Several studies have shown that adolescent and adult drinking patterns differ, with adolescents drinking less frequently than adults, but consuming more alcohol per drinking session (Johnston, et al., 2019. Adolescence, a developmentally sensitive period of increased vulnerability for developing AUD, is known for being a time when alcohol use first starts and escalates (rather than decreases) over time for most individuals (Hammond et al., 2014; Tarter and Vanyukov, 1994). In addition to the significant heterogeneity in drinking behaviors, in our supplementary analyses we also found that the largest differences in function and ADHD outcomes were between those groups with the greatest reduction vs. the greatest increase in drinking level during treatment. Based upon these findings future studies could employ the WHO risk levels to examine the bidirectional effects of change in risky drinking on health outcomes in the general population across different age groups, examining both significant increases and decreases in risky drinking over time. This would be a valuable topic for future research and would help us to better understand developmental differences.

Results from our primary analyses indicate that youth who achieved at least a 2-level reduction in WHO risk level following treatment showed significant improvements in global functioning, indexed by the CGAS, with this effect being driven predominantly by youth diagnosed with AUD. This suggests that reductions in WHO drinking risk level may be a valid predictor of global functional improvement in adolescent AUD populations. Our results are consistent with findings in the adult alcohol literature showing that non-abstinent drinking reduction, defined by the EMA as having at least a 2-level reduction in WHO risk level following treatment, confers clinically meaningful benefits (Hasin, et al., 2017; Witkiewitz et al., 2017). Non-abstinent 2-level or greater reductions in WHO risk levels have been shown to predict lower risk for alcohol-related psychosocial problems and medical consequences, including liver disease and even mortality, and improved functioning and well-being in adults (Kline-Simon, et al., 2013; Laramée, et al., 2015; Witkiewitz, 2013; Witkiewitz et al., 2017). Further, our exploratory analyses showed that youth who experienced at least a 1-level reduction of WHO risk level experienced improved global functioning compared to those who did not change or increased. While this should be interpreted cautiously given small proportion of the sample with a 1-level reduction, it preliminarily suggests that even modest reductions in alcohol risk may confer functional benefits in youth. It is also important to note that the association between WHO risk level reduction and improved global functioning observed in the sample was less consistent and less robust than what has been reported in adult studies. For example, our analyses only identified this association in relation baseline to end-of-treatment change, with during treatment changes (based upon our GEE analyses) not achieving statistical significance. Inconsistencies between our results and findings from adult studies may be secondary to heterogeneity in WHO risk levels obfuscating a signal in a subgroup of adolescents who reduced their drinking. For example, given the smaller proportion of participants in our sample that showed at least a 2-level reduction in WHO risk level compared to adult alcohol studies, our analyses may be underpowered to detect a relationship between risk reduction and improved functioning. The low proportion of youth who significantly decreased and high proportion of youth who showed no change or significantly increased their risky drinking during treatment also calls into question the efficacy of the combined ADHD pharmacotherapy with CBT in reducing alcohol consumption in youth with ADHD and comorbid SUD. The high variance in risk levels found in our sample suggests that WHO drinking risk levels at their current thresholds may not be sensitive enough to detect group-level differences in health outcomes during adolescent AUD clinical trials, especially for non-specific

interventions with modest effect-sizes and in samples with comorbidity or polydrug use. The original WHO risk levels were based on cohort studies of Australian adults recruited in the early 1990s (English et al., 1995), and may not be generalizable to American youth today. Alternate thresholds and different risk strata re-calibrated to account for the increased variance in developmental samples and polydrug users may be necessary in order for the WHO risk levels to have utility as a non-abstinent treatment target for youth AUD. Further research is needed in this area.

Our findings showed that youth who achieved at least a 2-level reduction in WHO risk level had greater reductions in ADHD symptoms following treatment. Regardless of AUD diagnostic status, participants showed significant reduction in ADHD symptoms during treatment. In parallel with our global function analyses, relationships between change in WHO risk level and ADHD outcomes were driven primarily by participants with AUD diagnoses who showed at least a 2-level reduction in risk level. Our results are consistent with a number of prior studies in individuals receiving treatment for ADHD and comorbid SUD that have shown a relationship between improving ADHD symptoms and reduction in drug use (Levin, Evans, Brooks, Kalbag, & Garawi, 2006; Levin et al., 2015; Levin et al., 2018; Riggs et al., 2011; Nunes et al., 2013; Luo et al., 2015) although null findings have also been reported (Carpentier and Levin, 2017; King et al. 1999; Wilens et al., 2008). Results also converge with the main NIDA-CTN-0028 study findings showing that ADHD treatment responders had significantly fewer non-tobacco substance use days at the end-of-treatment compared to non-responders (Riggs et al., 2011). Taken together, these results suggest that ADHD symptom response may track with reduction in alcohol use and non-tobacco substance use in general during combined treatment for ADHD and comorbid SUD in adolescents. Given the high propensity for polydrug use among this population, future research should investigate change trajectories of different substances during combined ADHD and SUD treatment in adolescents (Peters and Hughes, 2010).

Regarding treatment, the present study was underpowered to detect intervention-related effects on alcohol outcomes and on the relationships between change in WHO risk level and functional and ADHD outcomes. Primary findings from the NIDA-CTN-0028 study suggest OROS-MPH is a safe and effective medication for treating ADHD but does not influence non-tobacco drug use outcomes in adolescents with ADHD and comorbid SUD. This is consistent with studies in adults with ADHD and comorbid SUD that show pharmacological treatment of ADHD may improve ADHD symptoms, but typically has minimal effect on drug use outcomes (Levin et al., 2006; Levin et al., 2009; Riggs, Thompson, Mikulich, Whitmore, & Crowley, 1996; Schubiner et al., 2002). In the only trial of ADHD and comorbid AUD conducted to date, Wilens and colleagues found that atomoxetine treatment of ADHD was associated with reductions in ADHD symptoms but did not influence alcohol outcomes (Wilens et al., 2008). Further research is needed to clarify the types and combinations of interventions that are most effective in treating alcohol use problems in youth with ADHD and comorbid SUD.

There are several limitations to this study, described below. The present paper is a secondary analysis of the CTN-0028 study. Thus, we were limited by the assessment tools and study procedures conducted by CTN-0028, along with its focus on adolescents with ADHD and comorbid non-tobacco SUD. The primary ADHD outcome from the NIDA-CTN-0028 study was adolescent's self-reported ADHD symptoms, which may not be the most reliable source for this information. Polydrug use within the sample along with the non-specific focus of the CBT and the non-specific primary SUD outcome (change in past 28 day non-tobacco substance use) made it unclear how study therapists dealt with patients who used alcohol in combination with other drugs. These factors also made it difficult to isolate the unique effects of alcohol consumption and alcohol-related consequences, which could have been better characterized using measures and biochemical assays specific to alcohol (e.g., the Drinker Inventory of Consequences) (Miller et al., 1995). Lastly, our findings should be viewed through the lens of ADHD comorbidity. All participants had ADHD, a condition known to affect AUD treatment response (Wilens et al., 2008). Other psychiatric conditions highly comorbid with ADHD (e.g. conduct disorder) also influence AUD outcomes. Adolescents without ADHD may exhibit different patterns of change in alcohol consumption during treatment. As such, these results may not be generalizable to the entire adolescent population or to adolescents who do not have ADHD. To address these shortcomings, future studies should characterize WHO drinking risk levels and their relationship to functioning and mental health outcomes in other adolescent samples, clinical and general population-based, mixed (polydrug users) and alcohol only, and with varying levels of psychiatric comorbidity.

Despite these limitations, our paper also has several important strengths. The study from which the current work derives is one of the largest controlled studies of adolescents with SUD and remains the largest study conducted to date examining treatment of ADHD and comorbid SUD in youth. Another strength of the study is its comprehensive phenotypic characterization of study participants, including, for example, SUD and psychiatric diagnoses based upon clinical-interviews and the use of both self-report and biochemical measures to assess substance use. Some of these data were collected at many different time points throughout the study, providing for deeper insights into symptom progression over time. Additionally, many of the participants involved presented with an AUD, allowing for a large experimental group. Lastly, a major strength of the present work is that it is the first in the literature to investigate change in WHO drinking risk level as a metric for alcohol use harm reduction in an adolescent population.

4.1. Conclusion

In conclusion, in this secondary analysis of the NIDA-CTN-0028 study, we sought to determine whether reduction in WHO drinking risk level during treatment is a valid measure of alcohol-related changes in functioning and mental health in a population of adolescents with ADHD and comorbid SUD. Despite the significant heterogeneity in alcohol consumption among youth in the sample, we found evidence that achieving at least a 2-level reduction in WHO drinking risk level during treatment was associated with a greater reduction in ADHD symptoms and better functional outcomes. The current findings provide preliminary support for the use of 2-level reductions in WHO risk levels for alcohol use during treatment as a clinically valid non-abstinent treatment target for youth with AUD and ADHD, and indicate the need for further study of non-abstinent outcomes and their health correlates in adolescents and polydrug users.

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Contributors: Dr. Hammond, Ms. Park, and Mr. Mitchell designed the study, wrote the study procedures, and in parallel conducted the statistical analysis and wrote the manuscript. Mr. Mitchell collected and organized the data, conducted the statistical analyses, and wrote the first draft of the manuscript. Ms. Park revised the manuscript and aided in statistical analysis. All authors contributed to and have approved the final manuscript.

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CRediT authorship contribution statement

Henry M. Mitchell: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing - original draft. **Grace Park:** Data curation, Writing - review & editing, Project administration. **Christopher J. Hammond:** Conceptualization, Supervision, Methodology, Formal analysis, Validation, Writing - review & editing, Funding acquisition.

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 paper.

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