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Reduction in non-abstinent World Health Organization (WHO) drinking risk levels and drug use disorders: 3-year follow-up results in the US general population

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ABSTRACT

Background: To provide information on the clinical relevance of a reduction in the World Health Organization (WHO) drinking risk categories, we examined their relationship to an important indicator of how individuals feel and function: drug use disorders (DUDs), i.e., those involving substances other than alcohol.

Method: Current drinkers in a U.S. national survey (n = 22,005) were interviewed in 2001-02 and re-interviewed 3 years later. WHO drinking risk levels and DSM-IV-defined DUD were assessed at both waves. The relationship of changes in WHO drinking risk levels to the presence of DUD were examined using adjusted odds ratios (aOR).

Results: At Wave 1, 2.5% of respondents were WHO very-high-risk drinkers, and 2.5%, 4.8%, and 90.2% were high-risk, moderate-risk, and low-risk drinkers, respectively. Among Wave 1 very-high-risk drinkers, significantly lower odds of DUD at Wave 2 were predicted by reductions in WHO risk levels of one, two or three levels (aOR = 0.15, 0.01, 0.24, respectively; all p-values < .0001). Among participants who initially were drinking at lower risk levels, reductions in drinking or abstinence were generally associated with significantly lower odds of DUD, although the results were less consistent.

Conclusions: Among very-high-risk drinkers, reduction in the WHO drinking risk categories were associated with lower risk of a DUD. These results add to findings indicating that reductions in WHO drinking risk levels are a meaningful indicator of how individuals feel and function and could therefore serve as informative outcomes in alcohol clinical trials. WHO risk levels can also guide treatment goals and clinical recommendations on drinking reduction.

1. Introduction

Heavy drinking and alcohol use disorders (AUD) have many adverse consequences (Centers for Disease Control and Prevention, 2018; Grant et al., 2015, 2017; Greenfield et al., 2015; Hasin et al., 2017b; Rehm et al., 2003, 2017; Room et al., 2005) and contribute substantially to global morbidity and mortality (Rehm et al., 2003, 2017; Room et al., 2005). In the past decade, increases have been observed in U.S. per capita alcohol consumption and the prevalence of heavy drinking (Grant et al., 2015, 2017), AUD (Grant et al., 2015, 2017; Sacco et al., 2015), alcoholic liver disease (Doycheva et al., 2017), and alcohol-related liver cirrhosis mortality (National Institute on Alcohol Abuse and

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Alcoholism, 2018). Many individuals with AUD do not receive treatment (Cohen et al., 2007; Grant et al., 2015, 2017; Hasin et al., 2007; Mann et al., 2017a, b; Shield et al., 2014). Engaging more individuals with AUD in treatment is an important public health priority (National Institute on Alcohol Abuse and Alcoholism, 2019).

Providers' goals in treating patients with an AUD commonly involve complete abstinence (DeMartini et al., 2014). However, many patients that could benefit from treatment do not want to stop drinking completely, deterring them from seeking treatment (Grant, 1997; Mann et al., 2017a, b; McKellar et al., 2012; Probst et al., 2015; Tucker et al., 2004). If drinking *reduction* short of abstinence also provides clinical benefit, then offering non-abstinent drinking reduction goals could broaden interest in treatment (Mann et al., 2017a).

Widening the array of effective medications could also broaden interest in treatment (National Institute on Alcohol Abuse and Alcoholism, 2017). At present, only 3 medications have been approved by the FDA, disulfiram, naltrexone and acamprosate. Clinical trials may have been hampered from detecting additional effective medications by overly conservative drinking outcome measures. The FDA accepts only two clinical trial outcomes as evidence of efficacy: abstinence and no heavy drinking days (HDD; > 3 drinks for females, > 4 for males) (Food and Drug Administration, 2015). These conservative drinking outcome measures are difficult to achieve by participants in clinical trials (Falk et al., 2019), and may limit the ability of clinical trials to detect effective medications due to poor sensitivity (Hasin et al., 2017b; Knox et al., 2018), contributing to the limited number that have been approved in the past 50 years (Anton et al., 2012; Witkiewitz et al., 2015). An alternative outcome to those currently accepted (Food and Drug Administration, 2015; Maisto et al., 2018; Wilson et al., 2016; Witkiewitz et al., 2017c), used by the European Medicines Agency (EMA) is a 2-level reduction in the World Health Organization (WHO) 4-category classification of drinking risk levels: very-high, high, moderate and low (European Medicines Agency, 2010; World Health Organization, 2000). For the FDA to accept reductions in the WHO drinking risk levels as an efficacy outcome, information is needed on the clinical benefit provided by such reductions, i.e., whether they predict an improvement in how individuals feel and function.

Clinical (Witkiewitz et al., 2017b) and epidemiologic studies (Hasin et al., 2017b) have shown that reductions in the WHO drinking risk levels provide clinical benefit. Using data from a large clinical trial of medications to treat alcohol dependence (Anton et al., 2006; Witkiewitz et al., 2017b), reductions in WHO drinking risk levels predicted: reductions in alcohol consequences and systolic blood pressure, improved mental health functioning, decreased liver enzyme levels, and enhanced quality of life. In drinkers re-interviewed after 3 years in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), reductions from the very high- and high-risk levels of the WHO drinking risk categories predicted decreased odds of alcohol dependence diagnoses and improved mental health functioning (Hasin et al., 2017b), and reduced odds of liver disease (Knox et al., 2018) and psychiatric comorbidity (Knox et al., 2019). These studies support reductions in the WHO drinking risk categories as a valid clinical trial outcome associated with clinical benefit, but more information is needed on the relationship of these reductions to improvement in how individuals feel or function (Stockings and Farrell, 2017).

DUDs involve clinically significant impairment caused by the recurrent use of drugs other than alcohol, including health problems, disability, and failure to meet major responsibilities at work, school, or home (Compton et al., 2003; Degenhardt and Hall, 2012; Grant et al., 2016; Kessler, 2004; Nock et al., 2008; O'Brien et al., 2004; Yuodelis-Flores and Ries, 2015). DUDs also result in additional societal burden through their association with crime, incarceration, poverty, homelessness, and suicide (Compton et al., 2003; Degenhardt and Hall, 2012; Nock et al., 2008; Yuodelis-Flores and Ries, 2015). Substance use is prevalent and has been increasing in the United States (Substance Abuse and Mental Health Services Administration, 2017). For example, past-year non-medical cannabis use and cannabis use disorder increased from 3.6% to 7.6% and 1.4% to 2.6%, respectively (Hasin et al., 2017a), and past-year non-medical prescription opioid use and opioid use disorder increased from 1.8% to 4.1% and 0.4% to 0.9%, respectively (Martins et al., 2017), between 2001 and 2013. Alcohol use and AUD are major risk factors for a DUD (Grant et al., 2016; Hasin et al., 2007). DUDs are important indicators of impaired health and functioning, and therefore their presence can be used to study the clinical benefit associated with a reduction in the WHO drinking risk levels. An additional reason to assess the relationship between drinking level reductions and DUDs is the concern about substance substitution (Blanco et al., 2014), i.e., whether individuals who reduce their drinking substitute other substances.

Accordingly, we used baseline and 3-year follow-up data from drinkers in a nationally representative sample to examine the relationship between reductions in WHO drinking risk levels and the risk for having a current (past-year) DSM-IV-defined DUD. We examined whether: 1) a reduction of one or more WHO drinking risk levels reduced the risk of a DUD over time; and 2) whether the benefits of a reduction in WHO drinking risk level varied as a function of initial baseline WHO risk level.

2. Method

2.1. Study design and participants

The NESARC provided the baseline (Wave 1, 2001–2002; (Grant et al., 2004)) and three-year follow-up (Wave 2, 2004–2005; (Grant et al., 2009)) data from face-to-face interviews in participants' homes. The NESARC target population was non-institutionalized civilians ≥ 18 years in households and group quarters (e.g., group homes, dormitories). Individuals who were Black, Hispanic, and ages 18–24 years were oversampled. Data were adjusted for oversampling and household- and person-level non-response (Compton et al., 2007; Grant et al., 2004, 2009). All procedures, including written informed consent, were reviewed and approved by the US Census Bureau and the Office of Management and Budget. The overall Wave 1 response rate was 81.0%. Excluding ineligible respondents (e.g., those who died before follow-up), the overall Wave 2 response rate among Wave 1 participants was 86.9% (Grant et al., 2009). The weighted cumulative Wave 2 response rate (i.e., Wave 1 × Wave 2 rates) was 70.2% (Grant et al., 2009). Wave 2 data were weight-adjusted for non-response and demographic factors to ensure that the Wave 2 sample approximated the target population (Grant et al., 2009). The present analytic sample included Wave 1 drinkers (participants who had ≥ 1 drink in the prior 12 months) who participated in Wave 2 and had drinking data available (N = 22,005). Wave 1 abstainers were excluded because they could not reduce their drinking between Waves 1 and 2.

2.2. Measures

The study assessment was the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV), a modularized structured interview covering numerous health topics administered by lay interviewers (Grant et al., 2003; Ruan et al., 2008). The outcome measure for the present study used AUDADIS-IV diagnoses of DSM-IV DUDs. Substances included sedatives/tranquilizers, painkillers (prescription opioids), marijuana, cocaine/crack, stimulants, club drugs, hallucinogens, inhalants and heroin. A DUD was diagnosed when respondents met criteria for dependence with or without abuse for ≥ 1 substance in the past year. Dependence required 3 or more of the 7 DSM-IV dependence criteria, except marijuana, hallucinogens and inhalants, which did not have a DSM-IV dependence criterion for withdrawal. Hence, for DUD diagnoses involving these three substances, 3 or more of the remaining 6 DSM-IV dependence criteria were required. In multiple test-retest reliability studies of AUDADIS-IV DUD

Table 1
Prevalence of Wave 1 drinkers by WHO drinking risk levels defined in terms of drinks[a] per day, and within these levels, prevalence of Wave 1 drug use disorder.

Wave 1 WHO drinking risk level	Definition	n	Percent of participants at each WHO risk level	Prevalence in each risk level with Wave 1 drug use disorder
Very high	> 100 g (> 7.1 drinks) for men, > 60 g (> 4.3 drinks) for women	512	2.5%	10.0%
High	60–100 g (4.3–7.1 drinks) for men, 40–60 g (2.9–4.3 drinks) for women	546	2.5%	1.4%
Moderate	40–60 g (2.9–4.3 drinks) for men, 20–40 g (1.4–2.9 drinks) for women	1,073	4.8%	1.4%
Low	1–40 g (< 2.9 drinks) for men, 1–20 g (< 1.4 drinks) for women	19,874	90.2%	0.5%

[a] American standard drinks (contains roughly 14 g of pure alcohol).

diagnoses, most reliability coefficients (kappa or κ) for DUDs were good to excellent (κ ≥ .60) (Canino et al., 1999; Chatterji et al., 1997; Grant et al., 1995, 2003; Hasin et al., 1997; Vrasti et al., 1998).

The AUDADIS-IV alcohol consumption module was used to derive the WHO drinking risk levels. Four WHO drinking risk levels are defined using estimated mean ethanol consumption (grams) per day in the prior 12 months (Table 1), incorporating information on non-drinking as well as drinking days. Risk levels are expressed in terms of US standard drinks (14 g of pure ethanol). The four levels include very-high-risk drinkers (> 100 g/day for men, > 60 gm/day for women, or > 7.1 or > 4.3 standard drinks for men and women), high-risk drinkers (60–100 g/day for men, 40-60 g/day for women, or 4.3–7.1 standard drinks for men and 2.9–4.3 for women), moderate-risk drinkers (40–60 g/day for men, 20–40 g/day for women, or 2.9–4.3 standard drinks for men and 1.4–2.9 for women), and low-risk drinkers (1–40 g/day for men, 1–20 g/day for women, or < 2.9 standard drinks for men and < 1.4 for women). Wave 2 full abstainers, i.e., non-drinkers for at least a year, were treated as a separate group. The reliability of AUDADIS-IV alcohol consumption measures is very good to excellent (e.g., intraclass correlation coefficient = 0.73–0.92 for mean daily ethanol consumption) (Grant et al., 2003; Ruan et al., 2008).

In addition to examining the four WHO risk levels in terms of mean drinks *per day*, studies have also examined a reduction in WHO drinking risk levels defined in terms of drinks *per drinking day* (Hasin et al., 2017b; Knox et al., 2018) because the WHO risk levels are sometimes defined this way. This definition indicates mean ethanol consumption (grams) on the days that participants drank in the prior 12 months, ignoring days that they did not drink. In sensitivity analyses, we also analyzed mean drinks per drinking day.

2.3. Statistical analysis

We first obtained weighted proportions of individuals in the four WHO drinking risk categories at Wave 1 and prevalence of individuals in these categories with Wave 1 DUDs. Then, logistic regression was used to test the interaction between initial Wave 1 drinking risk level and change in drinking level from Wave 1 to Wave 2 on the prevalence of a DUD at Wave 2. The 2-way interaction was significant ($p < .001$), indicating that there were differential effects by baseline WHO drinking level. This indicated that the use of logistic regression was warranted to test the association of changes between Wave 1 and 2 WHO drinking risk levels with Wave 2 DUDs by each initial Wave 1 drinking risk level. The number of possible reduction levels at Wave 2 depends on participants' Wave 1 level. Wave 1 very-high-risk drinkers could remain unchanged, decrease one, two, or three levels (non-abstinent reductions), or reduce to abstinent. Wave 1 high-risk drinkers could increase one level, remain unchanged, decrease one or two levels (non-abstinent reductions), or reduce to abstinent. Wave 1 moderate-risk drinkers could increase, remain unchanged, decrease one level (non-abstinent reduction), or reduce to abstinent. Low-risk drinkers could increase, remain unchanged, or reduce to abstinent. We fit logistic regression models among Wave 1 drinkers that included each of these combinations of WHO risk categories, controlling for potential confounders (sex, age, education, race and ethnicity, smoking, body-mass index, health insurance). We calculated adjusted odds ratios (aORs) and 95% confidence intervals (Cis) of Wave 2 DUDs for each level of change in WHO drinking risk, using as the reference group those people whose WHO drinking risk level remained unchanged. The adjusted prevalence of Wave 2 DUDs was calculated using covariates fixed at their marginal distribution as found in the sample. All tests were 2-sided, with significance set at a p-value of 0.05. In all analyses, Proc Surveylogistic (SAS version 9.4) was used to incorporate the NESARC's complex clustered design and sampling weights.

We also conducted four sets of sensitivity analyses. First, we repeated the main analyses additionally controlling for DSM-IV alcohol dependence at Wave 1. Second, we restricted the analyses to

participants who had a diagnosis of alcohol dependence at Wave 1. Third, we defined the WHO drinking risk levels in terms of drinks *per drinking day*, because this measure may be more relevant to acute harms from drinking than drinks per day (World Health Organization, 2000). Eighty participants did not have the necessary information to calculate drinks per drinking day and were excluded from those analyses. Fourth, to determine specificity of the results on DUD to disorders involving specific substances, we re-ran the main analyses twice, replacing the DUD outcome variable with cannabis dependence and with prescription opioid dependence. We chose these because cannabis and prescription opioids are the substances most widely used non-medically.

3. Results

At Wave 1, 2.5% of respondents were very-high-risk drinkers, 2.5% were high-risk drinkers, 4.8% were moderate-risk drinkers, and 90.2% were low-risk drinkers (Table 1). The prevalence of Wave 1 DUDs was 10.0% in very-high-risk drinkers, and 0.5%–1.4% in the other drinking risk groups.

3.1. Very-high-risk drinkers

The rate of DUD at Wave 2 by change in WHO drinking risk level is shown in Table 2. Among Wave 1 very-high-risk drinkers with no change in drinking level, 2.8% had a Wave 2 DUD. Among those whose drinking decreased one, two, or three WHO risk levels at Wave 2 (non-abstinent drinking reductions), 0.4%, 0.03%, and 0.7%, respectively, had a Wave 2 DUD. The prevalence of DUD was 0.0% among individuals who became abstinent. Compared to respondents with no change in drinking level (the reference group), each non-abstinent decrease in WHO risk level predicted significantly lower odds of a Wave 2 DUD (p-values < .0001).

3.2. High-risk drinkers

In Wave 1 high-risk drinkers with no change in drinking level, 0.5% had a DUD, while those whose drinking decreased one or two WHO risk levels had a DUD prevalence of 0.7% and 0.6%, respectively. Prevalence of DUD was 0.0% among individuals who became abstinent. Compared to respondents with no change in drinking level (the reference group), the odds of DUD were significantly higher in those with a one-level decrease in WHO risk level predicted (p-value < .001).

3.3. Moderate-risk drinkers

In Wave 1 moderate-risk drinkers with no change in drinking level, 0.3% had a DUD, while 0.2% had a DUD among those whose drinking decreased one WHO risk level. Prevalence of DUD was 0.0% among those who became abstinent. Compared to respondents with no change in drinking level (the reference group), the odds of Wave 2 DUD were significantly lower in those with a one-level decrease in WHO risk level (p-value < .0001).

3.4. Low-risk drinkers

In Wave 1 low-risk drinkers with no change in drinking level, 0.4% had a DUD. Prevalence of DUD was 0.2% among those who became abstinent. Compared to respondents with no change in drinking level (the reference group), the odds of Wave 2 DUD were significantly lower in those who became abstinent (p-value = .0001).

3.5. Covariates

Wave 1 DUD, sex, age, education, race/ethnicity, insurance status, Wave 1 smoking and Wave 1 psychiatric disorder were significantly associated with Wave 2 DUD.

3.6. Sensitivity analyses

(1) Controlling for whether participants had a diagnosis of DSM-IV alcohol dependence at Wave 1 had virtually no effect on the results (not shown). (2) Restricting the sample to participants with a diagnosis of DSM-IV alcohol dependence at Wave 1 (N = 1152) did not substantively affect the results (Supplementary Table 1). (3) Re-defining WHO risk levels in terms of drinks per *drinking day*, results were similar to the main analyses. The prevalence of Wave 1 DUD was 3.5% in the

Table 2
Drug use disorder at Wave 2 by Wave 1 WHO drinking risk level (drinks per day) and change in WHO risk level between Waves 1 and 2.

Wave 1 WHO risk level and change by Wave 2	All Wave 1 drinkers (n = 22,005)			
	n	Prevalence of Wave 2 drug use disorder[a]	Adjusted OR (95% CI)	p-value
Wave 1 Very high risk				
No change	139	2.8%	Reference	
Decreased by one level	75	0.4%	0.15 (0.09-0.23)	< **.0001**
Decreased by two levels	59	0.0%[c]	0.01 (0.01-0.02)	< **.0001**
Decreased by three levels	198	0.7%	0.24 (0.12-0.50)	< **.0001**
Became abstainer	41	0.0%	NA[b]	
Wave 1 High risk				
Increased	77	1.8%	3.40 (1.40-8.26)	**0.0069**
No change	84	0.5%	Reference	
Decreased by one level	105	0.7%	1.37 (1.10-1.69)	**0.0043**
Decreased by two levels	246	0.6%	1.04 (0.81-1.33)	0.7818
Became abstainer	34	0.0%	NA[b]	
Wave 1 Moderate risk				
Increased	141	0.7%	2.65 (2.16-3.24)	< **.0001**
No change	259	0.3%	Reference	
Decreased by one level	628	0.2%	0.65 (0.57-0.75)	< **.0001**
Became abstainer	45	0.0%	NA[b]	
Wave 1 Low risk				
Increased	1,014	2.0%	4.94 (3.80-6.42)	< **.0001**
No change	15,999	0.4%	Reference	
Became abstainer	2,861	0.2%	0.56 (0.42-0.76)	**0.0001**

[a] Prevalence values are calculated from the same logistic regression used to obtain adjusted OR values which controls for a priori control covariates (sex, age, education, race and ethnicity, smoking, body-mass index, health insurance).
[b] Contrast cannot be computed since the prevalence of Wave 2 drug use disorder is 0.0%.

very-high-risk drinkers and 0.3%-0.8% in the other drinking risk groups (Supplementary Table 2)*. DUD at Wave 2 by change in WHO drinking risk level is shown in Supplementary Table 3. Again, results were most consistent among Wave 1 very-high-risk drinkers. Compared to respondents with no change in drinking level (the reference group), each non-abstinent decrease in WHO risk level predicted significantly lower odds of Wave 2 DUD (p-values < .001 to < .0001) as did becoming (p-value < .0001). Unlike the main analyses, among the Wave 1 high-risk drinkers, those with a one-level reduction in WHO drinking level had significantly lower odds of Wave 2 DUD than respondents with no change in drinking level (p-value = .0035). Among the Wave 1 moderate-risk drinkers, those with a one-level decrease in WHO drinking level had higher odds of Wave 2 DUD compared to those with no change in drinking level (p-value < .0001). (4) The Wave 1 prevalences of cannabis and non-medical prescription opioid dependence were low (Supplementary Table 4)*. Nevertheless, results for these drug disorders were very similar to those of the main analysis (Supplementary Table 5)*. Where cell counts were greater than zero, decreases in WHO risk levels predicted significantly lower odds of Wave 2 cannabis and prescription opioid dependence compared to participants whose WHO risk levels remained unchanged.

4. Discussion

Using data from a large national survey with a 3-year follow-up, we examined whether non-abstinent drinking reduction, defined by reductions in the WHO drinking risk levels, conferred clinically meaningful benefit by reducing risk for having a drug use disorder (DUD), an important indicator of how individuals feel and function. Of particular interest in this study were respondents who were initially in the WHO very-high-risk and high-risk drinking categories, i.e., those of greatest clinical concern.

Results indicate that among the very-high-risk drinkers, one-, two-, or three-level non-abstinent reductions in WHO drinking risk levels were associated with significantly lower odds of DUD, regardless of whether WHO risk levels were defined by drinks per day or drinks per drinking day and whether or not individuals in these groups met criteria for alcohol dependence initially. These findings provide robust support for the clinically meaningful benefit of non-abstinent reduction in WHO drinking risk levels among individuals whose drinking is of greatest concern (Falk et al., under review). In high-, moderate-, and low-risk drinkers, reductions in drinking or abstinence were also associated with significantly lower odds of a DUD, although the results were less consistent. Notably, among Wave 1 high-risk drinkers, a one-level decrease in Wave 2 WHO drinking risk levels predicted significantly greater risk for a DUD at Wave 2. Although in some cases there was a suggestion of a substitution effect, wherein decreased drinking was associated with increased risk for DUD (Moore, 2010), it is important to note that the difference in DUD risk for individuals who reduced their drinking by one level (versus the no-change reference group) was an increase of only 0.2%, which is not a clinically meaningful increase in DUD risk.

Our findings show that for very-high-risk drinkers, i.e., those whose drinking is most like participants in treatment trials for AUD, even a one-level reduction in WHO drinking risk levels (from very-high-risk to high-risk) offers meaningful and important clinical benefit. Furthermore, finding address a concern about reductions in drinking being offset by an increased risk of using other drugs (Hasin et al., 2007). Although this may be possible among high-risk drinkers, among very-high-risk drinkers, our results indicate the opposite, i.e., that drinking reduction as defined by the WHO risk levels was associated with a reduction in the risk of DUD within a 3-year period. This finding was most pronounced among very-high-risk drinkers but was generally found among moderate and low-risk WHO levels as well.

Clinically, individuals who are not interested in abstinence can be offered an initial drinking reduction goal that is described in specific terms, including reductions in WHO drinking risk levels and their associated benefit. These risk levels can be readily translated into goals involving the approximate numbers of drinks per day or drinks per drinking day using the standard drink equivalents to grams of alcohol of the country in which the intervention occurs (Hasin et al., 2017b). Our findings also support the use of non-abstinent reductions in WHO drinking risk levels as an outcome measure in clinical trials of medications for AUD. Our results are consistent with other findings (Anton et al., 2006; Dawson et al., 2008; Hasin et al., 2017b; Knox et al., 2018, 2019; Rehm and Roerecke, 2013; Roerecke et al., 2013, 2015; Witkiewitz et al., 2017a) showing that non-abstinent drinking reduction confers clinically meaningful benefit. This includes drinking reductions defined with the WHO drinking risk levels, which were shown to predict lower risk of many adverse consequences of heavy drinking, including alcohol dependence, poor mental health functioning (Hasin et al., 2017b), alcohol-related psychosocial consequences (Hasin et al., 2017b; Witkiewitz et al., 2017a), liver disease (Knox et al., 2018), and mortality (Roerecke et al., 2015). The consistency of the present results to previous findings supports the robustness of the present findings, and therefore the value of the WHO drinking risk levels as a means of defining drinking reductions that can be used to guide clinical recommendations and assess efficacy in clinical trials.

Study limitations are noted. Data were based on self-report, and alcohol use and DUDs may have been under-reported. Diagnoses were not made by clinicians, who cannot be used as field interviewers in large-scale epidemiologic surveys. However, the test-retest reliability of DUDs has been reported to be good to excellent (Canino et al., 1999; Chatterji et al., 1997; Grant et al., 1995, 2003; Hasin et al., 1997; Vrasti et al., 1998), supporting their use as a diagnostic measure in epidemiological studies. In addition, the focus of the present paper is drinking reduction (i.e., the potential clinical benefits of non-abstinent drinking reductions using the WHO 4-category classification of drinking risk levels). However, clearly, change in drinking can also include drinking increases. Using a similar model to address the effects of drinking increases would be a valuable topic for future research. Also, while this study addresses non-abstinent drinking reductions, it does not address the durability of such reductions over time or how this durability might compare to the durability of abstinence over time.

Study limitations are offset by several strengths. The study capitalized on a large and rigorously assessed epidemiological sample. The NESARC had high response rates; detailed assessment of drinking at both waves; a 3-year follow-up period; and the use of a national sample with a high representation of participants across demographic groups that was large enough to analyze WHO-defined risk groups, including very-high-risk levels. The need to widen the options available for treating AUD (e.g., non-abstinent goals and additional medications) has grown increasingly acute given national increases in drinking and AUD prevalence (Grant et al., 2017) and the fact that so many individuals with these disorders remain untreated (Cohen et al., 2007; Grant et al., 2015, 2017; Hasin et al., 2007; Shield et al., 2014). Understanding the potential benefits of non-abstinent drinking reductions in individuals initially drinking at “unsafe levels” will help inform the public, treatment providers, patients, investigators conducting clinical trials, and public health officials about treatment goals and potential health improvement and cost savings. As AUD poses an increasingly high public health burden (Grant et al., 2015, 2017), reduced drinking leading to decreased health problems has huge cost-benefit implications.

4.1. Conclusions

Problem drinkers and individuals with an AUD who do not want to stop drinking are less likely to voluntarily enter treatment that requires an abstinence goal from all patients compared to treatment that also works with patients with non-abstinent goals. Thus, broadening the range of acceptable treatment goals could help to engage individuals who need alcohol treatment. Further, non-abstinent drinking

reductions defined by the WHO drinking risk levels can also serve as valuable outcome indicators in treatment trials for AUD, as already accepted by the European Medicines Agency (European Medicines Agency, 2010). Our results suggest that such drinking reductions offer considerable benefit to very heavy drinkers by encouraging the reduction of other drug use, such that even those that reduce their WHO-defined drinking risk by only one level get such benefit. Thus, this data supports other findings that suggest that such WHO drinking risk reductions can be valid clinical trial outcome indicators and serve as valuable treatment goals to be discussed with patients. The information provided in this study is important for the public, public health officials, treatment providers, patients, and investigators conducting clinical trials.

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Contributors

All authors have approved the final manuscript. *Study concept and design:* Wall, Witkiewitz, Kranzler, Falk, Litten, Mann, O'Malley, Anton, Hasin. *Acquisition, statistical analysis, and interpretation of data:* Knox, Wall, Scodes, Hasin. *Drafting of the manuscript:* Knox, Hasin. *Critical revision of the manuscript:* All authors. *Intellectual content:* All authors. *Administrative support and study supervision:* Hasin.

Conflict of interest

Witkiewitz, Kranzler, Mann, Hasin, Falk, Litten, O'Malley, and Anton are members of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE Workgroup), which during the time in which this paper was developed, was supported by Abbvie, Alkermes, Arbor, Amygdala, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, and Pfizer. Mann has received speaker's fees from Lundbeck and the advisory board of Pfizer, Germany. Kranzler has served as a consultant, advisory board member, and CME lecturer for Alkermes, Lundbeck, and Indivior. Anton previously was a consultant for Lilly, Lundbeck, Novartis, Indivior, Laboratorio Farmaceutico CT, and Alkermes; served on advisory boards for Alkermes, Indivior, and Lundbeck; and received grant funds from Lilly and Laboratorio Farmaceutico CT. Hasin is Principal Investigator of a study funded by a contract from InVentiv Health Consulting that combines support from Actavis, Endo Pharmaceuticals, Janssen Pharmaceuticals, Mallinckrodt, Pfizer, Purdue Pharma, Rhodes Pharmaceuticals, Roxane Laboratories, and Zogenix. All other authors (Knox, Wall, Scodes) have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.03.020.

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