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Reduction in non-abstinent WHO drinking risk levels and depression/anxiety disorders: 3-year follow-up results in the US general population

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Abstract

Background: Non-abstinent drinking reductions that predict improvement in how individuals feel or function, such as the World Health Organization (WHO) drinking risk levels, may be useful outcomes in clinical trials for alcohol use disorders (AUD).

Methods: Current drinkers in a U.S. national survey (n=22,005) were interviewed in 2001–02 (Wave 1) and re-interviewed 3 years later (Wave 2). WHO drinking risk levels, a 4- level categorization system (very-high-risk, high-risk, moderate-risk, and low-risk drinkers) defined using estimated mean ethanol consumption (grams) per day in the prior 12 months, and DSM-IV depressive and anxiety disorders were assessed at both waves. Logistic regression was used to

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produce adjusted odds ratios (aOR) testing the associations of changes between Wave 1 and Wave 2 WHO risk levels to the presence or persistence of depression and/or anxiety disorder by each initial Wave 1 risk level.

Results: Among Wave 1 very-high-risk drinkers, lower odds of depression and/or anxiety disorders at Wave 2 were predicted by reductions in WHO risk levels of one-, two- or three-levels (aOR=0.42, 0.37, 0.67, p-values .04-<.0001), as was the persistence of depression and/or anxiety disorders among those with such disorders at Wave 1 (aOR=0.37, 0.29, 0.51, p-values .03-<.0001). Results were less consistent for participants initially drinking at lower risk levels.

Conclusions: Among very-high-risk drinkers, reductions in the WHO drinking risk categories were associated with lower risk of depression and/or anxiety disorders. These results add to findings indicating reductions in WHO risk levels are a meaningful indicator of how individuals feel and function.

Keywords

alcohol; alcohol use disorder; drinking reduction; depression; anxiety

1. Introduction

Heavy drinking and alcohol use disorders (AUD) have many adverse consequences (Centers for Disease Control and Prevention, 2018; Grant et al., 2015; Grant et al., 2017; Greenfield et al., 2015; Hasin et al., 2017; Rehm et al., 2003; Rehm et al., 2017; Room et al., 2005) and contribute substantially to global morbidity and mortality (Rehm et al., 2003; Rehm et al., 2017; Room et al., 2005). In the past decade, U.S. per capita alcohol consumption, the prevalence of heavy drinking (Grant et al., 2015; Grant et al., 2017), AUD (Grant et al., 2015; Grant et al., 2017; Sacco et al., 2015), alcoholic liver disease (Doycheva et al., 2017), and alcohol-related liver cirrhosis mortality (National Institute on Alcohol Abuse and Alcoholism, 2018) have increased. Many with AUD do not receive treatment (Cohen et al., 2007; Grant et al., 2015; Grant et al., 2017; Hasin et al., 2007; Mann et al., 2017a; Mann et al., 2017b; Shield et al., 2014). Engaging more individuals with AUD in treatment is an important public health priority (National Institute on Alcohol Abuse and Alcoholism).

In treating patients with AUD, provider goals 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; Mann et al., 2017b; 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. Widening the array of effective medication options could also broaden interest in treatment (National Institute on Alcohol Abuse and Alcoholism, 2017). Overly conservative drinking outcome measures may hamper the ability of clinical trials to detect effective treatments (Anton et al., 2012; Witkiewitz et al., 2015). Recognizing that abstinence may be an overly narrow, insensitive outcome, the Food and Drug Administration (FDA) now accepts an additional outcome, i.e., no heavy drinking days (HDD; >3 drinks for females, >4 for males) (Food and Drug Administration, 2015), with the percentage of participants having no HDD

compared between treatment arms. However, the no-HDD outcome may also be overly narrow and insensitive, since it classifies patients as treatment failures after any HDD, although some of these patients substantially reduce their drinking and improve in how they feel and function (Maisto et al., 2018; Wilson et al., 2016; Witkiewitz et al., 2017c). An alternative clinical trials outcome to those currently accepted (Food and Drug Administration, 2015; Maisto et al., 2018; Wilson et al., 2016; Witkiewitz et al., 2017c), which is used by the European Medicines Agency (EMA), is a 2-level reduction in the World Health Organization (WHO) 4-category classification of risk drinking 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 improvements in how individuals feel and function.

Benefit from reductions in the four-level WHO drinking risk levels has been shown in clinical and epidemiologic studies (Hasin et al., 2017). Using data from a large clinical trial of medications to treat alcohol dependence (Anton et al., 2006; Witkiewitz et al., 2017b), reductions in WHO risk drinking levels predicted reductions in alcohol consequences and improved mental health functioning. In drinkers re-interviewed after 3 years in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Hasin et al., 2017), 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, as measured by the Mental Component Summary of the Short-Form 12, version 2 (SF-12v2) Health Survey(Hasin et al., 2017). In the same sample, reductions in WHO drinking risk level were associated with reduced odds of liver disease. These studies support reductions in the 4-level WHO risk drinking categories as a valid clinical trial outcome, but more information is needed on the relationship of these reductions to improvement in how individuals feel or function (Stockings and Farrell, 2017), such as internalizing disorders, complex variables that combine symptomology and require some degree of impaired functioning. Mental functioning is a global term that does not provide clinical clarity or diagnostic accuracy. Therefore, to further define and focus the original findings in this analysis, we evaluated the more clinically meaningful and transportable concepts of depression and anxiety.

Diagnoses of internalizing disorders, i.e., depressive (major depression, dysthymia) and anxiety disorders (panic, generalized anxiety, social or specific phobia) are made in individuals with persistent, disabling low affect and/or high levels of anxiety (American Psychiatric Association, 2000, 2013) and as such, are important indicators of how individuals feel and function. Collectively, these highly comorbid disorders form the internalizing dimension in the transdiagnostic model of common mental disorders (Eaton et al., 2015). The internalizing disorders are common in US adults (Hasin and Grant, 2015; Hasin et al., 2018) and highly comorbid with AUD (Grant et al., 2004a; Grant et al., 2015; Hasin et al., 2005; Hasin et al., 2007; Hasin et al., 2018). Additionally, depression and anxiety symptoms are associated with greater alcohol relapse risk among those who receive alcohol treatment (Witkiewitz and Villarroel, 2009). Depressive and/or anxiety disorders are thus important indicators of health and functioning, and can therefore be used to study the clinical benefit associated with a reduction in the 4-category WHO drinking risk levels.

Accordingly, we used baseline and three-year follow-up data from drinkers in a nationally representative sample to examine the relationship between reductions in WHO risk drinking levels and 1) the risk for having a current (past-year) DSM-IV depressive and/or anxiety disorder and 2) the risk for having a persistent (past-year) DSM-IV depressive and/or anxiety disorder among those with a DSM-IV depressive and/or anxiety disorder at baseline. We examined whether: 1) the benefits of WHO risk drinking level reductions varied as a function of initial baseline WHO risk level; and 2) a reduction of one or more WHO risk drinking levels reduced the risk of prevalence and persistence of a depressive and/or anxiety disorder over time. We hypothesized that reductions of WHO risk drinking levels would reduce the risk of a depressive and/or anxiety disorder across all groups, but more so among those who were initially at the very-high-risk and high-risk drinking levels. We also hypothesized that the reduced risk of the prevalence and persistence of a depressive and/or anxiety disorder would be greater among those with larger reductions in their drinking levels.

2. Materials and Methods

2.1 Study design and participants

The NESARC (Grant et al., 2004b) provided the baseline (Wave 1, 2001–2002) and three-year follow-up (Wave 2, 2004–2005) data from face-to-face interviews in participants' homes (Grant et al., 2009). The NESARC target population was non-institutionalized civilians ≥18 years in households and group quarters (e.g., group homes, dormitories). Black individuals, Hispanic individuals, and those 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., 2004b; Grant et al., 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=21,925). Wave 1 abstainers were excluded because they could not reduce their drinking between Waves 1 and 2.

2.2 Measures

The measure for the study was the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV), a modularized structured interview administered by lay interviewers (Grant et al., 2003; Ruan et al., 2008) covering numerous health topics.

The outcome measure for the present study used AUDADIS-IV diagnoses of DSM-IV depressive disorders (major depression, dysthymia) and anxiety disorders (panic, generalized anxiety, social or specific phobia). Depressive disorders were diagnosed when ≥2 weeks of

persistent depressed mood or anhedonia occurred, accompanied by ≥5 of the 9 DSM-IV symptoms of major depression. Anxiety disorders similarly followed DSM-IV criteria. Reliability of DSM-IV depressive disorders was good (kappa=0.58–0.65), and fair for DSM-IV anxiety disorders (kappa=0.41–0.52) (Grant et al., 2003). Given the high comorbidity between depressive and anxiety disorders (Hasin et al., 2005; Hasin and Grant, 2015; Hasin et al., 2018), their clustering within the internalizing dimension of the transdiagnostic model (Eaton et al., 2015), our prior work examining the internalizing disorders in the NESARC data, and to increase the statistical power in the analyses, we combined them into a single variable, "depression and/or anxiety disorders," coded positive if any of the disorders were present in the prior 12 months. Prior work with the NESARC data found the internalizing construct based on the presence of depression and/or anxiety disorders was invariant across gender (Eaton et al., 2012) and race/ethnicity groups (Eaton et al., 2013).

The AUDADIS-IV alcohol consumption module was used to derive the WHO risk drinking levels. The 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 grams of pure ethanol). The four levels include very-high-risk drinkers (>100 gm/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 gm/day for men, 40–60 gm/day for women, or 4.3–7.1 standard drinks for men and 2.9–4.3 for women), moderate-risk drinkers (40–60 gm/day for men, 20–40 gm/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 gm/day for men, 1–20 gm/day for women, or <2.9 standard drinks for men and <1.4 for women). Full abstainers, i.e., non-drinkers for at least a year, are treated as a separate group. 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., 2017; 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 depression and/or anxiety disorders. 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 DSM-IV depressive and/or anxiety disorder at Wave 2 and persistence of a DSM-IV depressive and/or anxiety disorder at Wave 2 among those with a DSM-IV depressive and/or anxiety disorder at Wave 1. 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 depression and/or anxiety disorders 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 depression and/or anxiety disorders for each level of change in WHO drinking risk, using as the reference group those people whose WHO risk drinking level remained unchanged. We also calculated aORs and 95% CIs of the persistence of depression and/or anxiety disorders among individuals with such disorders at Wave 1, using a similar logistic regression model with each combination of WHO risk level change. The adjusted prevalence or persistence of Wave 2 depression and/or anxiety disorders 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 three sensitivity analyses. First, we repeated the main analyses additionally controlling for alcohol dependence at Wave 1. Second, we restricted the analyses to participants that had a diagnosis of DSM-IV alcohol dependence at Wave 1. The rationale for these sensitivity analyses was to see whether the results were similar when taking into account alcohol dependence, a diagnosis that would indicate the need for a reduction in drinking levels. Third, we defined the WHO risk drinking levels in terms of drinks *per drinking day*, since this measure may be more relevant to acute harms from drinking than to chronic harms; whether psychiatric disorders should be considered acute vs. chronic harm is unclear. Eighty participants did not have the necessary information to calculate drinks per drinking day and were excluded from those analyses.

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 depression and/or anxiety disorders was 29.3% in very-high-risk drinkers, and 16.6%−19.5% in the other drinking risk groups.

3.1 Very-High-Risk Drinkers

The rate of depression and/or anxiety disorders at Wave 2 by change in WHO risk drinking level is shown in Table 2. Among Wave 1 very-high-risk drinkers with no change in drinking level, 29.1% had Wave 2 depression and/or anxiety disorder. Among those whose drinking

decreased one, two or three WHO risk levels at Wave 2 (non-abstinent drinking reductions), 14.8%, 13.2%, and 21.6%, respectively, had Wave 2 depression and/or anxiety disorder. Prevalence of depression and/or anxiety disorder was 18.6% among those 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 Wave 2 depression and/or anxiety disorder (p-values .016 - <.0001). Reduction to abstinent predicted significantly lower odds of Wave 2 depression and/or anxiety disorder (p-value .004). Table 2 also shows Wave 2 *persistence* of depression and/or anxiety disorder among respondents with such disorders at Wave 1. The prevalence of persistent depression and/or anxiety disorder at Wave 2 was 67.8% among individuals with no change in drinking level, 43.5%, 37.6%, and 51.5% in those whose drinking decreased one, two or three levels, respectively, and 21.4% in those who became abstinent. Compared to respondents with no change in drinking level, each decrease in WHO risk level predicted significantly lower odds of persistent Wave 2 depression and/or anxiety disorder (p-values .017 −.031). Reduction to abstinent predicted significantly lower odds of Wave 2 depression and/or anxiety disorder (p-value <.0001).

3.2 High Risk Drinkers

Results for high-risk drinkers were less consistent (Table 2). In Wave 1 high-risk drinkers with no change in drinking level, 15.7% had a depression and/or anxiety disorder, while 19.7% and 11.5% had depression and/or anxiety disorder among those whose drinking decreased one or two WHO risk levels. Prevalence of depression and/or anxiety disorder was 7.0% among those 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 Wave 2 depression and/or anxiety disorder (p-values . 027 and .028). Reduction to abstinent predicted significantly lower odds of Wave 2 depression and/or anxiety disorder (p-value <.0001). No results were significant for *persistence* of depression and/or anxiety disorder.

3.3 Moderate and Low Risk Drinkers

In Wave 1 moderate-risk drinkers with no change in drinking level, 13.3% had a depression and/or anxiety disorder, while 13.4% had depression and/or anxiety disorder among those whose drinking decreased one WHO risk levels. Prevalence of depression and/or anxiety disorder was 7.3% among those who became abstinent. The only change that predicted lower odds of the prevalence or persistence of depression and/or anxiety disorder was becoming abstinent (p-values <.001 and .031, respectively) (Table 2).

In Wave 1 low-risk drinkers with no change in drinking level, 13.9% had a depression and/or anxiety disorder. Prevalence of depression and/or anxiety disorder was 14.8% among those who became abstinent. Significantly *higher* odds of depression and/or anxiety disorder were found in individuals who became abstinent (p-values <.0001 and .038, respectively).

3.4 Sensitivity Analyses

In our first sensitivity analysis, we added a control variable to the models indicating whether participants had a diagnosis of DSM-IV alcohol dependence at Wave 1. The addition of this variable had virtually no effect on the results (not shown).

In our second sensitivity analysis, we restricted the analyses to participants that had a diagnosis of DSM-IV alcohol dependence at Wave 1. The use of this sub-sample had virtually no effect on the results (Supplementary Table 1).

In our third sensitivity analysis, re-defining WHO risk levels in terms of drinks per *drinking day*, results were similar to the main analyses. The prevalence of Wave 1 depression and/or anxiety disorders was 24.7% in the very-high-risk drinkers and 14.0%−19.4% in the other drinking risk groups (Supplementary Table 2). Depression and/or anxiety disorders at Wave 2 by change in WHO risk drinking level is shown in Supplementary Table 3. Again, results were most consistent among Wave 1 very-high-risk drinkers. Rates of depression/anxiety disorder among those with no change in drinking level, or who decreased one, two or three WHO risk levels at Wave 2 (non-abstinent drinking reductions), were 41.8% 37.8%, 34.2% and 32.6%, respectively, and 23.8% among those 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 Wave 2 depression and/or anxiety disorder (p-values .031 - <.0001). Reduction to abstinent did not predict significantly lower odds of Wave 2 depression and/or anxiety disorder. Supplementary Table 3 also shows Wave 2 *persistence* of depression and/or anxiety disorder among respondents with such disorders at Wave 1. The prevalence of persistent depression and/or anxiety disorder at Wave 2 among individuals with no change in drinking level and whose level decreased one, two or three levels, was 17.3% 14.8%, 14.0%, and 12.0%, and 16.4% in those who became abstinent. Compared to respondents with no change in drinking level, decreases in two and three WHO risk levels predicted significantly lower odds of persistent Wave 2 depression and/or anxiety disorder (p-values .026, .003). Reduction to abstinence predicted significantly lower odds of Wave 2 depression and/or anxiety disorder (p-value <. 0001). Similar to the main analyses, results were less consistent among Wave 1 high-risk, moderate-risk and low-risk drinkers (Supplementary Table 3).

4. Discussion

Using data from a large national survey with a 3-year follow-up, we examined drinking reduction, defined by reductions in the 4-category WHO drinking risk levels, and becoming abstinent conferred clinically meaningful benefit in terms of reduced risk for having a depression and/or anxiety disorder, an important indicator of how individuals feel and function. Of particular interest in this study were respondents who initially were in the WHO very-high-risk and high-risk drinking categories, i.e., those of greatest clinical concern.

Table 3 summarizes the results of this study. Results indicate that among the very-high-risk drinkers, one-, two- or three-level non-abstinent reductions in WHO risk drinking levels were associated with significantly lower odds of depression and/or anxiety disorder, regardless of whether WHO risk levels were defined by drinks per day or drinks per drinking

day and whether 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 risk drinking levels among individuals whose drinking is of highest concern.

In high-risk drinkers, a 2-level reduction in drinking and a reduction to abstinence were associated with significantly lower odds of depression and/or anxiety disorder, as hypothesized. However, a 1-level reduction in drinking was associated with significantly higher odds of depression and/or anxiety disorder; we do not know of any clinical explanation for this unexpected result. Also, in high-risk drinkers, reductions in drinking had no association with persistence of depression and/or anxiety disorder among those with depression and/or anxiety disorder at baseline. Reductions in drinking also had less consistent relationships to the odds of depression and/or anxiety disorder across sensitivity analyses. These results are unexpected because high-risk drinkers report high levels of alcohol consumption, and many of these individuals would likely meet inclusion criteria for level of drinking in a clinical trial. In moderate-, and low-risk drinkers, reductions in drinking or abstinence showed less consistent relationships to the odds of depression and/or anxiety disorder, which may have occurred because at these initial drinking levels, issues other than drinking may have been more salient to the occurrence or persistence of depression and/or anxiety disorder than in drinkers in the very-high-risk group. The inconsistencies in findings were particularly notable among Wave 1 low-risk drinkers, in whom both increases and decreases (becoming abstinent) in Wave 2 WHO risk drinking levels predicted significantly greater risk for depression and/or anxiety disorder at Wave 2.

Our findings show that for very-high-risk drinkers 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 just high-risk) offers meaningful and important clinical benefit, with potentially important implications for improved work and social performance, decreased suicide risk, and better health outcomes.

Clinically, for individuals who are not interested in abstinence, initial drinking reduction goals can be offered and 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 of the country in which the intervention occurs (Hasin et al., 2017). Our findings also support the use of non-abstinent reductions in WHO drinking risk levels as an outcome measure in clinical trials of treatments for AUD. This is also important for several reasons. First, the use of less conservative and more discriminating outcome measures than full abstinence or subjects with no-HDD may enable the field to identify additional treatments that could benefit individuals with AUD. Second, by identifying more participants in trials who improved than the abstinent or no-HDD outcome measures, reduction in WHO risk drinking levels may identify more treatment “successes,” presenting a more realistic, nuanced picture of treatment efficacy than the rates of complete abstinence or no-HDD often found in trials to date. This information is important in educating the public and health professionals that treatment for AUD can be effective and therefore worthwhile, counterbalancing considerable, widespread skepticism and misperception. As

such more individuals who could potentially benefit from treatment could be motivated to receive help.

Our results are consistent with other studies (Anton et al., 2006; Bradley et al., 2016; Dawson et al., 2008; Hasin et al., 2017; Knox et al., 2018; Rehm and Roerecke, 2013; Roerecke et al., 2013; Roerecke et al., 2015; Witkiewitz et al., 2017a) that non-abstinent drinking reduction confers clinically meaningful benefit. This includes drinking reductions defined with the 4-category WHO risk drinking levels, which were shown to predict lower risk of many adverse consequences of heavy drinking, including alcohol dependence and poor mental health functioning (Hasin et al., 2017), psychosocial consequences (Hasin et al., 2017; Witkiewitz et al., 2017a), liver disease, and mortality (Dawson et al., 2008; Rehm and Roerecke, 2013; Roerecke et al., 2013; Roerecke et al., 2015). The consistency of previous findings with the present results adds further support to the robustness of our present findings on internalizing disorder diagnoses. These disorders are important indicators of clinical benefit because they are common in US adults (Hasin and Grant, 2015; Hasin et al., 2018), highly comorbid with AUD (Grant et al., 2004a; Grant et al., 2015; Hasin et al., 2005; Hasin et al., 2007; Hasin et al., 2018), and associated with greater alcohol relapse risk among those who receive alcohol treatment (Witkiewitz and Villarroel, 2009). They are important indicators of how individuals feel and function that go beyond some of the clinical outcomes that have already been demonstrated, such as alcohol use disorder (Dawson et al., 2008), high-density lipoprotein cholesterol (HDL) (Bradley et al., 2016), liver disease (Knox et al., 2018), and mortality (Rehm and Roerecke, 2013; Roerecke et al., 2013; Roerecke et al., 2015). A limitation of the NESARC measures of depressive/anxiety disorders is that they are not diagnoses made by clinicians. However, these diagnoses, based on self-reported symptoms ascertained by highly-trained field interviewers, have been shown to be reliable and valid. In summary, the present and previous findings confirm 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 psychiatric disorders may have been under-reported. Diagnoses of depression and/or anxiety disorders were not made by clinicians, who cannot be used as field interviewers in large-scale epidemiologic surveys. However, the test-retest reliability of the depression and anxiety diagnoses was fair to good (Grant et al., 2003), supporting their use as diagnostic measures. Also, the number of people who reported drinking and had a persistent depressive and/or anxiety disorder at Wave 2 was small for some drinking risk levels. 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 risk drinking 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. Lastly, our study addresses non-abstinent drinking reductions, but does not address the ability to maintain such reductions or how this compares to one’s ability to maintain abstinence.

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 treatments) 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; Grant et al., 2017; Hasin et al., 2007; Shield et al., 2014). Understanding potential benefits of non-abstinent drinking reductions in individuals at unsafe drinking levels is important to inform the public, treatment providers, patients, investigators conducting clinical trials, and public health officials. As AUD poses an increasingly high public health burden (Grant et al., 2015; Grant et al., 2017), reduction of drinking leading to decreased health problems has huge cost-benefit implications.

4.1 Conclusions

Our results suggest that non-abstinent drinking reductions defined by the 4-category WHO risk drinking levels offer considerable benefit to very heavy drinkers, even those that reduce their WHO-defined drinking risk by only one level. Thus, such reductions can be valid clinical trial outcome indicators for AUD, as already accepted by the European Medicines Agency (European Medicines Agency, 2010), and serve a valuable clinical use as treatment goals to be discussed with patients, especially those who do not want to stop drinking and are therefore unlikely to enter treatment otherwise. The information provided in this study is important to inform the public, public health officials, treatment providers, patients, and investigators conducting clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Wave 1 drinkers by WHO drinking risk levels defined in terms of drinks[a] per day, and depression and/or anxiety disorders

Wave 1 WHO drinking risk level	Definition	n	Percent of participants at each WHO risk level	Prevalence in each risk level with Wave 1 depression and/or anxiety disorders
Very high	>100 g (>7.1 drinks) for men, >60 g (>4.3 drinks) for women	512	2.5%	29.3%
High	60–100 g (4.3–7.1 drinks) for men, 40–60 g (2.9–4.3 drinks) for women	546	2.5%	17.7%
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%	19.5%
Low	1–40 g (<2.9 drinks) for men, 1–20 g (<1.4 drinks) for women	19,874	90.2%	16.6%

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

Table 2.

Depression and/or anxiety disorders at Wave 2 by Wave 1 WHO drinking risk level (drinks per day) and change in WHO risk level between Waves 1 and 2

	All Wave 1 drinkers (n=22,005)				Wave 1 drinkers with Wave 1 depressive and/or anxiety disorders (n=4,018)			
Wave 1 WHO risk level and change by Wave 2	**n**	**Prevalence of Wave 2 depressive and/or anxiety disorder[a]**	**Adjusted OR (95% CI)**	**p value**	**n**	**Prevalence of Wave 2 persistent depressive and/or anxiety disorders[b]**	**Adjusted OR (95% CI)**	**p value**
Wave 1 Very high risk								
No change	139	29.1%	Reference		35	67.8%	Reference	
Decreased by one level	75	14.8%	0.42 (0.29–0.63)	**<.0001**	20	43.5%	0.37 (0.15–0.91)	**0.031**
Decreased by two levels	59	13.2%	0.37 (0.22–0.62)	**<0.001**	19	37.6%	0.29 (0.10–0.80)	**0.017**
Decreased by three levels	198	21.6%	0.67 (0.49–0.93)	**0.016**	65	51.5%	0.51 (0.28–0.91)	**0.023**
Became abstainer	41	18.6%	0.56 (0.37–0.83)	**0.004**	13	21.4%	0.13 (0.07–0.25)	**<.0001**
Wave 1 High risk								
Increased	77	20.8%	1.41 (0.89–2.23)	0.144	17	45.5%	1.57 (0.49–5.02)	0.448
No change	84	15.7%	Reference		11	34.7%	Reference	
Decreased by one level	105	19.7%	1.32 (1.03–1.69)	**0.027**	22	33.9%	0.97 (0.39–2.41)	0.940
Decreased by two levels	246	11.5%	0.70 (0.51–0.96)	**0.028**	44	40.5%	1.28 (0.47–3.50)	0.631
Became abstainer	34	7.0%	0.40 (0.28–0.57)	**<.0001**	6	31.6%	0.87 (0.31–2.42)	0.786
Wave 1 Moderate risk								
Increased	141	12.9%	0.96 (0.69–1.35)	0.833	36	35.1%	0.84 (0.48–1.47)	0.550
No change	259	13.3%	Reference		55	39.1%	Reference	
Decreased by one level	628	13.4%	1.01 (0.84–1.20)	0.942	134	35.3%	0.85 (0.61–1.19)	0.344
Became abstainer	45	07.3%	0.51 (0.35–0.75)	**<0.001**	9	19.2%	0.37 (0.15–0.91)	**0.031**
Wave 1 Low risk								
Increased	1014	18.0%	1.36 (1.24–1.49)	**<.0001**	191	46.4%	1.59 (1.32–1.91)	**<.0001**
No change	15999	13.9%	Reference		2806	35.2%	Reference	
Became abstainer	2861	14.8%	1.07 (1.00–1.14)	**0.039**	535	33.3%	0.92 (0.80–1.05)	0.222

[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] Prevalence values are calculated from the same logistic regression used to obtain Adjusted OR values, controlling for the same control covariates and Wave 1 presence of depression and/or anxiety disorders

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Table 3.

Depression and/or anxiety disorder at Wave 2 by WHO drinking risk level (drinks per drinking day and drinks per day) at Wave 1 and change in WHO risk level between Waves 1 and 2

Wave 1 WHO risk level and change by Wave 2	Drinks/drinking day		Drinks/day	
	Prevalence	Persistence	Prevalence	Persistence
Very high risk				
No change	r	r	r	r
Decreased by 1 level	↓	-	↓	↓
Decreased by 2 levels	↓	↓	↓	↓
Decreased by 3 levels	↓	↓	↓	↓
Became abstainer	-	↓	↓	↓
High risk				
Increased	-	↓	-	-
No change	r	r	r	r
Decreased by one level	↓	↓	↑	-
Decreased by two levels	↓	↓	↓	-
Became abstainer	-	↓	↓	-
Moderate risk				
Increased	↑	-	-	-
No change	r	r	r	r
Decreased by one level	↓	↓	-	-
Became abstainer	-	-	↓	↓
Low risk				
Increased	↑	-	↑	↑
No change	r	r	r	r
Became abstainer	↑	-	↑	-

↓ = decreased risk of dep/anx disorder

↑ = increased risk of dep/anx disorder

blue arrows = statistically significant

black arrows = trend towards significance

- = not statistically significant difference

r = the reference group