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Algorithm Analysis of the DSM-5 Alcohol Withdrawal Symptom

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Abstract

Background—Alcohol withdrawal (AW) is an important clinical and diagnostic feature of alcohol dependence. AW has been found to predict a worsened course of illness in clinical samples, but in some community studies AW endorsement rates are strikingly high, suggesting false positive symptom assignments. Little research has examined the validity of the DSM-5 algorithm for AW, which requires either the presence of at least 2 of 8 sub-criteria (i.e., autonomic hyperactivity, tremulousness, insomnia, nausea, hallucinations, psychomotor agitation, anxiety, and grand mal seizures), or, the use of alcohol to avoid or relieve these symptoms.

Method—We used item and algorithm analyses of data from waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; current drinkers, $n = 26,946$ at wave 1) to study the validity of DSM-5 AW as operationalized by the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV).

Results—A substantial proportion of individuals given the AW symptom reported only modest to moderate levels of alcohol use and alcohol problems. Alternative AW algorithms were superior to DSM-5 in terms of levels of alcohol use and alcohol problem severity among those with AW, group difference effect sizes, and predictive validity at a three-year follow-up. The superior alternative algorithms included those that excluded the nausea sub-criterion; required withdrawal-related distress or impairment; increased the AW sub-criteria threshold from 2 to 3 items; and, required tremulousness for AW symptom assignment.

Conclusions—The results indicate that the DSM-5 definition of AW, as assessed by the AUDADIS-IV, has low specificity. This shortcoming can be addressed by making the algorithm for symptom assignment more stringent.

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Introduction

Chronic heavy drinking often leads to neuroadaptations that manifest as alcohol withdrawal (AW). AW has long been observed in detoxification settings (Gross et al., 1974) and is one of the primary symptoms of the Alcohol Dependence Syndrome (Edwards & Gross, 1976). AW can emerge within a few hours of heavy drinking being stopped or sharply curtailed, and is usually characterized by intense craving as well as affective, cognitive and physical disturbance. The avoidance and relief of AW symptoms plays a role in maintaining compulsive drinking (Baker et al., 2004; Koob & Le Moal, 2008). AW is common in addictions treatment settings, affecting near 70% in some patient groups (Saitz et al., 1994). Patients differ markedly in AW liability, with risk conferred by liver disease, acute illness, older age, other drug use, and past history of withdrawal episodes and detoxification (Saitz, 1998).

Among diagnostic criteria for Alcohol Use Disorders (AUDs), AW is especially important because it is predictive of illness severity and worsened future course in clinical samples. AW tends to onset late in the course of both adolescent (Martin et al., 1996) and adult problem drinking (Langenbucher & Chung, 1995). Hasin et al. (2000) found that AW in a community sample of persons with alcohol dependence predicted symptom severity at 1-year follow-up. Langenbucher et al. (2000a) found that an algorithm in which AW was necessary and sufficient for the diagnosis of alcohol dependence, outperformed the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) in terms of diagnostic reliability, syndrome staging, and concurrent and predictive validity. Among relatives of alcohol dependent probands, Bucholz et al. (1996) found that AW, alone among 37 signs and symptoms, occurred nearly exclusively among those with the most severe alcohol problems. Using a large clinical sample, Schuckit et al. (1998) found that alcohol problem severity was strongly associated with AW (but not tolerance). AW predicted alcohol outcomes at a 5-year follow-up in this sample (Schuckit et al., 2003). It should be noted that these latter three studies employed the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994), an interview whose assessment of AW is psychometrically severe compared to some other survey instruments (Lane et al., 2016).

At the same time, endorsement rates for AW seem implausibly high in many community samples (Caetano & Babor, 2006). In nationally-representative adult samples in the 1980s–1990s, some AW sub-criteria were endorsed by as many as 6% (e.g., anxiety) to 10% (e.g., nausea) of drinkers (Caetano et al., 1998). In other community samples AW was associated with only moderate levels of alcohol problem severity compared to some other AUD symptoms and signs (e.g., Kahler & Strong, 2006; Krueger et al., 2004; Saha et al., 2006). In some community samples of youth, AW was one of the most commonly endorsed AUD symptoms (Chung et al., 2002).

High rates of endorsement in community samples suggest potential problems with the definition of AW (although method effects associated with diagnostic instrument likely explain part of this variation; Lane, et al, 2016). In DSM-5 (APA, 2013), AW is one of eleven symptoms of AUD, which requires the presence of two or more criteria for diagnosis. DSM-IV (APA, 1994) and DSM-5 define the AW symptom in the same way: a cessation or reduction in heavy and prolonged alcohol use, accompanied by the presence of at least 2 of 8 AW sub-criteria—autonomic hyperactivity, tremor, insomnia, nausea, hallucinations, psychomotor agitation, anxiety, and seizures—or, the use of alcohol to avoid or relieve such withdrawal symptoms. DSM-5 does not require that the AW symptom is associated with clinically significant distress or impairment¹.

Little research has critically examined the DSM-5 AW algorithm. Langenbucher et al. (2000a) utilized a “sharpened” definition of AW that excluded anxiety and withdrawal-relief drinking, but did not systematically contrast different algorithms. Hasin et al. (2000) found that the predictive validity of AW among those with alcohol dependence was increased when the sub-criterion of tremulousness was required for symptom assignment. In an adult clinical sample, Langenbucher et al. (2000b) found that nausea and anxiety were the least discriminating sub-criteria and did not predict variance in severity beyond the other items. To our knowledge, research has not systematically examined the performance of alternative AW algorithms in community samples.

Given the importance of AW as a central clinical feature of alcohol dependence and as a predictor of future illness severity, additional work is required to enhance the utility of the sub-criteria and algorithms that define AW. This study used data from waves 1 and 2 of the National Epidemiologic Study on Alcohol and Related Conditions (NESARC) to examine item and algorithm performance for AW using DSM-5 and alternative definitions, in the context of concurrent and predictive validity analyses. We used NESARC because it is a large nationally representative survey with data on AW sub-criteria. Further, there are concerns that the AUDADIS-IV interview used in NESARC does not specify that AW is preceded by “heavy and prolonged” alcohol use, as described in DSM-5. Instead, the interview describes symptoms that occur when “the effects of alcohol are wearing off, including the morning after drinking...” This may contribute to over-diagnosis of AW by leading some participants to report effects of hangover (Boness et al., 2016).

We hypothesized that alcohol use to avoid AW, in the absence of any AW sub-criteria, would be associated with relatively low levels of alcohol use and problems. It is conceptually problematic that such reports qualify for DSM-5 AW, as this formulation does not involve the actual presence of AW symptoms and assumes that a person can accurately know that they would get AW in the absence of drinking. It seems more likely that those who report

¹DSM-5 has a diagnostic category of Alcohol Withdrawal Syndrome that is separate from the category of Alcohol Use Disorder. As with the alcohol withdrawal symptom, the Alcohol Withdrawal Syndrome is defined by cessation or reduction in heavy prolonged alcohol use, and by the presence of two or more of eight withdrawal sub-criteria. However, there are two important differences between the AW syndrome and the AW symptom. First, the symptom can be diagnosed via withdrawal-relief or withdrawal-avoidance in the absence of withdrawal sub-criteria, whereas this cannot be done for the syndrome. Second, the syndrome requires “clinically significant distress or impairment in social, occupational or other important areas of functioning”, but distress or impairment is not required for the symptom. This paper focuses on the alcohol withdrawal symptom, which aside from detoxification settings is used far more widely in treatment and research compared to the Alcohol Withdrawal Syndrome.

avoidance drinking and no AW sub-criteria are providing responses that are inconsistent with the question's intended focus. We also predicted that the sub-criteria of anxiety and nausea would have low specificity for AW (Langenbucher et al., 2000b), and that excluding these items would increase the concurrent and predictive validity of AW. Anxiety may perform poorly because it has many determinants other than heavy drinking, and nausea may be a poor item because it commonly occurs with simple hangover (Boness et al., 2016; Slutske et al., 2003). We predicted that several other alternative algorithms for AW also would be associated with a greater concurrent and predictive validity, compared to DSM-5 AW. One such definition required reports of AW-related distress or impairment, which conveys information about clinical significance (APA, 1994; 2013). Another alternative increased the threshold for symptom assignment from 2 to 3 AW sub-criteria to better avoid false positive reports (Caetano & Babor, 2006). Based on the findings of Hasin et al. (2000), a final AW algorithm required the presence of the tremulousness sub-criterion for AW symptom assignment. We also predicted that making the AW algorithm more stringent would reduce rates of DSM-5 AUD.

Method

Participants

Participants were those in waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Grant et al., 2003; Grant & Kaplan, 2005), funded by the National Institute of Alcoholism and Alcohol Abuse and conducted by the U.S. Census Bureau. The wave 1 sample was representative of United States residents 18 years and older. The survey oversampled Blacks, Hispanics, and those 18 to 24 years old. Face-to-face interviews were conducted during 2001–2002 with 43,093 respondents. The dataset is weighted to approximate the United States population. For the purposes of this paper we analyzed data from 26,946 past-12-month (i.e., “current”) alcohol users from wave 1. This sample had a mean age of 42.7 years ($SD=16.13$), was 47.4% female, 75.3% White/non-Hispanic, 9.0% African-American, 10.6% Hispanic, 3.2% Asian, and 1.9% American Indian. All participants from wave 1 were recruited to participate in a wave 2 assessment three years later, when they were age 21 years and older. The primary sample from wave 2 used here for predictive validity analyses ($n = 22,245$; 83.4% of wave 1 current drinkers) had a similar ethnic composition, a mean age of 45.9 years ($SD=16.12$), and was 47.5% female. We also calculated the prevalence of AW and DSM-5 AUD among wave 2 current drinkers ($n=22,177$).

Measures

Alcohol Use Disorders—Alcohol Use Disorders were assessed by the Alcohol Use Disorders and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV; Grant et al., 2001). Symptoms were assessed for both past-year and prior to past year time frames; we utilized past-year data. Studies have shown adequate reliability of AUD diagnoses using the AUDADIS-IV (Grant et al., 1995; Grant et al., 2003). At wave 1, the AUDADIS-IV assessed the DSM-IV criteria for Alcohol Dependence (seven criteria) and Alcohol Abuse (four other criteria). At wave 2, a craving symptom was added to the interview, allowing the assessment of DSM-5 AUD (defined by 2+/11 symptoms, including

10 DSM-IV criteria and craving). Thus, we were able to estimate the effects of various AW definitions on the prevalence of DSM-5 AUD for wave 2 data, but not wave 1 data.

Alcohol Withdrawal—To assess AW (defined exactly the same way in DSM-IV and DSM-5), the AUDADIS-IV queried 11 separate items that referenced the past year. The stem question was “The next few questions are about the bad after-effects of drinking that people may have when the effects of alcohol are wearing off. This includes the morning after drinking or in the first few days after stopping or cutting down”. The eight AW sub-criteria were “have trouble falling asleep or staying asleep”; “find yourself shaking”; “feel anxious or nervous”; “feel sick to your stomach or vomit”; “feel more restless than is usual for you”; “find yourself sweating or your heart beating fast”; “see, feel or hear things that weren’t really there”; and, “have fits or seizures”. A withdrawal relief item stated “Did you take a drink or use any drug or medicine, other than aspirin, Advil or Tylenol, to get over any of these bad after effects of drinking?” A withdrawal avoidance item asked “Did you take a drink or use any drug or medicine, other than aspirin, Advil or Tylenol to keep from having any of the bad after effects of drinking?” Importantly, while the relief item referred to “these bad after effects of drinking”, referencing AW sub-criteria, the avoidance item was worded as “the bad after effects of drinking”, which makes reference to the AW sub-criteria ambiguous. The AUDADIS-IV also contained an impairment/distress item asked only if 1+ sub-criteria were reported: “You just mentioned that you experienced some bad physical after-effects of drinking in the last 12 months. Were any of these bad after-effects uncomfortable or upsetting to you or did they cause problems in your life—like at work or school or with family or friends?” As defined by DSM-5, the AW symptom was coded as present in NESARC if participants reported two or more of the eight AW sub-criteria, or, if they endorsed the withdrawal-relief item or the withdrawal-avoidance item.

Other variables—A number of variables related to alcohol use and alcohol problems were used as concurrent validators (wave 1) and predictive validators (wave 2): past-year alcohol symptom count for DSM-IV (wave 1) and DSM-5 (wave 2) (not including AW; range for both variables = 0 to 10); past-year diagnoses of DSM-IV Alcohol Dependence (waves 1 and 2) and DSM-5 Alcohol Use Disorder (wave 2); past-year maximum drinks/occasion; lifetime maximum drinks/occasion; past-year average drinks/occasion; and, past-year frequency of binge drinking (defined as 5+ drinks/occasion). Age was categorized into seven strata for some prevalence analyses.

Data Analysis

NESARC utilized a complex survey sampling design. We used SUDAAN to adjust for the sampling weights in the calculation of parameter estimates (statistical package version 11; Research Triangle Institute, 2012). SUDAAN’s PROC CROSSTAB and PROC VARGEN were used to estimate prevalence rates, medians and quartiles. PROC REGRESS and PROC RLOGISTIC were used for linear and logistic regressions, respectively. Analyses based on a given subset of the entire sample used the SUBPOPN statement to ensure correct variance estimates. SUDAAN used a Taylor linearization method for the computation of confidence intervals.

Because alcohol use and problem variables tended to be skewed to the right, central tendency and dispersion were described via medians and inter-quartile range for continuous variables. Nominal variables were described using percentages and confidence intervals. In group difference analyses, a panel of alcohol use and problem measures served as dependent variables, and group differences were tested using the Wald F statistic². We used Bonferroni corrections, and in some cases an alpha = .01 and .001, to account for multiple comparisons.

Using wave 1 data, we computed rates of past-year DSM-5 AW, and tested for differences in alcohol use and problems between those with and without AW. We characterized rates of the 8 AW sub-criteria in different age strata, to examine whether any sub-criteria were improbably high in younger respondents who might conflate some AW queries with hangover. We used two-parameter Item Response Theory analysis to identify sub-criteria with relatively low discrimination of a latent trait of AW severity. Next, using those with DSM-5 AW, we tested whether a series of alternative AW definitions increased the level of alcohol use and problem severity associated with the symptom, by contrasting groups who did and did not have AW when the alternative was employed. These alternative definitions 1) excluded those who reported only 0 or 1 sub-criteria along with withdrawal-relief or withdrawal-avoidance drinking; 2) excluded nausea; 3) required reports of AW-related distress or impairment; 4) increased the number of sub-criteria required for symptom assignment; and 5) excluded those who did not report tremulousness. Next, we contrasted the validity of DSM-5 AW with alternative algorithms that were nested and that progressively restricted AW endorsement. In this case we computed the likelihood that “AW” and “not AW” group members were above the median on continuous alcohol variables, and tested for group differences using Odds Ratios. These methods were used to examine concurrent validity in wave 1 data, and predictive validity using wave 2 data. Finally, we used wave 2 data to calculate the effects of alternative AW algorithms on the prevalence of past-year DSM-5 AUD using current drinkers age 21+.

Results

Rates and Characteristics of DSM-5 AW

In wave 1, the rate of AW in current drinkers age 18+, as defined by DSM-5 and operationalized in the AUDADIS-IV, was 7.15% (CI = 6.70% – 7.61%). In wave 2, the rate of AW in current drinkers age 21+ was a similar 7.89% (CI = 7.40% to 8.40%). Table 1 shows wave 1 demographic and alcohol use and alcohol problem variables for those with DSM-5 AW (n = 1,846) and other current drinkers (n = 25,100). The results show that, compared to other drinkers, those with AW were more likely to be male and were younger. All of the alcohol use and problem variables were significantly higher among those with AW compared to other current drinkers. However, the data also indicate that many of those with DSM-5 AW reported only moderate levels of alcohol use and problems. For example, those with AW reported a median of only 1.91 alcohol symptoms (out of a possible 10). Of those with AW, 14.6% reported no other alcohol symptoms. The median maximum number of drinks/occasion in the past year was 7.82, with the bottom quartile of the AW group

²We also ran all of our primary analyses using gender and age as covariates, and the results were very similar to analyses that did not employ covariates. The latter are presented here.

reporting a maximum of fewer than 5 drinks/occasion. The median average number of drinks/occasion was just 3.65. The median number of past-year binge drinking days among those with AW was only 21.85, and, 19.4% of this group reported zero past-year binge drinking days. Of those with AW, 56.28% had past-year DSM-IV alcohol dependence, and 28.44% reported AW-related distress or impairment. Only 2.66% of those in the DSM-5 AW groups reported detoxification treatment in the past year.

Withdrawal-relief and Withdrawal-avoidance Drinking

There were a number of patterns of reported AW-related relief or avoidance drinking without 2 AW sub-criteria; each pattern meets criteria for DSM-5 AW. Some respondents reported 1 sub-criterion along with relief drinking (but not avoidance drinking; $n=119$), avoidance drinking (but not relief drinking; $n=45$), or both relief and avoidance drinking ($n=49$). More problematically, others reported no AW sub-criteria along with avoidance drinking ($n=65$), relief drinking ($n=145$), or both ($n=32$). Relief drinking without AW symptoms is illogical since there are no symptoms to relieve via alcohol use, and avoidance drinking without AW symptoms assumes knowledge of what would have occurred in hypothetical situations. Those with relief and/or avoidance drinking and no AW sub-criteria (total $n=242$) had significantly lower alcohol use and problems than others with AW ($n=1604$) (data not shown). Excluding these endorsement patterns reduced the rate of AW from 7.15% to 6.23%.

Endorsement of AW sub-criteria by Age Strata

For the entire sample and by age strata, Table 2 shows the percentage of current drinkers who endorsed each AW sub-criterion, and who had DSM-5 AW. Endorsement rates varied widely by sub-criterion and age. Overall rates ranged from 0.11% for seizures to a strikingly high 9.02% for nausea. Among those without DSM-5 AW, 4.67% endorsed the nausea sub-criterion—more than the other 7 sub-criteria combined. Table 2 shows that pairwise comparisons of age strata within each sub-criterion, using $p = .001$ to control for multiple comparisons, indicated significant differences in prevalence for some sub-criteria and age groups. There was much higher endorsement of nausea relative to other sub-criteria in the younger age strata, and this was the only sub-criterion with significantly lower prevalence among those age 30–39 compared to all younger strata. Among those aged 18–20, 29.39% endorsed nausea, a rate almost three times higher than the next most prevalent sub-criterion. The rate of the AW symptom was 18.03% for ages 18–20, and 16.34% for ages 21–24.

Item Response Theory (IRT) analysis of AW sub-criteria

We conducted two-parameter IRT analyses (Embretson & Reise, 2000) of the eight AW sub-criteria to identify items that may show relatively poor discrimination of a latent trait of AW severity. A two-parameter model demonstrated an excellent fit to the data (fit indices estimated using ML estimator: RMSEA = .012[CI = .010–.014]; CFI = .994; TLI = .992). Table 3 shows item difficulty and item discrimination values for the eight sub-criteria. Results showed the sub-criterion of nausea had the lowest item threshold value, and along with seizures had the lowest discrimination value, indicating nausea showed relatively poor discrimination of the latent trait of AW severity modeled in the IRT analysis.

Excluding Nausea

Because the nausea item had low overall discrimination and appeared improbably high in younger drinkers, we tested the effects of removing nausea from the algorithm for AW (such that 2+ of the 7 other AW criteria, or relief or avoidance drinking, are required). Table 4 shows that those who no longer had AW when nausea was removed from the algorithm (n=435) had significantly less alcohol use and problems compared to others who still had AW (n = 1411). Excluding nausea decreased the prevalence of AW from 7.15% to 5.23%.

Distress-Impairment

Table 5 shows alcohol use and problem variables for those persons with DSM-5 AW who did (n=522) and did not (n=1324) report AW-related distress or impairment. The results indicate that for all of the validators, those with distress-impairment had significantly greater alcohol use and problems than those without distress-impairment. All group differences remained significant when Wald F tests adjusted for the presence/absence of any past-year wave 1 Axis I disorder (other than AUDs). When the AW algorithm was changed to require distress or impairment, the rate of AW dropped from 7.15% to 2.03%.

Sub-criteria Threshold for Defining AW

We next examined the effects of using various thresholds for the number of AW sub-criteria required for symptom assignment. Table 6 shows alcohol use and problem variables, and the percentage with AW distress-impairment, among those participants who reported different numbers of AW sub-criteria. (Those with only 1 sub-criterion are included in Table 6, but they do not have DSM-5 AW unless they reported relief or avoidance drinking). The data tend to show roughly monotonic and usually significant increases in alcohol use and problems as the number of sub-criteria increases, as well as increases in the proportion who reported distress-impairment. Although there is no clean break in the distribution of variables, it does appear that the increase in alcohol use and problems from 2 to 3 AW items tends to be relatively larger compared to other possible cut-points. Increasing the threshold for symptom assignment from 2 to 3 sub-criteria decreased the rate of AW from 7.15% to 4.83%.

Tremulousness

Table 7 shows drinking and alcohol problem variables, and the proportion with AW distress-impairment, for those with DSM-5 AW who did (n = 379) and did not (n=1467) report the AW sub-criterion of tremors. All of the alcohol use and problem variables were significantly higher in the group that reported tremulousness. AW-related distress-impairment was reported by 49.72% of those with tremulousness and 22.61% who did not report tremors. Requiring tremulousness in the AW algorithm reduced the prevalence of past-year AW from 7.15% to 1.54%.

Contrasting Effect Sizes for Alternative AW Algorithms: Concurrent Validity

Up to this point we separately examined various changes to the AW algorithm. Next, we tested how these changes work in concert, by examining a series of nested algorithms in which the definition of AW became progressively restrictive and AW rates progressively

lower. The nested algorithms were 1) DSM-5 AW (prevalence among current drinkers = 7.15%); 2) excluding relief-avoidance drinking without AW sub-criteria (prevalence of 6.23%); 3) excluding nausea and using a 2+/7 sub-criteria threshold to define AW (4.52%); 4) requiring distress or impairment (1.66%); 5) requiring 3+/7 sub-criteria (1.30%); and 6) requiring tremulousness (0.57%).

For each of these algorithms, Table 8a shows wave 1 median values for each alcohol use and alcohol problem variable among those with and without AW, and the percentage of those with AW with DSM-4 Alcohol Dependence. For example, Table 8a shows that, as AW algorithms become more restrictive, the median number of alcohol symptoms among those with AW increased from 1.91 to 6.38. The data indicate similar increases in median values among those with AW for every alcohol use and problem variable. In addition, Table 8a shows Odds Ratios (ORs) and Confidence Intervals (CIs) that quantify the effect size of group differences between those who have AW based on a given algorithm, and all other current drinkers. The results indicate significant differences between those with and without AW for all algorithms. Further, in all cases ORs and the percentage of those with DSM-IV Alcohol Dependence became higher as AW definitions became more stringent. While we did not directly contrast alternative algorithms shown in Table 8a, in many cases CIs for ORs did not overlap, indicating significant differences in effect sizes between different AW definitions.

Contrasting Effect Sizes for Alternative AW Algorithms: Predictive Validity

Predictive validity analyses examined how wave 1 AW algorithms were associated with wave 2 alcohol use and problems measured three years later, using the same AW algorithms and analytic methods employed in the concurrent validity analyses. Participants were all wave 1 current drinkers with available wave 2 data, regardless of drinking status at wave 2. Predictive validity analyses involved the same alcohol use and problem variables as those used in concurrent validity analyses, with the exception that we did not test the lifetime maximum drinks/occasion variable. Wave 2 alcohol use and problem variables were adjusted using wave 2 sampling weights. Table 8b shows that median values for alcohol use and problems at wave 2 became greater as AW algorithms computed in wave 1 became more stringent. For example, median past-year alcohol symptoms at wave 2 ranged from 0.80 to 2.48 as wave 1 AW definitions became more stringent. Table 8b also shows ORs and CIs indicating group difference effect sizes for each AW definition and every alcohol variable. Overall, while effect sizes tended to be smaller for predictive compared to concurrent validity analyses, the pattern of results was similar. All of the CIs in Table 8b showed significant differences between those with and without AW for all algorithms. Further, in almost all cases ORs became higher as AW definitions became more stringent.

Effects of Different Alcohol Withdrawal Algorithms on the Prevalence of DSM-5 AUD

Using data from current drinkers in wave 2, which allowed us to make DSM-5 AUD diagnoses, we determined the effects of the various AW algorithms in Table 8b on the past-year prevalence of DSM-5 AUD. The prevalence of past-year DSM-5 AUD among wave 2 current drinkers was 16.3%. This figure was reduced when more restrictive AW algorithms were used, with prevalence rates of DSM-5 AUD ranging from 15.9% down to 14.9%. These

changes are not trivial: compared to the DSM-5 AW algorithm, more restrictive algorithms reduce the number of persons with a past-year DSM-5 AUD by as much as 8.6%.

Discussion

Alcohol Withdrawal (AW) is a key clinical and diagnostic feature of AUDs and thus it is critical to optimize the algorithm used to define the symptom. Using the AUDADIS interview and the DSM-5 definition of AW—two or more of eight AW sub-criteria, or, reports of withdrawal-relief or withdrawal-avoidance drinking—we found a past-year rate of 7.15% among current drinkers aged 18 years and older in NESARC wave 1. Those with DSM-5 AW had significantly higher levels of alcohol use and problems than other drinkers. In this sense, these data indicate some degree of validity of DSM-5 AW. At the same time, descriptive data indicate that many persons given DSM-5 AW have modest levels of drinking and alcohol problems, likely indicating false positive symptom assignments—i.e., persons who do not actually have AW. This motivated a search for patterns of AW endorsement associated with low levels of alcohol use and problems, in order to identify ways in which to increase the validity of the AW algorithm.

One pattern of DSM-5 AW endorsement that is empirically and conceptually problematic is reports of withdrawal-related relief or avoidance drinking among those who report no AW sub-criteria, which was associated with relatively low levels of alcohol use and problems. This pattern of endorsement does not involve unambiguous reports of actual AW. Avoidance drinking in the absence of AW symptomatology is conceptually problematic as it assumes persons can accurately know that they would have gotten AW symptoms in the absence of drinking. Further, it seems likely that those who report relief drinking and no AW symptoms did not understand the intended meaning of the item. In this regard, there is a methodological problem in how the AUDADIS-IV queries relief drinking when referencing AW sub-criteria, asking about “the bad after-effects of drinking” rather than the less ambiguous “these bad after-effects of drinking”. We conclude that the definition of DSM-5 AW should be revised to exclude avoidance or relief drinking in the absence of AW symptoms, and that relief drinking without AW symptoms in NESARC likely reflects a measurement artifact.

Other patterns of endorsement associated with relatively low alcohol use and problems, and likely false positive AW assignments, involve the AW sub-criterion of nausea. Nausea had relatively poor discrimination of AW severity in IRT analyses and was far more common than the next most prevalent sub-criteria in the younger age strata. Removing nausea from the algorithm reduced rates of AW by around one-quarter; those who were removed had substantially less drinking and alcohol problems than others with AW. These results support the hypothesis that nausea is often endorsed by those without AW who have experienced hangover or otherwise felt sick after drinking—after-effects that are known to be more common in younger drinkers. False positive reports related to hangover or other non-AW factors may also have occurred for sub-criteria such as insomnia and autonomic hyperactivity, but the data did not support our hypothesis that anxiety would be a relatively common AW sub-criterion. We conclude that nausea should not be a sub-criterion for AW. It is likely that nausea-related AW and hangover are especially likely to be conflated when the

stem question does not specify a prior pattern of heavy prolonged alcohol use, as is the case in the AUDADIS-IV (Boness et al., 2016).

We found strong evidence that those who reported AW-related distress or impairment had significantly greater alcohol use and problems than those without impairment. These group differences remained significant after adjusting for other Axis I disorders, suggesting that these effects are not due to comorbid psychopathology. These results indicate that distress-impairment conveys important information about alcohol problem severity. AW could be defined to require distress or impairment, as is the case in DSM-5 for the separate diagnostic category of the Alcohol Withdrawal Syndrome. Requiring distress or impairment for the AW symptom increases specificity but may result in a non-trivial loss of sensitivity, as some of those in the non-impairment group had very high levels of alcohol use and problems, and because this change by itself reduces the prevalence of AW by around three-quarters.

Results also indicate that the DSM-5 AW threshold of 2 or more of 8 sub-criteria assigns the symptom to many persons with relatively low levels of drinking and related problems, perhaps because criteria such as nausea, insomnia and autonomic hyperactivity are often endorsed due to hangover or other non-specific influences. The data suggest that this problem can be effectively reduced by increasing the number of AW sub-criteria required for symptom assignment. For example, alcohol use and problems tended to be greater among those with 3 AW sub-criteria compared to those with 2 sub-criteria.

The level of drinking and alcohol problem severity indexed by AW is greatly increased by requiring tremulousness for symptom assignment, as was the case in DSM-III-R (Hasin et al., 2000). Tremor holds promise because it is likely more specific to AW than some of the other more common sub-criteria, yet is far more prevalent than the very rare AW sub-criteria of hallucinations and seizures. Requiring tremor for AW may be effective when the specificity of assessment is especially important.

The data indicated concurrent and predictive validity when various AW algorithm changes were studied in concert. Overall, effect sizes contrasting those with and without AW increased as AW definitions became more restrictive. These results show that the alternative algorithms studied here are not redundant; each tends to produce incremental effects of the severity of AW. The effect sizes for the predictive validity analyses showed associations with alcohol use behavior three years after the baseline assessment. Also of note, we found that employing more strict definitions of AW produces non-trivial changes in the prevalence of past-year DSM-5 AUD. We believe that more rigorous assessment of all diagnostic criteria will provide more realistic estimates of the prevalence of AUDs in the general population and other nonclinical samples (Caetano & Babor, 2006).

There are a number of limitations of this study. Research is needed to see if the current results replicate in the NESARC-III study, which used the relatively recent AUDADIS-V interview (Hasin et al., 2015; Grant et al., 2015). Some potentially problematic issues with the assessment of AW are the same in both versions of the AUDADIS. Also, we were not able to study the performance of the ICD-10 algorithm for AW (WHO, 1992) using NESARC data because the AUDADIS-IV does not assess all ICD-10 AW sub-criteria.

NESARC used face-to-face interviews; we cannot address what patterns of endorsement may occur when AW is assessed via questionnaire. Another limitation is that all of the data came from self-reports. AW sub-criteria and their time course were not directly observed, such that there was no “gold standard” to assess AW. There is a valid observer rating scale for AW—the CIWA (Sullivan, Sykora, Naranjo & Sellers, 1989)—which has been used to study AW among detoxification patients in clinical settings. Future research should contrast different algorithms for AW in the context of using observer-rating data as a validator.

There also are limitations to our use of effect sizes to describe and contrast different algorithms for AW. Increased effect sizes are to be expected statistically as one takes more of an extreme groups approach to defining a symptom, disorder, or other characteristic. That is, simply maximizing group difference effect sizes cannot be the only criterion used to judge AW algorithms. Researchers and clinicians must choose among the various AW algorithms studied here based on the needs of a particular research and treatment setting. Because clinical research indicates AW is a severe symptom with prognostic significance, our view is that specificity should usually take precedence over sensitivity in choosing an algorithm for AW. In this regard, we did not study the effect of removing the AW sub-criterion of nausea, despite its low discrimination in IRT analyses, because it was relatively rare and associated with severe levels of alcohol problems. Future research should examine the utility of the seizure sub-criterion to convey important information about AW severity and medical management.

A final limitation is that the DSM-5 algorithm is not the only factor that can influence the validity of AW, and we did not study how assessment methods affect AW reports. Future research should compare specific patterns of AW endorsement across interviews and questionnaires in relation to how AW is queried. An important example is that although DSM-5 defines AW as something that happens after “heavy and prolonged” drinking, this language is not used in the AUDADIS-IV or the AUDADIS-V, which use less specific stem questions regarding the “after-effects” of drinking. We speculate that such language produces over-diagnosis of AW in diagnostic assessments. It seems likely that many endorsements of AUDADIS-IV AW sub-criteria are Type I errors owing to respondents endorsing symptoms of hangover (Boness et al., 2016). The idea that many reports of AW sub-criteria are likely misidentified hangover symptoms is becoming increasingly established in the literature (Karriker-Jaffe et al., 2015) and great pains should be taken to minimize this problem. Compared to instruments like the SSAGA, the AUDADIS operationalization of withdrawal represents a relatively low threshold determination (Lane et al., 2016). Consequently, it is important to attempt to replicate the current findings using diagnostic instruments and questionnaires that take greater precautions to avoid potential false positive symptom reports. Nevertheless, we believe that the analyses provided here provide clear evidence that reports of DSM-5 AW are inflated in NESARC, and shows ways in which this problem can be addressed by refining the AW algorithm.

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Table 1

Demographic, alcohol use and alcohol problem variables from NESARC wave 1 among current drinkers aged 18 and older with a current DSM-5 alcohol withdrawal (AW) symptom, and those without current DSM-5 AW. Reported descriptive statistics are medians (and interquartile ranges) for continuous measures and percentages (and confidence intervals) for nominal variables.

Demographic and alcohol variables	Alcohol Withdrawal (n=1,846)	No Withdrawal (n=25,100)	Wald <i>F</i> (df=1,65)
Age *	29.25 (22.18–39.71)	41.17 (30.18–53.40)	895.35 *
% Female *	39.00 (36.42–41.63)	48.05 (47.15–48.96)	40.35 *
% White	73.05 (68.47–77.18)	75.47 (72.54–78.19)	2.91
% DSM-IV Alcohol Dependence past year *	56.28 (53.80–58.73)	1.93 (1.70–2.19)	2980.35 *
Alcohol Symptom Count past year *	1.91 (0.50–4.00)	0.00 (0.00–0.00)	1275.21 *
Max drinks/occasion lifetime *	9.50 (5.36–14.73)	3.05 (1.34–6.10)	514.75 *
Max drinks/occasion past year *	7.82 (4.69–13.37)	2.21 (1.06–4.51)	725.41 *
Average drinks/occasion past year *	3.65 (2.04–5.73)	1.32 (0.00–2.32)	579.46 *
Binge drinking days past year *	21.85 (1.22–102.53)	0.00 (0.00–0.78)	473.74 *
% Detoxification treatment past year *	2.66 (1.84–3.83)	.11 (0.07–0.17)	127.81 *
% AW Relief Drinking	33.23 (30.46–36.11)	-	
% AW Avoidance Drinking	19.36 (17.16–21.78)	-	
% AW-related Distress-Impairment *	28.44 (25.75–31.29)	.56 (0.45–0.69)	1057.00 *

Note:

* $p < .0045$;

DSM-IV and DSM-5 AW algorithms are the same

Table 2

Percentage of Current Drinkers who Endorsed Each of the Eight Current AW Sub-Criteria and Met DSM Alcohol Withdrawal Criterion, for the Entire Sample, for those with and without DSM-5 AW, and by Age Strata

Past Year Sub-criteria and Withdrawal Criterion	Total Sample	Among AW	Among Non-AW	18-20	21-24	25-29	30-39	40-49	50-59	60+
Insomnia	4.26	41.26	1.41	5.49 _a	6.94 _a	5.95 _a	4.65 _{ab}	4.77 _a	3.03 _b	1.23 _c
Tremulousness	1.65	21.50	0.13	3.26 _a	2.74 _a	2.96 _a	1.69 _a	1.70 _a	0.62 _b	0.54 _b
Anxiety	1.97	25.12	0.19	3.51 _a	2.77 _a	2.32 _{ab}	2.28 _a	2.34 _a	1.10 _{bc}	0.69 _c
Nausea	9.02	65.54	4.67	29.39 _a	25.66 _a	15.44 _b	8.47 _c	5.73 _d	2.08 _e	0.85 _f
Restlessness	3.42	40.31	0.58	9.98 _a	6.68 _{ab}	4.72 _b	3.26 _b	3.31 _b	1.42 _c	0.79 _c
Autonomic hyperactivity	3.11	35.51	0.61	8.07 _a	6.27 _{ab}	4.17 _b	3.12 _b	2.94 _b	1.45 _c	0.79 _c
Hallucinations	0.56	6.90	0.07	2.28 _a	1.41 _{ab}	0.48 _{bc}	0.48 _{bc}	0.47 _{bc}	0.16 _c	0.14 _c
Seizures	0.11	1.05	0.04	0.15 _a	0.03 _a	0.30 _a	0.13 _a	0.10 _a	0.04 _a	0.05 _a
DSM Withdrawal Symptom Criterion Met	7.15			18.03 _a	16.34 _a	10.93 _b	7.55 _c	5.98 _c	2.79 _d	1.20 _e

Within rows, columns not sharing a common subscript differ from each other at $p < .001$ using the Wald F statistic

Table 3
Item difficulty and item discrimination values from Item Response Theory analysis of AW sub-criteria

Past Year Subcriteria and Withdrawal Criterion	Item Difficulty	Item Discrimination
Insomnia	2.133	2.479
Tremulousness	2.382	3.619
Anxiety	2.236	4.236
Nausea	1.730	2.180
Restlessness	2.030	3.732
Autonomic hyperactivity	2.140	3.242
Hallucinations	3.100	2.679
Seizures	4.219	2.148

Table 4

Alcohol Use and Alcohol Problems among Current Drinkers with Past-Year DSM-5 Alcohol Withdrawal who Do and Do Not Continue to Meet Withdrawal Criterion when the Nausea Sub-criterion is Removed from the Algorithm. Medians (and interquartile ranges) are presented for continuous variables; percentages (and confidence intervals) are presented for nominal variables.

Alcohol Use and Problem Variables	Alcohol Withdrawal With Nausea Removed (n=1,411)	No Alcohol Withdrawal When Nausea Removed (n=435)	Wald F (df=1,65)
Alcohol Symptom Count past year	2.13 (0.56–4.49)	1.41 (0.37–2.91)	39.62 *
Maximum drinks/Occasion lifetime	9.72 (5.46–14.86)	9.14 (5.14–14.25)	12.28 *
Maximum drinks/Occasion past year	7.99 (4.80–14.11)	7.32 (4.46–11.48)	8.67 *
Average Drinks/Occasion past year	3.82 (2.10–5.87)	3.11 (1.88–5.25)	19.29 *
Number of Binge Drinking Days past year	28.95 (1.51–122.57)	10.60 (0.70–50.45)	41.74 *
% Detoxification Treatment past year	3.36 (2.30–4.89)	0.41 (0.10–1.75)	7.85 *
% Reporting Alcohol Withdrawal-related Distress-Impairment	30.54 (27.59–33.65)	21.77 (17.12–27.27)	8.40 *

Note:

* p < .007

Table 5

Alcohol Use and Alcohol Problems among Current Drinkers who Reported that Past Year Alcohol Withdrawal Did or Did Not Cause Distress or Impairment in Social, Occupational, or Other Important Areas of Functioning. Values are medians (interquartile ranges) for continuous variables. For nominal variable (detoxification) values are percentages (confidence interval).

Alcohol Use and Problem Variables	No Impairment (n=1324)	Impairment (n=522)	Wald F (df=1,65)	Wald F adjusted for any Axis I disorder
Alcohol Symptom Count past year	1.41 (0.27–2.96)	4.05 (1.65–6.52)	227.75 *	194.45 *
Max drinks lifetime	8.98 (5.05–14.26)	11.47 (7.01–17.92)	26.81 *	22.72 *
Max drinks past year	7.50 (4.40–11.91)	9.54 (5.34–14.73)	13.50 *	11.20 *
Avg. drinks/occasion past year	3.41 (1.93–5.55)	4.42 (2.37–6.54)	17.76 *	15.52 *
Binge drinking days past year	14.80 (0.71–80.16)	45.09 (5.35–163.26)	34.63 *	30.70 *
% Detoxification Treatment past year	0.59 (0.26–1.35)	7.86 (5.27–11.55)	32.62 *	24.33 *

Note:

* $p < .008$

Table 6

Alcohol Use and Problems among Current Drinkers who Reported Different Numbers of Past-Year Alcohol Withdrawal (AW) Sub-criteria.

Number of AW sub- criteria (N)	Alcohol symptom count	Maximum drinks/occasion lifetime	Maximum drinks past year	Drinks/occasion Past year	Number of Binge drinking days past year	% Detox treatment past- year	% AW Distress- Impairment
1 (n=2037) [*]	0.68 (0.00–1.90) _a	7.24 (4.43–11.64) _a	6.07 (3.86–11.03) _a	2.82 (1.70–4.98) _a	8.06 (0.00–47.33) _a	0.35 (0.17–0.73) _a	8.67 (7.30–10.28) _a
2 (n=707)	1.47 (0.37–3.16) _b	9.11 (5.09–14.30) _{ab}	7.18 (4.28–11.71) _b	3.13 (1.86–5.36) _{ab}	10.88 (0.45–62.21) _b	1.14 (0.37–3.42) _a	22.91 (18.85–27.54) _b
3 (n=355)	2.31 (0.91–4.02) _c	9.50 (5.32–14.24) _b	8.48 (4.78–11.96) _{bc}	3.76 (1.92–5.75) _b	27.68 (1.29–120.10) _c	1.22 (0.43–3.41) _{ab}	35.71 (29.58–42.34) _c
4 (n=151)	3.73 (1.90–5.92) _d	11.85 (7.01–19.51) _c	10.57 (5.84–15.30) _c	5.08 (2.87–7.91) _c	55.56 (9.59–209.71) _d	2.92 (0.92–8.84) _b	47.71 (38.46–57.13) _{cd}
5 (n=87)	4.05 (2.35–6.20) _d	11.06 (6.88–19.74) _{bc}	10.28 (6.35–14.64) _{bc}	5.18 (2.59–7.84) _c	62.00 (4.99–206.12) _d	9.00 (3.72–20.19) _{bc}	48.46 (36.36–60.74) _{cd}
6 (n=54)	6.83 (4.08–7.83) _{de}	14.30 (9.19–22.43) _{bc}	14.04 (5.78–17.65) _c	6.03 (3.77–8.82) _c	105.41 (57.05–228.70) _d	15.13 (5.37–35.90) _{cd}	74.73 (50.55–89.53) _d
7 (n=33)	6.36 (5.23–8.21) _e	11.57 (9.87–23.71) _c	10.02 (4.99–20.13) _{bc}	5.74 (2.95–11.15) _c	99.82 (30.90–268.68) _d	24.26 (11.08–45.18) _d	80.50 (52.83–93.83) _d

Note: Because of very small sample size (n=4), data are not shown for those with all eight Alcohol Withdrawal sub-criteria. Medians (and interquartile ranges) are provided for continuous variables and percentage (and confidence intervals) for nominal variables. Within columns, rows not sharing a common subscript differ from each other at $p < .01$ using the Wald F statistic.

* Not all participants who report one withdrawal sub-criterion meet criteria for alcohol withdrawal (this depends on endorsing relief or avoidance drinking).

Table 7

Alcohol Use and Alcohol Problems among those who Did and Did Not Report Alcohol Withdrawal-Related Tremors. Reported statistics are medians (and interquartile ranges) for continuous measures and percentages (and confidence intervals) for nominal variables.

Alcohol Use and Problem Variables	No Tremors (n=1467)	Tremors (n=379)	Wald F (df = 1,65)
Alcohol Symptom Count past year	1.57 (0.34–3.36)	3.77 (1.60–6.33)	117.84 *
Maximum drinks lifetime	9.10 (5.13–14.17)	11.96 (7.16–22.41)	46.04 *
Maximum drinks past year	7.38 (4.37–11.77)	11.29 (5.89–19.04)	34.22 *
Average drinks/occasion past year	3.28 (1.90–5.44)	5.23 (2.93–8.41)	46.33 *
No. of days binge drinking past year	12.58 (0.65–77.39)	78.13 (10.37–218.97)	77.56 *
% Detoxification Treatment past year	1.09 (0.56–2.12)	8.38 (5.38–12.84)	25.57 *
% with Alcohol Withdrawal-related Distress-Impairment	22.61 (19.88–25.59)	49.72 (43.87–55.57)	73.35 *

Note:

* p<.007

Table 8a

Concurrent Validity of Different (Nested) Algorithms for Alcohol Withdrawal (AW) using Alcohol Use and Alcohol Problem Variables from Current Drinkers in NESARC Wave 1. Values in parenthesis are confidence intervals for Odds Ratios.

Wave 1 Alcohol Use and Alcohol Problem Variables												
Wave 1 AW algorithm (% past-year DSM-IV Alcohol Dependence [AD] at wave 1)	Alcohol Symptom Count past year		Max Drinks/Occasion lifetime		Max Drinks/Occasion past year		Average Drinks/ Occasion past year		Binge Drinking Days past year		Detox Treatment past year	
	OR	Mdn	OR	Mdn	OR	Mdn	OR	Mdn	OR	Mdn	OR	%
No DSM-5 AW (n=25,100)		0.00		3.05		2.21		1.32		0.00		0.11
DSM-5 AW (n= 1,846) (% AD=56.28)	25.68 (22.02–29.94)	1.91	8.67 (7.33–10.26)	9.50	12.32 (10.44–14.54)	7.82	7.50 (6.57–8.56)	3.65	10.81 (9.44–12.37)	21.85	24.76 (14.05–43.65)	2.66
Exclude relief-avoid only (n=1,604) (% AD=60.20)	31.22 (25.96–37.55)	2.14	9.26 (7.70–11.13)	9.69	13.80 (11.42–16.68)	8.33	7.67 (6.63–8.89)	3.78	11.75 (10.04–13.75)	25.16	24.25 (13.68–42.99)	2.86
Exclude nausea (2+/7 sub-criteria) (n=1,169) (% AD=65.20)	32.40 (25.46–41.24)	2.53	9.97 (8.02–12.39)	10.64	14.61 (11.51–18.54)	9.19	8.06 (6.81–9.53)	4.06	12.00 (10.14–14.20)	35.41	31.07 (17.53–55.06)	3.79
Require impairment (n=425) (% AD=81.29)	80.38 (41.61–155.25)	4.92	18.69 (11.92–29.31)	11.69	19.27 (11.81–31.45)	11.03	9.74 (7.32–12.97)	4.87	17.63 (12.16–25.56)	67.97	74.05 (41.37–132.55)	9.36
Require 3+/7 sub-criteria (n=334) (% AD=84.99)	110.49 (55.70–219.19)	5.43	22.01 (13.34–36.30)	11.99	24.13 (12.46–46.75)	11.33	12.23 (8.76–17.07)	5.09	20.01 (12.67–31.60)	95.91	93.67 (52.26–167.90)	11.74
Require tremors (n=144) (% AD=92.20)	458.72 (61.62–3414.86)	6.38	30.17 (13.88–65.58)	14.27	17.31 (6.64–45.15)	11.41	24.39 (13.55–43.88)	5.91	22.06 (9.87–49.29)	147.40	127.21 (65.00–248.94)	19.01

Note: OR = Odds Ratio; Mdn = Median; AD=Past-year DSM-IV Alcohol Dependence at wave 1

Table 8b

Predictive Validity of Different (Nested) Algorithms for Wave 1 Alcohol Withdrawal (AW) Definitions Over Three Years using Alcohol Use and Alcohol Problem Variables from NESARC Wave 2 Assessment. Values in parenthesis are confidence intervals for Odds Ratios.

Wave 1 AW algorithm (wave 2 n size) (% with past-year DSM-IV Alcohol Dependence [AD] at wave 2)	Wave 2 Alcohol Use and Alcohol Problem Variables						Detox Treatment past year	
	Alcohol Symptom count past year		Max Drinks/Occasion past year		Average Drinks/Occasion past year		Binge Drinking Days past year	
	OR	Mdn	OR	Mdn	OR	Mdn	OR	%
No DSM-5 AW (n=20,764)		0.00		2.76		1.40		0.09
DSM-5 AW (n=1,481) (% AD=29.71)	5.61 (4.90–6.42)	0.80	6.49 (5.50–7.65)	7.28	4.57 (3.96–5.28)	2.95	5.95 (5.16–6.85)	17.29 (7.96–37.54) 1.48
Exclude relief-avoid only (n=1,280) (% AD=31.74)	6.19 (5.37–7.13)	0.96	6.86 (5.73–8.23)	7.42	4.72 (4.01–5.57)	3.05	6.09 (5.18–7.16)	16.10 (7.26–35.69) 1.54
Exclude nausea (2+7 sub-criteria) (n=922) (% AD=36.27)	6.66 (5.63–7.87)	1.25	7.86 (6.27–9.85)	7.95	5.50 (4.56–6.64)	3.35	6.99 (5.74–8.51)	22.92 (10.30–50.99) 2.14
Require impairment (n=331) (% AD=42.89)	6.81 (5.13–9.04)	1.70	7.38 (5.01–10.86)	8.40	5.30 (3.90–7.22)	3.34	7.23 (5.10–10.25)	39.14 (15.73–97.39) 4.40
Require 3+7 sub-criteria (n=256) (% AD=49.20%)	7.39 (5.28–10.34)	2.03	8.31 (5.25–13.13)	9.42	6.19 (4.31–8.88)	3.58	8.16 (5.53–12.04)	42.50 (15.98–113.03) 5.04
Require tremors (n=110) (% AD=55.16%)	8.03 (4.67–13.81)	2.48	7.59 (3.74–15.41)	11.41	9.71 (5.08–18.56)	4.34	9.12 (4.82–17.26)	76.48 (24.84–235.50) 9.32

Note: OR = Odds Ratio; Mdn = Median; AD=Past-year DSM-IV Alcohol Dependence at wave 2