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A meta-analysis of topiramate's effects for individuals with alcohol use disorders

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Abstract

Background—Influenced by several trials and reviews highlighting positive outcomes, topiramate is increasingly prescribed as a treatment for alcohol use disorders (AUDs). The only previously published meta-analysis of topiramate for AUDs was limited by a sample of only 3 randomized, placebo-controlled trials (RCTs).

Methods—A systematic search identified 7 RCTs (including a total of 1,125 participants) that compared topiramate to placebo for the treatment of AUDs. This meta-analysis estimated the overall effects of topiramate on abstinence, heavy drinking, craving, and γ -glutamyltranspeptidase (GGT) outcomes, and included several sensitivity analyses to account for the small sample of studies.

Results—Overall, the small to moderate effects favored topiramate, although the effect on craving was not quite significantly different from zero. The largest effect was found on abstinence ($g = 0.468$, $p < .01$), followed by heavy drinking ($g = 0.406$, $p < .01$), GGT ($g = 0.324$, $p = .02$), and craving ($g = 0.312$, $p = .07$) outcomes. Sensitivity analyses did not change the magnitude or direction of the results, and tests did not indicate significant publication bias. The small sample size did not allow for examination of specific moderators of the effects of topiramate.

Conclusions—Topiramate can be a useful tool in the treatment of AUDs. Its efficacy, based on the current sample of studies, seems to be of somewhat greater magnitude than that of the most commonly prescribed medications for AUDs (naltrexone and acamprosate). Further research will help to identify the contexts in which topiramate is most beneficial (e.g., dose, concurrent psychotherapy, patient characteristics).

Keywords

topiramate; meta-analysis; alcohol use disorders; treatment

Introduction

Recent reviews have highlighted the antiepileptic medication topiramate as a promising treatment for individuals with alcohol use disorders (AUDs; Aubin and Daeppen, 2013; Kenna et al., 2009), including those who are actively drinking when they begin treatment (Johnson et al., 2007). Topiramate is now off-patent, so it is unlikely to be put through the FDA-approval process as a treatment for AUDs, even with additional evidence of its efficacy. Nonetheless, it is increasingly (though still uncommonly) prescribed off-label as an AUD treatment (e.g., Del Re et al., 2013a).

Topiramate is hypothesized to “decrease alcohol reinforcement and the propensity to drink” (Johnson et al., 2007) by reducing craving for alcohol through antagonizing the glutamate receptors and inhibiting dopamine release (Olmsted and Kockler, 2008). An earlier meta-analysis examining topiramate's effects for individuals with AUDs (k [number of studies] = 3) found support for topiramate in reducing heavy drinking and increasing abstinence relative to placebo (Arbaizar et al., 2010). However, the analysis was limited by the small sample of studies.

This report presents an updated and more detailed meta-analysis of topiramate's effects. We identified 4 additional topiramate trials, more than doubling the previous sample size to 7 randomized, placebo-controlled trials (RCTs). We focus on abstinence and heavy drinking outcomes, as well as craving and the biomarker γ -glutamyltranspeptidase (GGT). We present overall effect sizes on these outcomes and additionally carry out several sensitivity analyses to account for the still small number of studies. The results allow the efficacy of topiramate to be compared to that of other medications used to treat AUDs (e.g., naltrexone and acamprosate) and provide information that clinicians can use in making decisions regarding treatment for individuals with AUDs.

Materials and Methods

Inclusion criteria

This meta-analysis included published reports of double-blind RCTs that assessed the efficacy of topiramate compared to placebo for the treatment of AUDs in adults. No limitations were placed on publication date. We excluded studies that assigned fewer than 5 participants to any condition, were not published in the English language, were primarily short-term lab studies, or did not report data on any drinking outcomes.

Literature search

Broad searches were carried out on the PubMed and Web of Science databases (last searched on July 15, 2013). For example, we searched the PubMed database using the string “topiramate AND (alcohol OR alcohol* OR drink*),” and did not set any limits on the search. All identified citations and abstracts were screened for relevance and the full text of relevant publications was reviewed to make final decisions regarding inclusion in the meta-analysis consistent with the eligibility criteria above. Additional searches of trial registries were carried out, including ClinicalTrials.gov, the BioMed Central clinical trials registry, and the World Health Organization international clinical trials registry. Subsequent database

searches were conducted for publications on trials identified in these registries, based on primary investigator and funding information. The results of one recent study were provided by that study's primary investigator (Kranzler et al., 2014).

Study selection

A total of 418 unique publications was screened as a result of database searching (see Figure 1 for details). Of 41 potentially relevant publications, 19 were excluded based on an examination of the full-text because they were not randomized trials ($k = 11$), they did not include a placebo group ($k = 6$), or they were primarily a laboratory study ($k = 2$). The remaining 22 publications reported the results of 7 RCTs that met the eligibility criteria and were included in the meta-analysis (i.e., 7 publications reported primary results and 15 reported secondary analyses).

Coding of studies

Study characteristics of the earliest 4 studies were coded by 2 coders who had reached adequate reliability (Kappas and intraclass correlations $> .70$) in a larger review of trials of pharmacotherapy for AUDs (Maisel et al., 2013). One of those coders (JB) independently coded the most recent 3 studies. The extracted information included the randomized medication groups and dosages, the number of participants assigned to each group, and the number completing treatment. We also recorded details of any psychosocial treatment provided to all participants and whether the study required participants to be abstinent for any length of time before participation.

Outcome measures

We calculated effect sizes for alcohol-related outcomes at the end of the planned treatment period and double-checked them for accuracy. Effect sizes in the first 4 studies were calculated by 2 coders who discussed any discrepancies, and 1 of those coders (JB) independently calculated the effect sizes in the most recent 3 studies. To account for statistical dependencies, Gleser and Olkin's (2009) weighted mean procedure was used to aggregate effects related to abstinence and heavy drinking, respectively, resulting in 1 overall effect size per study for each of those 2 outcome domains. For the abstinence aggregated effect size, we calculated effect sizes for the abstinence rate (i.e., the percent of participants who were continuously abstinent during the assessment period), the number of days until first drink, and/or the percent days abstinent. For the heavy drinking aggregated effect size, we calculated effect sizes for the heavy drinking rate (i.e., percent of participants with at least 1 day of heavy drinking during the assessment period), the number of days until the first heavy drinking day, the percentage of heavy drinking days, and/or drinking quantity (defined as the number of drinks per drinking day). Additionally, we calculated effect sizes for alcohol craving (the most commonly used measure to assess craving was the Obsessive Compulsive Drinking Scale; Anton et al., 1996) and the biomarker GGT, which is commonly used as a laboratory measure of drinking reduction.

For continuous outcomes, we calculated the standardized mean difference using the formula for Cohen's d (Cohen, 1988) in the computer program ES: A Computer Program for Effect Size Calculation (Shadish et al., 1999). We then applied the Hedges g correction for small

sample bias (Borenstein, 2009; Hedges and Olkin, 1985). For dichotomous outcomes, we calculated the odds ratio for 2×2 tables (Haddock et al., 1998) and then converted them to *gs* for comparison purposes (Borenstein, 2009). When proportions or means and standard deviations were not presented, a *p*-value, if provided, was transformed into a standardized mean difference (Borenstein, 2009; Shadish and Haddock, 2009). Scores on “negative” outcomes (e.g., drinking quantity) were reversed, so that a positive effect size always indicates that the topiramate group had a better outcome than the placebo group. In order to calculate the aggregated effects described above, we combined the effect sizes within each study related to abstinence and heavy drinking, respectively, using the weighted aggregation procedures in MAd (Del Re and Hoyt, 2010) and RcmdrPlugin.MA (Del Re, 2013). Effect size values of 0.20 were considered small, values of 0.50 were considered moderate, and values of 0.80 were considered large (Cohen, 1988).

Meta-analysis

We calculated overall effect sizes under a restricted maximum likelihood random-effects model (Viechtbauer, 2005), given our goal of generalizability and our assumption of heterogeneity of effects (Raudenbush, 2009). With the small number of studies that could be included in this review ($k = 7$), we utilized several procedures to reduce the uncertainty in the model estimates. They included the Knapp and Hartung (2003) procedure and sensitivity analyses, including a permutation test (Good, 2005) and Hedges et al.'s (2010) robust standard error procedure. The Knapp and Hartung (2003) procedure adjusts the standard errors of the overall effect size estimate, thus accounting for the overall uncertainty in the model (residual heterogeneity). Permutation tests provide a robust alternative to potential violations of the assumptions of parametric tests, which help to control for Type I error and the limited power associated with the *Q* homogeneity test. Hedges et al.'s (2010) robust standard error procedure adjusts for dependence at the researcher/lab level.

Although we did not anticipate having a sufficient number of studies to test moderators, we evaluated the heterogeneity of effect sizes using the *Q*-statistic and the I^2 statistic (Borenstein and Hedges, 2009; Higgins et al., 2003). We considered an effect to be heterogeneous if the *Q*-statistic was significant and I^2 indicated at least low to moderate heterogeneity (>35%; e.g., Cuijpers et al., 2009). Finally, we evaluated publication bias by examining funnel plots (showing the relationship between effect size and standard error across the sample of studies) and the results of Duval and Tweedie's (2000) Trim-and-Fill procedure.

Results

Study characteristics

The 7 studies included a total of 1,125 randomized participants (excluding those participants in 1 study who were randomized to receive naltrexone; Baltieri et al., 2008), with a mean of 160.7 participants per study (SD: 98.3, range: 76-371). Six studies had a planned medication period of 3 months and 1 had a planned medication period of 4 months. All of the studies began with a ramp-up period (range: 35-56 days) prior to the full dose of topiramate; those ramp-up periods were included in the planned medication period. Most of the studies had a

target dose of 300 mg of topiramate. Four of the 6 studies required that individuals complete some period of abstinence before participating in the trial (Baltieri et al., 2008; Kampman et al., 2013; Likhitsathian et al., 2013; Rubio et al., 2009). All of the studies provided psychosocial treatment in addition to the randomized medication (see Table 1). Importantly, only 1 study included a sample whose members had a drug use disorder (i.e., cocaine dependence) in addition to an AUD (Kampman et al., 2013).

Overall effects

The results for individual studies as well as the overall results are presented in Table 2 and Figure 2. All 7 studies were included in the estimation of the overall effect on the pre-specified abstinence and heavy drinking aggregate measures, whereas 6 of the studies were included in the estimate on craving outcomes and 5 studies were included in the estimate on GGT. The overall effects across domains were small to moderate, although the craving effect was not quite significantly different from zero. The largest effect was found on abstinence outcomes ($g = 0.468, p < .01$), followed by heavy drinking ($g = 0.406, p < .01$), GGT ($g = 0.324, p = .02$) and craving ($g = 0.312, p = .07$). Some indications of heterogeneity were found in the sample, although due to the small sample size, we did not formally test any moderators. Heterogeneity of effects was highest for the craving outcome, with $I^2 = 72.3\%$ and a significant Q-value ($p < .05$; see Table 2), and also was significant for the abstinence aggregate ($I^2 = 55.22\%, p < .05$).

Sensitivity analyses

Due to the small number of studies included in this review ($k = 7$), we conducted several sensitivity analyses. Permutation tests, which provide more realistic estimates of the ‘true’ effect size and can be especially useful when an estimate is calculated from a small number of studies, did not substantially change the overall results. The effect size estimates did not change (the overall effect for the abstinence and heavy drinking aggregates remained significant, the overall craving estimate remained non-significant, and the GGT estimate was no longer significant (p -value increased from .02 to .13). Additionally, we used the robust standard error procedure to account for possible dependency across 2 studies from the same research group (i.e., Johnson et al., 2003; Johnson et al., 2007). The overall estimate and significance level did not change as a result of this adjustment.

Publication bias

Overall, there was little indication of publication bias. The Trim and Fill test showed significant bias only among the heavy drinking aggregate outcomes (not among the abstinence aggregate, craving, or GGT outcomes), and filled in only 2 additional study estimated effect sizes, and did not change the significance of the estimate.

Discussion

Summary of evidence

According to the current evidence, the overall effect of topiramate for the treatment for AUDs is moderate for abstinence, heavy drinking, craving, and GGT outcomes, significantly so for abstinence, heavy drinking, and GGT. However, because the overall estimate for GGT

did not remain significant in the permutation test, it should be interpreted with caution. Some indication of heterogeneity was found among the 7 studies included in this meta-analysis on craving and abstinence outcomes. Although the sample size was too small to carry out formal moderator tests, we qualitatively compared study features to identify possible moderators of effect sizes that could be examined in future meta-analyses after more studies accrue.

For the drinking-related aggregate outcomes, the effects in both the Kampman et al. (2013) and Likhitsathian et al. (2013) studies were noticeably smaller than the effects found in the other studies (and were not significantly different from zero). Both of these studies had unique characteristics that may have reduced the effect size. Kampman et al. (2013) was the only study that included a sample of participants with comorbid drug dependence (i.e., cocaine dependence). Although all participants in that trial met criteria for alcohol dependence, Kampman et al. (2013) indicated that the severity of dependence and level of alcohol consumption was lower than in the alcohol-dependent samples in previous topiramate trials, perhaps limiting room for improvement.

On the other hand, the differences in outcomes between the topiramate and placebo groups in Likhitsathian et al. (2013) may have been limited by the intensity of other treatment provided to all participants. Participants in this study were recruited after completing inpatient detoxification and beginning a residential treatment program where they received a mean of 25 days of treatment. The intensity of this treatment provided to all participants may have washed out treatment differences in the subsequent outpatient medication period, as participants overall were doing well at the end of the study (e.g., they were drinking on only 5.9% of days; Likhitsathian et al., 2013).

Regarding an initial period of abstinence, however, the effects in the 3 studies that included participants who were actively drinking at the start of the trial (Johnson et al., 2003; Johnson et al., 2007; Kranzler et al., 2014) did not seem to systematically differ from those in studies in which all participants had completed some period of abstinence prior to beginning the medication. Overall, these results imply that some aspects of the treated population and context of care may contribute to the efficacy of topiramate, though further research is necessary to understand the specific contexts in which topiramate is more and less beneficial.

The largest overall effect in our analysis was for the abstinence aggregate outcome, although the magnitude was similar to that of the heavy drinking aggregate ($g = 0.468$ vs $g = 0.406$). However, this does not necessarily reflect an increase in complete abstinence. The abstinence aggregate effect may largely reflect a reduction in frequency of drinking (i.e., more abstinent days), rather than an increase in complete abstinence. All 7 of the studies contributed an effect size for drinking frequency to the overall effect estimate, whereas only 3 of them also included a measure of the proportion of participants who were completely abstinent.

The overall effect sizes found in this analysis compare favorably to effect sizes in comparable outcome domains in a meta-analysis of the 2 most frequently studied

medications currently approved by the FDA for the treatment of AUDs (i.e., naltrexone and acamprosate; Maisel et al., 2013). Though sample differences should be taken into consideration, for each of the 3 outcome domains that were in both analyses (abstinence aggregate, heavy drinking aggregate, and craving), the overall effect of topiramate (g s from 0.312 to 0.468) was larger than the overall effects of naltrexone (g s from 0.116 to 0.189) and acamprosate (g s from 0.034 to 0.359). Furthermore, we calculated effect sizes for topiramate versus naltrexone for 3 randomized trials that directly compared topiramate to naltrexone, including 1 double-blind trial (Baltieri et al., 2008) and 2 open-label trials (Florez et al., 2008; Florez et al., 2011). The effects favored topiramate on all 3 outcomes, though the overall effect size did not reach significance for the abstinence aggregate (i.e., abstinence aggregate: $g = 0.149$, $p = .30$; heavy drinking aggregate: $g = 0.284$, $p = .04$; and craving: $g = 0.297$, $p = .04$).

Topiramate is generally well tolerated, but some patients do experience concerning adverse side effects, especially at higher doses and without gradual dose titration. Across 896 participants in a review of studies of topiramate for psychiatric disorders, the most commonly reported adverse events were paresthesia/numbness (12.9%), nausea/vomiting (6.2%), cognitive impairment (5.4%), headache (5.1%), and dizziness (5.0%; Arnone, 2005). Across the 4 studies in our sample that reported the number of participants who dropped out due to adverse events, 42 of 342 (12.3%) participants assigned to topiramate, compared to 16 out of 348 (4.6%) participants assigned to placebo dropped out for this reason (Johnson et al., 2003; Johnson et al., 2007; Likhitsathian et al., 2013; Rubio et al., 2009). On the other hand, the overall drop-out rates (i.e., drop-out for any reason) were similar (37.2% for topiramate vs 38.1% for placebo) and not significant in an omnibus test ($g = 0.122$, $p = .47$) across the 5 studies in our sample that reported this information (Baltieri et al., 2008; Johnson et al., 2003; Johnson et al., 2007; Kampman et al., 2013; Likhitsathian et al., 2013).

Limitations and strengths

The main limitation of this analysis is the small number of included studies ($k = 7$), which precluded any formal moderator analyses. Heterogeneity tests indicated that further research into moderators (e.g., severity of dependence, whether initial abstinence was required, and characteristics of concurrent psychotherapy, such as intensity and goal) might provide useful information on correlates of variation in effect sizes and about how best to use topiramate to treat AUDs. Additionally, the studies in this meta-analysis all had a target topiramate dosage of at least 250 mg, but a recent randomized trial compared psychotherapy alone to psychotherapy plus low-dose topiramate (up to 75 mg) and found that participants in the topiramate group were more likely than those in the psychotherapy only group to remain continuously abstinent during a 4-month follow-up period (33.3% compared to 14.5%, $p = .04$; Paparrigopoulos et al., 2011). Future trials could evaluate the effects of various doses of topiramate.

Furthermore, the magnitude of the effect sizes reported here should be considered in the context of the small number of studies included in the analyses. For example, effect sizes in published trials of naltrexone for AUDs have declined over time (Del Re et al., 2013b; Feinn and Kranzler, 2005). Using data from our meta-analysis of naltrexone studies, we calculated

the overall effect size (on abstinence aggregate, heavy drinking aggregate, and craving outcomes) for the first 7 published naltrexone trials. The effects in those 7 trials (gs from 0.166 to 0.305) were larger than the overall effects in the final sample of 45 trials (gs from 0.116 to 0.119; Maisel et al., 2013), although they are smaller than the effect sizes for parallel outcomes in the 7 currently available topiramate trials (gs from 0.312 to 0.468). Decreased overall effects over time may reflect publication bias, or a tendency for early and presumably smaller trials of an intervention to be more likely to be published if they find larger, statistically significant, effects, with subsequent regression to the mean (Finney, 2008; Trikalinos et al., 2004). Accordingly, some decline in effect sizes over time for topiramate also is likely as studies include more diverse samples and are more likely to be published, regardless of findings.

Nonetheless, this meta-analysis has several strengths. It provides an up-to-date estimate of the efficacy of topiramate for treating AUDs, focusing on high quality (randomized, double-blind, placebo-controlled) trials. This meta-analysis included a sample of 7 RCTs, relative to the sample of 3 trials included in a previous meta-analysis (Arbaizar et al., 2010). The additional studies provide some variation in the contexts in which topiramate has been tested, including with participants who had co-occurring cocaine and AUDs (Kampman et al., 2013), with participants completing inpatient or residential treatment (Likhitsathian et al., 2013), and with heavy drinking participants whose goal was to reduce drinking (Kranzler et al., 2014). This created a more varied sample on which to judge the effects of topiramate on drinking-related outcomes. We also employed more sophisticated estimation procedures, and carried out several checks and analyses to consider the implications of the still small number of available studies included in this review.

Conclusion

This meta-analysis provides additional support for the efficacy of topiramate for AUDs, which appears to be of somewhat greater magnitude than that of the most commonly prescribed medications for AUDs (naltrexone and acamprosate). These results demonstrate significant, though moderate, benefits of topiramate for abstinence and heavy drinking outcomes. Topiramate also appears to have a positive, although smaller (and not consistently significant), effects on GGT and alcohol craving. Clinicians should consider using topiramate in the treatment of AUDs.

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Fig. 1.
Literature search flow chart.

Fig. 2.

Forest plots of the effects of topiramate compared with placebo (random effects models; Hedges g and 95% CI).

Table 1
Characteristics of randomized, placebo-controlled trials included in the meta-analysis.

First author (year)	Medication groups (desired daily dosage)	N randomized	N completers*	Months of planned treatment	Required initial abstinence?	Psychotherapy provided
Johnson (2003)	Topiramate (300 mg) Placebo	78 80	55 48	3	no	Weekly sessions of manual-guided brief behavioral enhancement therapy
Johnson (2007)	Topiramate (300 mg) Placebo	183 188	112 144	4	no	Weekly sessions of manual-guided Brief Behavioral Compliance Enhancement Treatment (BBCET)
Baltieri (2008)	Topiramate (300 mg) Naltrexone (50 mg) Placebo	52 49 54	33 29 23	3	yes	Weekly sessions of standardized relapse prevention counseling
Rubio (2009)	Topiramate (250 mg) Placebo	n/a ¹ n/a ¹	31 32	3	yes	Weekly sessions of supportive group therapy
Kampman (2013)	Topiramate (300 mg) Placebo	83 87	54 46	3	yes	Weekly sessions of manual-guided CBT (adapted from MATCH manual)
Likhitsathian (2013)	Topiramate (100-300 mg) Placebo	53 53	28 25	3	yes	3-5 sessions of motivational enhancement therapy ²
Kranzler (2014)	Topiramate (200 mg) Placebo	67 71	55 62	3	no	9 sessions of manual-guided medical management.

¹ 76 randomized overall, group sample size not specified.

² Participants were recruited from inpatient detoxification and residential treatment programs (mean length of stay: 25 days). Topiramate or placebo was initiated a mean of 3.7 days prior to discharge.

* Number of participants who continued to take their assigned pills throughout the planned medication period.

Table 2

Effects of topiramate compared with placebo.

Outcome	Study/overall effect and variables that were aggregated	g	lower limit	upper limit	Top N	Pla N	Test of heterogeneity		
							Q-value	p-value	I ²
Abstinence aggregate	Johnson (2003) ¹	0.562	0.170	0.954	55	48			
	Johnson (2007) ^{1,2}	0.774	0.597	0.950	181	186			
	Baltieri (2008) ^{1,2}	0.496	0.163	0.829	52	54			
	Rubio (2009) ¹	0.478	-0.012	0.968	31	32			
	Kampman (2013) ¹	0.201	-0.093	0.495	83	87			
	Likhitsathian (2013) ¹	0.056	-0.473	0.585	28	25			
	Kranzler (2014) ^{1,2}	0.441	0.149	0.733	67	71			
Heavy drinking aggregate	Overall effect	0.468	0.250	0.687	497	503	14.75	0.02	55.22
	Johnson (2003) ^{3,4}	0.609	0.276	0.942	55	48			
	Johnson (2007) ^{3,4,5}	0.288	0.112	0.465	182	187			
	Baltieri (2008) ^{4,6}	0.553	0.220	0.886	52	54			
	Rubio (2009) ^{3,4}	0.560	0.129	0.992	31	32			
	Kampman (2013) ^{3,4}	0.140	-0.114	0.395	83	87			
	Likhitsathian (2013) ^{3,4,5,6}	0.212	-0.160	0.585	38	34			
	Kranzler (2014) ^{4,5}	0.623	0.345	0.901	67	71			
	Overall effect	0.406	0.215	0.600	508	513	11.55	0.07	49.81
	Johnson (2003) ⁷	0.502	0.248	0.757	75	75			
Craving	Johnson (2007) ⁷	0.530	0.275	0.785	112	144			
	Baltieri (2008) ⁷	-0.055	-0.428	0.317	52	54			
	Rubio (2009) ⁸	0.736	0.226	1.245	31	32			
	Kampman (2013) ⁹	0.301	0.007	0.595	83	87			
	Likhitsathian (2013) ¹⁰	-0.172	-0.583	0.240	47	42			
	Overall effect	0.312	-0.042	0.666	400	434	16.14	0.01	72.31

Outcome	Study/overall effect and variables that were aggregated	g	lower limit	upper limit	Top N	Pla N	Test of heterogeneity		
							Q-value	p-value	I ²
GGT	Johnson (2003)	0.417	0.095	0.739	75	75			
	Johnson (2007)	0.480	0.286	0.674	148	166			
	Baltien (2008)	0.171	-0.208	0.550	52	54			
	Likhitsathian (2013)	-0.085	-0.617	0.446	28	25			
	Kranzler (2014)	0.245	-0.087	0.580	67	71			
	Overall effect	0.324	0.082	0.567	370	391	5.69	0.22	28.79

Note. GGT= γ -glutamyltranspeptidase.

¹ Drinking frequency (percent days abstinent/percent days with any drinking).

² Percent abstinent.

³ Drinks per drinking day.

⁴ Heavy drinking frequency (percent heavy drinking days or number of heavy drinking weeks).

⁵ Percent with no heavy drinking days.

⁶ Time to first heavy drinking day.

⁷ Obsessive Compulsive Drinking Scale (Anton et al., 1996).

⁸ Craving scale score (not further specified).

⁹ Penn Alcohol Craving Scale (Flannery et al., 1999).

¹⁰ Visual Analogue Scale.