Effectiveness of Gabapentin in Reducing Cravings and Withdrawal in Alcohol Use Disorder:
A Meta-Analytic Review

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ABSTRACT

Objective: The current meta-analysis synthesizes previous findings on the effect of gabapentin on alcohol withdrawal and craving.

Data Sources: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, a search for relevant English-language literature published between January 1999 and February 2019 was conducted using PubMed and Google Scholar with the keywords *alcohol use disorder*, *alcohol dependence*, *alcohol withdrawals*, *alcohol craving*, "*gabapentin in alcohol use*, *consumption*," and "*gabapentin in alcohol withdrawals*."

Study Selection and Data Extraction: Studies were included wherein gabapentin was used as an adjunctive or primary treatment of alcohol dependence/withdrawal. Studies included participants diagnosed with alcohol use disorder using *DSM-IV*, *DSM-IV-TR*, *DSM-5*, or the *International Classification of Diseases*, Tenth Revision (*ICD-10*). The search, as well as data extraction, was carried out by 3 blinded authors to preserve precision, using a template in Microsoft Excel to extract the needed data. Following the review of the initial 65 returns, 2 authors independently judged each trial by applying the inclusionary and exclusionary criteria, and any remaining disagreements were resolved by involving a third independent author. A total of 10 studies met the inclusion criteria and were selected for analysis. Subjects in these 10 studies were pooled using standard techniques of meta-analysis.

Data Synthesis: Three sets of meta-analyses examined outcomes from (1) single-group pretest-posttest changes, (2) posttest differences between independent groups, and (3) differences in pretest-posttest change scores between independent groups. Statistically significant effect sizes were found for craving ($P < .01$) and withdrawal ($P < .01$, $P < .001$) in the meta-analysis of single-group pretest-posttest outcome changes and were associated with a high level of heterogeneity. In contrast, the meta-analyses of posttest differences between independent groups—that of differences in pretest-posttest change scores between independent groups—did not yield significant effect sizes.

Conclusions: Our analysis of pooled data provides evidence that the use of gabapentin to manage alcohol withdrawal symptomatology and related cravings is at least moderately effective. However, given the limited number of available well-designed studies, these findings require further support through more rigorously designed studies.

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Alcohol withdrawal occurs as a result of cessation of or reduction in alcohol use, particularly after a period of heavy and prolonged drinking. The diagnosis requires the presence of ≥ 2 of a set of 8 criteria: autonomic hyperactivity (eg, sweating or pulse rate > 100 beats per minute); increased hand tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; or generalized tonic-clonic seizures. The symptoms develop within several hours to a few days after this cessation or reduction in alcohol use and can be potentially life-threatening.[1] The "protracted abstinence" phase of withdrawal causes negative affective changes that are associated with increased cravings and relapse risk.[2]

At present, benzodiazepines (BZDs) serve as a standard of care in the treatment of alcohol withdrawal and mediate primary γ-aminobutyric acid (GABA) effects of alcohol by targeting the GABA-A receptors. While most patients with alcohol withdrawal respond to standard treatment that includes benzodiazepines, there is a subgroup of this patient population in whom deficiency of endogenous GABA or acquired conformational changes in GABA-A receptor may resist therapy (resistant alcohol withdrawal).[3] These patients require large doses of BZD (ie, ≥ 50 mg of intravenous diazepam in the first hour of treatment) and additional sedatives adjunctive to BZDs such as phenobarbital,

Clinical Points

- While benzodiazepines are considered the standard of care for alcohol withdrawal, gabapentin is a valuable alternative that can also help with cravings and abstinence long term.
- Larger, double-blinded studies are needed to more reliably demonstrate gabapentin's efficacy in the management of alcohol withdrawal and cravings.

dexmedetomidine, or propofol and some may undergo complicated hospitalizations.[4–6]

Although BZDs are the standard treatment for managing withdrawal, BZDs are approved for a diverse set of clinical indications and are increasingly prescribed. In 2012, for every 100 Americans, 37.6 BZD prescriptions were written by prescribers. The rise in overuse, misuse, and addiction increased overdose deaths involving BZDs from 1,135 in 1999 to 8,791 in 2015.[7]

The results from the National Epidemiologic Survey on Alcohol and Related Conditions report[8] estimated the US prevalence of *DSM-5* 12-month alcohol use disorder among adults aged 18 years and older was 13.9%, while the lifetime estimate was 29.1%. Evidence suggests that the US Food and Drug Administration (FDA)–approved relapse preventive medications are currently underused in the management of alcohol use disorder.[9] In the context of such a high prevalence of alcohol use disorder, this underutilization by prescribing health care professionals raises concern.

Gabapentin, or 1-(aminomethyl)cyclohexane acetic acid, is a nonbenzodiazepine anticonvulsant with high affinity for voltage-gated calcium channels. Its mechanism of action is believed to be blocking of a specific α-2d subunit of the voltage-gated calcium channel at selective presynaptic sites, thereby indirectly modulating GABA neurotransmission via a downstream cascade of resulting events.[10,11] Gabapentin has also been reported to enhance GABA activity by possibly stimulating GABA synthesis directly.[12] Although its FDA indication is for treatment of epileptic seizures and neuropathic pain, gabapentin has been increasingly used off-label in recent years. A rising number of reports[10,11] support its use for alcohol dependence as well as alcohol withdrawal symptomatology. Possible mechanisms include normalization of stress-induced GABA activation in the amygdala, which is associated with alcohol dependence. During withdrawal, it also potentially reduces withdrawal excitability in the hippocampus.[13] Studies[11] have also reported that gabapentin reduces alcohol craving as well as sleep and mood disturbances in alcohol-dependent individuals. Continued use of gabapentin has also been associated with reduced relapse rates and reduced risk of return to heavy drinking.[12] Furthermore, gabapentin has been reported to be non–habit forming and to have low abuse potential when compared to BZDs.

Despite the numerous studies involving off-label use of gabapentin for alcohol use disorder, there have been no meta-analyses conducted to assess its efficacy in reducing craving and withdrawal symptoms. Multiple studies[14] suggest gabapentin has some efficacy in reducing alcohol dependence, withdrawal, and craving, but current evidence is complicated by the challenges of the variable dosing of gabapentin between trials, the heterogeneity of diagnoses, and absence of clear and comprehensive primary study outcomes. Craving, as a criterion in the diagnosis of alcohol use disorder, was added in the *DSM-5* and was unlikely to be considered as a primary outcome in pre–*DSM-5* studies. Additionally, most studies were small or conducted in limited treatment settings. With this in mind, we decided to perform a meta-analysis of all available studies to assess the efficacy of gabapentin for craving and withdrawal symptoms. Our findings from these analyses are hypothesized to complement conclusions already drawn from systematic reviews.[12,14,15]

METHODS

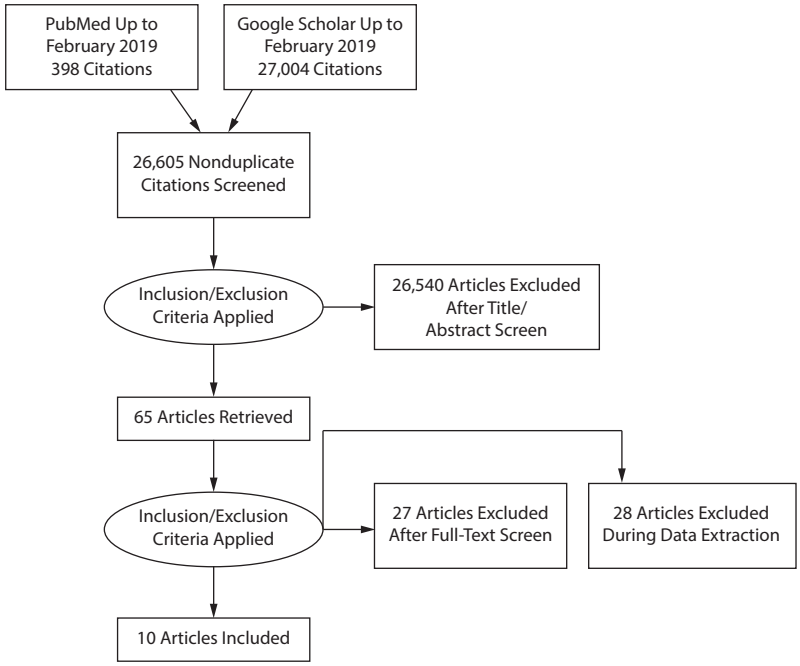
Data Sources and Searches

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology,[16] a search for relevant English-language literature published between January 1999 and February 2019 was conducted using PubMed and Google Scholar (Figure 1) with the following keywords: *alcohol use disorder*, *alcohol dependence*, *alcohol withdrawals*, *alcohol craving*, "*gabapentin in alcohol use*, *consumption*," and "*gabapentin in alcohol withdrawals*."

Inclusion Criteria

1. We included studies from the past 20 years until the final search was conducted in February 2019.
2. Studies had to be published in the English language.
3. Gabapentin was used as an adjunctive or primary treatment of alcohol dependence/withdrawal. Thus, studies could have included other medications or psychotherapy in addition to gabapentin.
4. Studies had to use a measure of either craving or withdrawal symptoms as one of the outcome measures, since these were the most frequently used scales across the studies we examined.
5. Studies had to include participants diagnosed with an alcohol use disorder using the *DSM-IV*, *DSM-IV-TR*, *DSM-5*, or *International Classification of Diseases*, Tenth Revision (*ICD-10*).
6. Eligible study designs included single-group pretest-posttest, independent-groups posttest, or independent-groups pretest-posttest designs. For the latter 2 designs, the design-specific effect sizes were calculated only if the comparison group received a placebo, rather than an alternative medication (since comparisons to alternative medications are beyond the scope of the current study). However, effect size calculations for

Figure 1. Flow Diagram Depicting Study Selection



studies that used an alternative medication for the comparison group were conducted using only the gabapentin group data and only for single-group pretest-posttest effect size calculations.

Exclusion Criteria

1. Studies published in any language other than English.
2. Gabapentin was used solely for illnesses other than alcohol dependence, such as seizure disorder, mood disorders, neuropathic pain, or any other neuropsychiatric illness.
3. Case reports, case series, and those studies in which there were no descriptive statistics or any statistics that could be converted to an effect size.
4. Review articles, commentaries, or opinion pieces.
5. Unpublished studies such as conference posters or presentations.

Data Extraction, Synthesis, and Analysis

The search was carried out by 2 independent authors (S.A. and S.B.). These researchers independently performed screening of titles and abstracts for initial exclusion based on publication type. Where required, the full texts were immediately screened to ascertain inclusion or exclusion. Following the initial exclusion screening, the researchers further evaluated the full-text articles for inclusion based on the 6 inclusion criteria. At each step, their results were compared, and any discrepancies were resolved through discussion. Any remaining disagreements were resolved by involving a third independent author (C.N.S.).

Means and standard deviations (SDs) of the withdrawal symptoms and craving measures were extracted from the studies by 2 independent volunteer researchers (S.A. and S.B.). For studies with more than 1 follow-up time point,[10,17–20] only data from the earliest measure were extracted to minimize loss of participants. In addition, there were 2 studies that divided their gabapentin treatment participants into subgroups of different treatment dosages and reported their results across these subgroups.[10,11] For these studies, the sample sizes, means, and SDs from these subgroups were combined, using the formula suggested in the Cochrane *Handbook for Systematic Reviews of Interventions*,[21] such that only 1 sample size and 1 set of means and SDs from all participants regardless of subtypes were obtained. If the means and SDs were not reported in a numeric format but were instead presented in graphs, these means and SDs were extracted from the graphs using a web-based application designed to facilitate data extraction from graphs.[22]

Design-specific standardized mean difference (SMD) scores were calculated for each study using 1 (or more when a study provided data that could be used in more than 1 of the meta-analyses conducted) of 3 formulas (Supplementary Appendix 1). In all cases of effect size calculations, the direction was coded so that negative effect sizes reflect favorable outcomes for the gabapentin group. Calculation of effect sizes was generally straightforward (some exceptions are discussed in Supplementary Appendix 1). Given the variability in types of trial designs, we aggregated only design-specific effect sizes across studies. Publication bias was assessed by funnel plots. In addition, a trim and fill analysis[23] was conducted to assess the degree to which

publication bias may have influenced the meta-analytic results. Finally, leave-one-out analyses were carried out for each of the 3 meta-analyses to assess the replicability and robustness of the results. Supplementary Appendix 1 provides a detailed description of these analyses.

Description of Studies

Information, where available, regarding the participants (age, sex, sample type, and clinical diagnoses) and the intervention design, dosage, and intervention interval for each study was obtained. Ten studies[10,11,17–20,24–27] were deemed eligible for inclusion. These studies utilized a variety of designs, the most common (6 studies) being that of a single-group pretest-posttest design. In all but 1 study,[24] participants were explicitly reported to have met *DSM-IV* or *ICD-10* diagnoses of alcohol dependence/withdrawal. This study[24] was included in the meta-analysis since it reported data on alcohol withdrawal from a US Veterans Affairs medical center between November 2001 and April 2002. Since the *DSM-IV* was published in 1994 and was widely used at the time of this study, we can infer that patients met *DSM-IV* criteria for alcohol withdrawal. In addition, the leave-one-out data analyses specifically address this issue of whether including this study impacted the meta-analytic results.

RESULTS

Treatment Outcomes

The meta-analyses of the single-group pretest-posttest results yielded significant SMDs for both cravings and withdrawal. However, the meta-analyses of the independent groups' posttest and independent groups' pretest-posttest outcomes on cravings did not result in any significant SMDs—studies that included withdrawal as an outcome variable had only a single-group pretest-posttest design, and no studies on withdrawal had either of the other 2 research design types. Substantial heterogeneity for all of the meta-analyses was demonstrated by the significant Q statistics and high I^2 values. Forest plots for all meta-analyses are shown in Figure 2. The results for each of the meta-analyses, together with the trim and fill–adjusted results, are presented in Table 1.

Sensitivity Analysis

Results of the leave-one-out analyses generally suggested reliable and robust results for the single-group pretest-posttest meta-analyses for both cravings and withdrawal symptoms. No one study affected the overall estimates by more than 15.35%. As for heterogeneity, the exclusion of Lembke et al[7] (this study was not included with the final 10 studies) impacted the Q statistic, which was no longer statistically significant ($P = .09$). Apart from this study, the exclusion of any other study did not significantly affect the heterogeneity results; the Q statistics remained significant ($P \leq .03$).

The leave-one-out analyses revealed less reliable results for the independent groups' posttest meta-analysis of cravings. First, the SMD for the independent groups posttest cravings became significant with the exclusion of Mason et al.[25] Next, the exclusion of Myrick et al[17] and Furieri and Nakamura-Palacios[20] each resulted in a 52.38% decrease in the SMD. Furthermore, the exclusion of Mason et al[25] resulted in a 90.48% increase in the SMD and rendered the Q statistic nonsignificant ($P = .32$)

Leave-one-out analyses were not carried out for the independent groups' meta-analyses since there were only 2 studies. The results of the leave-one-out analyses are presented in Table 2.

Trim and Fill Analyses

The funnel plots for the single-group pretest-posttest meta-analyses for cravings and withdrawal, as well as the funnel plot for the independent groups' posttest analyses for cravings, are shown in Figure 2. The funnel plot for the independent groups' pretest-posttest meta-analysis is not shown since there are too few studies for it to be meaningful. Using the trim and fill analysis, 2 studies were imputed in the meta-analysis of the single-group pretest-posttest results for cravings, 1 study was imputed in the meta-analysis of the independent groups' posttest results for cravings, and 1 study was imputed in the meta-analysis of the single-group pretest-posttest results for withdrawal symptoms. If the asymmetry is due to publication bias, the results suggest that the true effect is slightly overestimated (Figure 3). Trim and fill analysis was not conducted for the independent groups' pretest-posttest meta-analysis of cravings because there were only 2 studies. The results of the trim and fill–adjusted results, together with the rest of the results of the meta-analyses, are presented in Table 1.

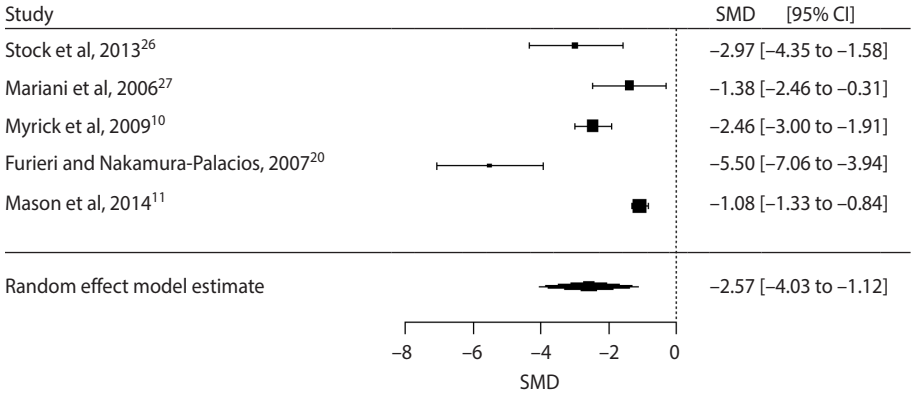
DISCUSSION

The significant pooled estimates obtained for the treatment outcomes in the single-group pretest-posttest meta-analytic results provide support for the use of gabapentin in treating alcohol craving and withdrawal. It has been suggested that it may be as effective as BZDs in treating the symptoms of alcohol withdrawal.[10,11,28–31] Patients might resume drinking if withdrawal symptoms are not adequately managed or if the medication given does not suppress the craving for alcohol or aggravates the craving. Some studies suggest that BZD use may increase craving and early relapse to alcohol use,[17] whereas other studies[28,32,33] have shown that gabapentin use did not trigger alcohol craving.

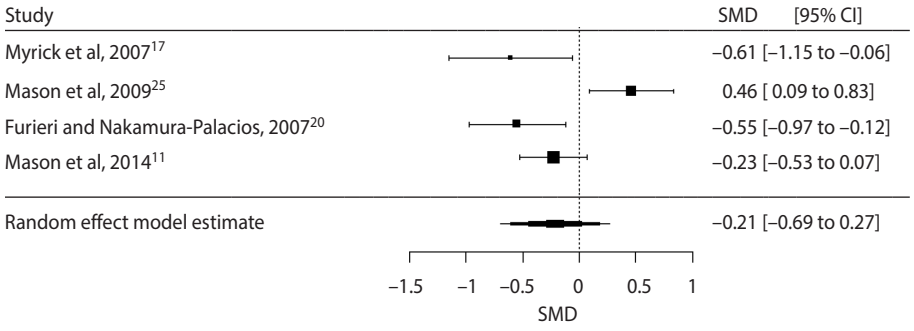
As described previously, barriers to the effective use of the FDA-approved agents in the management of alcohol use disorder include medical and psychiatric comorbidities, poor medication adherence, and problems with tolerability. As the body of research on alternatives to these agents continues to grow, we sought to improve the understanding of gabapentin's strategic role in the management of alcohol dependence and withdrawal. Gabapentin is not hepatically metabolized,[14] making it preferable to current FDA-approved agents, especially in a population with a high

Figure 2. Forest Plots of Meta-Analyses

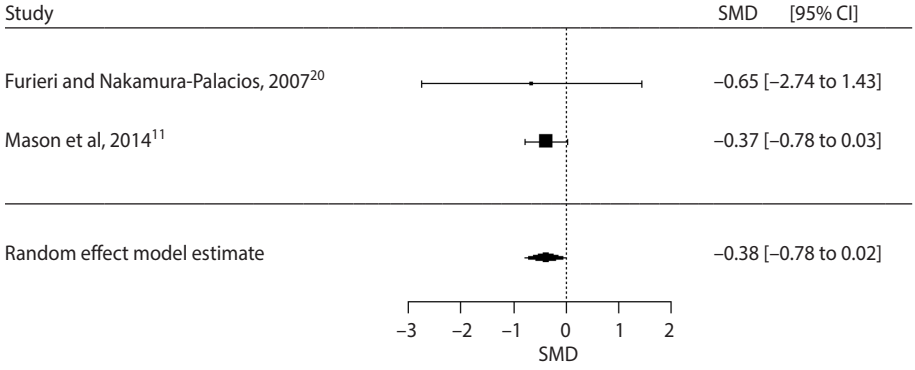
A. Cravings: Single-Group Pretest-Posttest



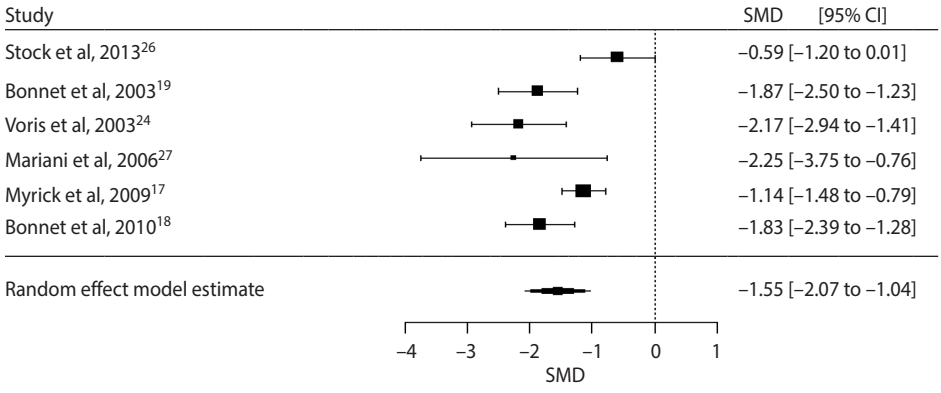
B. Cravings: Independent Groups Posttest



C. Cravings: Independent Groups Pretest-Posttest



D. Withdrawal: Single-Group Pretest-Posttest



Abbreviation: SMD = standardized mean difference.

Table 1. Meta-Analyses of the Effects of Gabapentin on Withdrawal Symptoms and Cravings, Separated by Research Design–Specific Analyses

Research Design	No. of Studies	$N_{Treatment}$	$N_{Control}$	SMD	SE	95% CI	*Q*	I^2
Cravings								
Single-group pretest-posttest	5	220		−2.54**	0.74	−4.03 to −1.12	51.94**	95.29
Independent groups posttest	4	163	107	−0.21	0.24	−0.69 to 0.27	16.68**	82.81
Independent groups posttest (TAF)	5			−0.10	0.22	−0.54 to 0.33	20.33**	81.63
Independent groups pretest-posttest	2	133	79	−0.38	0.20	−0.02 to 0.78	0.07	0
Withdrawal								
Single-group pretest-posttest	6	187		−1.55**	0.26	−2.06 to −1.03	18.66***	75.31
Single-group pretest-posttest (TAF)	7			−1.49**	0.25	−1.97 to −1.01	19.40***	71.11

**$P < .01$. ***$P < .001$.
Abbreviations: SMD = standardized mean difference, TAF = trim and fill.

Table 2. Results of the Leave-One-Out Analyses

Study Excluded	Year	Estimate	SE	95% CI	*Q*	I^2
Cravings: single-group pretest-posttest						
Stock et al[26]	2013	−2.51**	0.95	−4.38 to −0.65	47.16***	97.07
Mariani et al[27]	2006	−2.89**	0.90	−4.65 to −1.13	51.93***	96.41
Myrick et al[10]	2009	−2.64**	0.99	−4.58 to −0.70	36.16***	93.87
Furieri and Nakamura-Palacios[20]	2007	−1.88***	0.44	−2.73 to −1.02	25.44***	85.35
Mason et al[11]	2014	−3.00***	0.83	−4.63 to −1.37	18.72***	89.40
Cravings: independent groups posttest						
Myrick et al[17]	2007	−0.10	0.29	−0.67 to 0.47	13.68***	86.66
Mason et al[25]	2009	−0.40**	0.13	−0.66 to −0.14	2.29	22.67
Furieri and Nakamura-Palacios[20]	2007	−0.10	0.30	−0.70 to 0.49	12.58***	85.55
Mason et al[11]	2014	−0.22	0.35	−0.91 to 0.48	16.34***	86.46
Withdrawal: single-group pretest-posttest						
Stock et al[26]	2013	−1.72***	0.23	−2.17 to −1.27	10.77*	59.58
Bonnet et al[19]	2003	−1.49***	0.31	−2.11 to −0.88	16.19***	78.73
Voris et al[24]	2003	−1.43***	0.28	−1.97 to −0.89	14.26*	74.91
Mariani et al[27]	2006	−1.49***	0.28	−2.04 to −0.94	17.36***	79.29
Myrick et al[17]	2009	−1.67***	0.32	−2.29 to −1.05	14.95***	72.47
Bonnet et al[18]	2010	−1.50***	0.32	−2.12 to −0.88	15.74***	78.00

*$P < .05$. **$P < .01$. ***$P < .001$.

predisposition to hepatic insufficiency. Unlike acamprosate, gabapentin can also be used in patients with renal function < 20 mg/dL. Gabapentin is a promising agent in alcohol use disorder treatment because it is generally well tolerated, has a favorable safety profile with few side effects, does not interact with other medications, and improves sleep, mood, and anxiety.[11,34,35] Unlike for carbamazepine and valproic acid, regular blood draws to determine gabapentin blood levels are not required. Furthermore, gabapentin has been shown to have some positive impact in the management of anxiety disorders and insomnia, which are frequent risks factors for alcohol use relapse.[12,14]

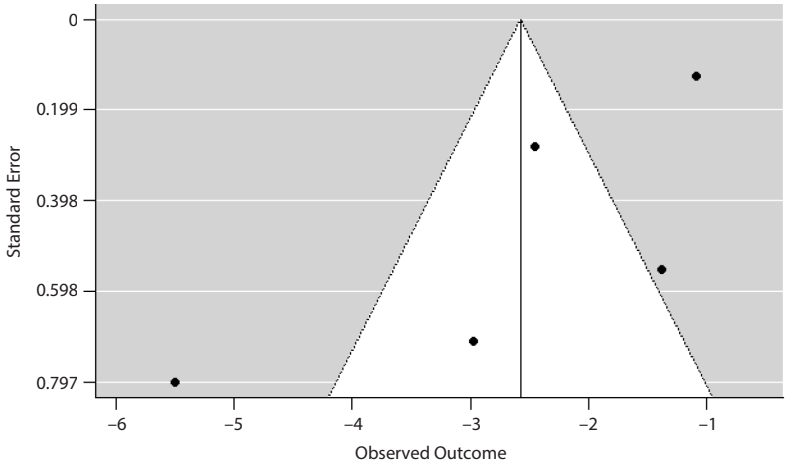
There is a general debate in clinical settings about the appropriate or recommended dose of gabapentin for alcohol dependence and withdrawal symptoms. Numerous clinical trials[10,11,17–20,24–27] have suggested several dosing regimens of gabapentin for the treatment of alcohol withdrawal, which range from 300 mg twice daily to 600 mg 3 times a day. There is no consensus, to our knowledge, on the recommended or optimum dose of gabapentin in alcohol use disorder.

By examining the studies included in this review, it is difficult to determine an optimum dose of gabapentin in patients with alcohol dependence and withdrawal symptoms. In this context, we suggest the randomized controlled trial by Mason and colleagues[11] as a model study for appropriate dosing while treating these patients. Mason et al[11] randomized patients to 3 groups to receive placebo, gabapentin 300 mg thrice daily (900 mg), or gabapentin 600 mg thrice daily (1,800 mg). The results indicated that gabapentin had a significant linear dose effect on complete abstinence rate and no days of heavy drinking. In the 1,800-mg group, the rate of sustained 12 weeks of abstinence was significant with concomitant manual-guided counseling. Also, linear dose effects related to relapse-related symptoms such as cravings, mood, and sleep were statistically significant in the 1,800-mg group compared with other groups.[11] Additional studies replicating this outcome would further establish gabapentin's role in the treatment of alcohol use disorder.

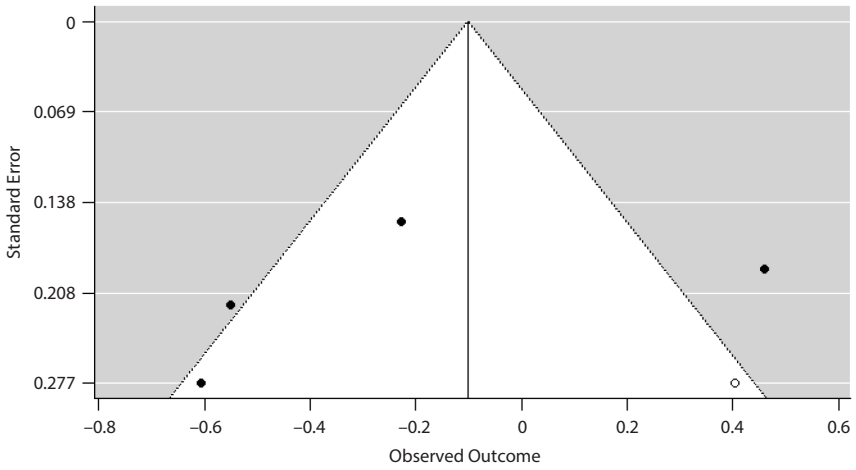
There is a growing concern that gabapentin is being misused. The misuse has increased rapidly in recent years, especially in patients with substance use disorder. Gabapentin is noted, especially in those using opioids, to produce a rapid euphoric effect or "high" and reduce withdrawals.[36] Patients with opioid use disorder misuse gabapentinoids to potentiate the effects of opioids in some cases, and patients also abuse it with prescription opioids such as methadone or buprenorphine/naloxone. The combined use of gabapentin and opioids also increases the risk of respiratory depression and deaths in this patient population.[37] Although, gabapentin has a beneficial role in some substance use disorders such as alcohol use disorder, clinicians should adopt a cautious approach when

Figure 3. Funnel Plots Assessing for Publication Bias in the Meta-Analyses of Cravings and Withdrawal Symptoms[a]

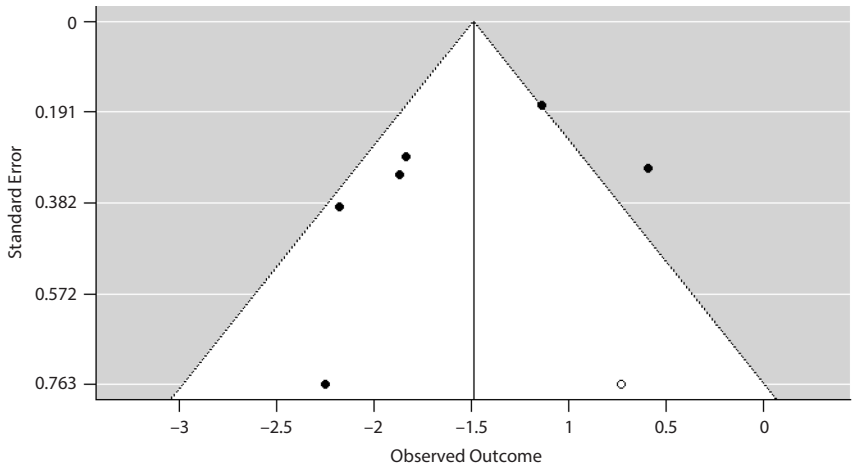
A. Cravings: Single-Group Pretest-Posttest



B. Cravings: Independent Groups Posttest



C. Withdrawal: Single-Group Pretest-Posttest



[a]Black and white spots represent actual and imputed studies, respectively.

considering prescribing gabapentin to patients with known prior history of drug dependence. Clinicians should educate their patients about the benefits and risks of gabapentin and its fatal interactions with other opioids (prescription opioids or illicit nonprescribed opioids).

Larger-sampled, double-blinded studies are required to more reliably demonstrate gabapentin's efficacy in the treatment of alcohol withdrawal and craving. The unique advantages of gabapentin offer an opportunity for the development of a fairly reasonable alcohol detoxification program. For instance, gabapentin could be used initially as a detoxification agent and subsequently used as a relapse prevention agent with a lower and more tolerable dose for several months of maintenance treatment. Because protracted alcohol withdrawal symptoms of insomnia, anxiety, dysphoria, and alcohol craving can complicate the immediate period of recovery after detoxification, short-term maintenance treatment with gabapentin may relieve these symptoms and reduce relapse rates. Given gabapentin's favorable safety profile, tolerability, and comparatively lower abuse potential than BZDs, it is an ideal candidate to study as a relapse prevention agent.

Limitations

One key limitation of this meta-analysis is that not all included studies were randomized controlled trials. In addition, there were several studies for which we were able to extract only pretest-posttest data, and these studies could, therefore, be included in only the single-group pretest-posttest meta-analyses. This meta-analysis does not, by definition of the eligibility criteria, compare the relative effectiveness of gabapentin with any alternative treatment.

In spite of the finding of significant single-group pretest-posttest effect sizes for both craving and withdrawal, there was a high degree of heterogeneity in both meta-analyses, as demonstrated by significant Q statistics and high I^2 values. In the absence of a comprehensive qualitative analysis of studies in the meta-analyses, possible explanations for this degree of heterogeneity include varying severities of alcohol use disorder in the various study participants, the presence of psychiatric comorbidities in studied participants, variations in gabapentin dosage across included studies, and that follow-up time points were not homogenous across the studies.

Another limitation to the present study is the small number of individual primary studies included in the meta-analyses, a factor that also contributes to the significant Q statistics and high I^2 values. The trim and fill analyses also point to some potential for publication bias in our findings, suggesting the possibility of a slight overestimate of the effect sizes in the meta-analyses. Given these limitations, one should exercise caution in generalizing the results of this study.

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Disclaimer: The findings of this meta-analysis are provided for educational purposes. These findings suggest conclusions based on analytical review of published data that should be interpreted cautiously in practical settings.
Ethics statement: The current meta-analysis identified published material and synthesized existing evidence that met prespecified eligibility criteria to answer specific questions regarding efficacy of gabapentin in alcohol withdrawal and cravings. The study was conducted entirely based on analytical interpretation of published papers. The authors did not require any consent from any human subjects.
Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Effectiveness of Gabapentin in Reducing Cravings and Withdrawal in Alcohol Use Disorder: A Meta-Analytic Review

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List of Supplementary Material for the article

1. Supplementary Appendix 1

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Appendix 1

Design-specific standardized mean difference (SMD) scores were calculated for each study, using one (or more, when a study provided data that could be used in more than one of the meta-analyses conducted) of three formulas. For studies that examined single group pretest-posttest changes, Formula 13 in Morris and DeShon[1] was used. For studies that examined posttest differences between independent groups, Formula 2 in Morris and DeShon[1] was used. Finally, for studies that examined differences in pretest-posttest change scores between independent groups, we used Formula 6 in Morris and DeShon.[1] In all cases of effect size calculations, the direction was coded so that negative effect sizes reflect favorable outcomes for the gabapentin group (either from pretest to posttest, relative to placebo at posttest, or amount of pretest-posttest change relative to placebo, depending on the design-specific meta-analyses).

In most cases, these calculations were done using means and standard deviations.[1] In one case[2] these data were not available. As a result, the between-group t-statistic was converted into SMD using Formula 27 from Morris and DeShon.[1]

Calculation of effect sizes were generally straightforward, with some exceptions. Three studies[3–5] involved independent groups, pretest-posttest designs, in which gabapentin treatment groups were compared to another drug instead of placebo. For the purposes of the present meta-analysis, only data from the gabapentin treatment group were extracted (as detailed in the text's Methods section), and the study was treated as a single-group pretest-posttest design in computing effect sizes. In addition, the baseline data for an independent groups' pretest-posttest study was unreported in one publication.[6] Consequently, only the posttest data was extracted, and the study was treated as an independent groups posttest study to compute its effect size.

Given the variability in types of trial designs, we aggregated only design-specific effect sizes across studies. That is, we meta-analyzed separately the (a) single-group pretest-posttest, (b) independent groups posttest, and (c) independent groups pretest-posttest results.

The sampling variances for the independent groups posttest effect sizes were calculated using formula A1.[1] An adapted version of this formula was used for the single-group pretest-posttest effect sizes, but—in contrast to the formula A1 in Morris and DeShon[1]—the effect size term was specifically defined by Formula 13 rather than Formula 4 in Morris and DeShon.[1] The rationale for this adaptation was that Formula 4 in Morris and DeShon[1] requires the standard deviation of the difference scores of outcome variables (or the pretest-posttest correlation of the relevant outcome variable, which can be algebraically transformed into the standard deviation of the difference score), which is information that is almost never reported by primary studies. As a result, it was preferable to use an adapted sampling variance formula for single-group pretest-posttest effect size that does not require this information, rather than impute an arbitrary estimate for the standard deviation of the difference scores. Calculation of sampling variances requires input of the sample size of study participants. As a result of attrition or missing data, however, the pre-test and posttest sample sizes for some studies with single-group

pretest-posttest effect sizes were different. We, therefore, used the pre-test sample sizes for calculation of the sampling variances.

For independent groups pretest-posttest studies, we first calculated single-group pretest-posttest sampling variances separately for the treatment and placebo arms of the study, using the calculations detailed above; both sampling variances were then summed to obtained the sampling variance for the independent groups pretest-posttest effect size.[7] As above, for instances in which pre-test and post-test sample sizes differed from each other, the sampling variances for each of the study arms were calculated using the pre-test sample sizes.

Effect sizes and their sampling variances were meta-analyzed with a random effects model using the metafor package in R.[8] Heterogeneity was measured using the Q and I^2 statistics. A significant Q statistic suggests that the variability among the effect sizes is larger than what is expected from participant sampling error alone. An I^2 value of 75% and above indicates a high degree of heterogeneity.[9] Publication bias was assessed by funnel plots. In addition, trim and fill analysis[10] was conducted to assess the degree to which publication bias may have influenced the meta-analytic results. Specifically, the trim and fill analysis use an iterative procedure to correct for potential publication bias by adjusting the weighted mean effect for studies at the extreme positive side of the graph until the distribution of studies is symmetric. Leave-one-out analyses were carried out for each of the three meta-analyses to assess the replicability and robustness of the results.

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