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REVIEW ARTICLE

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Gabapentinoids for treatment of alcohol use disorder: A systematic review and meta-analysis

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Abstract

Objective: Gabapentin (GBP) and pregabalin (PGB) have been used to treat alcohol use disorder (AUD) and alcohol withdrawal, but with inconsistent results. In this meta-analysis, we explored the effects of GBP/PGB treatment on AUD and their effects on withdrawal, craving, depression, and sleep disturbance in AUD patients.

Methods: We carried out a systematic review and meta-analysis of randomized controlled trials comparing the effects of GBP/PGB on AUD with those of a placebo or control treatment. Electronic databases were searched for relevant articles published before September 2019. The primary outcome was defined as the efficacy measure on achieving abstinence or reducing alcohol consumption in a hierarchical order. We included 16 studies in our meta-analysis.

Results: Overall, GBP had no significant benefit comparing to placebo or control treatment (Hedges' $g = 0.0725$, $p = 0.6743$). For specific alcohol-related outcome, GBP had significant effect on percentage of heavy drink (Hedges' $g = 0.5478$, $p = 0.0441$) and alcohol withdrawal symptoms (Hedges' $g = 0.2475$, $p = 0.0425$). GBP/PGB did not have significant beneficial effect on craving, depressive symptoms, or sleep disturbance. Instability was shown in sensitivity analyses of some above results.

Conclusions: GBP may be helpful to reduce AUD patients' heavy drinking behavior and withdrawal, but more studies are needed for drawing conclusions.

KEYWORDS
alcohol use disorder, alcohol withdrawal, craving, gabapentin, pregabalin

1 | INTRODUCTION

Many psychological and pharmacological treatments have been developed to manage alcohol use disorder (AUD; R. Ahmed et al., 2018; Imel, Wampold, Miller, & Fleming, 2008; Kranzler & Soyka, 2018; Swift & Aston, 2015). AUD is challenging to treat due to the symptoms of withdrawal and craving. At present, the most common pharmacological treatments for AUD are naltrexone, acamprosate, and disulfiram (Kranzler & Soyka, 2018; Liang & Olsen, 2014). Naltrexone is a blocking drug for reducing the euphoric effect of alcohol consumption; disulfiram works via aversive effect; and acamprosate has been shown to treat protracted withdrawal symptoms (Anton, 2008; Garbutt, 2010; Jorgensen, Pedersen, & Tonnesen, 2011; Kranzler & Soyka, 2018; Maisel, Blodgett, Wilbourne, Humphreys, & Finney, 2013; Mason & Goodell, 2015). Several other drugs have been reported to have the potential to reduce alcohol consumption, including topiramate, baclofen, gabapentin (GBP), and pregabalin (PGB; Kranzler & Soyka, 2018; Manhapra, Chakraborty, & Arias, 2019).

GBP and PGB are both gabapentinoids and have a similar structure to γ-aminobutyric acid (GABA; Calandre, Rico-Villademoros, & Slim, 2016; Uchitel, Di Guilmi, Urbano, & Gonzalez-Inchauspe, 2010). They can lower the excitability of thecentral nervous system and were developed to treat epilepsy (Delahoy, Thompson, & Marschner, 2010), but subsequent research revealed that they could also be useful in other disorders, such as neuropathic pain, fibromyalgia, and restless leg syndrome (Arnold et al., 2018; Straube, Derry, McQuay, & Moore, 2008; Tzellos et al., 2010; Wijemanne & Jankovic, 2015). Alcohol withdrawal is a state involving hyperexcitability of the central nervous system; therefore, drugs that reduce the excitability may be helpful for reducing withdrawal symptoms (al Qatari, Khan, Harris, & Littleton, 2001; Jesse et al., 2017). Several anticonvulsants have been found to be beneficial on alcohol withdrawal; it is hence rational to hypothesize that GBP and PGB may also be useful. Some patients with AUD suffer from protracted withdrawal symptoms (Maisel et al., 2013), and acamprosate has been found to improve protracted withdrawal symptoms by modulating the GABA–glutamate balance and alleviating excitotoxicity (al Qatari et al., 2001; Daoust et al., 1992). It would therefore be of interest to determine whether gabapentinoids have similar effects on protracted withdrawal and the abstinence.

Many studies have explored the effects of GBP and PGB on AUD. Some have indicated that these drugs reduce the symptoms and behaviors associated with AUD (Brower et al., 2008; Chompookham et al., 2018; Furieri & Nakamura-Palacios, 2007; Guglielmo, Martinotti, Clerici, & Janiri, 2012; Rentsch, Fiellin, Bryant, Justice, & Tate, 2019; Saitz, 2014). But not all studies have produced positive findings (Falk et al., 2019; Freynhagen et al., 2016). Improving withdrawal symptoms and reducing craving are beneficial to abstinence. Therefore, assuming that gabapentinoids are helpful in treatment of AUD, it would be useful to know which pathway (managing withdrawal or craving) is mainly responsible for their therapeutic effect, though craving and withdrawal are not totally independent (Jung & Namkoong, 2006). We considered that analyzing the effects of gabapentinoids on both withdrawal and craving would provide insight into the mechanism of action of gabapentinoids. As with the effects on alcohol consumption, the effects of gabapentinoids on alcohol withdrawal and craving have been somewhat inconsistent and various outcome indicators have been used (Addolorato & Leggio, 2010; Becker, Myrick, & Veatch, 2006; Bonnet et al., 1999, 2003, 2010; Bozikas, Petrikis, Gamvrula, Savvidou, & Karavatos, 2002; Di Nicola et al., 2010; Forg et al., 2012; Guglielmo et al., 2012; Leung, Hall-Flavin, Nelson, Schmidt, & Schak, 2015; Leung et al., 2018; Martinotti et al., 2008; Myrick et al., 2009; Oulis & Konstantakopoulos, 2012; Prince & Turpin, 2008; Voris, Smith, Rao, Thorne, & Flowers, 2003; Wilming, Alford, & Klaus, 2018). Some studies have also explored the effects of GBP and PGB on depression and insomnia in AUD patients (Malcolm, Myrick, Veatch, Boyle, & Randall, 2007; Mason et al., 2014; Mason, Quello, & Shadan, 2018; Wilming et al., 2018) and adverse reactions to these drugs (Di Nicola et al., 2010; Mason, Light, Williams, & Drobes, 2009; Rustembegovic, Sofic, Tahirovic, & Kundurovic, 2004; Voris et al., 2003). On the same time of performing this analysis in 2019, we noticed that two meta-analyses about the application of GBP on AUDs were published; GBP were found to be effectively reducing heavy drinking days, withdrawal, and craving (S. Ahmed et al., 2019; Kranzler, Feinn, Morris, & Hartwell, 2019). But the approaches of those two articles were somewhat different to ours, such as the different included studies and statistical methods, not analyzing the additional effects on depression, sleep disturbance and adverse reactions, and not considering PGB studies. Therefore, we believe that our analysis with different scopes and approaches is still clinically meaningful.

This study had five aims. First, to investigate whether GBP reduces alcohol consumption in AUD patients. For this purpose, we combined the outcomes of each study with a hierarchical approach according to previous meta-analyses (Bschor, Henssler, Muller, & Baethge, 2018). The advantage of this principle is able to include as many data as possible. Second, to analyze whether GBP ameliorates alcohol withdrawal syndrome. Third, to examine whether GBP reduces craving for alcohol. Fourth, to analyze GBP effects on negative emotions and sleep disturbance in AUD patients. Fifth, to compare the incidence of adverse reactions to GBP and placebo in patients with AUD. Separate analyses were carried out on the effects of GBP only and all gabapentinoids.

2 | METHODS AND MATERIALS

2.1 | Data sources and search strategy

This systematic review and meta-analysis were prepared according to the PRISMA statement guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Three researchers (Y.-C. Cheng, Y.-C. Huang, and W.-L. Huang) searched PubMed, the Cochrane Library, EMBASE, and

PsychINFO from the earliest available date to September 2019. Unpublished studies were also searched for the ClinicalTrials.gov website.

Three sets of key terms were used without any additional restrictions: ("*GBP*" or "*PGB*" or "*gabapentinoid*") and ("*AUD*" or "*alcohol dependence*" or "*alcoholics*" or "*alcoholism*" or "*alcohol abuse*" or "*alcohol withdrawal*" or "*alcohol*") and ("*controlled clinical trial*" or "*randomized study*" or "*randomized trial*"). We searched keywords, text, titles, and subject headings in all databases for a wide variety of terms representing the above concepts. The full texts of all titles meeting the inclusion criteria were retrieved and reviewed. Original studies investigating the effects of GBP or PGB on AUD or acute alcohol withdrawal were eligible for review. We searched the reference lists of primary articles and relevant reviews in order to identify any eligible studies that had not been retrieved through the electronic search.

2.2 | Inclusion and exclusion criteria

We aimed to evaluate the efficacy of GBP and PGB in the treatments for AUD. Eligible studies have the following features: (1) randomized clinical trials; (2) patients with alcohol dependence or AUD, diagnosed using standardized criteria, such as The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Fourth Edition, Text Revision; Fifth Edition (DSM-IV; DSM-IV-TR; DSM-5), and The International Statistical Classification of Diseases and Related Health Problems, 9th Revision; 10th Revision (ICD-9; ICD-10); (3) clinical studies compared GBP or PGB with placebo or treatment as usual (TAU); (4) being published in English, and (5) reporting statistics that could be converted to effect sizes. We excluded series of cases, case reports and conference abstracts, and review articles.

2.3 | Data extraction and quality assessment

Three investigators (Y.-C. Cheng, Y.-C. Huang, and W.-L. Huang) independently extracted relevant information from the included studies and evaluated their methodological quality using the Cochrane Collaboration risk of bias tools (Higgins et al., 2011). The following data on studies were obtained: last name of first author; year of publication; participant characteristics; study design; duration of interventions; sizes of intervention and control groups; efficacy outcome variable. In cases where some of these data were missing, the study authors were contacted to request the necessary information. If outcome data were available from figures only, we employed Plot digitizer software (version 2.6.8) to extract numbers. All potentially relevant manuscripts were independently reviewed by two investigators (Y.-C. Cheng, Y.-C. Huang), and areas of disagreement or uncertainty were adjudicated by a third investigator (W.-L. Huang). The Cochrane Collaboration's tool was used to evaluate seven domains of risk of bias: selection bias (sequence generation and concealment), performance bias (blinding of participants and assessors), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective outcome reporting, and other biases. Studies were classified as having a low, high, or unclear (if there was insufficient information to make a judgement) risk of bias in each domain. The final risk of bias assessment was a consensus judgement by two reviewers following the guidelines for the Cochrane Collaboration's tool (Higgins et al., 2011; disagreements between the two investigators were resolved through discussion).

2.4 | Outcome measures

In order to calculate the aggregated effects of GBP and PGB, the primary outcome was defined as the efficacy measure on achieving abstinence or reducing alcohol consumption. The operationalized outcome was chosen by the investigators of each study. Where more than one outcome was reported, we prespecified the order of the outcomes with the following hierarchy: (1) cumulative days of abstinence, (2) abstinence rate at study endpoint, (3) time to relapse, (4) percentage of heavy drinking days, (5) number of heavy drinking days per week, and (6) amount of alcohol consumption (Bschor et al., 2018). The following predefined subgroup analysis were conducted separately as secondary outcome: (1) percentage of heavy drinking days; (2) the amount of alcohol consumption; (3) percentage of abstinence days; (4) abstinence rate; (5) severity of alcohol withdrawal, rated with the Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised or the Michigan Alcohol Withdrawal Severity; (6) craving, rated with the Obsessive Compulsive Drinking Scale rated or using another craving scale; (7) negative affect, rated by any clinically validated rating scale for negative emotion; (8) sleep, measured with the Pittsburgh Sleep Quality Index or sleep-problem questionnaire; and (9) safety of the treatment, measured as the difference between the number of participants report >0 adverse events in the intervention and placebo arms.

2.5 | Data synthesis and statistical analysis

To calculate the overall effect on the prespecified abstinence and drinking aggregate measures, we calculated standardized mean differences (SMDs) using the formula for Hedges' g with 95% confidence intervals for continuous outcomes (e.g., percent of abstinent days, percentage of heavy drinking days, time to relapse, number of drinking days, and amount of alcohol consumption). For dichotomous outcomes (e.g., abstinence rates), we calculated the odds ratio (OR) and then converted them to Hedges' for comparison purpose. Hedges' g is related to Cohen's d and can be interpreted using the same conventions: small (0.2), medium (0.5), and large (0.8) (Cohen, 1988). An added benefit of Hedges' g is that it is robust against biases found in small samples.

For drinking outcomes representing negative consequences (e.g., drinking quantity and percentage of heavy drinking days), the efficacy measures were reversed, so the positive effect size indicates that the

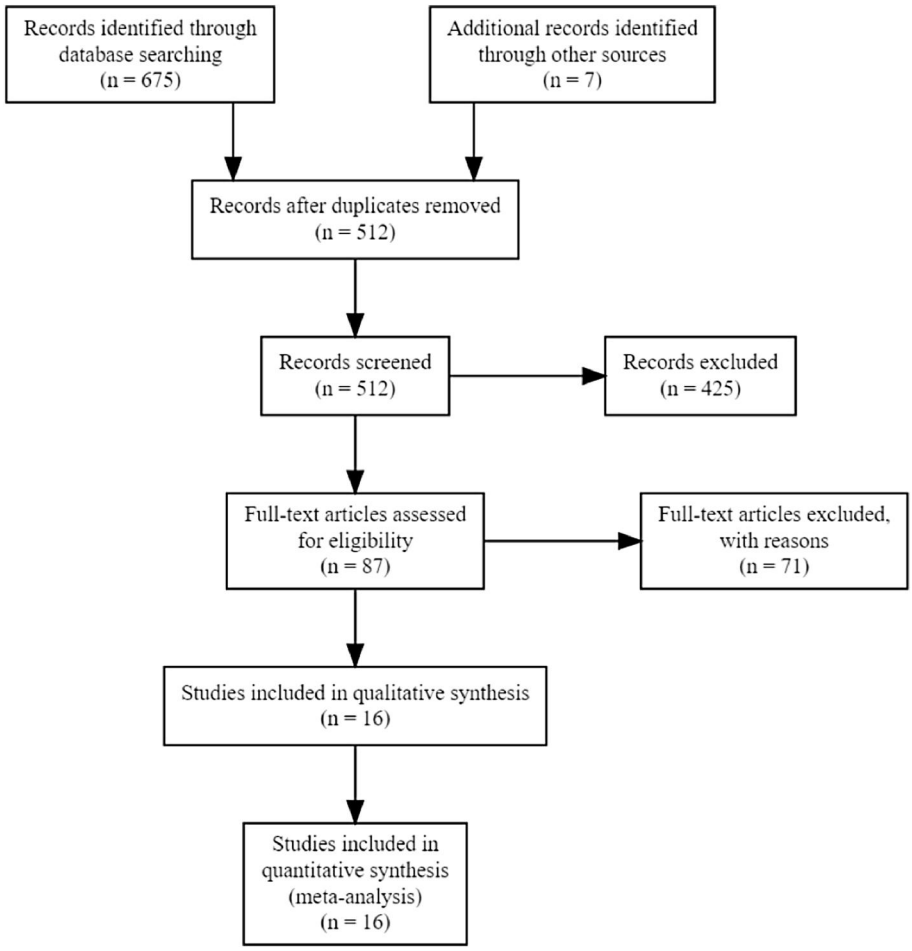

FIGURE 1 PRISMA flow diagram of selection of studies included in the present systematic review and meta-analysis

effect of the intervention was superior to that of the control treatment. For continuous outcomes measured using scales (e.g., craving, withdrawal, depression, and sleep disturbances), SMDs were calculated for the difference between pre- and postintervention scores in the intervention and placebo groups. The standard deviations (SDs) of changes from baseline were calculated using the formula (SD = square root [(SD pretreatment)^2 + (SD post-treatment)^2 − (2R × SD pretreatment × SD post-treatment)], assuming a correlation coefficient (R) = 0.5) if this value was not reported. When only standard error of the mean (SEM) was reported, we calculated the SD by multiplying the SEM by the square root of the sample size. In the case of studies reporting medians and ranges, we estimated means and SDs using the formula given in the Cochrane guidelines (Higgins & Green, 2011; Hozo, Djulbegovic, & Hozo, 2005). In the case of studies where multiple doses of the intervention treatment were used, we combined the means and SDs for the different dosage groups to give single values for the intervention group. For the binary outcomes as abstinence rate and adverse effects, effect size was calculated using the OR similarly.

Possible sources of heterogeneity or inconsistency in the magnitude or direction of effects in trials were investigated. Heterogeneity was assessed using the I^2 test (Higgins & Thompson, 2002). A random effect model was used to assume given the methodological variation between studies. Leave-one-study-out sensitivity analysis was performed by excluding one trial at a time and examining whether the pooled effects remained robust. Because of the presence of heterogeneity, we conducted subgroup analyses to assess source of heterogeneity based on suspected variables. Publication bias was examined using a funnel plot of effect size against the standard error for asymmetry. Egger's regression test was also used to assess publication bias (Egger, Smith, Schneider, & Minder, 1997). All meta-analytic computations were performed with the R software (using meta package version 3.5.1).

3 | RESULTS

3.1 | Baseline characteristics of included studies

Figure 1 summarizes the review flowchart in accordance with the PRISMA statement. Sixteen of the 512 original studies screened met the inclusion criteria for qualitative synthesis (Anton et al., 2009; Bonnet et al., 2003; Brower et al., 2008; Chompookham et al., 2018; Chourishi, Raichandani, Chandraker, & Chourishi, 2010; Di Nicola et al., 2010; Falk et al., 2019; Forg et al., 2012; Furieri & Nakamura-Palacios, 2007; Malcolm et al., 2007; J. Mariani, 2018; J. J. Mariani,

TABLE 1 Meta-analysis result of gabapentinoids effect on patients with alcohol use disorder

	Study no.	Patients/ Control	Effect size	Effect estimate (95% CI)	Effect size *p*-value	Heterogeneity I^2 (%)
Only gabapentin						
Groups by primary outcome	8	413/356	Hedges' *g*	0.0725 (−0.2655; 0.4105)	0.6743	64.9%
Groups by percentage of heavy drinking days	7	395/339	Hedges' *g*	0.5478 (0.0145; 1.0812)	0.0441	89.0%
Groups by alcohol consumption	4	314/252	Hedges' *g*	0.1446 (−0.3452; 0.6344)	0.5628	82.2%
Groups by percentage of abstinence days	3	214/207	Hedges' *g*	0.4951 (−0.1740; 1.1642)	0.1470	81.9%
Groups by abstinence rate	4	306/246	Odds ratio	1.4704 (0.8154; 2.6514)	0.2000	2.0%
Groups by withdrawal scales	5	142/102	Hedges' *g*	0.2885 (0.0286; 0.5483)	0.0296	0.0%
Groups by craving scale	9	425/328	Hedges' *g*	0.1276 (−0.0188; 0.2740)	0.0876	0.0%
Groups by sleep scale	6	354/281	Hedges' *g*	0.3030 (−0.9154; 1.5215)	0.6259	97.4%
Groups by depression scale	6	364/292	Hedges' *g*	0.3302 (−1.0847; 1.7451)	0.6474	98.0%
Groups by event of side effects	8	6785/6628[a]	Odds ratio	1.0679 (0.9127; 1.2494)	0.4121	16.9%
Gabapentin and pregabalin						
Groups by withdrawal scales	6	162/123	Hedges' *g*	0.2475 (0.0083; 0.4868)	0.0425	0.0%
Groups by craving scale	11	468/370	Hedges' *g*	0.1282 (−0.0103; 0.2667)	0.0695	0.0%
Groups by depression scale	8	421/350	Hedges' *g*	0.3079 (−0.7683; 1.3841)	0.5750	97.4%
Groups by event of side effects	10	6842/6686[a]	Odds ratio	1.0895 (0.9780; 1.2136)	0.1196	0.0%

[a]Odds ratio were calculated from proportion of reported adverse event in the intervention arm compared to the placebo arm.

Rosenthal, Tross, Singh, & Anand, 2006; Mason et al., 2009; Stock, Carpenter, Ying, & Greene, 2013; Trevisan et al., 2008). A summary of the studies included in the qualitative review is presented in Table S1. Nine studies evaluated the efficacy of gabapentinoids as a treatment for AUD (Brower et al., 2008; Chompookham et al., 2018; Falk et al., 2019; Furieri & Nakamura-Palacios, 2007; J. Mariani, 2018; Mason et al., 2009, 2014; Myrick, Anton, Voronin, Wang, & Henderson, 2007; Trevisan et al., 2008) and seven studies evaluated the effects of gabapentinoids on acute withdrawal symptoms specifically (Bonnet et al., 2003; Chourishi et al., 2010; Forg et al., 2012; J. J. Mariani et al., 2006; Martinotti et al., 2010; Myrick et al., 2009; Stock, Carpenter, Ying, & Greene, 2013). Eight studies were chosen for inclusion in the primary meta-analysis (Brower et al., 2008; Chompookham et al., 2018; Falk et al., 2019; Furieri & Nakamura-Palacios, 2007; J. Mariani, 2018; Mason et al., 2014; Myrick et al., 2007; Trevisan et al., 2008); their sample sizes ranged from 10 to 170 subjects and the duration of interventions from 8 days to 26 weeks. The results of quality assessment of the trials included in the meta-analysis, based on the Cochrane Collaboration tool and the authors' judgements about each risk of bias item, are presented in Figures S1 and S2.

3.2 | Primary outcome

Table 1 displays the full results of all meta-analyses of the effects of gabapentinoids on AUD. The main meta-analysis covered eight studies involving a total of 413 patients with AUD and indicated that GBP had no different effect comparing to placebo or TAU (Hedges' $g = 0.0725$, 95% CI [−0.2655; 0.4105], $p = 0.6743$; Figure 2). Visual inspection of a funnel plot (Figure S3) did not suggest the presence of publication bias.

3.3 | Secondary outcome and subgroup analysis

Secondary analysis showed that GBP had an significant advantage on percentage of heavy drinking days (Hedges' $g = 0.5478$, 95% CI [0.0145; 1.0812], $p = 0.0441$; Figure 3). A significant advantage of GBP was found on withdrawal symptoms (Hedges' $g = 0.2885$, 95% CI [0.0286; 0.5483], $p = 0.0296$; Figure 4). GBP had no effect on craving (Hedges' $g = 0.1276$, 95% CI [−0.0188; 0.2740], $p = 0.0876$; Figure S4), symptoms of sleep disturbance (Hedges' $g = 0.3030$, 95% CI [−0.9154; 1.5215], $p = 0.6259$; Figure S5), or depression (Hedges' $g = 0.3302$, 95% CI [−1.0847; 1.7451], $p = 0.6259$; Figure S6). Eight studies reported the incidence of side effects, there was no difference between the incidence of side effects in subjects receiving GBP and placebo (OR = 1.0679, 95% CI [0.9127; 1.2494], $p = 0.4121$; Figure S7). Running the analyses again after incorporating the studies using PGB (Di Nicola et al., 2010; Forg et al., 2012) produced similar results (Figures S8–S11).

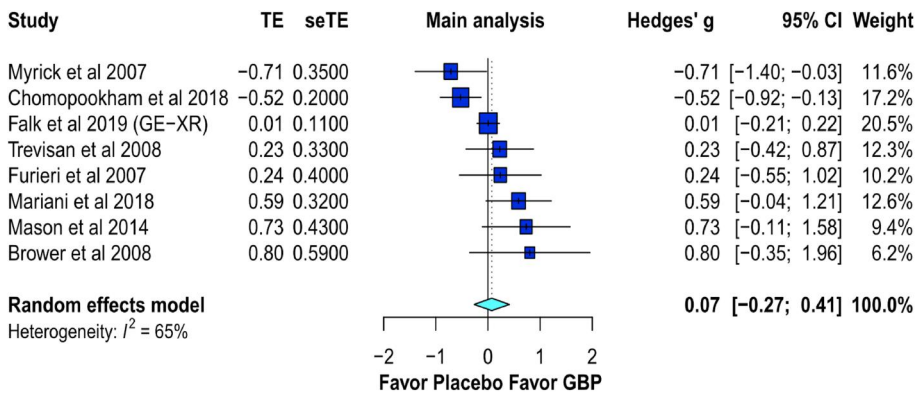

FIGURE 2 Forest plot of meta-analysis on gabapentin (GBP) effect on alcohol use disorder

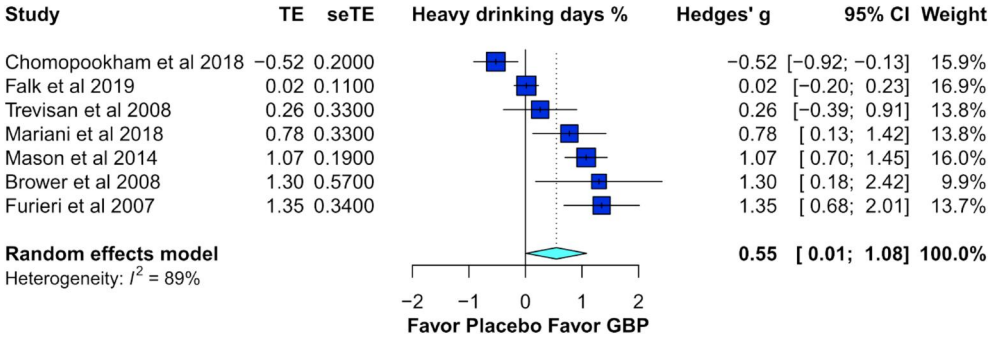

FIGURE 3 Forest plot of meta-analysis on gabapentin (GBP) effect on heavy drinking days

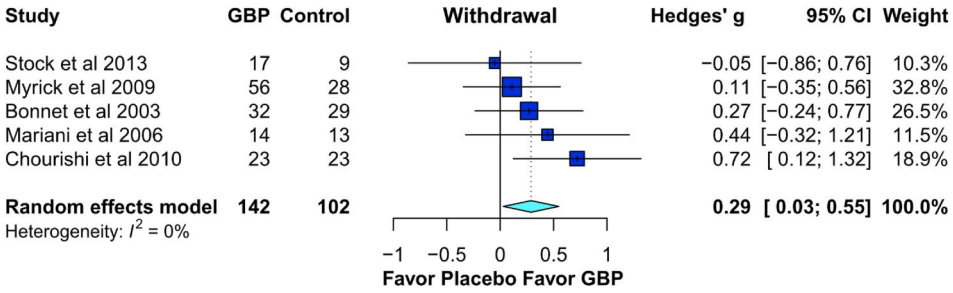

FIGURE 4 Forest plot of meta-analysis on gabapentin (GBP) effect on withdrawal

3.4 | Sensitivity analysis

In the following subgroup analyses, the sensitivity analysis indicated instability, and so these results should be treated with caution: percentage of heavy drink; percentage of abstinence days; and withdrawal symptoms and craving in GBP and PGB group (Table S2).

4 | DISCUSSION

Our analyses produced five major findings. First, GBP did not reveal a beneficial effect on the main outcome of reducing alcohol consumption (indexed as the combination of days of abstinence, amount of alcohol consumed, heavy drinking days, etc.). Separating different indices, only the effect of reducing heavy drinking days of GBP is significantly higher than that of placebo. Second, GBP had a greater beneficial effect on symptoms of alcohol withdrawal than placebo treatments. Third, GBP was not more effective than placebo in reducing craving in AUD patients. Fourth, GBP did not improve depression or sleep disturbance in patients with AUD. Finally, the incidence of adverse reactions was similar in AUD patients receiving GBP and placebo. The latter four results did not change if GBP and PGB data were both included. But instability of the results indicated by sensitivity analyses should be noticed.

Our results indicate that GBP helps to reduce heavy drinking days, which is similar to the finding of Kranzler et al. (2019). Detailed comparison of our findings and previous meta-analyses with overlapping topic was shown in Table S3. However, its effect on elevating abstinence rate or abstinence days is not significantly higher than

which of placebo. It implies that GBP is helpful for decreasing alcohol consumption rather than abstinence. The small number of studies and the heterogeneity of outcome variables may have influenced the results. Most studies examined the effects of monotherapy with GBP, but clinical considerations would suggest that GBP should be used in combination with other medication to treat AUD (Anton et al., 2011; Schacht et al., 2011; Wilming et al., 2018).

We found that gabapentinoids are helpful in the treatment of acute alcohol withdrawal symptoms; it was also similar to the result of S. Ahmed et al. (2019). It was true for the situations "only GBP" and "combining GBP and PGB". Taken together with the above finding of "decreasing heavy drinking days," which pathway should be mainly relieving of withdrawal symptoms. The doses used to manage withdrawal symptoms are 300–1200 mg/day for GBP and 100–450 mg/day for PGB. This effect can be understood in terms of the known central nervous system effects of gabapentinoids: they act on GABA pathways to reduce excitotoxicity (Sills, 2006). Some comparative studies have found that gabapentinoids and lorazepam have similar effects on alcohol withdrawal symptoms (Addolorato & Leggio, 2010; Martinotti et al., 2010; Myrick et al., 2009). Other anticonvulsants have been shown to be effective in managing alcohol withdrawal symptom and preventing seizure and delirium during withdrawal (Hammond, Niciu, Drew, & Arias, 2015). Several studies suggest that combining GBP or PGB may decrease the dose of benzodiazepines required during alcohol withdrawal, although the results are controversial (Morrison, Udeh, & Burak, 2019; Nichols, Robert, Taber, & Cluver, 2019; Vadiei, Smith, Walton, & Kjome, 2019). Gabapentinoids could be used in AUD patients for whom benzodiazepines are unsuitable and should improve withdrawal symptoms within days.

In our analysis, gabapentinoids have no significant effect on craving. This differs to the finding of S. Ahmed et al. (2019). We noticed two different aspects between the previous meta-analysis and ours: (1) We focused on the delta values of pre- and post-treatment craving level and performed an intergroup analysis between individuals with and without gabapentinoids treatment. Two different approaches were used in the previous meta-analysis: single group pre- and post-treatment comparison, and comparison for post-treatment values between ones receiving GBP and not receiving GBP. We fell that our approach should be more straightforward and can prevent the placebo influence. (2) The number of included studies and samples is higher in our analysis; 9 studies for only GBP and 11 for combining GBP and PGB. Larger sample size should have higher meaning for a meta-analysis. Focusing on the pleasure-seeking basis of craving, reward system is involved with its mechanism, and dopamine and opioids are the main neurotransmitters of the reward system (Jung & Namkoong, 2006; Robinson & Berridge, 1993). Drugs that reduce the rewarding effects of alcohol often act on the dopamine or opioid systems (Tek, 2016). GBP and PGB do not have direct effects on the dopamine or opioid systems, so it is not surprising that their blocking effect is limited. However, if we assume that craving is not totally independent of withdrawal, we would expect a drug that improves withdrawal symptoms to produce a modest decrease in craving (de Bruijn, Korzec, Koerselman, & van Den Brink, 2004; Jung & Namkoong, 2006).

Regarding the studies about withdrawal and craving, some used placebo and others used TAU as the controls. For investigating the potential influence of this factor, we performed subgroup analyses for studies with placebo control and TAU control. The results are shown as Figure S12. No any subgroup analyses revealed significant intergroup difference. This may be explained by the reduced sample size under the subgroup analyses. Although in the original analysis, the gabapentinoids effect on withdrawal had a significant intergroup difference, its effect size is not very high. It is more difficult to reach significant level under similar effect size but decreased sample size.

Gabapentinoids do not affect sleep disturbance and symptoms of depression in AUD patients. Outside the addiction field, they have been found to have meaningful effects on pain, negative emotions, and sleep disturbance (Arnold et al., 2018; Biyik et al., 2013; Straube et al., 2008; Tzellos et al., 2010; Wijemanne & Jankovic, 2015). A review noted that gabapentinoids are beneficial for AUD patients with these comorbidities (Mason et al., 2018). Most of the research showing that gabapentinoids can have a beneficial impact on sleep disturbance or emotional disturbance have been carried out in patients with fibromyalgia and restless leg syndrome, which are different to the situation of AUD patients with these symptoms. Our results indicate that gabapentinoids should not be a first-line treatment for emotional disturbance or sleep disturbance in patients with AUD.

Our results revealed that GBP and PGB are well tolerated when all adverse reactions were considered in a whole. Dizziness and somnolence are common adverse reactions to gabapentinoids (Eidy et al., 2017); when these two side effects were separated and estimated with relative risk, individuals receiving gabapentinoids showed higher value than controls (Figure S13). Other side effects (fatigue, nausea/vomiting, and headache) did not reveal significant intergroup difference. The incidences of developing dizziness and somnolence in individuals taking gabapentinoids are both around 10%–20% according to the included studies. In summary, we consider that this result supports that gabapentinoids can be considered for AUD treatment in clinical contexts if dizziness and somnolence are observed carefully. However, in the studies we incorporated, GBP and PGB were usually used in a short duration. The literature suggests that there is potential for misuse or abuse of PGB (Freynhagen et al., 2016; Schwan, Sundstrom, Stjernberg, Hallberg, & Hallberg, 2010), so caution and careful monitoring would be required in long-term use of gabapentinoids.

Several limitations of this analysis should be taken into consideration. First, the number of studies included in our review was small, and the number involving PGB was even smaller. Because there are only two PGB studies, it should be not so meaningful for making a conclusion to PGB. But the analyses regarding PGB all revealed similar results to which with only GBP imply that PGB have comparable effects on AUD with GBP. It supports the future research of PGB on AUD to be rational. Second, the designs and outcomes used in the included studies were somewhat heterogeneous. The results would be different

when adopting distinct indices of alcohol use. Although we tried to manage the issue of heterogeneity with subgroup analyses and meta-regression, some factors cannot be analyzed via these approaches. For example, the prescribing dose of gabapentinoids may affect the results; however, because the dose titration protocol is quite different across studies, the dosing effect is hard to be analyzed with meta-regression or subgroup analyses. As GBP is a short-acting drug with nonlinear pharmacokinetic features, it is difficult to decide an optimal dosing pattern or to estimate the dosing effect on the results. Third, some studies reported several outcome variables or reported outcomes at several time points. In our main analysis, we managed this use through a hierarchical approach. A similar method was adopted in another meta-analysis of AUD medications (Bschor et al., 2018). It remains possible, however, that results vary depending on the outcome variable or time point used. Fourth, most studies of alcohol withdrawal have focused on the acute stage and their findings on the effects of gabapentinoids on alcohol withdrawal cannot be directly extended to protracted withdrawal. The statement that GBP reduces alcohol use behavior via improving protracted withdrawal remains somewhat speculative. To our knowledge, only several studies have investigated the effects of gabapentinoids on protracted withdrawal (Mason et al., 2009; Sanchez-Alavez, Wills, Amodeo, & Ehlers, 2018). Fifth, the results of sensitivity analyses indicate instability in some of our analyses. It implies that our findings should not be viewed conclusively. It maybe a little premature to conduct a meta-analysis on this topic; more studies are needed for overcoming the instability. Finally, the positive findings about heavy drinking days and withdrawal are under nonadjusted alpha values (set as 0.05). If the alpha values are adjusted under the consideration of multiple testing, the statistical significance may diminish. Again, it reminds us that the results about heavy drinking days and withdrawal are not very robust.

In summary, adopting distinct approaches to previous meta-analyses, our results indicate that gabapentinoids may be useful in the treatment of AUD, such as improving withdrawal symptoms and reducing heavy drinking days. But the effect of gabapentinoids on craving was not replicated; besides, their effects on depression and sleep disturbance in AUD patients did not reach statistical significance. But the above findings did not indicate robust conclusions because the numbers of included studies were limited, and instability was revealed in sensitivity analyses. Moreover, only a small number of studies have examined the effects of PGB or looked at the effect of gabapentinoids generally on protracted withdrawal symptoms. Further research in these areas is required.

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CONFLICT OF INTEREST

W.-L. Huang has received presentation honoraria from Pfizer during the past 12 months.

AUTHOR CONTRIBUTIONS

Y.-C. Cheng and W.-L. Huang reviewed the literature and designed the study. Y.-C. Cheng and Y.-C. Huang analyzed and interpreted the data. Y.-C. Cheng and W.-L. Huang drafted the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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