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Gabapentin as an Effective Treatment Option for Alcohol Use Disorder

Monica Hurst
University of North Dakota

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by

Monica Hurst, PA-S, PT, DPT

Bachelor of Science, University of Florida, 2013

Doctor of Physical Therapy, University of Miami, 2017

Contributing Author: Russell Kauffman, MPAS, PA-C

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Abstract

The purpose of this literature review is to determine whether gabapentin is an effective treatment option for alcohol use disorder (AUD). Utilizing data sourced primarily from published clinical trials, gabapentin's effect on heavy drinking, abstinence, withdrawal symptoms and alcohol cravings will be explored. This review will also compare gabapentin's efficacy against currently approved AUD treatment options, along with what dosages are most efficacious while contributing the fewest adverse effects. The data presented in this literature review undeniably demonstrates a positive effect of gabapentin on alcohol use disorder; Specifically, the data shows that gabapentin at multiple dosages helps to decrease heavy drinking days (HDD), total drinking days, and alcohol cravings. Further research should be performed to evaluate whether gabapentin is more efficacious used as a monotherapy vs an additive therapy, what long term effects gabapentin has on AUD, and to define the most effective dosage and treatment duration.

Key words: gabapentin, alcohol use disorder, alcoholism, GABA, gabapentinoids, alcohol withdrawal, benzodiazepines, lorazepam, naltrexone, and acamprosate.

Introduction

Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), Alcohol Use Disorder (AUD) is defined as a problematic problem of alcohol use leading to clinically significant impairment or distress, and the manual lists 11 manifestations of the disorder of which the individual being diagnosed needs to demonstrate two in a 12-month period (5th ed.; DSM–5; American Psychiatric Association, 2013). Diagnostic features include behavioral and physical symptoms, and finding methods of reducing these symptoms has been the goal of targeted research for decades. A review written in 2018 revealed the shocking statistic that 14% of U.S. adults are suffering from AUD, and that 88,000 U.S. deaths are associated with alcohol consumption (Kranzler, 2018). Fifty percent of AUD risk is genetic, with the other half being attributed to environmental factors including childhood abuse of any form, parental psychiatric illness, and household instability.

Three medications have been approved for the treatment of AUD, which include acamprosate, naltrexone and disulfiram, however, less than 9% of patients who would qualify for medication management of AUD received a prescription (Kranzler, 2018). All three of these approved medications carry either strong side effects, have significant interactions if combined with ethanol, or do not reduce the likelihood of binge drinking, therefore studies continue to be performed to determine whether there are more effective medications that can reduce binge drinking, promote abstinence, and decrease intensity of withdrawal symptoms (Kranzler, 2018).

Statement of Question

In patients with alcohol use disorder (AUD), is gabapentin effective in reducing cravings and withdrawal symptoms as a primary treatment option?

Methods

Multiple databases were searched in order to compile this literature review including PubMed, Science Direct, ClinicalKey, and Medline. Common search phrases, key terms and MeSH terms included "gabapentin" "alcohol use disorder" "alcoholism" "GABA" "gabapentinoids" "alcohol withdrawal" "benzodiazepines" "lorazepam" "naltrexone" and "acamprosate". Originally the search was limited to the past three years (2019-2022), however the search was expanded to include an article from 2007 due to its important findings, therefore the search was expanded to include articles from 2007-2022. Exclusion criteria included articles written in a language other than English, articles that had high drop-out rates (>60%), systematic reviews and meta-analyses, and articles that failed to provide statistically significant data. Using these criteria, a total of 6 articles were included in this literature review.

Literature Review

Gabapentin and Measures of Alcohol Use

In 2021, Mariana et al. published a randomized, placebo-controlled trial outlining the effects of high-dose gabapentin on patients suffering from AUD (Mariani et al., 2021). Out of 254 individuals being assessed for eligibility, 40 were enrolled in the study. The most common exclusion criteria included not meeting Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for current alcohol dependence or meeting DSM-IV-TR criteria for an Axis I psychiatric disorder. Sixty-seven and a half percent of the sample was male (27/40), 55% was white (22/40), and 27.5% was Hispanic (11/40). The 40 participants were randomized via a computer-generated process that stratified by gender and severity of alcohol use into either a treatment (n=19) or placebo group (n=21). The placebo group received capsules that appeared identical to the gabapentin capsules, while the treatment group was titrated over a 5-day period up to the target dose (3600mg/day) of gabapentin, which they remained at for 8 weeks, and were then tapered off of the medication over a period of a week. Adherence to the study was assessed by a weekly pill count interview. All study participants also engaged in behavior treatment sessions with a research psychiatrist, with interventions focusing on abstinence and medication compliance. As the gabapentin dose was increased, the behavior treatment sessions were tapered down to a frequency of bi-weekly.

Results of the trial, specific to HDD, demonstrate a significant difference in the proportion of HDD per week between the placebo and treatment groups F (7,215) = 3.33; p = 0.002, suggesting that gabapentin is an effective intervention strategy to reduce HDD at a dose

of 3600mg/day. Interestingly, gabapentin was not shown to demonstrate a decrease in withdrawal symptoms when compared to placebo $F(1,220) = 0.03$; $p= 0.871$, however, there was a significant week-specific difference in withdrawal pattern in both placebo and treatment groups $F(7,220) = 4.48$; $p< 0.001$. This study had several limitations, with the most influential being its small sample size. This subjects the study to skewing of results by outliers. The study also has limited clinical significance, as there was only a 67.5% retention rate at the end of 8 weeks, with few patients achieving abstinence. Additionally, the participants were exposed to gabapentin for a relatively brief period of time, leaving the additional question of what effect a longer exposure, or a larger loading dose followed by a lower dose would have on this population. Finally, no biological markers of medication adherence and alcohol abstinence were utilized, leaving results largely dependent on participant self-reporting. Ultimately, this study identified that gabapentin does have a positive effect on individuals suffering from AUD, and, when dosed appropriately, can limit HDD. This study also demonstrated that high doses (3600mg/day) of gabapentin can be studied safely in this setting (Mariani et al., 2021).

In 2014, Mason et al. published a double-blind, randomized clinical trial studying the dose-dependent effects of gabapentin on multiple outcomes used to assess the efficacy of AUD treatment vs a placebo (Mason et al., 2014). The study was conducted over 12 weeks and included 150 randomized participants, with common inclusion criteria being over 18 years old, meeting the DSM-IV criteria for alcohol dependence, and being abstinent from alcohol for 3 days prior to randomization. Common exclusion criteria included CIWA-Ar score >9, longer than 1 month of abstinence, significant psychiatric disorder or other drug dependency. Participants

were randomized using a computer generated randomization code and placed in either a placebo group, gabapentin 900mg group or gabapentin 1800mg group. The two gabapentin groups were tapered up to their respective doses over 4-6 days, maintained at the active dose for 11 weeks, then titrated down by the end of week 12. All participants attended weekly visits with study physicians which included assessments of alcohol use, craving, mood, sleep and safety, along with counseling aimed at improving motivation, abstinence and medication compliance. Primary outcome measures considered during the study included the rate of complete abstinence, rate of no heavy drinking days (HDD), number of drinks per week, and GGT as a biomarker of drinking reduction. Additional outcome measures included a subjective report of craving, sleep and mood.

The results of the study reveal a strong dose-dependent response of gabapentin increasing rates of complete abstinence ($p = .04$) and decreasing HDD ($p=.02$). The rate of sustained abstinence throughout the 12 week study was 4.1% in the placebo group, 11.1% in the 900mg group and 17% in the 1800mg group. The study outlines that the NNT with 1800mg gabapentin for abstinence is 8 with an OR of 4.8, “indicating a large effect size for abstinence” (Mason), and the NNT for no HDD with 1800mg gabapentin is 5 with an OR of 2.8, “indicating a medium effect size” (Mason). In regards to secondary outcome measures, gabapentin demonstrated significant effects on craving, mood and sleep using the Alcohol Craving Questionnaire, Beck Depression Inventory and Pittsburgh Sleep Quality Index for assessment. There were no serious adverse reactions to gabapentin throughout the study, however there were nine participants that dropped out of the study due to adverse events including headache, fatigue, and euphoria. There were complaints of fatigue, insomnia and headache in both the

placebo and gabapentin groups, without a significant difference between treatment and placebo groups. Following active treatment, there was no evidence of rebound alcohol use when participants were tapered off of the medication. Overall, gabapentin demonstrated a favorable safety profile without serious adverse events and there was no evidence of misuse or abuse of gabapentin during the trial. One of the biggest limitations of this study is that it did have a high dropout rate, with only 85 of the original 150 participants completing the entire 12 weeks; however this 56% completion rate is comparable to other trials on alcohol dependence. Another limitation of this study is that it was conducted at one single institution, which limits its generalizability to the public; all participants in this study were able to remain abstinent from alcohol for 3 days prior to study initiation without requiring detoxification, which brings the question of how those requiring a detox period would respond to gabapentin during their AUD treatment. One aspect of this study that separates it from other studies assessing drug treatment for AUD is that it used an objective biomarker, GGT, to confirm participant self-reported use of alcohol, which strengthens the reliability of the study results. This study provides results that favor the use of gabapentin to successfully and safely treat AUD, with data that clearly demonstrates that gabapentin reduces HDD along with mood, sleep and craving disturbances, and increases abstinence rates (Mason et al., 2014).

Gabapentin and Alcohol Withdrawal

In 2020, Anton et al. published a randomized, double-blind, placebo-controlled trial discussing the efficacy of gabapentin as a single therapy to promote abstinence and reduce alcohol withdrawal symptoms in those diagnosed with alcohol use disorder (Anton et al., 2020). 145 individuals met the DSM V criteria for alcohol use disorder, and of those, 96 met alcohol

withdrawal criteria as well. The participants were between 18-70 years old, had a minimum of 5 drinks/day in the 90 days leading up to the study, and had to be abstinent at least 3 days prior to randomization. Other exclusion criteria included meeting criteria for drug use disorder, using psychoactive drugs, meeting criteria for major depressive disorder, bipolar disorder, psychotic disorder or eating disorder, women being pregnant or breastfeeding, and a CIWA-Ar score of >10 during assessment. The 96 participants were randomized into either a placebo group (n = 50) or a treatment group (n = 46). The treatment group received a ramp up period of 5 days to achieve a daily gabapentin dose of 1200 mg, and the placebo group underwent a similar process with placebo capsules. The treatment dose of gabapentin was continued for 15 weeks. Participants also attended medical management sessions during which they received educational and supportive information, as well as were assessed for adherence and adverse effects. The primary outcome measure of this study was the percentage of participants with no heavy drinking days, and the secondary outcome measure was percentage of participants who remained fully abstinent throughout the study. Participants' adherence to the gabapentin was confirmed using riboflavin detection, and their reported alcohol intake was also confirmed using multiple biomarkers, with the most sensitive being percentage of disialo carbohydrate-deficient transferring (%dCDT).

The study results demonstrated that no heavy drinking days confirmed by %dCDT was significantly lower in the gabapentin group vs placebo group (18.6% difference, p=0.02). The secondary outcome measure of total abstinence was also statistically significant, with a 13.8% difference between the gabapentin and placebo group (p = 0.04). An interesting data comparison that this study also drew was the difference in relapsing to heavy drinking or losing

abstinence between those participants who began the study with an alcohol withdrawal score (AWS) of either greater or less than 8.5. Results demonstrated that those with high alcohol withdrawal scores had less relapse to heavy drinking ($p = 0.02$) and more total abstinence ($p = 0.003$) when treated with gabapentin compared to placebo, while there was no statistically significant difference between gabapentin and placebo groups in the participants with low alcohol withdrawal scores. The only significant side effect of gabapentin during the study was mild to moderate dizziness ($p = 0.02$). These outcomes strongly suggest that gabapentin at a dose of 1200mg/day is efficacious in preventing relapse and in promoting abstinence in individuals who experience intense withdrawal symptoms, and that it can reduce heavy drinking days and total drinking days in this population. One large limitation of this study, as with many of the other studies cited in this paper, is the high drop-out rate. 30% of the gabapentin group and 39% of the placebo group did not complete the trial. One unique factor of this study that increases the validity of the data is that not only were biomarkers used to confirm participant's self-reported number of drinks per week (ie GGT, %dCDT), but biomarkers, specifically riboflavin, were also used to assess adherence to the medication. The gabapentin and placebo capsules were coated in riboflavin, which was measured at each medical visit. This helps to further validate the adherence to the medication regimen throughout the study. In conclusion, this study provides sufficient evidence to suggest that gabapentin can help an individual with alcohol use disorder sustain abstinence, especially an individual with a history of severe alcohol withdrawal symptoms (Anton et al., 2020).

In 2007, Furieri et al published a randomized, double-blind, placebo-controlled trial assessing the efficacy of a 28 day gabapentin treatment program in individuals with alcohol use

disorder (Furieri et al., 2007). The study enrolled 152 participants undergoing alcohol dependence treatment, and 60 of these individuals met inclusion criteria. Inclusion criteria for this study included age between 18 and 65 years old, consuming an average of 35 drinks per week for the past year, being abstinent from alcohol for no longer than 14 days from start of treatment, meeting DSM- IV criteria for alcohol dependence, along with multiple other considerations. Of the 60 participants, 30 were randomly assigned to the placebo group, and 30 to the treatment group. Participants in both groups were instructed to take two tablets orally, for a total of 600mg gabapentin daily, and subjects were evaluated weekly for vital signs, adverse effects, and treatment compliance. This study focused on drinks per day, drinks per drinking day, percentage of heavy drinking days and percentage of days abstinent as primary outcome measures.

Data revealed that the decrease in the number of drinks per day was significantly higher in the gabapentin group when compared to placebo ($p = 0.02$). It was also noted that subjects in the gabapentin group consistently decreased alcohol consumption each week more than those in the placebo group ($p < 0.01$). The percentage of heavy drinking days was also significantly lower in the gabapentin group when compared to placebo ($p= 0.02$), and the percentage of days abstinent was significantly higher in the gabapentin group when compared to placebo ($p = 0.008$). There were no significant side effects with gabapentin reported in the study. One limitation of this study is that it did not assess gabapentin's efficacy at reducing acute withdrawal symptoms, but rather its effect on longer term withdrawal symptoms, otherwise known as protracted withdrawal syndrome. While the data remains relevant and important, it is slightly skewed in that the participants in the study still underwent a 7-day

withdrawal treatment that included use of diazepam; the results of this study should be interpreted with caution as it is possible that the success of gabapentin treatment was largely due to the initial curbing of withdrawal symptoms by the use of benzodiazepines. Despite this challenge, the results of the study still do show an undisputed improvement in abstinence, heavy drinking days and total drinking days in individuals using 600mg of gabapentin for 28 days when compared to placebo (Furieri et al., 2007).

Gabapentin versus Other Medications for AUD

In 2009, Myrick et all conducted a double-blind trial comparing the effects of Gabapentin versus Lorazepam in the treatment of alcohol withdrawal. This study was conducted in an academic medical center in Charleston, South Carolina with participants being recruited through media ads and clinical referrals (Myrick et al., 2009). Inclusion criteria included meeting DSM-IV definition of alcohol dependence and alcohol withdrawal, having a blood-alcohol level of equal to or less than 0.1 g/dL, mini-mental status exam score of greater than or equal to 26, and a CIWA-Ar score of greater than or equal to 10. Exclusion criteria included additional substance use disorders, Axis I psychiatric disorder, use of medication for alcohol withdrawal within the past 30 days, and medical instability. Interestingly, this study did not exclude participants with a history of alcohol withdrawal seizures, which again broadens its applicability to a more generalized population of individuals suffering from alcohol use disorder. The medication administration period in this study only lapsed over a 4 day period, with participants randomly being assigned to either a gabapentin or lorazepam group. The participants were randomized to different dosing regiments of gabapentin (either 300mg t.i.d or 400mg t.i.d), or lorazepam (2mg t.i.d), and were also provided rescue packs of either drug in

the event they needed additional treatment for withdrawal symptoms. Participants were seen every day for the first five days of the trial, then at day 7 and day 12 for compliance assessment as well as to check breath alcohol levels. Multiple other measures were obtained at each visit that assessed withdrawal symptoms, depression, anxiety, and sleep. The primary outcome measures of the study were drinks per day, CIWA-Ar scores and relapse drinks.

Over the span of 12 days, the high dose gabapentin group demonstrated significantly lower CIWA-Ar scores than the lorazepam group (p=0.009), and the high-dose gabapentin group was the only group that showed a continued downward trajectory of CIWA-Ar score after discontinuing medication treatment vs the low-dose gabapentin and lorazepam groups. In comparing day by day drinking habits, participants in the gabapentin group were more likely to drink on the first day of treatment, however then demonstrated a downward trend in drinking days as the study progressed, whereas in the lorazepam group, virtually no participants drank alcohol on the first day of initiating treatment, however demonstrated an upward trend in drinking as the study progressed, particularly when the medication treatment was discontinued. There was a significant difference noted between the gabapentin and lorazepam groups on days 2,3, and 6 (p = 0.027, 0.019 and 0.0009 respectively). When discussing the secondary outcome measures, the study notes that overall, the high-dose gabapentin group demonstrated less self-reported anxiety, craving for alcohol and daytime sedation compared with the lorazepam group, however no statistical values were provided for this comparison. In overall discussion, this study provides reasonable support for the hypothesis that gabapentin is equally effective at treating alcohol use disorder, particularly in the early withdrawal period, as benzodiazepines, specifically lorazepam. An interesting finding of this study is that initially, it

was meant to measure the effects of three different dosages of gabapentin, with the lowest being 200mg t.i.d. however at the start of the study, those in the lowest dose group experienced seizure-like events and therefore this dose was discontinued. While only a small sample, this does provide evidence that the efficacy of gabapentin in treating alcohol use disorder is dose dependent, and a minimum dose must be established in future research for safety reasons. This study also did not contain a placebo group, as it included those with higher CIWA-Ar scores when compared to similar studies, therefore it does not speak to whether gabapentin is more effective than no treatment in alcohol use disorder. Some of the limitations of this study include that it was a small sample size and had a low completion rate (68 moving to completion vs 100 randomized to treatment). This study was also conducted at a single site, therefore limiting the expanse to which the results can be generalized. There was only one dosing schedule of lorazepam vs multi-dosing schedule of gabapentin, therefore possibly skewing the results. Despite these limitations, this study does provide important literature on the use of non-benzodiazepines in the treatment of alcohol use disorder, particularly during the withdrawal period (Myrick et al., 2009).

In 2013, Stock et al. conducted a double-blind study comparing gabapentin with chlordiazepoxide for treatment of alcohol use disorder in an outpatient setting on United States veterans (Stock et al., 2013). The aim of the study was to assess various measures affected by alcohol use and alcohol withdrawal, including the Epworth Daytime Sleepiness Scale (ESS), Penn Alcohol Craving Scale (PACS, and Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) scores, and how they are affected by gabapentin and chlordiazepoxide. The study was conducted over seven days, and all participants were recruited from the George E Wahlen

VA Medical Center's Mental Health Outpatient Detoxification Clinic. Inclusion criteria included meeting the DSM-IV definition of alcohol withdrawal. Exclusion criteria included any acutely unstable medical or psychiatric condition requiring emergency care, seizure disorder, or using other drug therapy likely to affect alcohol withdrawal symptoms. Using these criteria, 26 participants were recruited, with 17 being assigned to the gabapentin group and 9 being assigned to the chlordiazepoxide group. For the gabapentin group, the dosing was as follows: 1200mg for days 1-3, 900mg day 4, 600mg day 5 and 300mg day 6. For the chlordiazepoxide group, the dosing was as follows: 100mg days 103, 75mg day 4, 50mg day 5 and 25mg day 6. The subjects and researchers were blind to the medication and the dose. During the trial, adherence to the medication was measured by pill counts and serum samples at each visit. At each visit, conducted daily throughout the study, assessments included CIWA-Ar score, ESS, PACS, physical exam assessing neurological function, and breath alcohol concentration (BAC). Eleven subjects in the gabapentin group and 6 subjects in the chlordiazepoxide group followed the study through to completion, with dropouts being attributed to worsening withdrawal and failure to return to follow-up appointment after demonstrating initial improvement in withdrawal symptoms.

In discussing results, ESS scores in the gabapentin group were significantly lower than the chlordiazepoxide group ($p = 0.04$) in the later stage of the trial. There was no significant difference between groups on the PACS or CIWA-Ar scores throughout all phases of the trial. There were also no clinically significant differences in neurological symptoms or vital signs when comparing the gabapentin and chlordiazepoxide groups. The results of this student demonstrate that the subjects receiving gabapentin experienced significantly reduced daytime

sleepiness that those receiving chlordiazepoxide. As the study explains, this result is not surprising considering that repeat intake of chlordiazepoxide leads to a buildup of metabolites which causes worsened sleepiness as time progresses, a property that gabapentin does not possess (Stock et al., 2013). Both treatment groups had similar reductions in withdrawal symptoms and vital signs, and the dropout rates and the reasons for dropping out were comparable between the two groups. A major limitation of this study is the small sample size; despite the small size, however, this study did demonstrate a high medication adherence rate of 96%. Considering the difference in the metabolic and pharmacokinetic profiles of gabapentin and chlordiazepoxide, it was difficult for the investigators to establish a dose equivalence between the two medications. This leads to difficulty in establishing whether the differences in daytime sleepiness experienced between the two groups are due to dose discrepancies and the possibility of poorer withdrawal management in the chlordiazepoxide group, or due to gabapentin truly demonstrating superiority in reducing daytime sleepiness. The results of this study are adequate to support further research into this comparison, and the use of gabapentin to manage alcohol withdrawal symptoms in an outpatient setting while reducing the risk of causing daytime sleepiness (Stock et al., 2013)

Gabapentin Dosing and Interaction with Alcohol and Sleep

All of the abovementioned studies focused on the efficacy of immediate-release gabapentin at different dosing schedules in the treatment of alcohol use disorder. A randomized, double-blind placebo-controlled trial from 2019 (Falk et al., 2019) questioned whether extended-release gabapentin would have the same effect on alcohol use disorder. The

benefits of assessing extended-release gabapentin were that this formulation reduced the variability in blood levels and bioavailability between participants, and as it only needs to be taken 2x/day, it has the potential to increase participant compliance with the medication regimen. Inclusion criteria for this study included DSM-V diagnosis of moderate alcohol use disorder, equal to or older than 21 years of age, an average consumption of at least 21 drinks per week for women and 28 for men, and 3 consecutive days of abstinence prior to study initiation. Exclusion criteria included underlying medical conditions for which gabapentin might be contraindicated, the use of psychiatric medications, and a diagnosis of additional substance use disorder (with the exception of nicotine). This study was a larger study comprising 346 participants total, randomized into two groups with 173 participants per group. The participants completed a baseline visit, 11 in-clinic visits, 17 phone visits and a follow-up phone visit 1-2 weeks after the last in-clinic visit. The gabapentin group was supplied the medication during their in-clinic visits, and titrated up to 600mg b.i.d for a total of 1200mg gabapentin daily; the second group was given a placebo. Compliance was assessed by pill counts during the treatment weeks of the trial (weeks 2-25), as well as gabapentin plasma levels checked at weeks 12,20, and 24. Primary outcome measures used were participant self reported drinking, and secondary outcomes measured included alcohol craving, alcohol related consequences, mood, sleep, anxiety and depression scales.

The extended-release gabapentin showed a slightly higher primary outcome level (no heavy drinking days) than the placebo group, however this number was not statistically significant ($p=0.157$). More participants in the extended-release gabapentin group actually discontinued medication than in the placebo group, however this number again proved to be

not statistically significant (p=0.158). During the 4-week maintenance period, the extended-release gabapentin and the placebo groups demonstrated similar outcomes on secondary measures including craving, alcohol-related consequences, cigarette smoking, sleep, and anxiety. This study ultimately demonstrated that extended-release gabapentin at 1200mg daily is not more effective than placebo at decreasing number of drinking days in individuals with alcohol use disorder who are attempting to stop drinking. Strengths of this study included that it was a multi-site study with a large population size, it included a long duration of treatment (6 months), and it had a high treatment retention when compared to other similar studies. Many limitations to this study exist; this study only utilized a single dosing schedule of gabapentin, and while at the time of the study this was a newly released formulation of gabapentin, it may not have been the ideal dose for alcohol use disorder. Another limitation which is a common limitation in most trials assessing alcohol use disorder, this study excluded participants with concurrent psychiatric diagnoses, which limits its generalizability to a small sub-population of individuals. (Falk et al., 2019).

A study conducted in 2006 evaluated how gabapentin interacts with alcohol at different doses, and if it is able to achieve similar subjective performance effects of alcohol, thus decreasing alcohol intake (Bisaga, 2006). Seventeen volunteers were recruited through advertisements; inclusion criteria included drinking between 20 and 60 drinks per week, while exclusion criteria included BMI lower than 19 or higher than 28, prescription medication use, diagnosis of other psychiatric disorder other than alcohol abuse or nicotine dependence, pregnancy, or seeking treatment for alcohol use disorder. Participants were brought to a testing facility for a total of three inpatient experimental phases, separated by a minimum of one week

each to avoid carryover effects. Each participant was provided an oral dose of gabapentin (at 0, 1000, or 2000mg), and 2.5 hours after administration of gabapentin, participants were given four alcoholic beverages, spaced 20 minutes apart. The amount of alcohol was dosed based on estimated total body water, to eliminate variables in alcohol pharmacokinetics between sexes. The timing of the alcohol administration was specific to the half life of gabapentin, with the aim of providing alcohol when gabapentin would be at its peak. There were multiple outcomes measured in this study, the first of which being a subjective effects battery consisting of the alcohol craving scale, the drug effects questionnaire, the clinician-administered dissociative states scale, word recall and recognition tasks and the balance test and the visual analog scale. These were measured at various intervals after consumption of alcohol to determine a variety of subjective effects of the combination of gabapentin and alcohol.

The only subjective or behavioral variable that was significantly affected by gabapentin alone was the ability to balance, particularly at the higher dose ($p < 0.05$), however pre-treatment with gabapentin had little effect on alcohol's effects on the aforementioned measures. The psychomotor effects of gabapentin were measured by a 3-minute digit enter and recall task, a 10-minute divided attention task, a 3-minute digit symbol substitution test and a time estimate task. These were measured at various intervals after the administration of gabapentin before alcohol administration, and then at various intervals after the administration of alcohol. Gabapentin alone had no effect on these tasks. Finally, the physiological measures collected during the study were systolic and diastolic blood pressure and heart rate, along with breath alcohol concentration. The only physiological measure that was affected by gabapentin was heart rate, which showed a significant increase after both gabapentin doses compared to

placebo ($p < 0.01$). All of the outcomes measured in the study were significantly affected by alcohol, as expected, however no notable difference was seen when alcohol was combined with gabapentin, with the exception of the statistically significant findings listed above. The findings of this study demonstrate that gabapentin did not have a significant effect on the behavioral, physiologic, and psychomotor effects of alcohol, and it also did not decrease alcohol craving when used as a pre-treatment. Strengths of this study include using a population of individuals that would benefit from using gabapentin as a pharmacological strategy to reduce alcohol consumption, along with the use of an inpatient setting to ensure consistency with the starting point of blood alcohol levels prior to administration of medication. The study also used doses of gabapentin that have previously been studied in the literature as effective doses to treat alcohol use disorder. Limitations of this study include not including participants who are suffering from alcohol dependence, as they felt it would be unethical to repeatedly expose these individuals to alcohol, which limits the application of the results to a subset of individuals who would likely benefit from pharmacological treatment. This study also did not follow participants for an extended period of time, therefore limiting results to explain short-term effects versus sustained effects of treatment. While the results of this study do not show that gabapentin is an effective pharmacological intervention to decrease alcohol craving or reduce the physiological, psychomotor or behavioral effects of alcohol, it does reveal the important consideration that it is safe to combine alcohol with gabapentin in treatment efforts (Bisaga, 2006).

In 2010, Brower et al. composed a randomized, double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia (Brower et al., 2010). It is

well understood that sleep disturbances are common for months to years during sobriety, with rates ranging from 36-91%, and insomnia is associated with relapse in alcohol-dependent individuals. Gabapentin is often used for its positive effect on sleep habits, however this effect has never been studied in the alcohol dependent population. This study comprised of twenty-one subjects who were recruited from an outpatient alcohol treatment center or from the surrounding community via advertising. Inclusion criteria included meeting the DSM-IV criteria for alcohol dependence, meeting study criteria for insomnia lasting at least 6 months prior to study onset, and desire to abstain from alcohol. Exclusion criteria included pregnancy, medication-induced insomnia, other pharmacologic treatment of alcohol use disorder, other substance use disorder, or other medical illness. The study consisted of a 1-2 week polysomnography screening phase, a 6-week trial of gabapentin versus placebo and a 6-week follow-up visit. Gabapentin was titrated up to the target dose of 1500mg taken prior to bedtime over a 10-day period, and then tapered off over 4 days at the completion of the 6-week trial. Subjects were also receiving six behavioral therapy sessions to enhance compliance with medication schedule. There were multiple subjective and objective measures included in the study to measure sleep quality as well as drinking and other substance use. Subjective frequency and quantity of alcohol consumption was collected with the timeline follow-back interview (TLFB), which was corroborated by breath tests at every study visit as well as blood level of gamma-glutamyl transferase. A urine drug screen was used to assess for other substance use. The severity of cravings was measured with the obsessive compulsive drinking scale (OCDS), and the consequences of drinking were measured with the short index of problems (SIP). The sleep problems questionnaire (SPQ) was used to assess subjective sleep, as

it is able to measure improvements in sleep over 4-6 week intervals and overnight polysomnography was used to obtain objective sleep measurements. These overnight studies were completed on three separate occasions; the first night assessed for any primary sleep disorders such as sleep apnea, while the second night supplied baseline data prior to the start of the study. The final night was completed after three weeks of medication treatment. The polysomnography recording was interpreted by authors who were blinded to all participant data with the exception of age and gender. This study included blood level of gabapentin as a measure of compliance with medication regimen, which was only the second study found throughout this literature review to use such an objective measure of compliance. Drinking outcome was measured by duration of time between study start and relapse into heavy drinking day.

Of the gabapentin group, three of 10 relapsed into heavy drinking during the 6-week trial, versus 9 of 11 in the placebo group. There was a statistically significant favorable difference between the gabapentin and placebo groups in relapse to heavy drinking ($p = 0.03$). At the 6-week follow-up visit, 6 of 10 subjects in the gabapentin group had relapsed to heavy drinking, while 11 of 11 in the placebo group had relapsed by the 6-week follow-up visit. This also revealed a statistically significant difference that favored the gabapentin group ($p=0.003$). While gabapentin did demonstrate superiority in reducing relapse to heavy drinking, it did not demonstrate statistically significant benefit in promoting full abstinence from alcohol during the entire 12-week study. Three participants from the gabapentin group and 1 participant from the placebo group remained abstinent during the 6-week study, and only 1 of 21 total participants remained fully abstinent for the entire 12 weeks. There were no significant differences

between treatment and placebo groups in self-reported sleep performance, and both groups subjectively reported improved sleep during the 6-week study trial. There were also no significant differences in polysomnography between the gabapentin and placebo groups, and neither group demonstrated objective changes in polysomnography that would indicate improved or prolonged refreshing sleep. It is statistically evident that gabapentin does prolong the time to relapse to heavy drinking, however since both treatment and placebo groups reported improved subjective sleep throughout the study, this finding cannot be attributed to gabapentin's effect on sleep. The authors reflect on the correlation between gabapentin and prevented relapse, however the conclusion reflects that the exact mechanism by which gabapentin has this effect was not measured in the study. Study limitations include a very small sample size (n=21), as well as a high drop-out rate (7 of 21 subjects). Considering this small sample size and strict inclusion criteria, the results of this study cannot be generalized to a broad population of individuals suffering from alcohol use disorder. Study strengths include using biochemical measurements to corroborate self-reported drinking as well as medication adherence, and obtaining subjective measure of sleep quality. Follow-up studies are warranted to further explore the relationship between gabapentin, sleep and alcohol use disorder (Brower, 2010).

Discussion

Gabapentin and Heavy Drinking Days

In analyzing pertinent literature, it became evident that gabapentin has an effect on alcohol use disorder. Mariani et al. (2021), Mason et all. (2014), Anton et al. (2020), Furieri et al. (2007), Falk et al. (2019), and Brower et al. (2010), all demonstrated a reduction of heavy drinking days (HDD) with administration of gabapentin throughout their respective trials. Doses as high as 3600mg/day (Mariani ,2021), and as low as 900mg/day (Mason, 2014) and 600 mg/day (Furieri, 2007) were shown to be effective at decreasing HDD, yet there was a dose-dependent response with higher doses demonstrating statistically significant superiority ($p= 0.02$) (2014). Mason's study was conducted over the longest time period of 12 weeks, which strengthens the validity of the results and gabapentin's ability to promote reduced drinking for a sustained period of time, while not leading to adverse side effects (2014).

Gabapentin and Abstinence from Alcohol

Gabapentin also demonstrates favorable effects on promoting full abstinence from alcohol, although the pharmacological properties that allow this response are not fully understood. Brower hypothesized that gabapentin would have a favorable effect on promoting abstinence and prolonging sobriety due to its positive effects on sleep behavior (2010). While his randomized double-blind study did demonstrate that gabapentin significantly reduced relapse into heavy drinking when compared to placebo ($p=0.03$), his hypothesis that this would be due to subjective and objective improvements in sleep were not well supported by his study design. Furieri's study, which was one of the larger studies enrolling 152 participants, demonstrated that gabapentin promoted a significantly higher percentage days abstinent

(p=0.008) at a dose of 600mg/day. While the results of this particular study were strongly favorable toward gabapentin, the study did include a 7-day withdrawal treatment with the use of diazepam, which does skew the generalizability of the results to a population that does not undergo a benzodiazepine-mediated withdrawal period.

In all of the aforementioned studies, the most common shortfalls include small sample size and low retention rates. The low retention rates are consistent with most studies related to addiction medicine, however do compromise the validity of the results. None of these studies look at long-term follow-up, which leaves the question of can gabapentin effectively treat AUD for extended periods of time.

Gabapentin vs Lorazepam in Alcohol Withdrawal

A question that has been posed multiple times is whether alcohol withdrawal can be mediated by substances that pose fewer addiction risks than benzodiazepines, which are most commonly used to manage alcohol withdrawal symptoms. There are few studies that address this question, mainly due to the ethicality of precipitating a dangerous withdrawal amongst study subjects, however one study was included in this literature review that revealed gabapentin may be a favorable substitute to a benzodiazepine to treat alcohol withdrawal (Myrick, 2009). Originally, the study was comparing various dosages of gabapentin to arrive at the smallest dose required to effectively treat withdrawal, however due to seizure like activity experienced in the low-dose gabapentin group, only 900mg/day and 1200mg/day doses were continued in the study. It was found that gabapentin demonstrated superiority in all outcome measures when compared to lorazepam when used at either 900mg/day or 1200mg/day, including CIWA-Ar scores, drinking days, and self-reported anxiety. One of the reasons this

study was included in this literature review is that it starkly contrasts many of the other studies in regard to acceptable CIWA-Ar score (this study is targeting participants with a higher likelihood of strong withdrawal symptoms), and this study also takes into account a mental status exam, which most of the other studies do not. This provides valuable information regarding the effects gabapentin can have on withdrawal symptoms, as well as on mental status. Follow-up studies are absolutely warranted to further explore the ability of gabapentin to mediate withdrawal symptoms and reduce risk of addiction to an additional substance.

Applicability to Clinical Practice

Gabapentin is a safe and effective pharmacologic intervention to treat those suffering from alcohol use disorder in an outpatient setting. Dosages as low as 600mg/day were shown to be effective in reducing heavy drinking days and promoting abstinence, with dosages of up to 3600mg/day showing adequate safety profiles. Dosages of less than 900mg/day should not be considered in those demonstrating high CIWA-Ar scores carrying a risk for seizure activity

Conclusion

An adequate amount of data exists to support the use of gabapentin to treat AUD. Gabapentin positively affects measures of heavy drinking including HDD, PDA, and withdrawal symptoms, it demonstrates a favorable safety profile with low risk of adverse effects, and it can provide successful treatment for AUD at a variety of doses. There remains room for further data compilation to answer more specific questions regarding the most appropriate patient population for treatment with gabapentin, how comorbidities affect the success of treatment, long-term effects and success of treatment with gabapentin and how to best determine dose

needed to treat, however sufficient data exists to support the use of gabapentin in treating outpatient AUD.

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