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The Efficacy of Gabapentin in the Treatment of Alcohol Use Disorder: A Comprehensive Review

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Abstract

Introduction:

Alcohol Use Disorder (AUD) is a significant medical condition characterized by an inability to control alcohol use despite adverse consequences, ranging from occasional excessive drinking to daily dependency. Treatment for AUD involves a combination of pharmacological and behavioral approaches. Common medications include Disulfiram, Naltrexone, and Acamprosate, with newer therapies like gabapentin providing additional options. This review aims to systematically evaluate and synthesize available research concerning the use of gabapentin in the treatment of AUD.

Methods:

This review was created based on 4 articles found in PubMed and Pubmed database based on keywords: "alcohol use disorder", "gabapentine in alcohol use disorder" and "gabapentine".

State of knowledge:

Gabapentin was originally developed for its anticonvulsant properties and tts primary use was to treat epilepsy by reducing the frequency of seizures in patients with refractory epilepsy. Gabapentin's effectiveness in treating Alcohol Use Disorder is founded on its ability to modulate neuronal excitability. Recent RCTs have demonstrated the efficacy of gabapentin in alcohol use disorder, especially for patients with a history of significant alcohol withdrawal symptoms, though the extended-release formulation of gabapentin proved ineffective.

Conculsions:

The overall findings suggest gabapentin holds promise as a treatment for AUD, particularly in individuals with significant withdrawal symptoms, but additional studies are required to fully establish its efficacy and optimal use.

Keywords: alcohol withdrawal syndrome, gabapentin, Alcohol Use Disorder

1. Introduction

Alcohol Use Disorder (AUD) is a medical condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. It encompasses a range of behaviors from occasional excessive drinking to daily alcohol dependency. Previously, AUD has been referred to as alcohol abuse, alcohol dependence, alcohol addiction, and colloquially, alcoholism. The terms “alcohol abuse” and “alcoholism” may increase stigma, whereas using the diagnostic term “alcohol use disorder” with patients may help reduce stigma.

The diagnosis of AUD is a careful process that involves the evaluation of both physical and behavioral criteria. The diagnostic criteria set by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) play a central role in this process. The DSM-5 defines AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 of the following 11 symptoms occurring within a 12-month period [1]. The number of symptoms determines the severity: 2 to 3 symptoms for mild AUD, 4 to 5 for moderate, and 6 or more for severe.

Alcohol Use Disorder is one of the most prevalent mental health disorders globally, with 100·4 million estimated cases in 2016 (age-standardised prevalence 1320·8 cases per 100 000 people, 95% uncertainty interval [95% UI] 1181·2-1468·0) [2]. The prevalence of AUD varies significantly between regions and is influenced by cultural, economic, and legislative factors. For example, European countries generally report higher rates of AUD compared to other regions. Studies such as those conducted within the European Union estimate that the prevalence of AUD can be as high as 3.4% among adults aged 18-64 years [3]. This variation often correlates with local drinking cultures and the availability of alcohol [3]. Although the

prevalence of AUD in men is still five times that in women, globally some signs exist of the gender gap narrowing globally over time [4].

AUD can have profound effects on nearly every organ system in the body, but the most significant impact is on the liver, where alcohol is metabolized. Chronic alcohol use can lead to liver diseases such as fatty liver, hepatitis, and cirrhosis [6]. Furthermore, it increases the risk of heart diseases including hypertension and heart failure [5-6]. Neurological complications can include cognitive decline and brain damage, while psychiatric conditions like depression and anxiety are commonly exacerbated by alcohol use [7]. Additionally, studies show dose-response associations between alcohol consumption and cancers of the oral cavity, pharynx, larynx, esophagus, colon, rectum, liver, and female breast [8]. AUD also leads to substantial economic costs related to healthcare, lost productivity, and alcohol-related crimes [9]. It affects family and social relationships, contributing to domestic violence and child neglect. AUD is also a factor in a significant proportion of traffic fatalities and violent crimes, placing a strain on public safety and healthcare resources [9].

Treatment for AUD requires a combination of pharmacological and behavioral therapies to address its complex spectrum of social, economic, and health outcomes. Approved medications like Disulfiram, Naltrexone, and Acamprosate are commonly used [10]. Disulfiram causes unpleasant reactions when alcohol is consumed by its inhibition of the enzyme aldehyde dehydrogenase, resulting in an increase in the plasma acetaldehyde concentration; Naltrexone reduces the euphoria associated with drinking, and Acamprosate acting by modulating receptors, reduces alcohol craving and unpleasant withdrawal symptoms [11-13]. Newer pharmacotherapies such as topiramate and gabapentin provide additional options for individuals unresponsive to traditional treatments. Gabapentin, originally developed for the treatment of epilepsy, has found a significant role in the management of AUD due to its unique pharmacological properties. It is not a direct GABA agonist; instead, it modulates GABA synthesis and glutamate synthesis through its action on the α2δ subunit of voltage-gated calcium channels in the brain. This modulation helps to restore the balance between excitatory and inhibitory neurotransmission that is often disrupted in AUD [14].

This review aims to systematically evaluate and synthesize available research concerning the use of gabapentin in the treatment of Alcohol Use Disorder (AUD).

2. Materials and method

This literature review is based on articles published in the PubMed database. The search was specifically limited to articles published from 2014 to 2024 to focus on the most current research. Keywords used in the search included "alcohol use disorder,", "gabapentin in alcohol use disorder" and "gabapentin."

Only studies that were clinical trials or randomized controlled trials were included. The studies needed to:

- Be published between 2014 and 2024.
- Specifically evaluate the use of gabapentin in the treatment of AUD.
- Include outcomes related to alcohol disorder, withdrawal symptoms or craving.

Studies were excluded if they:

- Did not focus on gabapentin as a primary intervention for AUD.
- Were published outside of the specified date range.
- Were not conducted in English.

Based on the exclusion criteria stated above from 23 results, 4 articles were included in this literature review.

3. State of knowledge

Gabapentin overview

Gabapentin was originally developed for its anticonvulsant properties and received FDA approval in 1993 for treating epilepsy by reducing the frequency of seizures in patients with refractory epilepsy. Over time, its use expanded to address neuropathic pain in 2004, a common and challenging type of pain resulting from nerve damage or dysfunction. In 2011, an extended-release (ER) prodrug, gabapentin enacarbil, was approved to treat restless legs syndrome.

Pharmacodynamics and pharmacokinetics

Gabapentin’s primary mechanism of action involves the modulation of voltage-gated calcium channels, particularly the alpha-2-delta subunit present in the central nervous system [15]. Gabapentin selectively inhibits Ca2+ influx through these voltage-operated Ca2+ channels, which results in its ability to reduce postsynaptic excitability and decrease the release of excitatory neurotransmitters [16-17]. Unlike traditional GABAergic drugs, Gabapentin does not directly interact with GABA receptors nor does it affect the synthesis or uptake of GABA

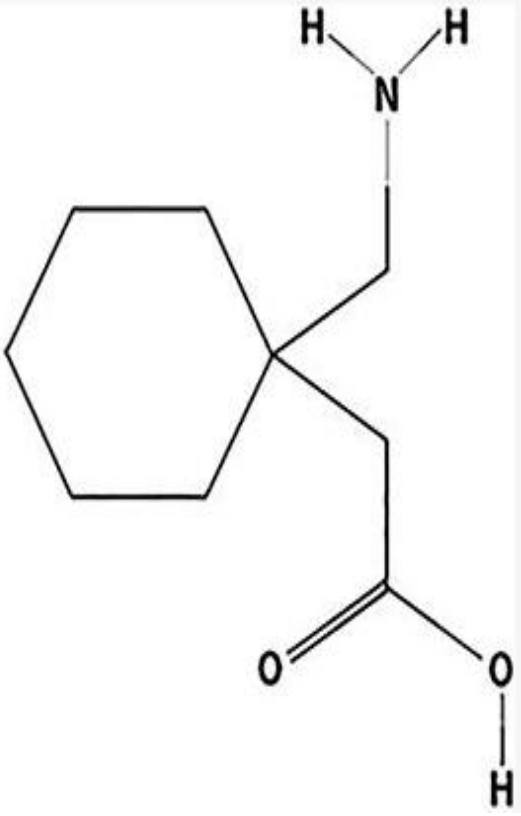
[18]. Instead, its action on calcium channels offers a distinct pathway for modulating neuronal excitability and transmission, contributing to its effectiveness in treating seizures and pain.

Gabapentin is absorbed from the gastrointestinal tract with a bioavailability of about 60% at lower doses, which decreases with higher doses. Maximum plasma concentrations are reached within 3 to 4 hours after oral administration. It is not bound to plasma proteins, allowing more of the drug to be available for action. It has a high volume of distribution, indicating extensive distribution into body tissues. Gabapentin is not metabolized by the liver, nor does it affect the metabolism of other drugs. This lack of hepatic metabolism reduces the risk of drug-drug interactions. It is excreted unchanged primarily through the kidneys, and its clearance is directly proportional to creatinine clearance. Therefore, dose adjustments are necessary in patients with impaired renal function [19]. The elimination half-life of gabapentin is about 5 to 7 hours, which can extend to 7 to 8 hours in patients with renal impairment. Due to its elimination profile, gabapentin is often administered in three divided doses per day to maintain steady plasma levels.

Fig. 1. Gabapentine basic information summary

Drug name: Gabapentine
Route of Administration: Oral
Bioavailability: 30% - 60% (depending on the dose)
Protein binding: Not binding to plasma proteins
Metabolism: Not significantly metabolized
Elimination half-life: 5 – 7 hours
Extraction:

Chemical structure:



Kidneys

Gabapentin and its alcohol-related mechanism of action

The rationale underlying gabapentin as a treatment for AUD is founded on preclinical evidence that gabapentin decreased the amplitudes of GABA receptor mediated inhibitory post synaptic currents (IPSCs) in the central nucleus of the amygdala (CeA), a stress-related brain region activated during early abstinence in alcohol dependence, and reduced alcohol intake in alcohol-dependent rats [20-21]. Additionally, a study from 2009 show that gabapentin antagonizes thrombospondin binding to alpha2delta-1 and powerfully inhibits excitatory synapse formation in vitro and in vivo [22]. Thrombospondin is an astrocyte-secreted protein that promotes central nervous system (CNS) synaptogenesis. These findings identify alpha2delta-1 as a receptor involved in excitatory synapse formation and suggest that gabapentin may function therapeutically by blocking new synapse formation [22]. Previous work from 2006 has shown that alpha-2-delta type 1 subunits are upregulated in reward related regions by all major drugs of abuse including alcohol [23]. Morover recent study from 2021 has shown that gabapentin-treatment promotes early abstinence partly by increasing dACC glutamate levels that are subsequently associated with gabapentin's efficacy in reducing drinking over an extended period in individuals with AUD and a history of AWS [24]. Findings also provide evidence for a biomarker of efficacious treatment (i.e., increased dACC glutamate levels) that may be used to evaluate other glutamatergic and/or GABAergic medications for individuals with AUD, and potentially other conditions marked by dACC glutamate and/or GABA deficiency [24].

Previous clinical trials

Human laboratory studies have provided insightful data on the effectiveness of gabapentin in managing Alcohol Use Disorder (AUD). For instance, one study investigated the safety of administering acute doses of gabapentin (0, 1000, or 2000mg) in combination with alcohol [25]. This study found that the combination did not alter the pharmacokinetics of alcohol, nor did it affect subjective and performance measures, including the intoxicating effects of alcohol or cravings in nondependent drinkers. The study underscored the safety of gabapentin and suggested further investigation into its efficacy in abstinent alcohol-dependent patients. Further information comes from a double-blind study where gabapentin did not impact blood alcohol levels or alcohol self-administration, affirming its safety, but highlighting that while the combination of gabapentin and alcohol is safe, the laboratory model may not effectively induce the neuroadaptations and clinical symptoms of early abstinence, such as craving, which gabapentin aims to treat [26]. Additionally, the efficacy of gabapentin was evaluated in a human laboratory model assessing risk factors for relapse, such as emotional triggers and

exposure to alcohol cues without consumption [27]. In this study, volunteers with AUD who were not seeking treatment were administered gabapentin (1200mg/d) or placebo for a week, with required abstinence from alcohol for three days prior to testing. Gabapentin was found to significantly reduce measures of craving in response to alcohol cues and improve sleep disturbances without increasing daytime drowsiness, compared to placebo.

Recent clinical trials

In the study published *JAMA Internal Medicine* in 2014, Mason et al. conducted a detailed analysis of gabapentin's efficacy in treating alcohol dependence [28]. This 12-week, double-blind, placebo-controlled, randomized dose-ranging trial was carried out at The Scripps Research Institute, a single-site outpatient clinical research facility. The trial included 150 adult participants, all diagnosed with current alcohol dependence according to DSM-IV criteria. Participants were randomized using a computer-generated randomization code and placed in either a placebo group, gabapentin 900mg group or gabapentin 1800mg group

The inclusion criteria for participants required them to be over 18 years old and diagnosed with current alcohol dependence according to DSM-IV criteria, ensuring a minimum of 3 days of abstinence prior to randomization. Potential participants were disqualified for a CIWA-AR score > 9, more than one month of abstinence prior to the study, dependency on substances other than alcohol or nicotine, significant medical or psychiatric conditions, use of medications that could affect study outcomes, and treatment mandated by a legal authority.

Gabapentin or placebo was administered orally in a divided dose regimen. For participants in the gabapentin groups, the dosage was gradually increased over the first few days to minimize side effects and adapt the body to the medication. After reaching the target dose by week 4-6, participants continued at that dose until the end of the 11th week, then titrated down by the end of week 12.

The study showed that gabapentin significantly increased abstinence rates in a dose-dependent manner, with the placebo group achieving a 4.1% abstinence rate, compared to 11.1% in the 900 mg gabapentin group and 17.0% in the 1800 mg group. Furthermore, rates of no heavy drinking were also higher in the gabapentin groups: 22.5% for placebo, 29.6% for the 900 mg group, and 44.7% for the 1800 mg group, evidencing a similar dose-response effect.

Secondary outcomes such as mood, sleep, and craving were also positively affected by gabapentin treatment. Improvements in mood and significant enhancements in sleep quality were observed, especially with the higher 1800 mg dose, as measured by standardized tools like the Pittsburgh Sleep Quality Index. Reductions in alcohol craving were most pronounced in the highest dosage group, reinforcing the dose-dependent efficacy of gabapentin.

Gabapentin exhibited a favorable safety profile throughout the trial. There were no serious drug-related adverse events, however there were nine participants that dropped out of the study due to adverse events including headache, fatigue, and euphoria.

This study had several limitations to consider. The biggest one was 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 [28]. Additionally, the single-site design limits the generalizability of the results to other populations and treatment settings. Furthermore, the study's duration was limited to 12 weeks, which does not provide information on the long-term efficacy and sustainability of gabapentin post-treatment. Lastly, the requirement for participants to have been abstinent for at least three days prior to randomization might have introduced a selection bias, favoring individuals with less severe withdrawal symptoms or higher motivation levels.

The study's findings have shown that gabapentin effectively treated alcohol dependence and relapse-associated symptoms involving craving, mood and sleep but also highlight its favorable safety profile and the clinical relevance of its use in higher doses. However, larger studies in more diverse populations of patients with alcohol dependence are needed to replicate and extend these findings.

In 2019 Falk, Daniel E et al performed a randomized, double-blind, placebo-controlled, multisite clinical trial to assess the efficacy and safety of GE-XR in treating AUD [29]. A total of 346 men and women diagnosed with at least moderate AUD, according to DSM-5 criteria, were recruited across 10 US clinical sites. Eligible individuals were at least 21 years old and reported significant alcohol consumption—women averaged at least 21 standard drinks per week, and men 28, with at least one heavy drinking day per week during the 28 days prior to consent. Additionally, participants were required to have achieved a minimum of three consecutive days of abstinence before randomization. The study excluded individuals with any current substance use disorder other than alcohol or nicotine, those with major psychiatric disorders, as well as those with medical conditions that could interact negatively

with gabapentin. Participants were randomly assigned, in a 1:1 ratio, to receive either GE-XR or matched placebo using a permuted block randomization procedure stratified by clinical site. The trial used a double-blind method to dispense GE-XR in 600 mg tablets, alongside identical matching placebo tablets, ensuring neither the participants nor the research staff knew which treatment was being administered. Participants started with 1 tablet (600 mg or placebo) during the first three days, increased to 2 tablets twice a day (1200 mg total) from days 4 to 7, and continued this target dose through weeks 2 to 25. In the final week (week 26), the dose was tapered back to 1 tablet. The choice of GE-XR over other forms of gabapentin was due to its increased bioavailability and less variability in blood levels, with twice-daily dosing that could potentially enhance treatment adherence—a key consideration in addiction treatments [30]. The specific dose of 600 mg twice a day was selected because it matches the highest approved dose for another FDA-approved indication. Efficacy was measured primarily by the percentage of subjects with no heavy drinking days during the last four weeks of treatment. Secondary measures included the percentage of heavy drinking days, days abstinent, weekly alcohol consumption, and the percentage of abstinent subjects. Additional assessments covered alcohol craving, alcohol-related consequences, sleep quality, mood, and smoking behavior.

The results revealed that GE-XR did not significantly reduce alcohol consumption compared to the placebo. Specifically, the primary efficacy outcome, which was the percentage of subjects with no heavy drinking days, showed no significant difference between the GE-XR and placebo groups (28.3% vs. 21.5%, respectively; p=0.157). In terms of secondary outcomes, the results were similarly inconclusive. There were no significant differences between the GE-XR and placebo groups across various drinking metrics, including the percentage of heavy drinking days, percentage of days abstinent, drinks per week, and drinks per drinking day. The study also evaluated the safety and tolerability of GE-XR, finding that it was generally well-tolerated, despite some participants reporting side effects like fatigue, dizziness, and somnolence more frequently than those receiving placebo.

There are several possible explanations for the lack of efficacy of GE-XR in this trial. Firstly, the dose used in the trial was the highest FDA-approved dose for another indication (postherpetic neuralgia), but it may not have been adequate for AUD. Secondly, alcohol may have reduced the bioavailability of gabapentin. Thirdly, the heterogeneity of the population obscured a potential treatment effect. To sum up, Additional studies may be needed to examine GE-XR at higher dosages, compare side-by-side GE-XR versus G-IR within the same RCT, and evaluate the effect of alcohol on the mechanism of action of the prodrug

formulation as well as identifying subtypes of patients who might be more likely to benefit from this medication.

In a randomized clinical trial examining the efficacy of gabapentin for the treatment of Alcohol Use Disorder (AUD), Anton et al. (2020) assessed its impact particularly on individuals with significant alcohol withdrawal symptoms [31]. The trial, which took place from November 2014 to June 2018, was designed to provide a comprehensive evaluation of gabapentin's potential benefits in a specific subset of the AUD population. The study enrolled 145 participants who met the DSM-5 criteria for AUD. Out of these, 96 participants who also exhibited recent alcohol withdrawal symptoms were selected for randomization.

Participants were community-recruited, treatment-seeking individuals who had not engaged in other AUD interventions and were required to maintain abstinence for at least three days before randomization. This abstinence was confirmed using breath analysis and urinary ethyl glucuronide testing. The study sample had a mean age of 49.6 years and included 69 men (77%) and 85 white individuals (94%).

The participants were randomly assigned to receive either gabapentin, up to a maximum dosage of 1200 mg/day, or a placebo, over a 16-week period. Participants in the gabapentin group received up to 1200 mg/day, following a structured dosing schedule: 300 mg at bedtime on day 1, 300 mg in the morning and at bedtime on day 2, 300 mg in the morning, at noon, and at bedtime on days 3 and 4, and from day 5 through day 112, 300 mg in the morning and at noon, and 600 mg at bedtime. The placebo group received identically encapsulated placebo capsules following the same schedule. Both groups attended nine medical management visits, each lasting 20 minutes, designed to provide educational support, enhance adherence, and monitor adverse effects. These visits were conducted at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16. The primary outcomes were measured by the percentage of participants who reported no heavy drinking days, and the secondary outcome measure was percentage of participants who remained fully abstinent throughout the study. These self-reported outcomes were verified using the percentage of disialo carbohydrate-deficient transferrin (%dCDT) in the blood, a biomarker for heavy drinking [32].

The primary outcomes revealed that 27% of participants in the gabapentin group reported no heavy drinking days, compared to 9% in the placebo group ($p = 0.02$; number needed to treat [NNT] = 5.4). Additionally, 18% of the gabapentin group achieved total abstinence, compared

to 4% in the placebo group (p = 0.04; NNT = 7.2). The efficacy of gabapentin was particularly notable among participants with high alcohol withdrawal symptoms, with 46% reporting no heavy drinking days and 41% achieving total abstinence, compared to 13% and 4% in the placebo group, respectively (p = 0.02 and p = 0.003, NNT = 3.1 and 2.7). Although gabapentin was associated with higher incidences of mild to moderate dizziness (25% vs. 15%; p = 0.02), this side effect did not diminish its overall efficacy.

The study had several limitations. Firstly, the trial had a significant noncompletion rate, with 30% of participants in the gabapentin group and 39% in the placebo group not completing the study. This dropout rate is comparable to other AUD gabapentin trials but still impacts the generalizability of the findings [28,29]. Additionally, the study relied on self-reported alcohol withdrawal symptoms prior to study entry, which may not fully capture the severity of withdrawal. The exclusion criteria were also stringent, ruling out individuals with complex psychiatric and medical conditions, including a history of alcohol withdrawal seizures, which limits the applicability of the results to a broader AUD population. Furthermore, while gabapentin is excreted through the kidneys and generally considered safe for individuals with liver disease, its efficacy and safety in patients with more severe liver conditions were not specifically addressed.

The study concluded that gabapentin is effective in promoting abstinence and reducing heavy drinking days in individuals with AUD, particularly in those with significant alcohol withdrawal symptoms. To further confirm this, future studies should specifically evaluate symptoms related to protracted alcohol withdrawal during gabapentin treatment.

In the most recent study from 2021 Mariani, John J et al. aimed to evaluate the efficacy of high-dose gabapentin (3600 mg/day) in reducing harmful alcohol consumption among actively drinking outpatients diagnosed with Alcohol Use Disorder (AUD) [33]. The trial enrolled 40 participants between August 2010 and December 2012, all of whom met the DSM-IV-TR criteria for current alcohol dependence. Inclusion criteria required participants to be between 18 and 65 years old, able to provide informed consent, and report drinking at least five standard drinks for men or four for women on at least four days per week over the past 28 days. Participants were excluded if they had a current Axis I psychiatric disorder that required intervention, moderate-to-severe alcohol withdrawal symptoms (CIWA-Ar ≥ 13), a history of alcohol withdrawal seizures or delirium, an allergic reaction to gabapentin, were pregnant or lactating, had unstable physical disorders, current dependence on substances other than

nicotine and caffeine, or were legally mandated to participate in an alcohol use disorder treatment program. Comprehensive evaluations, including the Structured Clinical Interview for DSM-IV (SCID), clinical psychiatric assessments, medical histories, physical examinations, and laboratory tests, were conducted to confirm eligibility and ensure participant safety. Participants were randomly assigned to receive either gabapentin or an identical-appearing placebo in a double-blind manner. Randomization was conducted using computer-generated blocks of four, stratified by gender and alcohol use severity, with the NYSPI research pharmacy managing treatment assignments. Gabapentin was administered in 400 mg capsules, titrated over five days to reach a target dose of 3600 mg/day, divided into three doses of 1200 mg each. Placebo capsules were titrated following the same schedule. Weekly supportive behavioral treatment sessions with a research psychiatrist were conducted for all participants, using a manual designed for pharmacotherapy trials in alcohol use disorders. These sessions aimed to promote abstinence, encourage attendance at mutual-support meetings, and ensure compliance with study medication and procedures. The study visits were structured as follows: daily visits for the first four days, then every other day for the rest of the first week, resulting in a total of five visits in the first week. During the second week, participants attended three visits (days 8, 10, and 12). For the remaining six weeks, participants had bi-weekly visits, culminating in a final post-taper visit after the study medication was discontinued. One visit per week included a Medical Management session with the research psychiatrist. Comprehensive evaluations were conducted throughout the study, including vital signs at every visit, alcohol consumption tracking using the Alcohol Timeline Follow-Back (TLFB) method, alcohol withdrawal symptom assessment with the CIWA-Ar scale, and adverse effects monitoring using the Systematic Assessment for Treatment and Emergent Events (SAFTEE). Laboratory tests, including complete blood counts, electrolytes, urinalysis, and liver function tests, were performed at screening. Pregnancy tests were conducted at screening, week 4, and week 8, and urine toxicology screens were collected at screening, week 4, and week 8 to detect any substance use. The primary outcome was the proportion of heavy drinking days (HDD) per week as a measure of alcohol consumption. The secondary outcomes were the percent days abstinent (PDA) and the CIWA-Ar score which is the outcome measure of alcohol withdrawal. Additionally, the SAFTEE was used to measure adverse effects.

The study's results indicated that gabapentin group exhibited a significantly lower proportion of heavy drinking days (HDD) per week compared to the placebo group ($F_{7,215}=3.33$,

p=.002). Additionally, the gabapentin group showed a significantly higher proportion of percent days abstinent (PDA) per week compared to the placebo group ($F_{7,215}=3.11$, p=.004). The overall retention rate for the study was 67.5%, with no significant difference in time-to-dropout between the gabapentin and placebo groups (log-rank p=.420). The mean retention period was 6.5 weeks (SD = 2.4) for the placebo group and 7.1 weeks (SD = 1.7) for the gabapentin group. The median number of weeks retained in the study was 8 weeks for both treatment groups. In terms of withdrawal symptoms, there was no significant difference between the treatment groups over time ($F_{7,213}=1.56$, p=.150). However, withdrawal symptoms varied significantly week by week ($F_{7,220}=4.48$, p<.001). No participants were removed from the trial due to the development of moderate-to-severe alcohol withdrawal (CIWA-Ar score ≥ 13). Adverse effects were similar between the two groups, with no significant differences in the proportion of participants experiencing individual adverse effects or in the number of adverse effects per participant. There were no serious adverse events reported during the trial. One participant in the placebo group discontinued due to a viral hepatitis infection, and one participant in the gabapentin group discontinued due to palpitations.

The study had several limitations that may influence the interpretation of the results. Firstly, the small sample size of 40 participants makes the study vulnerable to skewing by a few individuals, warranting conservative interpretation of the results. Secondly, the brief eight-week duration of gabapentin exposure raises questions about the long-term efficacy and safety of the treatment. It remains unclear whether longer exposure to the 3600 mg/day dose would yield different results or if a gradual dose reduction over time would be beneficial.

Overall, the results indicate that gabapentin at a dose of 3600 mg/day is associated with a reduction in heavy drinking days and an increase in abstinent days among outpatients with AUD. Further research is needed to confirm these findings and explore the long-term effects and optimal dosing of gabapentin for treating AUD.

4. Discussion

Efficacy of Gabapentin

Gabapentin has shown potential in reducing alcohol consumption and promoting abstinence among individuals with AUD. Notably, the study by Mason et al. (2014) demonstrated a dose-dependent increase in abstinence rates, with the highest dose group achieving a significant

reduction in heavy drinking days. Similarly, Anton et al. (2020) reported substantial benefits of gabapentin among participants with severe alcohol withdrawal symptoms, indicating its effectiveness in this subgroup. Mariani et al. (2021) further supported these findings, showing that high-dose gabapentin reduced heavy drinking days and increased abstinent days.

Despite these positive outcomes, the trial by Falk et al. (2019) did not show significant efficacy of gabapentin extended-release (GE-XR) compared to placebo. This discrepancy highlights the potential influence of formulation and dosing on treatment outcomes. The lack of efficacy in this trial could be attributed to the specific characteristics of GE-XR or the dosage used, suggesting that further investigation into the optimal formulation and dose is necessary.

Safety Profile

Gabapentin generally exhibited a favorable safety profile across the studies, with common adverse effects including dizziness, fatigue, and somnolence. These side effects were mostly mild to moderate and did not significantly impact the overall efficacy of the treatment.

Limitations and Future Directions

Several limitations were noted in the reviewed studies, which must be addressed in future research. The high dropout rates and relatively short duration of most trials limit the generalizability and long-term applicability of the findings. Future studies should aim for longer follow-up periods to assess the sustained efficacy and safety of gabapentin in treating AUD.

The heterogeneity of the study populations also poses a challenge. Differences in the severity of AUD, presence of withdrawal symptoms, and comorbid psychiatric conditions can influence treatment outcomes. Identifying specific patient subgroups that are more likely to benefit from gabapentin treatment could enhance its clinical utility.

Conclusion

The evidence reviewed suggests that gabapentin holds promise as a treatment for AUD, particularly in individuals with significant withdrawal symptoms. Future research should focus on optimizing dosing regimens, exploring long-term effects, and identifying patient

subgroups most likely to benefit from gabapentin. Addressing these aspects will be essential in establishing gabapentin as a reliable pharmacotherapy for AUD.

Disclosure

Author's contribution

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Conflict of interest

The authors deny any conflict of interest.

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