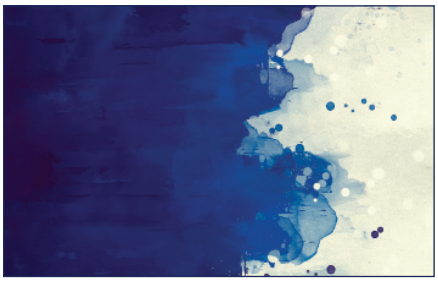

Psychiatric Uses of Gabapentin

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ABSTRACT

Objective: This article reviews evidence-based psychiatric uses of gabapentin, along with associated risks. **Method of Research:** An extensive literature review was conducted, primarily of articles searchable in PubMed, relating to psychiatric uses, safety, and adverse effects of gabapentin. **Results:** Evidence supports gabapentin as a treatment for alcohol withdrawal and alcohol use disorder. There is sufficient evidence to consider gabapentin as a third-line treatment for social anxiety disorder and severe panic disorder. Evidence does not support the use of gabapentin for bipolar disorder, major depressive disorder (MDD), posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), stimulant use disorder, or opioid withdrawal. Risks of gabapentin use are highest among those with a history of a substance use disorder and those concurrently taking opioids. **Conclusion:** While gabapentin has a place in psychiatry for a select few indications, the literature does not support its use for many studied diagnoses.

KEYWORDS: Gabapentin, neurontin, alcohol use disorder, alcohol withdrawal, opioids

Gabapentin has been approved by the United States (US) Food and Drug Administration (FDA) for postherpetic neuralgia and as adjunctive therapy for focal seizures.[1] However, a recent analysis of US physician office-based prescription practices between 2011 and 2016 found that less than one percent of gabapentin prescriptions are for such indications.[2] In 2020, gabapentin was reported to be the sixth most prescribed medication in the US.[3] Gabapentin is often used off-label for psychiatric indications, with varying levels of evidence-based support. Off-label prescribing does not necessarily signify that the medication is being used improperly, and in some cases, reliable research might validate its use. Nonetheless, prescribing gabapentin for off-label use might also result in negative consequences, including adverse drug effects, liability concerns, and a lack of reimbursement due to the paucity of evidence.[4] This article seeks to review the evidence supporting gabapentin for various mental health indications, as well as the risks of prescribing this medication.

METHODS

The authors conducted electronic searches, primarily using PubMed. Search parameters included all English-language articles published up to April 2021. Search terms included "gabapentin" or "Neurontin" in conjunction with terms such as "psychiatric," "psychiatry," "mental health," "substance abuse," "major depressive disorder," "depression," "bipolar," "anxiety," "generalized anxiety disorder," "social anxiety disorder," "social phobia," "panic disorder," "panic," "PTSD," "posttraumatic stress disorder," "OCD," "obsessive compulsive disorder," "alcohol," "alcohol use disorder," "alcohol dependence," "alcohol withdrawal," "stimulant use disorder," "stimulant," "cocaine," "methamphetamine," "opioid," "opioid use disorder," "opioid withdrawal," "cannabis," "cannabis use disorder," "cannabis withdrawal," "risks," "adverse effects," "side effects," "abuse," "misuse," and "withdrawal."

Among search results with relevant titles, abstracts were reviewed. Full-text articles were retrieved for further investigation as needed. All relevant randomized, controlled trials (RCTs) identified were included in this review. For areas in which no RCTs were identified, less robust studies, such as non-RCTs or retrospective cohort studies, were included. Individual case reports were excluded. References in retrieved articles were reviewed for additional relevant articles. References to clinical textbooks and other online databases were also utilized for supplemental information as appropriate. Articles that were not subject to peer-review and articles published in languages other than English were excluded.

RESULTS

Mood disorders. Mood disorders are complex conditions that in some individuals can be refractory to FDA-approved pharmacotherapies. While some case series and open-label studies have provided evidence of efficacy of gabapentin for bipolar disorder, four RCTs assessing treatment efficacy for nonspecific overall symptom severity, as well as more specific symptoms of mania, hypomania, and mixed state, have failed to support the use of gabapentin for bipolar disorder.[5] For major depressive disorder (MDD), there are no RCTs assessing the efficacy of gabapentin.[5,6] One retrospective chart review conducted by Yasmin et al[7] in 2001 examined 27 patients with depressive disorders refractory to standard

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antidepressant therapy. These patients were started on adjunctive gabapentin with a mean gabapentin trial duration of 15±7.8 weeks, with a mean final dose of 904±445mg/day (range: 300–1,800mg/day). Clinician-rated measures (Clinical Global Impressions [CGI], Global Assessment of Symptoms, and Social and Occupational Functioning Assessment) improved significantly in 10 patients from baseline to endpoint. One unblinded, non-RCT with 40 adult patients diagnosed with epilepsy (not MDD) found that those with gabapentin add-on therapy (doses ranging from 100–3,600mg/day) had a reduction in Cornell Dysthymia Rating Scale scores after three months (p=0.04), but not the Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory scores.[7]

Anxiety disorders. Previously presumed to have a low abuse and misuse potential, gabapentin has been commonly prescribed for the treatment of anxiety disorders.[10,11] While pregabalin has shown efficacy for generalized anxiety disorder (GAD) in two RCTs,[12,13] the authors could find no such RCTs done for gabapentin.[9] One randomized, double-blind, placebo-controlled, 14-week trial of 69 patients with social phobia (the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* [DSM-IV] equivalent of social anxiety disorder) showed that those randomized to gabapentin, compared to those randomized to placebo, showed a significant decrease in social phobia symptoms (p<0.05) in both clinician- and patient-rated scales, including the Liebowitz Social Anxiety Scale (LSAS) and the CGI Scale of Change.[14] For the treatment of panic disorder, one RCT of 103 patients lasting eight weeks failed to demonstrate a significant difference between gabapentin and placebo in Panic and Agoraphobia Scale (PAS) scores (p=0.606). However, a *post-hoc* analysis found that patients with severe panic disorder who received gabapentin treatment showed a significant improvement in PAS scores (p=0.04), compared to the placebo group.[15] The authors could not find any RCTs assessing the efficacy of gabapentin in the treatment of posttraumatic stress disorder (PTSD).[5,6,16] In one retrospective study of 30 patients who had been diagnosed with PTSD and had been prescribed gabapentin as an adjunctive medication, 77 percent showed improvement in sleep duration and more than half showed an improvement in nightmares, as measured by a CGI scale.[17] One RCT with 40 outpatients diagnosed with obsessive compulsive disorder (OCD) found short-term improvement in OCD symptoms in a group taking fluoxetine with adjunct gabapentin, compared to a group taking fluoxetine alone, as measured by Yale–Brown Obsessive Compulsive Scale (Y-BCOS) (p=0.002) and CGI (p=0.024) scores, but this effect was not sustained past four weeks.[18]

Substance use disorders. *Alcohol use disorder.* Multiple RCTs have demonstrated the efficacy of gabapentin for alcohol dependence, both as monotherapy and adjunctive therapy. One RCT with 150 participants demonstrated that, over the course of 12 weeks, gabapentin 1,800mg daily resulted in a 17-percent abstinence rate, compared to a 4.1-percent abstinence rate with placebo, and a 44.7-percent rate of no heavy drinking, compared to a 22.5-percent rate of no heavy drinking with placebo.[19] Of significance, a daily dose of gabapentin 900mg also demonstrated efficacy in increasing abstinence and decreasing heavy drinking, but less so than the 1,800mg daily dose. In another 28-day RCT with 60 participants with alcohol dependence, those receiving gabapentin 300mg twice daily demonstrated a significant reduction in number of drinks per day (averaging <1 drink per day vs. ~3 drinks per day, with t=2.31 and p=0.02) and number of heavy drinking days (averaging ~6% of days vs. ~22% of days, with t=2.352 and p=0.02), with a significant increase in the percentage of days abstinent (averaging ~93% of days vs. ~72% of days, with t=2.750 and p=0.008), compared to placebo.[20] In an RCT of 90 participants with alcohol use disorder and previous alcohol withdrawal, those treated with gabapentin up to 1,200mg daily were significantly more likely than those treated with placebo to have no heavy drinking days (27% of participants on gabapentin vs. 9% on placebo) and were significantly more likely to have total abstinence through the 16-week study (18% of participants on gabapentin vs. 4% on placebo).[21] These differences were most pronounced in patients who reported more severe alcohol withdrawal symptoms when discontinuing alcohol leading up to the study (defined as >8.5 on the Alcohol Withdrawal Symptom Checklist). There were no significant differences in outcomes of gabapentin versus placebo in patients with mild alcohol withdrawal symptoms upon discontinuation of alcohol.

A relationship between the severity of alcohol withdrawal symptoms and response to gabapentin for alcohol dependence was further revealed in an RCT in which 60 patients with alcohol dependence received either intravenous (IV) flumazenil 2mg for two days, followed by gabapentin up to 1,200mg daily for 39 days, or placebo.[22] Patients with more severe alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment Alcohol Scale Revised [CIWA-Ar] score of ≥7) at the start of the study had more days abstinent and longer duration of time until their first heavy drinking day after initiating treatment when taking gabapentin compared to placebo (medication group averaging ~95% days abstinent vs. ~63% for placebo group, and ~73% of medication group with no heavy drinking days by end of study vs. ~42% of placebo group). Those with less alcohol withdrawal symptoms (CIWA-Ar score of <7) had better outcomes on the aforementioned measures when taking placebo. Assessing gabapentin as an adjunctive treatment, one RCT with 150 participants with alcohol dependence found that, compared to naltrexone alone, naltrexone plus gabapentin up to 1,200mg/day for the first six weeks of the 16-week study resulted in fewer heavy drinking days (averaging ~4% vs. ~8% for the first 6 weeks, and ~6% vs. 12% for the remainder of the 16 weeks) and fewer drinks per drinking day (averaging ~3.8 vs. ~5.7 drinks per day for the first 6 weeks, with no significant difference after gabapentin discontinuation).[23] Despite these studies supporting the use of gabapentin for alcohol dependence, it should be noted that one RCT with 346 participants showed contrary results.[24] In this study, gabapentin encarbil extended-release, dosed at 600mg twice daily, failed to differ significantly from placebo on multiple measures, including percent of subjects abstinent throughout duration of study, percent of subjects with no heavy drinking days throughout duration of study, percent of days abstinent, percent of heavy drinking days, drinks per week, and drinks per drinking day.

Alcohol withdrawal. Multiple studies have shown gabapentin to be effective in the treatment of alcohol withdrawal. In one double-blind, dose-response RCT, 100

participants with CIWA-Ar scores of 10 or greater were randomized to receive either gabapentin 900mg/day for three days, followed by gabapentin 600mg/day on the fourth day; gabapentin 1,200mg/day for three days, followed by gabapentin 800mg/day on the fourth day; or lorazepam 6mg/day for three days, followed by lorazepam 4mg/day on the fourth day.[25] CIWA-Ar scores decreased over time in all groups, with the high-dose gabapentin group showing a statistically superior (p=0.009), though clinically similar, response, compared to the lorazepam group. Furthermore, those treated with gabapentin had less craving (as measured by Visual Analogue Scales [VASs]), anxiety (measured by the Zung Anxiety Scale), and sedation (measured by the Epworth Sleepiness Scale) compared to lorazepam, and had less probability of drinking (measured by the Timeline Followback) during post-treatment follow-up. Another RCT of 26 patients with alcohol withdrawal compared treatment with gabapentin 1,200mg/day tapered down to 300mg/day over six days to chlordiazepoxide 100mg/day tapered down to 25mg/day over six days. CIWA-Ar scores averaged 7.7 (gabapentin) and 8.8 (chlordiazepoxide) at baseline and declined gradually and similarly in both groups, with the gabapentin group experiencing less sedation toward the end of the seven-day trial, as measured by the Epworth Daytime Sleepiness Scale.[26] This study was limited by its small sample size. A retrospective cohort study examined 50 patients who received high-dose gabapentin (≥1,800 mg/day) in the first 48 hours of hospital admission and compared them to 50 propensity-score matched patients who did not receive gabapentin. This study found that patients who received high-dose gabapentin for severe alcohol withdrawal required significantly less total amount of benzodiazepines (mean±standard deviation [SD]: 109.5±53.4mg vs. 88.5±35.6mg [lorazepam equivalents], p=0.023) and had a significantly lower mean CIWA-Ar score (10.1±4.7 vs. 7.7±3.9, p=0.010) compared to those who did not receive gabapentin.[27] These findings are challenged by a RCT in which 61 patients, who all received a symptom-triggered regimen of clomethiazole, were randomized to receive either gabapentin 1,600mg/day or placebo in a seven-day trial.[28] There was no significant difference in the amount of clomethiazole required in the first 24 hours between groups, nor was there a significant difference in level of alcohol withdrawal symptoms in the first 48 hours. It should be noted that there is an absence of evidence showing gabapentin being effective for delirium tremens or withdrawal seizures in alcohol withdrawal,[29] except for one retrospective cohort study of adults admitted to the hospital for alcohol withdrawal syndrome.[30] This study categorized patients into a gabapentin group, a benzodiazepine group, and a combination group and found no statistical differences among incidence of seizure, intensive care unit (ICU) transfer, or delirium tremens.

Stimulant use disorder. Gabapentin has consistently been shown to be ineffective for stimulant use disorder. Multiple RCTs have shown gabapentin to be ineffective at reducing cocaine use in cocaine use disorder.[31–34] One RCT with 99 participants with cocaine use disorder compared gabapentin 3,200mg/day to placebo over 12 weeks and found no significant difference in number of days of cocaine use, cravings, or retention in treatment.[35] Another RCT with 88 participants also showed gabapentin to be ineffective for methamphetamine dependence.[36] In this study, those receiving gabapentin 2,400mg/day over 16 weeks showed no significant decrease in methamphetamine use, as measured by urine samples, compared to those receiving placebo. However, one 30-day RCT found that flumazenil plus gabapentin significantly reduced cravings (measured by a combination of 6 VASs on Days 6, 13, 20 and 30, p=0.02) and frequency of use of methamphetamine (averaging use 29–42% of days vs. 35–47% of days, p=0.02), compared to placebo.[37] A later 108-day RCT comparing flumazenil plus gabapentin to placebo for methamphetamine use disorder showed no significant difference in methamphetamine use between the two groups, based on urine samples.[38]

Opioid withdrawal. Gabapentin has been studied as an add-on treatment for alleviating symptoms of acute opioid withdrawal in multiple RCTs, with mixed results. One three-week RCT studied patients going through methadone-assisted detoxification and showed no significant difference in withdrawal symptoms, as measured using the Subjective Opiate Withdrawal Scale (SOWS), between add-on gabapentin 900mg/day and add-on placebo.[39] However, a follow-up, three-week, open-label study imitated this design with gabapentin 1,600mg/day and showed a significant decrease in withdrawal measures among those taking gabapentin (average SOWS scores: 7.5–9.2 after treatment for those receiving gabapentin vs. 11.4–13.4 for those receiving placebo).[40] Another four-week, double-blinded RCT compared gabapentin 1,600mg/day to placebo for add-on treatment in buprenorphine-assisted detoxification, and though there was some decrease in withdrawal symptoms in the gabapentin group, it was not statistically significant.[41] A five-week RCT compared add-on gabapentin 1,600 mg/day to placebo in buprenorphine-assisted detoxification, and again showed no significant difference in withdrawal symptoms between the two groups (though withdrawal ratings in both groups were low overall).[42] In one RCT comparing add-on gabapentin 900mg/day to add-on placebo in methadone-assisted detoxification, those on gabapentin showed significantly decreased withdrawal symptoms (0% vs. 38.5% of participants experiencing withdrawal syndrome), as well as less total methadone consumption (averaging 58.9±11mg vs. 73.8±19.5mg, p=0.001).[43]

Cannabis use disorder. One RCT studied 50 adults with cannabis dependence who were randomized to gabapentin 1,200mg/day or placebo, in addition to individual counseling.[44] Over the course of the 12-week study, those receiving gabapentin demonstrated significantly less cannabis use, based on self-report and confirmed by urine toxicology, and significantly less withdrawal symptoms, as measured by the Marijuana Withdrawal Checklist.

RISKS ASSOCIATED WITH GABAPENTIN

Gabapentin and alcohol. While safety is of concern when multiple central nervous system (CNS) depressants are used concurrently, studies have shown that gabapentin and alcohol do not potentiate the harmful effects of each other. One RCT with 17 participants who drank heavily demonstrated that gabapentin dosed up to 2,000mg did not acutely alter the pharmacokinetics, subjective effects, performance effects, intoxicating

effects, or physiological effects of alcohol (other than enhancing alcohol-induced tachycardia).[45] An eight-day RCT found that patients on gabapentin 1,200mg/day did not experience differences in subjective high or intoxication compared to patients on placebo, nor did gabapentin have a significant effect on blood alcohol levels, stimulation, or sedation.[46] Additionally, gabapentin has typically been found to be safe and well-tolerated throughout 11 studies, lasting up to 12 weeks in duration, involving a total of 655 participants with alcohol use disorder, with no deaths or serious adverse events reported.[47]

Gabapentin and opioids. There are significant causes for concern in regard to the safety of concurrent use of gabapentin and opioids. The FDA issued a warning that "serious breathing difficulties may occur in patients using gabapentin . . . and opioid pain medications."[48] One population-based study, with case-control, found that among patients receiving prescription opioids, gabapentin use of 900mg/day or greater was associated with a 60-percent increased risk of opioid-related death, compared to no concurrent gabapentin use.[49] Another retrospective cohort analysis found that sustained overuse of gabapentin, defined as greater than 3,600mg/day, plus opioids resulted in quadrupled odds of all-cause inpatient hospitalization, drug-related inpatient hospitalization, and hospital visits for altered mental status.[50]

The FDA has clarified that "buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks."[51]

Gabapentin abuse. Gabapentin has the potential for abuse, especially in those with a history of other substance use disorders, including alcohol, opioid, and cocaine use disorders.[52] One systematic review of 106 studies concluded that while there is not "convincing evidence of a vigorous addictive power of gabapentinoids . . . in patients without a prior abuse history . . . the principal population at risk for addiction of gabapentinoids consists of patients with other current or past substance use disorders."[53] Another systematic review found that those who misused gabapentin were most often individuals with a history of disordered substance use.[11] This was confirmed by a third systematic review, which found a 1.6-percent prevalence of gabapentionoid abuse among the general public, compared to a 3- to 68-percent prevalence of gabapentinoid abuse among patients who abused opioids.[54] One survey of 162 patients with opioid dependence admitted to a detoxification program found that 13 percent had used gabapentin without a prescription, and, of those prescribed gabapentin, 40 percent used more than the amount prescribed.[55] In one survey of 503 adults using nonprescribed opioids, 15 percent reported using gabapentin specifically "to get high" in the past six months.[56]

Gabapentin withdrawal. While there have been multiple case reports of gabapentin withdrawal,[57] it is uncommon.[58] When it does occur, onset is usually between 24 and 48 hours of discontinuation, and symptoms include agitation, confusion/disorientation, diaphoresis, gastrointestinal upset, tremor, tachycardia, hypertension, and insomnia.[57] Reinitiation of gabapentin is the most effective treatment for this. When discontinuing gabapentin, it is typically recommended to taper over a minimum of one week to avoid withdrawal symptoms.[57]

CONCLUSION

While gabapentin is frequently used in practice for a wide array of psychiatric diagnoses, its use is evidence-based for only a few indications. Multiple RCTs have shown gabapentin to be ineffective for bipolar disorder. There is insufficient evidence to recommend the use of gabapentin for MDD, GAD, PTSD, or OCD. There is sufficient evidence to consider the use of gabapentin for social anxiety disorder and, potentially, severe panic disorder after other treatment options have failed.

Multiple 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. Thus, gabapentin may be considered in patients with contraindications to first-line treatments for alcohol use disorder. However, this should be weighed against the risk of gabapentin abuse. Overall, the literature shows gabapentin to be effective for alcohol withdrawal, and as such, it is a reasonable treatment option for patients with contraindications to benzodiazepines, which have a more robust evidence base, and who are not at high risk for withdrawal seizures or delirium tremens, as there is a lack of evidence showing gabapentin to be effective for treating or preventing these complications.

There are mixed results in RCTs evaluating the efficacy of gabapentin for opioid withdrawal, with many of these studies yielding negative results. Regardless of its level of efficacy, safety risks with concurrent use of gabapentin and opioids outweigh potential benefits, and as such, gabapentin is not recommended for opioid withdrawal. The combination of gabapentin and opioids has been associated with increased rates of hospitalization and even death. Finally, while the rate of gabapentin abuse in the general population appears to be low, there is a much higher risk for abuse of gabapentin in patients with a history of a substance use disorder, especially opioid use disorder. The risk of the addictive use of gabapentin is sufficient cause for pause when considering prescribing gabapentin to patients with a history of a substance use disorder, regardless of the indication.

DISCLAIMER

This article does not necessarily represent the views of the US Air Force.

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