Gabapentin: an old anticonvulsivant with new potential, may reduce withdrawal symptoms and contribute to alcohol abstinence

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ABSTRACT

Alcohol abuse is one of the most common causes of substance dependence, representing an area of interest in continuous development. In terms of treatment, Gabapentin (GBP) has shown in published studies that it is an important therapeutic agent, especially in the case of alcohol withdrawal syndrome. The main objective of this article is to carry out a detailed evaluation of studies on the effectiveness of Gabapentin in the treatment of numerous mental disorders and also substance use disorders. Although it belongs to the category of anticonvulsants, it has been shown that Gabapentin has many therapeutic properties due to its mechanism of action involving the GABAergic system. Thus, a new therapeutic vision in the treatment of abstinence and withdrawal syndrome is outlined.

KEYWORDS:

Gabapentin, alcohol use disorder, withdrawal symptoms, alcohol dependence, GABAergic system, abstinence.

INTRODUCTION

Alcohol use disorder (AUD) is a complex syndrome with multiple consequences in terms of socio-familial environment and health status. The World Health Organization estimates alcohol consumption is responsible for 5.1% of disease burden and for 5.9% of

deaths, especially through liver cirrhosis, cancers and organ injuries (1).

ICD-10 (2) and DSM-IV (3) define alcohol related disorders by a cluster of psychological, somatic and behavioral symptoms. DSM-5 (4) has introduced 11 criteria for substance use disorders: (1) large

amounts consumed; (2) desire or inability to reduce use; (3) significant time spent obtaining, using, or recovering from use; failing to meet role obligations; (4) continued use despite problems; (5) reduced/ceased societal activities as a result of use; (6) results in physically dangerous situations; (7) cravings; (8) continued use despite insight to dangers; (9) tolerance develops; (10) withdrawal. Therefore 2 or 3 positive symptoms define a mild substance use disorder, 4 or 5 a moderate, and 6 or more a severe one.

This psychiatric problem with different degrees of severity is typically a chronic disorder characterized by compulsive heavy alcohol drinking (4). The occurrence of an acute withdrawal syndrome due to marked reduction in drinking is typically followed by a prolonged withdrawal phase with a high risk of relapse. Preventing relapsing after an acute withdrawal is a leading concern of alcoholism research (5). Gabapentin is an oral anticonvulsant with anxiolytic properties shown to have beneficial effects in a multitude of areas pertaining to optimal treatment of alcohol withdrawal, as well as alcohol dependence (6). A Cochrane review (2014) found evidence supporting the use of gabapentin for multiple health conditions (8) and pointed out that gabapentin has statistically positive effects in reducing alcohol consumption, but not in maintaining abstinence or reducing cravings (8). Gabapentin is a calcium channel GABAergic modulator that is widely recommended for neuropathic pain. Numerous medical studies have shown that gabapentin promotes a reduction of alcohol consumption in patients with depression or sleep disorders (7).

PHARMACOKINETIC PROPERTIES

A couple of FDA-approved anticonvulsants, including Gabapentin, that exert action on

GABA synthesis in the brain, have been studied for their ability in treating AUD and alcohol withdrawal syndrome (9). In individuals with alcohol related disorders, gabapentin significantly reduced alcohol consumption and cravings by improving the symptoms associated with the abstinence syndrome. The results highlight some findings that indicate that gabapentin is more effective in people with a history of alcohol withdrawal (9). Gabapentin is an amino acid designed as a structural analogue of GABA (10) interacting with type 1 alpha-2-delta subunit of closed voltage calcium channels (11, 12) and selectively inhibits the influx of calcium (13) which results in decreased ability to reduce postsynaptic excitability (14). By blocking excitatory neurotransmission, gabapentin increases the concentration of GABA in the brain (15, 16). The mechanism involved in the psychoactive effects of GBP is not fully understood (17).

At concentrations up to 100 μ M, gabapentin has no affinity for a number of receptor sites, including benzodiazepine, NMDA, alpha 1, alpha 2 or beta-adrenergic, glutamate, adenosine A1 or A2, cholinergic, dopamine D1 or D2, muscarinic or nicotinic, histamine H1, opiates μ , serotonin S1 or S2, cannabinoid 1, delta or kappa. Gabapentin has not been shown to significantly influence the cellular action of dopamine, norepinephrine or serotonin. The half-life of gabapentin is 5-7 hours and no dose adjustment is required. Regarding the renal elimination, the clearance is directly proportional to the creatinine clearance, so that in patients with renal injury, the clearance of gabapentin is low, and dose adjustment is required.

The bioavailability of gabapentin is not directly related to the dose taken, and serum levels do not directly correlate with ingested doses (18). Gabapentin has minimal drug-

drug interactions compared with previously studied anticonvulsants (carbamazepine, oxcarbamazepine, valproate, phenytoin, phenobarbital, topiramate) and a favourable safety profile (19).

THERAPEUTIC EFFECTS OF GABAPENTIN

Gabapentin has been indicated to treat many psychiatric and medical conditions, such as migraines, fibromyalgia and chronic pain syndromes. It is also widely prescribed for off-label psychiatric disorders (19,20) originally developed to treat epileptic seizures, it is also recommended now to relieve neuropathic pain and restless legs syndrome. It is especially used as a first-line therapy for neuropathic pain as encountered in post-herpetic neuralgia, central neuropathic pain and diabetic neuropathy. Studies in rats and human subjects have shown an increase in GABA biosynthesis and in vitro neurotransmission, and the conclusion suggests that its modulation has the effect of sedating or calming the nervous system. Another mentioned mechanism involves the binding to the $\alpha 2\delta$ -1 subunit of calcium ion channels with voltage, which supports its analgesic effects.

Preclinical studies report the benefits of gabapentin related to seizures and anxiety. Moreover, gabapentin has been shown to be effective in reducing the excitability of the hippocampus, and in long-term administration has proven to have benefits in reducing recurrence and maintaining abstinence. This new potential makes him an attractive agent to explore these indications for managing alcohol withdrawal and addiction (21).

GABAPENTIN AND WITHDRAWAL SYMPTOMS

Benzodiazepines are considered the first choice for treating alcohol withdrawal, but

Gabapentin has been studied as a potential treatment, based on its modulatory action on brain inhibitory mechanisms (i.e., GABAergic).

One of the most common disorders of substance use is alcohol use disorder, including both alcohol consumption and addiction (22). Three drugs are approved and used in the treatment of alcohol abuse, and these are disulfiram, acamprosate and naltrexone, and a fourth drug called "nalmefene" is being approved. Numerous randomized studies have evaluated the role of GBP in the treatment of alcohol abuse and alcohol addiction. A number of 13 studies with a total of 807 patients (23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35) were highlighted in the literature. Published studies illustrate the therapeutic effects of GBP in alcohol consumption disorders, by using relatively high doses of 1,200–3,200 mg GBP per day with a positive effect on cravings, depression, insomnia, withdrawal symptoms and in maintaining abstinence (28, 29). Sleep disorders such as insomnia are often associated with recurrence of consumption in alcohol-dependent patients, with rates ranging from 36-91%. It can be hypothesized that treating insomnia in these patients may minimize recurrence rates. Studies show that GBP addresses the signs and symptoms of insomnia and recurrences in alcohol-dependent patients (28).

Studies of alcohol-dependent animal models have shown that gabapentin decreases the amplitudes of GABA receptor-mediated post-synaptic inhibitory currents in the central amygdala (CeA), which results in a decrease in alcohol-induced dependence (36). Surprisingly, the effects of gabapentin seem to be identical to the effects of a corticotropin-releasing factor (CRF) antagonist (37, 38). These results suggest a significant GABA-

CRF interaction in GABAergic neurotransmission that has the ability to adapt during the development of alcohol dependence and therefore GABA-CRF neuroadaptations induced by ethanol dependence may represent the differential effects of gabapentin observed in CeA (36).

Other mechanisms of action involve blocking the effects of thrombospondin on the alpha 2 delta type 1 subunit (38). Type 1 subunits have the ability to modulate closed-channel calcium channels, but can simultaneously perform functions independent of calcium. Astrocytes secrete a protein, named thrombospondin, with a role in promoting synaptogenesis, and gabapentin antagonizes the binding of thrombospondin to the alpha-2 delta subunit resulting in inhibition of excitatory synapse formation, action independent of the calcium channel (38). Previous research and studies have shown that alpha-2-delta type 1 subunits are regulated in reward-related regions by all major drugs of abuse, including alcohol (39).

A 12-week placebo-controlled dose study in 150 patients (40) indicated that Gabapentin has beneficial therapeutic effect on abstinence rates (placebo: 4.1%; gabapentin 900 mg: 11.1%; gabapentin 1800 mg: 17.0%). In this study there were no side effects when taking the medicine. Used in combination with the benzodiazepine antagonist flumazenil, it did not show satisfactory results (41). The recent editorial by JAMA (Journal of the American Medical Association) (42) regarding current perspectives in alcohol pharmacotherapy highlights positive results from a 6-month study in a group of 348 patients who used either 1200mg of gabapentin, either placebo, with good results in the treatment of alcohol disorder.

Jonathan G. Leung's study was performed, at Mayo Clinic, Rochester, on 77 patients included in the primary evaluation of the gabapentin protocol, with a mean age of 48.7 ± 11.4 years, with the predominance of the male sex, respectively 72.7%. The mean PAWSS(Prediction of Alcohol Withdrawal Severity Scale) scale for these patients was 4.7 ± 1.4 , with 62 (80.5%) patients with a PAWSS score of at least 4 indicating a high risk of complicated withdrawal. In this gabapentin protocol, 51.9% of patients received an average of 2.3 ± 1.6 mg lorazepam in the emergency department, and 4 of them received diazepam in doses between 10-20 mg (26). The results offer a new direction of treatment and include the use of gabapentin in the future, but this requires a well-established protocol, as well as further research into the safety of this anticonvulsant treatment (GBP) vs benzodiazepine (43).

Another study by JAMA Internal Medicine, on a group of 96 patients, divided into placebo-group and gabapentin treated group, conducted over a period of 16 weeks, showed that Gabapentin prevented alcohol consumption and promoted alcohol abstinence among patients. Subsequently, a marker of alcohol consumption was collected, the percentage of transferrin disialo-carbohydrate was found to be deficient in the blood during treatment. Total abstinence was also higher in the gabapentin group - 18% compared to 4% in placebo group. However, about 33% of the participants in each group did not complete the process, a major limitation (44). Gabapentin was equally safe and tolerable, with no significant differences between the batch groups. These studies provide preliminary evidence that there may be a role for gabapentin on its own in the treatment of mild to moderate alcohol withdrawal syndrome.

CONCLUSIONS

This article presents preliminary, but potentially convincing evidence collected from the scientific literature in support of Gabapentin therapy for alcohol withdrawal syndrome and abstinence. Early initiation of high-dose gabapentin was associated with a significant reduction in benzodiazepine requirements, but also a faster stabilization of symptoms related to discontinuation of alcohol consumption and a shorter hospital stay. This anticonvulsant is unlikely to replace benzodiazepines, the first line therapy, but may play an appropriate role and may be useful as monotherapy for milder cases with a lower risk of complications. The current indication for this drug remains for the treatment of alcohol withdrawal syndrome complicated with seizures, refractory forms, in association with benzodiazepines. Therefore, more clinical trials are needed to investigate the efficacy of this anticonvulsant, Gabapentin, in both psychiatric and substance use disorders, but also its grade of tolerance and safety.

ACKNOWLEDGE AND DISCLOSURE

The authors declare that they have no potential conflicts of interest to disclose.

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Submission: 22 feb 2020
Acceptance: 17 apr 2020