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REVIEW ARTICLE

Anticonvulsant drugs for alcohol-related disorders

Leki przeciwdrgawkowe stosowane w zaburzeniach związanych z nadużywaniem alkoholu

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Abstract

Introduction and Objective. This study was designed to review the literature in search of current anticonvulsants for the treatment of alcohol-related diseases. As an alternative to the currently applied medicaments, antiepileptic drugs have become the focus of research so that patients can achieve permanent abstinence or reduce the bothersome alcohol-induced symptoms.

Review Methods. The literature review was conducted using the PubMed and Google Scholar database. Publications from 2015–2024 were analyzed and the following keywords were used as search criteria: „alcohol use disorder," „alcohol withdrawal syndrome," „anticonvulsant drugs."

Brief description of the state of knowledge. Alcohol use disorder (AUD) can manifest itself as either a recurrent and violent desire to consume alcohol or chronic heavy drinking. While attempting to stop drinking, patients experience the symptoms of alcohol withdrawal syndrome (AWS). Alcohol abuse can be clinically diagnosed on the basis of DSM-5 or ICD-11 criteria. The pathogenesis of AUD is connected with the increased amount of ethanol consumed, the excess of which leads to increased activity of GABAergic receptors and decreased activity of glutamatergic receptors. The AUDIT test was created to screen for problems with significant alcohol abuse, while the negative effects of alcohol withdrawal are assessed by the CIWA-AR protocol. Anticonvulsants are currently second-line drugs for the treatment of alcohol-related disorders. The most promising study results have been observed with gabapentin and topiramate.

Summary. Currently, some benefits of administering antiepileptic drugs in alcohol-related diseases have been noted, but due to lack of sufficient research their routine use is not recommended. Anticonvulsants can be considered an option when the patient has comorbidities and when there are no contraindications to the drugs applied.

Key words

alcoholism, anticonvulsants, alcohol-related disorders

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Streszczenie

Wprowadzenie i cel pracy. Niniejszy artykuł miał na celu przegląd piśmiennictwa w poszukiwaniu leków przeciwdrgawkowych stosowanych w leczeniu zaburzeń związanych z nadużywaniem alkoholu. Stały się one przedmiotem badań jako alternatywa dla obecnej terapii, której celem jest uzyskanie trwałej abstynencji lub zmniejszenie uciążliwych objawów wywołanych alkoholem.

Metody przeglądu. Przeglądu literatury dokonano przy użyciu bazy danych PubMed i Google Scholar. Przeanalizowano publikacje z lat 2015–2024, a jako kryteria wyszukiwania zastosowano następujące słowa kluczowe: „zaburzenia związane z używaniem alkoholu", „zespół abstynencyjny", „leki przeciwdrgawkowe".

Opis stanu wiedzy. Zaburzenia związane z używaniem alkoholu mogą objawiać się jako nawracające i gwałtowne pragnienie jego spożywania, a także jako przewlekłe intensywne picie, a wszelkie jego ograniczenia prowadzą do zespołu abstynencyjnego. Nadużywanie alkoholu można zdiagnozować na podstawie kryteriów DSM-5 lub ICD-11. Patogeneza AUD jest związana ze zwiększoną ilością spożywanego etanolu, co prowadzi do nadmiernej aktywności receptorów GABAergicznych i zmniejszonej aktywności receptorów glutaminergicznych. Narzędziem przesiewowym stosowanym w celu wykrywania problemów związanych z nadużywaniem alkoholu jest test AUDIT, podczas gdy negatywne skutki jego odstawienia oceniane są za pomocą protokołu CIWA-AR. Leki przeciwdrgawkowe są aktualnie lekami drugiego rzutu w leczeniu, a najbardziej obiecujące wyniki badań zaobserwowano w przypadku gabapentyny i topiramatu.

Podsumowanie. Obecnie odnotowuje się pewne korzyści z podawania leków przeciwpadaczkowych w chorobach związanych z nadużywaniem alkoholu, ale ze względu na brak wystarczających badań w tym zakresie nie zaleca się ich rutynowego stosowania. Mogą one być brane pod uwagę, gdy u pacjenta występują choroby współistniejące i nie ma przeciwwskazań do ich przyjmowania.

Słowa kluczowe

leki przeciwdrgawkowe, alkoholizm, zaburzenia związane z nadużywaniem

INTRODUCTION AND OBJECTIVE

The impact of alcohol on human health has been widely discussed in recent years. One of the most frequently observed conditions involving psychoactive drug abuse is alcohol use disorder (AUD) [1]. Alcohol abuse can manifest itself as intermittent episodes of compulsive binge drinking to days of heavy drinking [2]. The result can be an alcohol withdrawal syndrome (AWS), the characteristic symptoms of which include insomnia, hallucinations, anxiety, tremors, convulsions and, in its most severe form – delirium. The gold standard for assessing these disorders is the CIWA-Ar scale. Pharmacotherapy plays a key role in alleviating the bothersome symptoms and complications of alcohol abuse, which also helps to prevent alcohol relapse [3, 4, 6]. Current reports focus on the search for drugs effective in AUD and AWS, having a good action profile and without their addictive potential.

In view of the above, anticonvulsants have become the focus of research. They are increasingly being used for treating both the symptoms of withdrawal syndrome and in chronic alcohol addiction recovery to achieve sustained abstinence. The decision concerning the pharmacological treatment is very complex, as it must take into account the efficacy of the drug with minimal side-effects [5].

MATERIALS AND METHODS

The literature was reviewed and analyzed by searching the PubMed and Google Scholar database. Articles were searched by using key words such as: 'alcohol use disorder', 'alcohol withdrawal syndrome', 'anticonvulsant drugs'. The review discusses articles published between 2015–2024, the majority after 2018. A few older papers were included as an exception, due to the lack of similar studies in recent years. Original papers, review papers, meta-analyses and some Internet websites mostly in English but also Polish, Portuguese and Korean, were included in the review.

STATE OF KNOWLEDGE

Pathogenesis and diagnosis. Alcohol use disorder (AUD) is a chronic and relapsing condition associated with compulsive alcohol abuse, the inability to stop drinking, and the resulting alcohol withdrawal syndrome [7]. DSM-5 is the Diagnostic and Statistical Manual by the American Psychiatric Association (APA), while ICD is the International Statistical Classification of Diseases by the World Health Organisation (WHO) [8].

Excessive alcohol consumption leads to increased GABAergic activity, decreased glutamatergic activity, and ultimately to central nervous system depression. Chronic ethanol abuse is associated with disturbed homeostasis, which in turn results in altered concentrations of various neurotransmitters. Adaptive downregulation of GABA receptors leads to an increased need for alcohol to achieve the same intoxicating effect – the phenomenon known as tolerance. Abrupt cessation of long-term alcohol consumption leads to excessive neuronal excitability, resulting in symptoms of AWS within approximately 4–72 hours [7,12–13].

Receptors. Ethanol is thought to affect the GABA-A receptor which is most often found in the postsynaptic cell membrane in the brain. The receptor subunits form a pentamer. This conformation allows neurotransmitter GABA binding to GABA-A receptors, which are permeable to chloride ions. Ethanol-induced changes in the receptor subunits are responsible for alterations in all GABAergic signalling in the brain, particularly in the region of mesolimbic neurons: amygdala, hippocampus and striatum. Chronic alcohol abuse contributes to their constant activation, which consequently leads to the increase of dopamine from neurons in the ventral tegmental area [13]. Learning and memory processes that develop habits of seeking and consuming alcohol also contribute to the development of alcohol dependence. NMDA (N-methyl-D-aspartate glutamate) receptors are involved in this process, against which ethanol has an antagonistic effect [13, 15].

Assessment scales. The Alcohol Use Disorders Identification Test (AUDIT) developed by the World Health Organisation (WHO) is a screening tool designed to identify alcohol problems. It consists of 10 questions with 3 or 5 possible answers for which 0–4 points can be given. Thus, scoring 40 points indicates the most problematic habits and behaviours related to alcohol abuse [16]. Alcohol withdrawal syndrome begins within hours of cessation or reduction of chronic and excessive alcohol consumption [12]. Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) is a 10-item rating scale with a maximum score of 67 that assesses clinically significant features of alcohol withdrawal. It assesses the following factors:

1. Nausea and vomiting;
2. Tremor;
3. Paroxysmal sweats;
4. Sensory disturbances;
5. Visual disturbances;
6. Auditory disturbances;
7. Anxiety;
8. Agitation;
9. Headache
10. Disturbance of orientation and/or consciousness.

This scale is a widely accepted assessment tool used to monitor the severity of AWS [11,15,18,20].

Treatment. The aim of AUD and AWS treatment is to alleviate or eliminate the bad habits as well as the bothersome clinical symptoms. Undoubtedly, psychosocial interventions play the most important role. These are the most common forms of treatment for alcohol use disorders and include, for example, cognitive behavioural therapy (CBT), support groups or the Twelve-Step Facilitation (TFS). When psychotherapy fails, pharmacotherapy is implemented and benzodiazepines (BZDs) used as the first-line drugs for acute withdrawal syndrome [3, 21]. The focus is the treatment of AWS and delirium tremens, which is one of the most dangerous complications of the syndrome. It is a short-lasting psychosis that is characterized by disturbances of consciousness, disorientation, and increased, potentially life-threatening somatic symptoms. Although this is one of the more important complications of AWS, this review is devoted to medications that are relevant in both AUD and AWS, and help to rid the patient of the habit of reaching for

alcohol, and with the nagging symptoms associated with its continued abuse. The management of acute alcoholic delirium was the focus of a review by Grover et al. [17].

Unfortunately, BZDs have significant side-effects as well as a potentially highly addictive effect [3, 21]. For this reason, other effective drugs are still being sought for the treatment of withdrawal syndrome and alcohol abuse disorders in general. Anticonvulsants have been placed in a new light due to their different mechanisms of action [3]. The American Psychiatric Association (APA) provides guidelines for the treatment of AUD-related disorders. The following drugs are approved by the U.S. Food and Drug Administration (FDA) for the AUD as first line treatment: naltrexone, acamprosate and disulfiram. Of the anticonvulsant drugs, only gabapentin and topiramate have been adjuvantly accepted by the FDA. The choice of these antiepileptic drugs in the treatment of AUD may be dictated by concurrent seizures or symptomatic neuropathy [24].

Carbamazepine. Carbamazepine inhibits voltage-gated sodium channels and calcium channels. Several studies have demonstrated its efficacy in the treatment of withdrawal syndrome, but due to a lack of sufficient statistical significance, carbamazepine is not recommended as a first-line drug [25, 27]. According to some experts, carbamazepine and valproate can be used adjunctively in the treatment of AWS when its symptoms persist despite the use of benzodiazepines, the drugs of first choice, but these data are not supported by enough studies. Carbamazepine can be used as a monotherapy for withdrawal syndrome, but it is not effective enough to counteract all the symptoms of AWS, such as delirium tremens. This is the reason why benzodiazepines are still the first-choice drugs [14].

According to APA guidelines, carbamazepine prevents alcohol withdrawal seizures, and its use is recommended primarily for mild to moderate alcohol withdrawal syndromes [19]. The most common side-effects of carbamazepine are fatigue, dizziness, drowsiness, nausea, vomiting, diplopia, hyponatraemia, Steven-Johnson syndrome and agranulocytosis [7]. In addition, carbamazepine can lead to an increase in hepatic aminotransferase activity and exacerbate the effects of alcohol intoxication, and in rarer cases, even liver failure. Therefore, its use is not completely safe for active alcohol users abusers [22, 23].

Valproic acid. Valproic acid blocks and modulates voltage-gated ion channels, mainly sodium, as well as potassium and calcium. In addition, it increases the concentration of the neurotransmitter GABA by inhibiting its degradation and increasing its synthesis [25]. Among patients with alcohol abuse disorder and co-occurring bipolar affective disorder (BAD), the addition of valproate to lithium, being the primary form of therapy, has the potential to reduce alcohol consumption. According to studies by Brady et al., Kemp et al. and Salloum et al., the combination of lithium with valproate improves the problem of alcohol abuse However, due to too small study samples and an insufficient number of experiments, the results are not reliable enough to conclude that this drug combination improves symptoms associated with BAD and AUD [26, 28]. A study by De Iuliis et al. shows that a valproate concentration at a minimum of 30 ug/ml is the optimal value for maintaining abstinence from alcohol. More interestingly, the use of doses >50 ug/ml shows the same efficacy as those within 31–50ug/ml, thus titrating VPA to a lower dose may reduce the likelihood of side-effects from this drug [26].

Most studies from the past century have demonstrated the potential benefits of valproate in the treatment of AUD by helping in the alleviation of the symptoms and complications of withdrawal syndrome by preventing and interrupting seizures. However, due to too many serious side-effects, it is not recommended for routine treatment [7, 14, 29]. The most frequent and serious side-effects of valproic acid are gastrointestinal irritation, weight gain, hair loss, ataxia, hepatotoxicity and thrombocytopenia [30]. A 2018 study using databases from Norway, Sweden and Denmark, noted that the use of valproate young men in the three months before conception by their partners, could expose the child to a potential increased risk of neurodevelopmental disorders [31, 34]. Moreover, valproate also leaves a stigma on procreation by young women, leading to an increased risk of teratogenesis and cognitive impairment in children. Its adverse effects are particularly evident in the early embryonic stage, as it is responsible for many abnormalities such as heart defects, skeletal anomalies, neural tube defects and limb deformities [36, 40].

Gabapentinoids. The gabapentinoids, namely gabapentin and pregabalin, modulate GABA transmission by binding to voltage-gated calcium channel subunits. For the use of pregabalin, few data are available in the literature supporting its use in the treatment of alcohol use disorder and alcohol sustained withdrawal [3]. In one of the few available studies, a group of alcohol-dependent patients were given pregabalin at a maximum dose of 150–450mg/d, which caused as many as half of them not to reach for alcohol throughout the study. In another study, in which doses of pregabalin 200–450mg/d were used, withdrawal symptoms and alcohol craving were reduced. Other studies conducted on patients with AWS examined the impact of pregabalin and other medications used for the condition. Researchers compared pregabalin with tiapride and lorazepam. After 2 weeks of treatment, all patients reported significant improvement in terms of withdrawal symptoms and alcohol craving. Pregabalin additionally had a beneficial effect on comorbid psychiatric symptoms such as anxiety. In another study comparing the effectiveness of pregabalin and naltrexone, both drugs made patients maintain abstinence from alcohol, and pregabalin was even more effective. In a study which compared the effects of pregabalin and placebo, the results were not significantly different between the 2 substances – they reduced withdrawal symptoms and alcohol craving to the same extent [43]. Mariani et al. in their study suggest that pregabalin in doses up to 600 mg daily (200mg in the morning and 400mg in the evening) is effective and well tolerated in patients with AUD. However, more experiments, preferably of the double-blind type, are still required to confirm all these considerations for this drug [48]. The most important adverse effects of pregabalin are weight gain, somnolence, peripheral edema, dizziness, ataxia [30, 32].

Gabapentin is much more commonly studied by researchers. It affects GABAergic and glutamatergic activity by binding to the α2δ subunit of presynaptic voltage-gated calcium channels. Its mechanism of action has been discussed in numerous scientific papers [33]. Anton et al., in a randomised clinical trial, showed that gabapentin,

compared to placebo, resulted in a significant increase in the number of people who reduced or gave up drinking alcohol, from which it can be concluded that it is effective in the treatment of AUD, especially in those with more withdrawal syndrome symptoms. Unfortunately, many of the subjects of this experiment did not make it to the end, which is a major limitation of the study [35]. In another study on this topic, Falk et al. examined the safety and efficacy of the extended-release prodrug gabapentin enacarbil in alcohol-abusing patients. The authors found that the proportion of participants without heavy drinking days in the last 4 weeks of the study did not differ significantly between the groups of patients taking gabapentin enacarbil and placebo. Unfortunately, the study sample did not include patients with comorbidities which are often observed in AUD sufferers. The safety and efficacy of the drug at higher doses needs further evaluation [37]. Mason et al. in turn administered gabapentin 1,800 mg, which effectively treated alcohol dependence and demonstrated a favourable safety profile in people who responded well to gabapentin during this study. In this study, the group of patients was also not representative as more than 1/3 of the participants dropped-out during the experiment. The results should not be applied to the general population, however, since the study was conducted in only one research centre. Mariani et al. on the other hand, showed that the use of gabapentin at a dose of 3,600 mg/day resulted in a lower percentage of heavy drinking days in chronic alcohol abusing patients, and a higher percentage of abstinence days per week. In the study the main limitation was the short exposure time of patients to gabapentin, and less restrictive alcohol assessment indicators [33].

Most studies and meta-analyses show that the mechanism of action of gabapentin has the potential to benefit patients suffering from AUD and AWS. However, given the limited number of available studies with too little statistical significance, these results need more confirmation in further experiments to define the exact role of gabapentin in the treatment of alcohol abuse [38, 39, 41]. The side-effects of gabapentin mainly affect the nervous system and include drowsiness, dizziness, ataxia and exacerbation of myoclonus [32].

Topiramate. Topiramate acts by inhibiting voltage-gated sodium channels and, in addition, has been shown to affect GABAergic and glutamatergic receptor activity [7, 25]. The neurobiological mechanism of action of topiramate was investigated by Wetherill et al. who performed MRI scans before patients started taking topiramate 6 weeks later. It was noted that topiramate weakened alcohol craving and alcohol-related brain activation. A limitation of this study, however, was the fact that the study sample was too small and the topiramate titration period was long, leading to the loss of an already too small number of patients on whom the study was conducted [42]. According to current scientific reports, topiramate at a dose of 300 mg/day has been shown to be effective in the treatment of AUD in actively-drinking patients, but the study results were based on the use of similar doses of topiramate on too small study samples; therefore, new studies should evaluate the effect of other doses of topiramate on AUD on a larger number of affected individuals [33]. In contrast, Kranzler et al. replicated the results of their previous study and showed that topiramate at a dose of 200mg/day was effective in the treatment of AUD and reduced the number of heavy drinking days, as well as contributing to the maintenance of alcohol abstinence. In the new study, in comparison to the previous one, the moderating effect of different genotypes was additionally assessed, but no statistically significant results were observed [39].

A study conducted by Goodyear et al. shed new light on alcohol addiction because a different criterion was taken into account, namely financial – the amount of money spent on alcohol, and not craving alcohol or heavy drinking days. In this study, behavioral indicators of alcohol demand confirmed that topiramate at 200mg/day lowered alcohol demand by reducing the cash spent on alcohol on a weekly basis. However, the research sample was too selective, focusing only on compulsive alcohol drinkers who do not seek treatment. Similar studies in the future should be conducted on more representative groups of patients [50]. However, there is still insufficient evidence for the use of topiramate in AUD and AWS because, despite its potential efficacy, in many studies it was poorly tolerated in some patients, causing more adverse events leading to treatment discontinuation [1, 3, 44]. The most frequent adverse effects of topiramate include cognitive impairment, depression, fatigue, paresthesia, anorexia, acute glaucoma [30, 32, 45].

Zonisamide. Zonisamide is a sulfonamide derivative, with its mechanism of action mainly based on blocking sodium channels, T-type calcium channels, and inhibiting carbonic anhydrase activity [5, 32]. Petrakis et al. observed that zonisamide at a dose of 400 mg/day reduced the need to drink alcohol in patients diagnosed with AUD and post-traumatic stress disorder (PTSD) [46, 47]. Using another randomized trial as an example, which compared zonisamide with diazepam in the treatment of alcohol withdrawal syndrome, patients were taking zonisamide 400–600 mg/day, and reducing it after 3 weeks to the endpoint of 100–300 mg/day. The patients had a lower desire to consume alcohol and recorded lower scores on the CIWA-Ar protocol, both in diazepam group and zonisamide group. These instances prove that zonisamide is a promising drug for people struggling with alcohol abuse, but there is still insufficient research to support the use of zonisamide for the treatment for this kind of disorder [5]. Among the side-effects of zonisamide, somnolence, fatigue, weight loss, cognitive slowing, and even psychosis have been noted [30, 32].

CONCLUSIONS

AUD is a devastating chronic disease that has a profound impact on patients and their families. Nowadays, a holistic approach to the treatment of alcohol use disorder and alcohol withdrawal syndrome is observed, which is a combination of psychosocial and pharmacological approaches. The drugs available on the market are those approved by the FDA and off-label options. The selection of an appropriate treatment should be guided primarily by the criterion of the effectiveness and safety of the drug for the specific patient; therefore, the doctor should engage in joint decision-making with the patient. Benzodiazepines, which are the first-choice drugs for AWS and alcoholic delirium, unfortunately have significant side-effects and a potentially highly addictive effect. For this reason, other drugs with a better action profile and greater efficacy are still being investigated. Choosing the

Table 1. DSM-5 and ICD-11 criteria

DSM-5 criteria:	ICD-11 criteria:
1) Frequent consumption of alcohol in greater amounts or for longer periods than intended. 2) Persistent desire, or unsuccessful attempts to reduce or control drinking. 3) Spending too much time on activities necessary for obtaining alcohol. 4) Alcohol craving. 5) Neglecting responsibilities in different spheres of life – work/school/home. 6) Social or interpersonal problems. 7) Limiting or giving-up important activities in favour of alcohol. 8) Recurrent alcohol consumption in situations of danger or emergency. 9) Continued alcohol use despite having social or psychological problems caused or exacerbated by alcohol abuse. 10) Developing alcohol tolerance. 11) Symptoms of withdrawal syndrome or attempts to alleviate and avoid them.	1) Impaired control of alcohol use, manifested in the amount of alcohol consumed and the circumstances of use, often but not necessarily accompanied by a subjective sensation of craving for alcohol. 2) Alcohol use increasingly dominates over other activities, responsibilities, health, or personal care. Alcohol begins to play the central role in the person's life and while activities in other areas of life are neglected**.** Alcohol use is often continued despite harmful health and/or negative effects on others and the self. 3) Physiological characteristics of addiction are manifested by: a) tolerance; b) withdrawal symptoms; c) repeated use of alcohol (or a pharmacologically similar substance) to alleviate or prevent withdrawal symptoms.
AUD is diagnosed when at least 2 of the above criteria are met within a 12-month period [8,9].	AUD is diagnosed when at least 2 of the above criteria are met within a 12-month period if alcohol use is continued for at least 1 month [8, 10].

Table 2. Treatment of Alcohol Use Disorder

MEDICATION	DOSAGE USED IN DIFFERENT STUDIES	CLINICAL SUMMARY	SIDE-EFFECTS
Carbamazepine	600–800 mg/day	Appropriate monotherapy in mild AWS	fatigue, dizziness, drowsiness, nausea, vomiting, diplopia, hyponatraemia, Steven-Johnson syndrome, agranulocytosis
	200mg every 8 hours or 400 mg every 12 hours	Adjunctive therapy with benzodiazepines in AWS	
Valproic Acid	300–500 mg every 6 hours	Adjunctive therapy with benzodiazepines in AWS	gastrointestinal irritation, weight gain, hair loss, ataxia, hepatotoxicity, thrombocytopenia, teratogenicity
Gabapentin	1200 mg/day	Mild to moderate AWS	drowsiness, dizziness, ataxia and exacerbation of myoclonus
	300–500 mg every 6 to 8 hours	Adjunctive therapy dosing in AWS	
	1800 mg/day or 3600 mg/day	AUD treatment	
Pregabalin	150–450 mg/day	Withdrawal, craving and psychiatric symptoms in AWS	weight gain, somnolence, peripheral oedema, dizziness, ataxia
	600 mg	AUD treatment	
Topiramate	200–300 mg/day	AUD treatment	cognitive impairment, depression, fatigue, paresthesia, anorexia, acute glaucoma
Zonisamide	400–600 mg/day	AUD and AWS treatment	somnolence, fatigue, weight loss, cognitive slowing and even psychosis

Sources: 7, 14, 30, 32, 33, 39, 43, 45, 46, 48, 49

right drug can be difficult, but for a decision to be appropriate, the presence of comorbidities, potential interactions and the cost of treatment, should be considered. Currently, the use of antiepileptic drugs is not recommended for the first line treatment of patients with AUD and AWS because there is still insufficient evidence to support the routine clinical use of these drugs for the aforementioned conditions. There is still a need for more studies on more representative groups of volunteers, including those with other comorbidities with AUD and AWS. Studies should also pay more attention to the appropriate duration of exposure to the drug and its side-effects, which can potentially be reduced by carefully titrating the drug to a specific dose. New studies should consider more varied drug doses, both low and high, that may be effective in treating alcohol abuse disorders. All anticonvulsants discussed in this review showed some therapeutic benefits, particularly gabapentin and topiramate. A wider investigation of these properties of antiepileptic drugs may open a path towards a more effective fight against alcohol abuse and withdrawal syndrome symptoms in the community.

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