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The effectiveness of novel antiepileptic drugs: levetiracetam, pregabalin, tiagabine and zonisamide in the treatment of addictions

Efektywność nowych leków przeciwpadaczkowych: lewetiracetamu, pregabaliny, tiagabiny i zonisamidu w leczeniu uzależnień

INTRODUCTION

Drug addiction is a chronically relapsing disorder characterized by the compulsion to seek and digest the drug, loss of control in limiting intake and, the emergence of a negative emotional state when access to the drug is withdrawn [18].

Treatment of addiction is a long and difficult process associated with many failures. The disadvantages of standard therapy also contribute to higher ratio of drop-outs. For instance, unfortunately, established pharmacologic treatments of alcohol addiction (disulfiram, naltrexone, benzodiazepines), usually combined with behavioural therapies, are often not effective or poorly effective in many patients [21]. Moreover, benzodiazepines (BDZs), a "gold standard" of alcohol withdrawal syndrome treatment, are associated with increased risk of excess sedation, memory deficits, severe interactions with ethanol, respiratory depression in patients with liver impairment and have abuse and addiction liability [7, 26]. It can be safely said that anticonvulsants offer a novel approach to alcoholism treatment, especially that they can be given to actively drinking individuals. Moreover, antiepileptic drugs (AEDs) are able not only to replace BDZs in some of their treatment indications, but are also used in the withdrawal therapy in BDZs' dependent patients [7]. Finally, many forms of addiction lack effective therapeutics and the prevalence of this disorder remains unacceptably high [19]. Therefore, there is still a growing necessity to introduce new, more potent and safe drugs in the addiction therapy schedule. AEDs seem to present suitable profile of action and are intensively studied towards anti-addiction application. The primary rationale for using anticonvulsants in substance-abuse patients are that they are relatively safe, devoid of addiction potential, inhibit "kindling" mechanisms in withdrawal syndrome, are efficacious in comorbid psychiatric disorders, as well as demonstrate mood stabilizing and anxiolytic properties [1, 61]. Older, established AEDs, are currently replaced by novel AEDs. Newer generation of antiepileptics

demonstrates exceptional mechanisms of action, better tolerability, better pharmacokinetic profiles and fewer drug-drug interactions compared to standard drugs.

In the current review four novel AEDs: levetiracetam, pregabalin, tiagabine and zonisamide are presented. Each of them demonstrates different mechanism of action that may be potentially helpful in the treatment of addiction disorders.

Although **levetiracetam** has been available since 1999 as an antiepileptic drug, its mechanism of action has not been still completely elucidated, and it does not appear to involve the main cellular mechanisms associated with classical antiepileptic drugs. The most probable mechanism of action is binding to the brain cells' protein SV2A. This protein is engaged in the release and transport of substances essential to proper functioning of neurotransmitter systems [42]. Furthermore, levetiracetam inhibits AMPA receptores [9], inhibits the delayed rectifier K^+ currents, reduces voltage-operated K^+ currents, and also N-type and P/Q-type high-voltage activated Ca^{2+} currents. Moreover, it has been revealed that levetiracetam suppresses an inhibitory action of zinc and β-carbolines on GABA-A- and glycine-gated currents, which consequently enhances GABA-ergic transmission [31, 42].

Pregabalin is an analogue of γ-aminobutyric acid (GABA) however devoid of GABA-ergic properties. It is not metabolically converted into GABA or a GABA antagonist, and does not alter the uptake or degradation of GABA. Thus, GABA-A and GABA-B receptors lack binding activity to pregabalin [7, 54]. In return, pregabalin binds to the alpha-2-delta subunit of the presynaptic neuron's voltage-gated calcium channels. Consequently, this reduces Ca^{2+} influx at presynaptic nerve endings and further, reduces the release of several neurotransmitters, which include glutamate, noradrenalin, substance P and calcitonin gene–related peptide [20, 33, 54]. This, in result leads to the decrease in stimulation of the postsynaptic receptors and restores the neurons to a normal physiologic state. The great advantage of pregabalin is its state-dependent activity and modulation of the activity of only "hyper-excited" neurons, which results in a decrease in the release of neuroexcitatory neurotransmitters and a return to normal physiologic state [20].

Tiagabine acts by blockade of GABA uptake via inhibition of GABA transporter, GAT-1, on presynaptic neurons and glial cells. In consequence, it prolongs the inhibitory action of GABA at synapses within the brain [28, 49,50].

Zonisamide is a benzisoxazole derivative, structurally unrelated to other existing AEDs. The antiepileptic mechanism of action of zonisamide involves blockade of voltage dependent Na^+ and T-type Ca^{2+} channels, enhancement of GABA function through interaction at allosteric or other binding sites and/or by influencing GABA transport, and also a weak inhibition of carbonic anhydrase [4, 29, 43]. Additionally, zonisamide facilitates dopaminergic and serotoninergic transmission by increasing extracellular levels of these monoamines [4, 53]. Interestingly zonisamide has biphasic effects on dopamine function dependent upon its doses, i.e. therapeutic doses of zonisamide (20 and 50 mg/kg) enhance dopamine function while supratherapeutic dose (100 mg/kg) inhibits dopamine function [37].

REVIEW

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in children and adults [22, 41]. Additionally, levetiracetam is also effective in headache, neuropathic pain, anxiety and movement disturbances [10, 42]. There is also the evidence of potential efficacy in alcohol addiction.

As ethanol and levetiracetam display some similarities in the mechanism of modulatory influence on the central nervous system, there also exists a potential risk of their interaction. The knowledge of interactions is very important during therapy of alcoholism, especially when the patient breaks abstinence. The studies of these two compounds have shown synergistic alteration in EEG pattern in rabbits treated with both ethanol and a high dose of levetiracetam (200 mg/kg) mainly in the frontal cortex and in midbrain reticular formation. Furthermore, the repeated administration of levetiracetam remarkably has decreased the sensitivity of the hippocampus to ethanol. Therefore, levetiracetam should be considered in the future as a potential compound for the treatment of alcohol addiction [42].

Another preclinical 2-week study has shown that application of levetiracetam (50 mg/kg or 100 mg/kg, twice daily) decreased voluntary alcohol consumption in rats in comparison with both the pretreatment period and in comparison with the vehicle-treated rats. Moreover, an increase of beta-endorphin levels induced by levetiracetam administration was noticed. It is known that genetic deficiency of beta-endorphin predisposes to alcohol addiction because alcohol enhances the level of this peptide. Thus, levetiracetam is a potential medication for preventing alcohol abuse. It is supposed that the increase of endogenous beta-endorphin level may be a result of protracted stimulation of GABA-ergic transmission in reward system that leads to reduction of dopamine release in nucleus accumbens, which in consequence results in increased beta-endorphin levels to restore the balance within the mesolimbic reward system. The second possible mechanism of effectiveness of levetiracetam in this study may be suppression of N-type high voltage Ca^{2+} channels [60].

The above data seem to be confirmed by the 10-week open-label study in 20 actively drinking alcohol patients who were taking levetiracetam at maximum dose 2000 mg/day. A group of patients either significantly reduced their drinking or achieved abstinence during levetiracetam treatment [47].

Additionally, Leopold et al. have shown that levetiracetam is able to reduce mild to severe alcohol withdrawal syndrome [27].

It has been also suggested by cases of three patients with co-existing alcohol addiction and anxiety that levetiracetam (500-1500 mg, twice daily) could be beneficial in these two comorbid conditions. All patients reported reductions in alcohol consumption and anxiety symptoms during the study period [32].

Moreover, levetiracetam has normalised chlordiazepoxide-induced anxiety in mice, which may point to its potential efficacy in the benzodiazepine withdrawal syndrome [25].

In all the presented studies levetiracetam was well tolerated by most subjects, did not impair cognition, and only mild adverse events were observed like sedation, nausea, insomnia or pruritus [27, 32, 47]. However, some data point to the occurrence of impulsive aggressiveness, especially in coexistence of comorbid psychiatric disorder [12].

Pregabalin is used as an adjunctive medication to standard AEDs in reducing seizure frequency in adult patients with previously uncontrolled partial-onset seizures [54]. Due to its unique mechanism of action pregabalin also appears to be effective in the treatment of neuropathic pain in patients with postherpetic neuralgia, diabetic peripheral neuropathy, fibromyalgia, anxiety and posttraumatic stress disorder [20, 40]. Numerous essays with the application of pregabalin in substance addiction, especially benzodiazepine and alcohol addiction, also give encouraging, however still preliminary, effects.

Recently, pregabalin has been reported to help prevent excessive use of BDZs. In the study of Norwegian Prescription Database, between 2004 and 2007, 15-29% of patients taking pregabalin or gabapentin stopped consumption of BDZs [7].

Oulis et al. [38-40] also presented two studies (3 to 7 and 3 to 14 weeks long) over respectively 4 and 15 benzodiazepine dependent patients, in which pregabalin revealed anxiolytic and probably antidepressant properties.

The next 12-week study engaging 282 dependent to benzodiazepines individuals has shown that pregabalin (the mean dose at the last week- 315 mg/kg) promoted cessation of benzodiazepines' intake. Moreover, patients benefited from a significant improvement in sleep outcomes, disability and symptoms of anxiety [6].

The preclinical study in a mouse model of chronic ethanol dependence indicated that pregabalin (50-200 mg/kg) may be effective in the management of alcohol withdrawal and, in particular, against withdrawal-related seizure activity [5].

Also clinical studies confirm the efficacy of pregabalin in alcohol dependent subjects. After the first stage of detoxification with diazepam, 20 participants (heavy-drinkers) were taking pregabalin (at target dose 150-450 mg/day) for 16-weeks. Half of treated with pregabalin participants satisfactory achieved and maintained abstinence from alcohol throughout the study period, and at the end of the study remained totally alcohol-free [33]. In other similar scheme study over 59 patients treated with naltrexone or pregabalin both compounds significantly decreased withdrawal and craving for alcohol with large effect. Patients treated with pregabalin remained abstinent from any amount of alcohol for significantly longer time in comparison with naltrexone. Moreover, the reduction of withdrawal symptoms was significantly superior and emerged earlier in the pregabalin group than in the naltrexone group [34, 40].

The same Italian group in the 2-week study also showed that pregabalin, in firstly flexible and then gradually tapering doses may be effective in mild to moderate alcohol withdrawal syndrome [11].

In the last multi-centre, randomized, single-blind comparison trial in patients with moderate to severe alcohol withdrawal syndrome including pregabalin, tiapride and lorazepam all drugs showed evidence of safety and efficacy with some particular differences. Overall, pregabalin and lorazepam has given comparable effects, but pregabalin in flexible doses was superior to both tiapride and lorazepam in the management of some symptoms of alcohol withdrawal syndrome (e.g. headache) [35].

It is worth noting that mechanisms involved in the efficacy of pregabalin in the above-mentioned trials in relapse prevention could be related both to the anti-craving effect and to the treatment of comorbid psychiatric symptoms [11, 35].

Preclinical study has also shown that pregabalin blocked the motor symptoms and anxiety associated with spontaneous cannabinoid withdrawal in mice. However, further investigations are needed to confirm its efficacy in the treatment of cannabis addiction [2].

Pregabalin is rather well tolerated and the most commonly reported adverse effects affect central nervous system with most often occurring somnolence, dizziness and headache [54]. The resemblance of the drug to GABA leads to awareness of its potential for abuse and dependence. If pregabalin was the drug of abuse, the benefits of reduced benzodiazepine use and alcohol intake might be questioned. Although, the literature data about potential abuse properties of pregabalin are small, further research on the subject is warranted [7].

Tiagabine has been shown to be effective against partial seizures in adults and adolescents [48, 49]. Additionally it is useful in neuropathic pain, migraine, insomnia, posttraumatic stress disorder and possibly in anxiety and mood disorders [51, 52]. The effectiveness of tiagabine in some types of drug dependence was also observed in humans.

In animals, preliminary studies over the effectiveness of tiagabine in cocaine addiction have not provided encouraging results. Tiagabine (2.5–10 mg/kg) proved ineffective in the rat model of cocaine-evoked hyperlocomotion and sensitization [15]. Tiagabine at the highest dose attenuated the cocaine (10 mg/kg)-induced hyperactivation, however it may be a result of the decrease of basal locomotor activation evoked by the drug. Tiagabine also did not inhibit the development of sensitization to cocaine in this study [15].

Similarly, the lack of significant effects was observed when cocaine-evoked self administration and discriminative stimulus effects were assessed in rats [14].

In baboons [56] tiagabine (1 mg/kg) reduced both cocaine self-administration and food-maintained behaviour with a trend towards greater reduction of cocaine-maintained behaviour. However, the significant decrease in food-maintained behaviour may be the result of motor impairment or other non-specific effects. Tiagabine given at a dose not producing non-specifying effects (0.32 mg/kg), also failed to reduce cocaine seeking [5]

In cocaine-dependent humans pregabalin has brought more encouraging results. Tiagabine (4 and 8 mg/day p.o.) did not alter the subjective or reinforcing effects of oral cocaine and cocaine induced cardiovascular effects [30]. However, when cocaine was administered intravenously (0.45 mg/kg, in two increasing doses) tiagabine attenuated some subjective ratings of “stimulated” and “crave cocaine”. The difference may be the result of way of administration, as time course after intravenous administration is faster than following oral route, and additionally intravenous cocaine is 10 times more potent than oral form [52].

Winhusen et al. [58, 59] obtained contradictory results in cocaine abusers, in whom tiagabine reduced cocaine (20 mg/day) use. Tiagabine (24 mg/day) significantly reduced cocaine use in cocaine-dependent, methadone treated participants, observed as an improvement in the index of cocaine-free urines [16, 17].

Data concerning efficiency of tiagabine activity in other substance-abuse-disorders are less available. In the ethanol challenge imaging study the influence of 1 week administration of tiagabine (15 mg/day) to healthy volunteers on intravenous ethanol challenge was measured [13]. Resultantly, despite prominent GABA-receptor stimulation, tiagabine did not prevent ethanol-induced activation of the mesolimbic reward system, but enhanced ethanol-induced hypometabolism within areas of visual cortex and the cerebellum.

On the other hand, tiagabine appeared promising in the treatment of alcohol withdrawal. In a retrospective chart review including 13 patients, tiagabine (2-4 mg/day) was equally efficient in reducing CIWA-Ar (The Clinical Institute Withdrawal Assessment for Alcohol-revised) scores as oxazepam and lorazepam. Furthermore, there was a trend for patients receiving tiagabine to report less post-detoxification drinking [36].

However, further studies are needed to assess if tiagabine demonstrates or does not demonstrate potential aptitudes to treat alcohol addiction.

Studying the role of tiagabine in the management of nicotine dependence it has been demonstrated that the administration of tiagabine (8 mg/kg) attenuated the ratings of "good effects" and "drug liking", the craving for cigarettes and enhanced the cognitive performance in Classical Stoop Test. Thus, these results suggest that tiagabine, GABA system enhancing drug, may diminish the reinforcing effects of nicotine and craving for cigarettes. However, further controlled clinical studies are needed [51].

Moreover, tiagabine has favourable side effects profile with low addictive potential [17, 49]. The most often occurring adverse effects related to nervous system contained dizziness, somnolence, nervousness, speech disorder, depression and tremor, and also asthenia and diarrhoea. What is important for patients, tiagabine does not cause any deterioration in cognitive performance [48]. Additionally, adverse events improve in time and during proper dose adjustment [28, 48].

Zonisamide represents many features desirable in an AED and therefore it is a valuable addition to the therapeutic options for treating epilepsy [4]. It is used in simple and complex partial seizures, generalized tonic clonic seizures, myoclonic epilepsies, Lennox – Gastaut syndrome, and infantile spasms [29]. Preliminary studies suggest that zonisamide may also be safe, effective and well tolerated in monotherapy of children and young adults with a variety of seizure types [57].

Based on exceptional mechanisms of action of zonisamide there is a growing interest in treating with zonisamide other non-seizure conditions like Parkinson's disease, intractable neuropathic pain, headache, obesity and binge eating disorder [43].

The therapeutic features of zonisamide indicate that it may be valuable in addiction. Some preclinical and clinical trials have shown zonisamide as promising drug in the prevention and treatment of alcohol withdrawal syndrome and alcohol dependence [3, 23, 24, 44].

Zonisamide at a dose of 50 mg/kg has decreased ethanol consumption in both mice and rats in the limited access model of drinking [24]. This effect of zonisamide was readily reversible after the discontinuation of drug administration. Also observed was the lack of significant influence of zonisamide (50 mg/kg) on weight and motor coordination in tested rodents. Therefore, it is concluded that the effects of zonisamide on ethanol consumption are not associated with a marked influence on the neuronal systems that are involved in the regulation of food consumption and motor coordination [24].

Clinical studies provided preliminary beneficial effects in the treatment of alcohol dependence with zonisamide.

In the 13-week open label trial zonisamide (400 mg/day) administered to 16 alcohol-dependent subjects significantly reduced the mean number of drinks consumed daily during the treatment period with reference to baseline levels [23].

In another 12-week open label trial over 22 patients, zonisamide (started at a dose of 50 mg/kg and titrated to a target dose of 300 mg/kg) revealed an improvement in alcohol craving and alcohol consumption scores [44].

There was also a 12-week long placebo-controlled double-blind trial of 40 alcohol dependent subjects. Initial dose of zonisamide 100 mg/kg was over 8 weeks gradually increased to the target dose 500 mg/day and the target dose was maintained through the last 4 weeks of the trial [3]. The results of this study are consistent with previous studies as zonisamide has significantly reduced intake of ethanol, and provide preliminary support for the use of zonisamide to treat alcohol dependence.

Zonisamide appeared also efficient in the management of alcohol withdrawal syndrome. In the 3-week, randomized, flexible-dose trial over 40 inpatients with alcohol dependence zonisamide or diazepam were used for detoxification gradually tapering doses scheme [46]. Despite both drugs equally reduced alcohol withdrawal symptoms, the decrease was more marked in the zonisamide group. Additionally, zonisamide produced less craving for alcohol, less anxiety, and less daytime sedation compared with the effects of diazepam.

It is worth mentioning that zonisamide is a well-tolerated AED during both short- and long-term treatment [8]. The most common adverse effects, reported by more than 10% of patients, are usually central nervous system related: agitation, irritability, confusion, depression, ataxia, dizziness, memory impairment, somnolence and diplopia. Appetite decrease and weight loss have also been reported [4].

CONCLUSIONS

Collected data have shown that levetiracetam and zonisamide are promising drugs in the treatment of alcohol addiction and alcohol withdrawal syndrome, and in prevention of alcohol overuse. Pregabalin, first of all has sucessfully reduced benzodiazepine abuse, besides giving encouraging effects in the management of alcohol dependence and withdrawal. Otherwise, tiagabine has mainly revealed its effectiveness in the treatment of cocaine addiction, and as preliminary studies show - in nicotine dependence and alcohol withdrawal syndrome.

The use of atypical antiepileptic drugs for the treatment of drug dependence has increased considerably in the last years. Many of these compounds inhibit hyperexcitation of neuronal activity abnormally increased in drug dependent patients [2]. As was previously mentioned, levetiracetam, pregabalin, tiagabine and zonisamide have unique albeit different mechanisms of action. Therefore, they exert their antidependence effects in various manners.

The facilitation of GABA-ergic inhibitory transmission is a well known way of addiction treatment, and at least three out of four drugs reviewed here present this mode of action.

What is important, the major inhibitory amino-acid - GABA, possesses extensive neuronal connections in mesolimbic regions and therefore it can modulate dopaminergic neurons. The use of addictive substances leads to an increase of dopamine level in striatum and nucleus accumbens, which is associated with the reward system of the brain, providing feelings of enjoyment and reinforcement to motivate a person [13]. Enhancing levels of GABA in the synaptic cleft is thought to reduce psychostimulant induced increase of dopamine in the nucleus accumbens, thereby reducing their reinforcing properties [18,56]. Thus, drugs that stimulate inhibitory GABA-ergic system in

turn attenuate dopaminergic effects i.e craving of addictive substances. Therefore, the indirect improvement of GABA-ergic neurotransmission by AEDs, may reduce the reward system response and, consequently, the perception of stimulus as pleasant [42]. That is of high importance on the way to successful control of addiction. However, it is thought not to be the only mechanism of action of AEDs in attenuating dependence.

Further investigation is needed in order to get to know their complete mode of action in dependence disorders.

Summing up, the above studies demonstrate that levetiracetam, pregabalin, tiagabine and zonisamide are prospective drugs in the treatment of various types of dependence. However, notable part of the presented research consists of the initial observations. Therefore, further, larger, multisite, randomized double-blind and placebo controlled studies to confirm and supplement previous findings in this area are needed.

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SUMMARY

It is commonly known that standard therapy of addiction still brings a high ratio of failures. According to the most recent studies, anticonvulsant drugs offer a novel approach in the treatment of dependence disorders. In this paper, four new antiepileptic drugs levetiracetam, pregabalin, tiagabine and zonisamide were reviewed considering their activity in various types of addiction. Collected data have shown that levetiracetam and zonisamide are promising drugs in the treatment of alcohol addiction and alcohol withdrawal syndrome, and in prevention of alcohol overuse. Pregabalin, first of all has sucessfully reduced benzodiazepine abuse, in addition to giving encouraging effects in the management of alcohol addiction and withdrawal. However, tiagabine has revealed its effectiveness mainly in the treatment of cocaine addiction, and as show preliminary studies, in nicotine dependence and alcohol withdrawal syndrome.

Levetiracetam, pregabalin, tiagabine and zonisamide exert antidependence effects in different ways due to various modes of action. One of the most probable, and present in at least three reviewed drugs, mechanism of antidependence action is facilitation of GABA-ergic inhibitory transmission, which in turn through modulation of dopaminergic neurons in mesolimbic system, reduces the rewarding properties of psychostimulants. Based on recent studies, levetiracetam, pregabalin, tiagabine and zonisamide are prospective drugs in the therapy of dependence. However, further investigation to confirm and supplement previous findings is needed.

Keywords: antiepileptic drugs, levetiracetam, pregabalin, tiagabine, zonisamide, dependence

STRESZCZENIE

Powszechnie wiadomo, że standardowe schematy leczenia uzależnień przynoszą wysoki odsetek niepowodzeń. Według najnowszych danych, leki przeciwpadaczkowe dają nowe możliwości leczenia uzależnień. W prezentowanej pracy oceniano skuteczność czterech leków przeciwpadaczkowych nowej generacji: lewetiracetamu, pregabaliny, tiagabiny i zonisamidu, w leczeniu różnych typów

uzależnień. Zebrane dane wykazały, iż lewetiracetam i zonisamid są obiecującymi lekami w leczeniu choroby alkoholowej i zespołu odstawienia alkoholu, oraz zapobiegają nadużywaniu alkoholu. Pregabalina, przede wszystkim znacząco zredukowała nadużywanie benzodiazepin, wykazując ponadto zachęcające wyniki podczas terapii zależności alkoholowej i odstawiania alkoholu. Zaś tiagabina wykazała głównie efektywność w leczeniu uzależnienia od kokainy i według wstępnych badań w nadużywaniu nikotyny i zespole odstawienia alkoholowego. Za skuteczność lewetiracetamu, pregabaliny, tiagabiny i zonisamidu w leczeniu uzależnień odpowiadają odmienne mechanizmy działania. Najbardziej prawdopodobna, i obecna w przynajmniej trzech z opisywanych leków, jest poprawa hamującego przekaźnictwa GABA-ergicznego, które z kolei poprzez modulację neuronów dopaminergicznych w układzie mezolimbicznym, zmniejsza nagradzające właściwości psychostymulantów. W oparciu o dostępne wyniki lewetiracetam, pregabalina, tiagabina i zonisamid są obiecującymi lekami w terapii uzależnień. Jednakże, wymagane są kolejne badania, aby potwierdzić oraz uzupełnić dotychczasowe dane.

Słowa kluczowe: leki przeciwpadaczkowe, lewetiracetam, pregabalina, tiagabina, zonisamid, uzależnienie.