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Review Article

Antiepileptic drugs in alcoholism: an update

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CONTENTS

Abstract

Alcohol dependence is a devastating health problem that is associated with significant morbidity and mortality and with negative social consequences for the patient and his/her family environment. Few drugs are available for the pharmacological treatment of alcoholism, and although disulfiram, naltrexone, acamprosate or benzodiazepines have been for years the mainstay treatments for alcohol dependence, there is a clear need for newer, more effective drugs. Antiepileptic agents have emerged as potential treatment alternatives with potential efficacy in treating alcohol-dependent patients, in particular those presenting with psychiatric co-morbidities. This article reviews current clinical evidence for the use of antiepileptic drugs in the treatment of alcoholism.

Introduction

Alcoholism is characterized by repetitive and compulsive consumption of alcohol that persists despite knowing the deleterious consequences of alcohol abuse. Alcohol-dependent patients experience a loss of control of their drinking behavior that results in physical and psychological consequences. In addition, alcohol dependence leads to tolerance —a need to increase alcohol intake to achieve the desired effect—, withdrawal syndrome and disruption of normal social, occupational or recreational activities (1). The complex nature of alcohol addiction requires medications used to treat symptoms of alcohol withdrawal during detoxification, as well as a combined treatment approach of pharmacotherapy and psychosocial measures, preferentially aimed at preventing relapse, once alcohol detoxification has been performed. Deterrent drugs such as disulfiram or drugs that reduce alcohol intake like acamprosate are frequently used in alcohol treatment programs. Understanding the biological basis of alcohol dependence, tolerance and withdrawal is key to achieve successful treatments.

Alcohol dependence, tolerance and withdrawal syndrome

Dependence

Increases in dopamine levels in the mesolimbic system are essential for the expression of the acute reinforcing effects of alcohol and other drugs of abuse. The dopamine mesolimbic pathway initiates in the ventral tegmental area (VTA), which sends out dopaminergic projections to the nucleus accumbens in the ventral striatum and limbic structures, including the amygdala, hippocampus and prefrontal cortex (2) (Fig. 1).

Dopaminergic activity is regulated by excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) signaling. The nucleus accumbens receives glutamatergic afferents from the prefrontal cortex, amygdala and hippocampus that synapse with GABAergic medium spiny neurons, which play a central role in the integration of excitatory and inhibitory signaling in the nucleus accumbens, regulating rewarding behavior (2). Acute ethanol promotes dopamine release into the nucleus accumbens by liberating dopaminergic VTA neurons from inhibitory GABAergic signaling and inducing positive reinforcement critical for the development of alcohol dependence.

Dopamine D3 receptors have been postulated as key players in mediating alcohol-induced addictive behavior, as their expression is elevated in the nucleus accumbens, D3 receptor polymorphisms have been associated with alcoholism and selective D3 receptor antagonists can reduce alcohol-taking and -seeking behaviors (3). Dopamine release in the amygdala is important to establish learned associations between the drug and other cues predictive of drug use. Furthermore, reward responses to alcohol consumption involve changes in synaptic plasticity of the dopamine mesolimbic system, similar to those

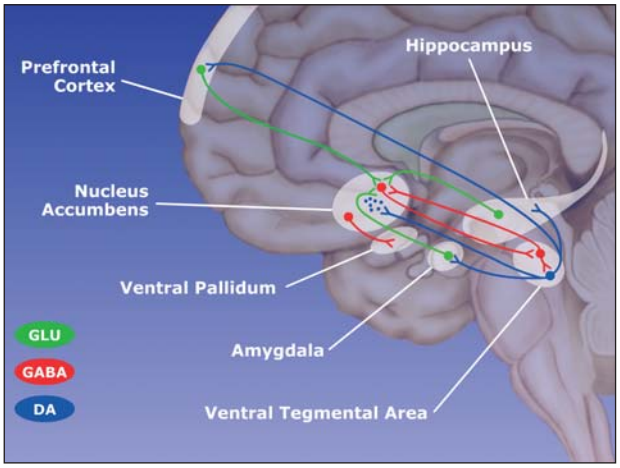

Fig. 1. Major structures of the brain reward circuit are the ventral tegmental area (VTA), the nucleus accumbens and the prefrontal cortex. Dopaminergic neurons in the VTA fire in response to a rewarding stimulus, such as alcohol, and induce dopamine (DA) release in the nucleus accumbens. Dopaminergic neurotransmission to the nucleus accumbens is modulated by excitatory and inhibitory inputs mediated by glutamatergic (GLU) and GABAergic signaling. Ethanol increases DA release in the nucleus accumbens primarily via inhibition of GABAergic neurotransmission, hence enhancing positive reinforcement and the development of dependence.

observed in learning and memory processes (4). Ethanol exposure promotes the phosphorylation of the transcription factor cAMP response element-binding protein (CREB), via activation of the cAMP protein kinase A (PKA) pathway, which, in addition to inducing the transcription of genes involved in synaptic plasticity and memory storage, has also been associated with the regulation of ethanol consumption and reward (5).

A persistent increase in the probability of GABA release in the ventral tegmental area is another form of plasticity related to enhanced ethanol self-administration (6). In addition, structural plasticity (changes in dendritic morphology, spine density, etc.) in different brain reward system areas has also been related to the development of addiction (2). A recent study demonstrated that chronic ethanol exposure is associated with enlargement of dendrites in rat hippocampus (7). These long-lasting changes in neuronal plasticity may partially explain the permanent nature of addiction, which places the alcoholic patient at constant risk of relapse despite prolonged periods of abstinence.

Tolerance and withdrawal syndrome

Alcohol targets different neurotransmitter systems within the brain that converge to decrease brain excitability. As previously mentioned, alcohol activates GABA signaling via $GABA_A$ receptors, which results in hyperpolarization of neuronal membranes and brain hypoexcitability. On the other hand, alcohol inhibits glutamatergic NMDA receptors, thus blocking neuronal calcium entry and decreasing glutamate excitatory effects. Chronic exposure leads to a reduction in $GABA_A$ receptor density and NMDA receptor upregulation to oppose alcohol depressor effects and results in the development of tolerance. Ethanol-induced inhibition of NMDA receptors in the nucleus accumbens has also been related to reinforcing behavior (2). Abrupt cessation or reduction of alcohol use after periods of sustained alcohol intake causes brain hyperexcitability, which leads to alcohol withdrawal syndrome involving anxiety, agitation, tremor, seizures and delirium tremens. The severity of symptoms is correlated with the amount of alcohol ingested, the duration of use and the presence of co-morbidity, in particular psychiatric conditions (8).

Investigational antiepileptic drugs in the management of alcoholism

Detoxification, pharmacological treatment of withdrawal and dependence and psychosocial counseling are strategies to enhance abstinence and prevent relapse in alcoholism rehabilitation programs. Benzodiazepines, disulfiram, naltrexone or acamprosate are commonly used drugs, although in recent years anticonvulsants have gained attention in treating substance withdrawal, including alcohol withdrawal, as well as alcohol dependence (9, 10).

As mentioned above, alcohol's depressant actions are mediated, at least in part, by potentiation of GABA via modulation of the $GABA_A$ receptor. Increasing GABAergic neurotransmission inhibits mesolimbic dopaminergic neurons, thus decreasing alcohol's reinforcing effects. The mechanism of action of anticonvulsant drugs appears adequate to counteract the neuronal processes underlying alcohol withdrawal and dependence, as they enhance inhibitory GABAergic neurotransmission and/or reduce excitatory neurotransmission. Their lack of addiction potential makes them attractive alternatives to benzodiazepines or other potentially addictive drugs. A systematic review of clinical studies evaluating the use of antiepileptics in treating alcohol withdrawal highlighted a positive trend towards therapeutic success in comparison to other drug treatments (11).

Here, we review the experimental evidence of antiepileptic drug use in the treatment of alcoholism. We have classified anticonvulsant drugs as GABA and non-GABA modulators, but most antiepileptic drugs share more than one mechanism of action (12).

GABA modulators

1. Gabapentin

Gabapentin is known to increase GABA concentrations via two GABA receptor-independent mechanisms: 1) increase of GABA synthesis; and 2) blockade of neuronal voltage-dependent calcium channels (12). The pharmacological treatment of alcohol dependence or withdrawal is a challenging task, especially due to the presence of severe hepatic or hematological complica-

tions or psychiatric co-morbidities in alcoholic patients. Gabapentin appears *a priori* as an attractive candidate for the treatment of alcoholism due to its lack of abuse potential, good safety and pharmacokinetic profile, and its lack of liver or renal metabolism, thus reducing the risk for drug-drug interactions. Indeed, two recent studies evaluating the safety and tolerability of gabapentin reported minimal interactions with alcohol intake in non-treatment-seeking alcoholic subjects (13, 14).

This lack of interaction with alcohol supports the use of gabapentin for the treatment of alcohol withdrawal in the outpatient setting, where alcohol is accessible to patients and concomitant psychiatric disorders are common. A number of studies have investigated the efficacy of gabapentin for the treatment of alcohol withdrawal. Initial observations described the beneficial action of gabapentin as add-on treatment to clomethiazole, a $GABA_A$ receptor modulator with sedative and anticonvulsant properties. The addition of gabapentin reduced the need for clomethiazole treatment during the detoxification period in 3 of 4 patients. The other patient was adequately controlled only with gabapentin. None of them experienced alcohol withdrawal-induced seizures (15). Gabapentin monotherapy for alcohol withdrawal was successfully used in 3 additional cases, where symptoms of alcohol withdrawal receded within 2 days after gabapentin initiation, without requiring adjuvant medications (16).

In further controlled studies, gabapentin led to different results, but it generally appears safe and potentially useful in treating alcohol withdrawal. Sixty-one patients suffering from alcohol dependence and no other co-morbidity were randomized to receive either gabapentin or placebo as adjunctive therapy to clomethiazole. The amount of clomethiazole required during the first 24 h of acute withdrawal syndrome was the primary efficacy measure. Gabapentin was found to be equally effective as placebo in reducing clomethiazole requirements and the severity of acute withdrawal syndrome over time (measured by the Mainz Alcohol Withdrawal Score [MAWS]) did not differ significantly between the two study groups. The authors attributed this lack of effect to the low entry dose of gabapentin (17). Further analysis of trial results revealed that gabapentin positively influenced the mood profile of patients with alcohol withdrawal by accelerating the improvement of vigor within the first 2 days of treatment (18).

In contrast, gabapentin appeared to be as effective as phenobarbital in treating alcohol withdrawal in a randomized, open-label trial, where 27 patients received gabapentin or phenobarbital for 4 days. Neither the percentage of individuals completing the treatment (71% and 62% in the gabapentin and phenobarbital groups, respectively) nor the percentage of subjects requiring rescue medication for breakthrough signs and symptoms of alcohol withdrawal (57% and 38%, respectively) differed significantly between groups. Withdrawal symptoms and psychological distress were similar in both groups, and gabapentin-treated patients who required rescue medication appeared to be those in more severe withdrawal (19).

Gabapentin has also shown efficacy in the treatment of psychiatric conditions concomitant to alcohol dependence. In patients with alcohol dependence and co-existing post-traumatic stress disorder (PTSD) refractory to selective serotonin reuptake inhibitors (SSRIs), gabapentin was well tolerated and induced significant improvement in clinical PTSD scores (20).

Gabapentin is currently being investigated in several ongoing clinical studies. A randomized, double-blind trial will evaluate the safety and efficacy of gabapentin as add-on to standard naltrexone therapy in treating patients with alcohol dependence (21). Also, the safety and efficacy of combined flumazenil and gabapentin in reducing early alcohol withdrawal symptoms and in preventing relapse in patients with alcohol dependence will be examined in a study that is expected to recruit 60 patients (22). Another study investigating the efficacy of gabapentin monotherapy in addition to behavioral counseling in outpatients with alcohol dependence is currently under way (23).

2. Vigabatrin

Vigabatrin, or γ-vinylaminobutyric acid, enhances GABA levels in the CNS via inhibition of its metabolic degradation by the enzyme GABA aminotransferase. It is commonly used to treat refractory epilepsy, such as infantile spasms and complex partial seizures (12). Preclinical observations in rats selectively bred for alcohol consumption reported a sustained decrease in alcohol use after vigabatrin treatment (24). In alcohol-dependent individuals, vigabatrin administration for 3 consecutive days led to a significant improvement in alcohol withdrawal syndrome clinical scores (*i.e.,* Clinical Institute Withdrawal Assessment for Alcohol Scale [CIWA-A]). Sudden vigabatrin withdrawal after 3 days did not result in worsening of symptoms (25).

A further double-blind, randomized trial evaluated the potential use of vigabatrin in the treatment of alcohol withdrawal syndrome in comparison to oxazepam. Thirty-eight inpatients were included in the 7-day trial. CIWA-A scores decreased on days 2, 3, 5 and 7 as compared to day 1 in both treatment groups, with no statistically significant difference between them. Thus, vigabatrin may represent an interesting treatment option for alcohol withdrawal syndrome, with the advantage of being a drug with no known abuse potential (26).

3. Tiagabine

Tiagabine blocks neuronal and glial GABA uptake via inhibition of the presynaptic GABA transporter GAT-1, thus increasing GABA concentrations at the synapse and enhancing GABAergic neurotransmission (12). The potential use of tiagabine as a modulator of ethanol reward was examined by Nguyen *et al.* in alcohol-preferring C57BL/6 mice. Pretreatment with subcutaneous tiagabine reduced appetitive behavior for ethanol reward upon chronic exposure, but did not influence reward responses induced by water or food at the same tiagabine doses (27).

In the clinical setting, tiagabine has provided controversial results. On the one hand, it was unable to prevent ethanol-induced activation of the human reward system when tested in nonalcoholic human volunteers (28). However, a retrospective chart review of patients treated for acute alcohol withdrawal determined that tiagabine was comparable to benzodiazepines in reducing withdrawal symptoms during the detoxification period. Tiagabine also showed a decreased trend for relapse (29).

4. Valproate

Valproate is an antiepileptic agent used for the treatment of both generalized and partial seizures in adults and children. It has been suggested that its activity in epilepsy is related to a variety of mechanisms, including increased GABAergic transmission due to inhibition of GABA aminotransferase-mediated metabolism, reduced release and/or effects of excitatory amino acids, blockade of voltage-gated sodium channels and modulation of dopaminergic and serotonergic transmission (12).

Evaluation of valproate in clinical studies has not led to promising prospects for the treatment of alcohol dependence and withdrawal in alcoholic patients with or without concomitant pathologies. Initial data from a small pilot study in alcoholic male patients revealed that valproate was well tolerated, with no liver, kidney or bone marrow function abnormalities reported. However, too few patients completed the full 6-month study period, which did not allow for any reliable conclusions on the safety and efficacy of valproate (30).

Another pilot clinical study in patients with alcohol dependence evaluated the use of valproate in the prevention of alcohol relapse. Despite the fact that there were no differences between the valproate and placebo groups in most drinking outcome variables, a trend towards a decreased percentage of patients who relapsed and reduced days of heavy drinking (more than 5 drinks per day) was reported in valproate-treated subjects. There was an additional trend for larger reductions in irritability and hostility (31).

According to an isolated report of a patient with alcohol dependence and type I bipolar disorder who experienced severe alcohol withdrawal, maintenance valproate treatment failed to protect against alcohol withdrawal, which was treated with diazepam. Interestingly, the addition of gabapentin allowed a reduction in diazepam dose (32).

Concomitant manifestation of bipolar disorder and alcoholism is particularly prevalent and involves increased morbidity, aggressivity and higher suicide risk (33). Among other drugs, the efficacy of valproate in managing this patient population has been investigated. A double-blind, randomized, placebo-controlled clinical trial assessed the effects and safety of valproate in 59 patients with bipolar I disorder and alcohol dependence. A few days after starting standard lithium carbonate therapy and psychosocial counseling, each patient was randomized to receive placebo or valproate for 24 weeks. Valproate induced a reduction in heavy drinking days compared to placebo at the end of the study (44% *vs.* 68%), reduced the average number of drinks per heavy-drinking day (5.6 *vs.* 10.2) and increased the average time to relapse to sustained heavy drinking (93 days *vs.* 63 days). A significant correlation was found between the increase in serum valproate levels and the reduction in drinking behavior. In general, the combination of valproate and lithium was well tolerated, with only an increase in nausea and vomiting compared to placebo (34).

A clinical trial is investigating the safety and efficacy of valproate in patients with alcohol dependence and mood and/or anxiety symptoms (35).

5. Topiramate

Topiramate displays multiple mechanisms of action: it enhances GABA-mediated currents via a putative binding site at the $GABA_A$ receptor; it blocks the AMPA receptor; inhibits voltage-dependent sodium and calcium currents; and it increases potassium conductance (12). Reports from preclinical studies evaluating the impact of topiramate on ethanol-induced reward have not been conclusive. Topiramate alleviated withdrawal symptoms in rats exposed to chronic intermittent ethanol by increasing the threshold of pentylenetetrazol-induced seizures and reducing anxiety (36). However, in other studies, topiramate did not substantially modify ethanol's rewarding effects (37, 38), although it has been reported to reduce ethanol consumption (39).

Results from clinical trials have been more encouraging. Compared to placebo, topiramate caused a reduction in self-reported drinking outcomes (number of drinks per day, drinks per drinking day, heavy-drinking days and proportion of abstinent days), which correlated with decreased plasma γ-glutamyltransferase, an objective drinking measure. Furthermore, topiramate attenuated craving, as measured by the Obsessive-Compulsive Drinking Scale (OCDS), which corresponded with reduced alcohol consumption (40). Interestingly, another study showed that topiramate had a positive impact on patient's quality of life, ameliorated general clinical condition and reduced the harmful consequences of drinking (41). In a small open clinical study, topiramate decreased alcohol consumption and improved craving scores in dependent patients who were taking other medications (SSRIs, atypical antipsychotics, lithium and anti-craving drugs) for concomitant psychiatric conditions, suggesting it could be useful as adjuvant therapy (42).

Besides its potential utility in treating dependence, topiramate has also been evaluated for the management of withdrawal symptoms. In an open, randomized study, topiramate showed comparable efficacy to lorazepam, as evidenced by nonsignificant differences in CIWA-A scores (43).

At present, topiramate is the subject of several ongoing clinical studies evaluating its efficacy in alcohol-dependent patients (44-47) and also in those displaying either concomitant addictions (cocaine dependence) (48) or eating disorders (49) (see Table I for a detailed description of these trials).

Table I: Clinical results for GABA-modulating antiepileptic drugs in the treatment of alcohol abuse (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Gabapentin	Randomized Double-blind	Gabapentin, 300 mg o.d. [night] x 1 d → b.i.d. x 2 d → t.i.d. x 2 d → 300/300/600 mg t.i.d. x 2 d → 300 mg o.d. [morning] Placebo	35	Although no effect on alcohol craving or subjective high or intoxication after drinking alcohol was noted with gabapentin, the drug proved safe and well tolerated when used with alcohol consumption in alcoholic individuals	13
	Randomized Double-blind	Gabapentin, 1000 mg p.o. + Ethanol, 0.75 mg/kg Gabapentin, 2000 mg p.o. + Ethanol, 0.75 mg/kg Placebo + Ethanol, 0.75 mg/kg	17	Gabapentin given with intoxicating doses of alcohol was safe and well tolerated in heavy drinkers, but it did not modify the effects of alcohol or reduce alcohol craving in these subjects	14
	Multicenter Randomized Double-blind	Gabapentin, 400 mg p.o. q.i.d x 3 d → t.i.d. x 1 d → b.i.d x 1 d → o.d. x 1 d + Clomethiazole [when BrAC = 0.15% or less] Placebo + Clomethiazole	61	Gabapentin was not superior to placebo in reducing clomethiazole requirements. The severity of acute withdrawal syndrome over time did not differ significantly between groups	17
	Multicenter Randomized Double-blind	Gabapentin, 400 mg p.o. q.i.d x 3 d → t.i.d. x 1 d → b.i.d x 1 d → o.d. x 1 d + Clomethiazole [when BrAC = 0.15% or less] Placebo + Clomethiazole	59	Gabapentin accelerated improvement of vigor, as measured by the Profile of Mood States subscore (POMS), within the first 2 days of treatment in patients with alcohol withdrawal syndrome	18
	Open Comparative Randomized	Gabapentin, 1200 mg p.o. → 600 mg p.o. → 600 mg p.o. on d 1 → 600 mg p.o. t.i.d. on d 2 → 600 mg b.i.d. on d 3 → 600 mg on d 4 Phenobarbital, 60 mg p.o. q.i.d. on d 1 → 60 mg p.o. t.i.d. on d 2 → 60 mg p.o. b.i.d. on d 3 → 60 mg b.i.d. on d 4	27	Gabapentin was as effective as phenobarbital in terms of the number of patients with alcohol dependence who required rescue medication for breakthrough signs and symptoms of withdrawal	19
	Open	Gabapentin x 12 wks	20	Gabapentin as adjunctive therapy demonstrated encouraging activity in patients with post-traumatic stress disorder with co-morbid alcoholism resistant to selective serotonin reuptake inhibitors	20
	Randomized Double-blind	Naltrexone, 50 mg/d x 16 wks + Gabapentin, 1200 [max.] mg/d x 6 wks + alcohol counseling Naltrexone, 50 mg/d x 16 wks + alcohol counseling	150	This study will evaluate the safety and efficacy of adjuvant gabapentin added to standard naltrexone therapy in treating patients with alcohol dependency	21
	Randomized Double-blind	Flumazenil i.v. x 2 d + Gabapentin p.o. + Hydroxyzine + Vitamins x 39 d Placebo + Hydroxyzine + Vitamins	60	This study will evaluate the safety and efficacy of combined flumazenil and gabapentin in reducing early alcohol withdrawal symptoms and in preventing relapse in patients with alcohol dependence	22
	Randomized Double-blind Dose-finding	Gabapentin x 12 wks Placebo	150	This study will evaluate the efficacy of gabapentin in outpatients with alcohol dependence	23
Vigabatrin	Open	Vigabatrin, 1 g p.o. b.i.d. x 3 d + Oxazepam, 75 [mean] mg/d	25	Vigabatrin significantly improved the CIWA-A score in patients with alcohol withdrawal syndrome	25
	Randomized Double-blind Comparative	Vigabatrin x 7 d Oxazepam x 7 d	38	CIWA-A scores decreased on days 2, 3, 5 and 7 as compared to day 1 in patients with alcohol withdrawal syndrome treated with either vigabatrin or oxazepam	26
Tiagabine	Randomized Single-blind	Tiagabine, 7.5 mg o.d. x 2 d → 15 mg o.d. x 5 d → Ethanol, 40 g i.v. over 15 min Placebo → Ethanol, 40 g i.v. over 15 min	20	Pretreatment with tiagabine did not prevent ethanol-induced stimulation of the mesolimbic system, but it augmented ethanol-induced hypometabolism in areas of the visual system and cerebellum	28

Continuation

Table I (Cont.): Clinical results for GABA-modulating antiepileptic drugs in the treatment of alcohol abuse (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Tiagabine	Retrospective Comparative	Tiagabine, 2 mg b.i.d. → increased to 4 [max.] mg b.i.d. x 5 d Oxazepam 30 mg b.i.d. → increased to 30 [max.] mg q.i.d. x 5 d	13	Tiagabine was well tolerated during acute ethanol withdrawal. Tiagabine was comparable to benzodiazepines in reducing withdrawal symptoms and showed a decreased trend for relapse	29
Valproate	Single-blind	Valproate, 5 mg/kg p.o. t.i.d. x 1 mo → Placebo x 1 mo → Valproate, 15 mg/kg p.o. t.i.d. x 1 mo	13	Low-dose sodium valproate was well tolerated and devoid of toxicity. Anxiety levels tended to fall during low-dose treatment, although no changes in the desire to drink were observed. Too few patients completed the trial to ascertain the safety and efficacy of valproate at a standard antiepileptic dose	30
	Randomized Double-blind	Valproate, 1500 mg/d p.o. x 12 wks Placebo	39	Valproate treatment was equivalent to placebo in reducing measures of heavy drinking, although a smaller percentage of patients treated with valproate relapsed to heavy drinking and greater reductions in irritability were observed in these patients	31
	Randomized Double-blind	Valproate, 750 mg/d [adjusted to C_{min} 50-100 μg/ml] + Lithium + Psychosocial interventions x 24 wks Placebo + Lithium + Psychosocial interventions x 24 wks	59	Valproate was well tolerated and significantly reduced heavy drinking in patients with bipolar I disorder and alcohol dependence	34
	Randomized Double-blind	Valproate-ER [C_{min} 70-120 μg/ml] x 12 wks Placebo	40	This clinical trial will examine the efficacy of extended-release valproate in the treatment of co-morbid mood and anxiety disturbances in alcohol-dependent subjects	35
Topiramate	Randomized Double-blind	Topiramate, 25-300 mg/d x 12 wks Placebo	150	Topiramate was more effective than placebo in reducing the number of drinks per day, drinks per drinking day and heavy-drinking days, and increasing abstinence rates in patients with alcohol dependence	40
	Randomized Double-blind	Topiramate, 25-300 [max.] mg/d x 8-12 wks Placebo	150	Topiramate improved drinking outcomes and the quality of life and decreased the severity of addiction and its deleterious effects in patients with alcohol dependence	41
	Open	Topiramate, 50-400 mg/d p.o. [titrated from 25 mg/d] x 12 wks	24	Topiramate was safe and well tolerated and may be a beneficial adjunctive therapy for the treatment of alcohol dependence	42
	Open Randomized Comparative	Topiramate, 50 mg + Trazodone p.o. PRN + Lorazepam PRN Lorazepam, 1 mg q.i.d. on d 1 → 1 mg b.i.d. on d 2 + Trazodone p.o. PRN + Lorazepam PRN	52	Preliminary results suggested that topiramate and lorazepam demonstrated similar efficacy on alcohol withdrawal symptoms	43
	Open	Topiramate x 13 wks	10	This study will investigate the efficacy of topiramate in reducing alcohol consumption in alcohol-dependent subjects, and whether alcohol consumption changes correlate with alterations in prefrontal cortex GABA concentrations	44
	Randomized Double-blind Crossover	Topiramate Placebo	134	This study will examine the dose-response relationship of the acute effects of topiramate on alcohol-induced craving, reward and euphoria. The effects of chronic treatment and whether topiramate interactions with alcohol are associated with neurocognitive impairment will also be assessed	45

Continuation

Table I (Cont.): Clinical results for GABA-modulating antiepileptic drugs in the treatment of alcohol abuse (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Topiramate	Randomized Double-blind	Topiramate, 25-300 mg/d [adjusted from 25 mg/d over 6 wks] x 14 wks Placebo	368	This study will provide data on the safety and efficacy of topiramate in reducing heavy-drinking days in patients with alcohol dependence	46
	Randomized Double-blind	Topiramate + Ondansetron x 13 wks Placebo	320	This study will evaluate whether the combination of topiramate and ondansetron is safe and effective in reducing alcohol consumption in patients with alcohol dependence	47
	Open	Topiramate	24	This study will test the potential utility of topiramate for reducing binge eating and drinking episodes in obese alcohol-dependent individuals with binge-eating disorder	49

BrAC: Breath alcohol concentration. CIWA-A: Clinical Institute Withdrawal Assessment for Alcohol Scale.

Non-GABA modulators

1. Carbamazepine

Carbamazepine is a sodium channel blocker that has been used for more than 40 years for the prophylactic management of epilepsy in adults and children, the symptomatic treatment of pain associated with trigeminal neuralgia and the treatment of psychosis. It has also been approved for the treatment of acute manic and mixed episodes associated with bipolar disorder. The drug's antiepileptic effects are attributed to the inhibition of voltage-sensitive sodium channels, which in turn stabilizes neuronal membranes, hence modifying the presynaptic release of excitatory amino acids (*i.e.,* glutamate). Carbamazepine's potential in the treatment of alcohol withdrawal seizures was first suggested more than two decades ago.

Several trials have investigated its effects in combination with other drugs, such as tiapride, a dopamine D2 receptor antagonist that has been used since 1977 for the treatment of delirium tremens, psychosis and Tourette syndrome. Combination therapy was hypothesized to provide improved control of withdrawal convulsions, anxiety, tremor and vegetative symptoms, while avoiding the risk of abuse or overdose. German researchers found a trend for a better control of withdrawal seizures with the combination of carbamazepine plus tiapride compared to clomethiazole monotherapy (50).

Further results from a prospective open study carried out by the same team of researchers showed similar improved CIWA-A scale scores with combined carbamazepine and tiapride, and also slightly more efficacy in reducing vegetative symptoms (tachycardia, hypertension) in both studies (50).

A pooled analysis of 540 patients demonstrated the safety of this combination and a decrease in withdrawal symptoms over time. Interestingly, approximately 19% of patients had a history of withdrawal-related delirium tremens, but during the detoxification period only 1.5% showed these symptoms (51).

In alcoholics subjected to an outpatient detoxification program, combined carbamazepine and tiapride therapy was well tolerated, with a clear decrease in withdrawal symptoms over time and excellent patient compliance (52). A larger study corroborated these findings, supporting the use of carbamazepine/tiapride combination therapy in the treatment of alcohol withdrawal on an outpatient basis (53). An additional open study found combined carbamazepine/tiapride to be as safe and effective as clomethiazole or diazepam in the management of moderate withdrawal symptoms in both intoxicated (breath alcohol concentration [BrAC] of 1 g/l or more) and nonintoxicated patients (BrAC < 1 g/l) (54).

In an outpatient setting, carbamazepine monotherapy demonstrated comparable efficacy to lorazepam for moderate alcohol withdrawal, but was superior in preventing rebound withdrawal symptoms and reducing post-treatment drinking, especially for patients with a previous history of multiple treated withdrawals (55). A small observational study confirmed the utility of carbamazepine monotherapy in alcohol withdrawal, indicating further improvement in mood symptoms and a reduction in hospitalization time (56).

In addition to its efficacy in treating withdrawal syndrome, a small study highlighted a positive effect on cognitive function, as carbamazepine treatment was associated with better verbal memory performance during the first days of treatment compared to clomethiazole (57).

2. Oxcarbazepine

Oxcarbazepine, a structural analogue of carbamazepine, exerts its antiepileptic activity by blocking voltage-sensitive sodium channels, inhibiting voltage-activated calcium currents and decreasing glutamatergic excitatory neurotransmission (58). Oxcarbazepine and carbamazepine were compared in an open pilot study in which oxcarbazepine was used alone or in combination with clomethiazole during alcohol withdrawal. Oxcarbazepine was better tolerated than carbamazepine and did not induce liver enzyme elevations in patients

with severe alcohol dependency (59). A further randomized, single-blind study compared oxcarbazepine and carbamazepine in 28 patients undergoing alcohol withdrawal therapy. Oxcarbazepine-treated patients showed a significant decrease in CIWA-A scores compared to the carbamazepine group. Also, patients receiving oxcarbazepine reported less perceived alcohol craving (craving intensity: 10.9%) compared to those treated with carbamazepine (50.2%) (60).

Case series observations regarding the safety and efficacy of oxcarbazepine in high-risk alcoholic patients who had often relapsed after detoxification and who were refractory to acamprosate treatment showed that 7 of 10 patients remained abstinent for the 3-month follow-up period. A marked reduction in craving was also reported (61). Oxcarbazepine was further compared to acamprosate in a 12-week open clinical trial in alcohol-dependent patients. Oxcarbazepine was well tolerated, even in patients taking alcohol concomitantly, and comparable to acamprosate in prolonging the time to severe relapse and time to first consumption of alcohol (62). In two additional reported cases, oxcarbazepine was successful in treating outpatient alcohol detoxification, resolving withdrawal symptoms and reducing craving (63).

3. Zonisamide

The anticonvulsant activity of zonisamide has been shown to be mediated by a variety of mechanisms, including blockade of voltage-dependent sodium channels, reduction of T-type-mediated calcium currents and, more recently, activation of large-conductance calcium-activated potassium (BK_{Ca}) channels (64). Zonisamide is effective in different types of epilepsy, such as focal or generalized seizures, as well as in other nonepileptic disorders (migraine, neuropathic pain) (65).

As zonisamide shares some structural and mechanistic similarities to topiramate, it has been hypothesized that it may also be beneficial in alcoholism. Preliminary findings by researchers at Boston University showed that zonisamide and topiramate had comparable efficacy in decreasing alcohol consumption in rats, and therefore prompted further clinical investigation of the effects of zonisamide in alcoholic patients (66, 67).

4. Levetiracetam

Levetiracetam (Keppra™; UCB Pharma) is an N-type calcium channel blocker approved as adjunctive therapy for partial or generalized epilepsy and currently under clinical investigation for panic disorder, obsessive-compulsive disorder and alcoholism, among other conditions. Preclinical findings showed that levetiracetam prevented spontaneous tremors and handling-induced convulsions in mice subjected to forced ethanol drinking and subsequent withdrawal (68). In humans, levetiracetam therapy for 6 days (doses ranging from 500 to 2000 mg) was well tolerated and induced rapid clinical improvement in withdrawal symptoms in patients with mild to severe withdrawal syndrome (69). According to this study, levetiracetam appears to be a potential alternative to benzodiazepines in treating alcohol withdrawal, since only 1 patient required additional diazepam therapy due to moderate withdrawal symptoms. These preliminary results will be further investigated in a larger randomized, double-blind, controlled clinical trial (70). Moreover, levetiracetam does not worsen liver function tests in patients with mild to moderate liver cirrhosis, thus appearing to be safe for treating alcoholic patients. However, caution should be exercised in severely cirrhotic patients, who should initially receive half of the recommended dose (71).

The appearance of anxiety in alcoholic patients who discontinue alcohol use may interfere with the treatment of alcohol dependence. Therefore, researchers at UCB are investigating, in collaboration with the New York State Psychiatric Institute, the efficacy of levetiracetam in treating alcohol-dependent patients with co-existing anxiety (72). In preclinical studies, levetiracetam was found to reduce anxiety symptoms associated with chlordiazepoxide withdrawal in mice (73).

5. Lamotrigine

The antiepileptic drug lamotrigine (Lamictal™; GlaxoSmithKline), a dual sodium channel blocker and glutamate release inhibitor, is also effective in treating bipolar disorder and is undergoing clinical investigation for the treatment of neuropathic pain, postherpetic neuralgia and multiple sclerosis. Some psychiatric conditions present concomitantly with alcohol dependence and are associated with increased alcohol relapse or worsening of psychiatric disease prognosis. A 12-week open-label study evaluated the effects of lamotrigine in ambulatory patients with bipolar disorder and alcohol dependence (74). Lamotrigine adjunctive treatment (up to a maximum dose of 300 mg/day) improved mood symptoms, as assessed by psychiatric rating scales, and also produced a reduction in weekly alcohol consumption and craving.

Although the efficacy of lamotrigine in schizophrenia has not been proven, evidence from isolated cases indicated a potentiation of clozapine-induced reduction of alcohol use. Kalyoncu *et al*. reported 3 schizophrenic patients presenting with co-morbid alcohol dependence who were treated with clozapine. Lamotrigine was added to their treatment and all 3 were included in psychosocial programs for both schizophrenia and alcohol dependence. The addition of lamotrigine was found to be safe and to reduce craving, which prolonged abstinence time in these patients (75).

Recently, a randomized, single-blind, placebo-controlled clinical study has reported efficacy in treating alcohol withdrawal syndrome for lamotrigine and other antiglutamatergic drugs, comparable to diazepam. In this study, lamotrigine was slightly better than memantine and topiramate in reducing withdrawal severity scores (76) (see Table II).

Conclusions

Alcohol dependence is an important public health problem that requires both pharmacological and psy-

Table II: Clinical results for non-GABA-modulating antiepileptic drugs in the treatment of alcohol abuse (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Carbamazepine	Pooled meta-analysis	Carbamazepine, 200 mg p.o. 1x/4 h → 800 [max.] mg/d in men or 600 [max.] mg/d in women + Tiapride, 300 mg p.o. 1x/4 h → 1200 [max.] mg/d → downtitrated over 10 d Clomethiazole, 384-768 mg p.o. → 384 mg p.o. 1x/1-2 h → 4608 [max.] mg/d → downtitrated over 10 d	140	The combination of tiapride and carbamazepine reduced heart rate and blood pressure in both retrospective and prospective studies. Withdrawal symptoms, as assessed by CIWA-Ar score, in the prospective study improved faster with tiapride/carbamazepine treatment than with clomethiazole	50
	Pooled meta-analysis	Carbamazepine, 543 [mean] mg on d 1 → 680 [mean] mg on d 2 → downtitrated over 10 d + Tiapride 796 [mean] mean on d 1 → 1035 [mean] mean on d 2 → downtitrated over 10 d	540	The combination of carbamazepine and tiapride was effective in the management of alcohol withdrawal in patients with alcohol dependence. Patient compliance was good and only a few patients suffered from delirium or seizures during treatment	51
	Open	Carbamazepine, 600 mg/d p.o. + Tiapride, 300 mg/d p.o. x 5-7d → downtitrated	50	Combined carbamazepine and tiapride therapy was well tolerated and effective in outpatient alcohol detoxification in patients with moderate withdrawal syndrome	52
	Open	Carbamazepine, 502 [mean] mg + Tiapride, 289 [mean] mg	116	The combination of carbamazepine and tiapride was safe, well tolerated and effective in the treatment of alcohol dependence	53
	Open	Carbamazepine, 1200 [max.] mg/d + Tiapride, 1800 [max.] mg/d x 9 d Clomethiazole, 3840 [max.] mg/d x 9 d Diazepam, 80 [max.] mg/d x 9 d	127	Carbamazepine/tiapride was safe and effective in the management of moderate withdrawal symptoms in intoxicated (BrAC = 1 g/l or more) patients; however, it was not effective in 6 of 28 nonintoxicated patients (BrAC < 1 g/l)	54
	Randomized Comparative	Carbamazepine, 600-800 mg/d p.o. → downtitrated to 200 mg/d p.o. over 5 d + Thiamine, 100 mg/d p.o. x 12 d Lorazepam, 6-8 mg/d p.o. → downtitrated to 2 mg/d p.o. over 5 d + Thiamine, 100 mg/d p.o. x 12 d	136	Carbamazepine and lorazepam showed comparable efficacy in treating alcohol withdrawal symptoms. Carbamazepine was superior to lorazepam in preventing rebound withdrawal symptoms and reducing post-treatment drinking, especially in patients with a previous history of multiple treated withdrawals	55
	Randomized Single-blind Comparative	Carbamazepine, 600 mg/d p.o. x 3d → 300 mg p.o. x 1 d → 100 mg p.o. x 1 d Clomethiazole, 378 mg p.o. 5x/d x 3 d → 378 mg p.o. 3x/d x 1 d → 378 mg p.o. x 1 d	37	Carbamazepine and clomethiazole were equally effective in controlling alcohol withdrawal symptoms, although carbamazepine provided a better clinical outcome in terms of verbal memory performance compared to clomethiazole	57
Oxcarbazepine	Open Comparative	Oxcarbazepine, 1200 mg/d p.o. x 3 wks Oxcarbazepine, 1200 mg/d + Clomethiazole [during withdrawal] x 3 wks Carbamazepine, 800 mg/d p.o. x 3 wks	20	Oxcarbazepine appeared to be better tolerated than carbamazepine and did not induce liver enzyme elevations in patients with severe alcohol dependency	59
	Randomized Single-blind Comparative	Oxcarbazepine, 900 mg p.o. x 3 d → 450 mg p.o. x 1 d → 150 mg p.o. x 1 d + Clomethiazole [if not sufficient response] Carbamazepine, 600 mg p.o. x 3 d → 300 mg p.o. x 1 d → 100 mg p.o. x 1 d + Clomethiazole [if not sufficient response]	29	Oxcarbazepine treatment produced a significant decrease in withdrawal symptoms and less craving for alcohol compared to carbamazepine treatment in patients with alcohol dependence	60
	Open	Oxcarbazepine 300 mg/d p.o. → increased to 900 [max.] mg/d p.o. over 1 wk → 1200 mg/d p.o. [adjusted to clinical response]	10	Oxcarbazepine treatment was effective in reducing craving in all patients with co-morbid alcohol and nicotine dependence	61
	Randomized Open Comparative	Oxcarbazepine, 150 mg/d p.o. → increased by 150 mg/d over 12 d → 1200 [max.] mg/d x 12 wks Acamprosate, 1998 mg/d p.o. x 12 wks	30	Oxcarbazepine was safe and well tolerated and showed similar efficacy to acamprosate in prolonging the time to severe relapse and time to first consumption of alcohol in patients with alcohol dependence	62

Continuation

Table II (Cont.): Clinical results for non-GABA-modulating antiepileptic drugs in the treatment of alcohol abuse (from Prous Science Integrity®).

Drug/Intervention	Design	Treatments	n	Conclusions/Objectives	Ref.
Zonisamide	Double-blind Crossover	Zonisamide Placebo	10	This pilot study will evaluate the effect of zonisamide on alcohol self-administration and on cognitive functioning in heavy alcohol users	66
	Open	Zonisamide x 13 wks	20	This study will investigate the effects of zonisamide on alcohol consumption in subjects with alcohol dependence	67
Levetiracetam	Open	Levetiracetam, 1000 mg/d p.o. x 1 d → 2000 mg/d p.o. x 2 d → 1500 mg/d p.o. x 1 d → 1000 mg/d p.o. x 1 d → 500 mg/d p.o. x 1 d + Diazepam, 5 mg/d p.o. → 30 [max.] mg/d p.o. [if persistent withdrawal symptoms or insomnia] + Clonidine, 75 mg/d p.o. → 400 [max.] mg/d p.o. [if hypertonia]	15	Levetiracetam therapy was well tolerated and resulted in rapid clinical improvement in alcohol withdrawal symptoms in all patients	69
	Open	Levetiracetam	30	This study will evaluate the efficacy of levetiracetam in treating alcohol dependence in patients presenting with associated anxiety symptoms	72
Lamotrigine	Open	Lamotrigine, 25 mg/d p.o. o.d. x 2 wks → 50 mg p.o. o.d. x 2 wks → 75 mg/d p.o. x 1 wk → 100 mg/d p.o. x 1 wk → escalated by 50 mg/wk up to 300 [max.] mg/d + Diazepam, 15-50 mg/d p.o. x 1 wk	28	Lamotrigine therapy improved mood clinical scores and reduced alcohol craving and consumption in patients with alcohol dependence and bipolar disorder	74
	Randomized Single-blind Comparative	Lamotrigine, 25 mg p.o. q.i.d. x 7 d Topiramate, 25 mg p.o. q.i.d. x 7 d Memantine, 10 mg p.o. t.i.d. x 7 d Diazepam, 10 mg p.o. t.i.d. x 7 d Placebo	25	Lamotrigine, memantine, topiramate and diazepam significantly reduced observer-rated and self-rated withdrawal severity, dysphoric mood and supplementary diazepam administration compared with placebo. The active medications did not differ from diazepam in treating alcohol withdrawal symptoms in alcohol-dependent men	76

BrAC: Breath alcohol concentration. CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale, revised. CIWA-A: Clinical Institute Withdrawal Assessment for Alcohol Scale.

chosocial treatment approaches specifically geared to maintain sobriety and avoid relapse. Ideally, drugs for the treatment of alcoholism should be devoid of addiction potential and promote abstinence by reducing alcohol craving and consumption and alleviating withdrawal symptoms. Antiepileptic agents, alone or in combination, have been shown to attenuate withdrawal syndrome, alcohol craving and consumption. In addition, antiepileptics appear to be particularly beneficial in treating alcoholic patients with psychiatric co-morbidities, a highly prevalent group among the alcohol-dependent population who are at increased risk of relapse. Currently ongoing clinical trials of gabapentin, valproate and topiramate will provide much needed information on the safety and efficacy of these drugs in the management of alcohol dependence.

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