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Anticonvulsants for the Treatment of Alcohol Withdrawal Syndrome and Alcohol Use Disorders

Christopher J. Hammond[1,2], **Mark J. Niciu**[3], **Shannon Drew**[4], and **Albert J. Arias**[2,4]

[1] Yale Child Study Center, Yale University School of Medicine, PO Box 207900, 230 South Frontage Road, New Haven, CT 06520, USA

[2] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[3] Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, Bethesda, MD, USA

[4] Veterans Affairs Connecticut Healthcare System-West Haven Campus, West Haven, CT, USA

Abstract

Alcoholic patients suffer from harmful allostatic neuroplastic changes in the brain causing an acute withdrawal syndrome upon cessation of drinking followed by a protracted abstinence syndrome and an increased risk of relapse to heavy drinking. Benzodiazepines have long been the treatment of choice for detoxifying patients and managing alcohol withdrawal syndrome (AWS). Non-benzodiazepine anticonvulsants (NBACs) are increasingly being used both for alcohol withdrawal management and for ongoing outpatient treatment of alcohol dependence, with the goal of either abstinence or harm reduction. This expert narrative review summarizes the scientific basis and clinical evidence supporting the use of NBACs in treating AWS and for reducing harmful drinking patterns. There is less evidence in support of NBAC therapy for AWS, with few placebo-controlled trials. Carbamazepine and gabapentin appear to be the most promising adjunctive treatments for AWS, and they may be useful as monotherapy in select cases, especially in outpatient settings and for the treatment of mild-to-moderate low-risk patients with the AWS. The body of evidence supporting the use of the NBACs for reducing harmful drinking in the outpatient setting is stronger. Topiramate appears to have a robust effect on reducing harmful drinking in alcoholics. Gabapentin is a potentially efficacious treatment for reducing the risk of relapse to harmful drinking patterns in outpatient management of alcoholism. Gabapentin's ease of use, rapid titration, good tolerability, and efficacy in both the withdrawal and chronic phases of

Albert J. Arias albert.arias@yale.edu.
Christopher J. Hammond christopher.hammond@yale.edu

[1]The term ‘reversibility’ refers to whether the drug binds but is capable of dissociating from the enzyme, or whether it permanently binds the enzyme, thus essentially destroying it. The term ‘selectivity’ refers to whether or not the drug affects either or both MAO-A and MAO-B enzymes.

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treatment make it particularly appealing. In summary, several NBACs appear to be beneficial in treating AWS and alcohol use disorders.

1 Introduction

Alcohol use disorders (AUDs) will affect approximately 30 % of the US population in their lifetime, and are associated with significant morbidity and mortality, costing the nation an estimated US $185 billion per year [1, 2]. Globally, AUDs (with an estimated average world lifetime prevalence of 4.1 %) are thought to cause somewhere between 2.3 and 3.3 million deaths each year (approximately 5 % of all deaths), more than HIV and tuberculosis, and are the third leading global risk factor for disease and disability [3, 4]. AUD pathophysiology is rooted in harmful allostatic neuroplastic changes that occur in the brain, especially in the ventral striatum, due to repeated heavy drinking [5]. These harmful changes result in a dependence syndrome characterized by an inability to control consumption, development of tolerance, withdrawal upon cessation, and also a protracted abstinence syndrome that can persist long after detoxification [6].

The major excitatory and inhibitory neurotransmitters in the brain, glutamate and GABA, respectively, and their receptors have been implicated in the pathophysiology of AUDs [7]. Alcohol is a $GABA_A$ receptor positive allosteric modulator and a NMDA (ionotropic glutamate) receptor negative allosteric modulator. In both preclinical models of AUDs and in clinical neuroimaging studies, glutamatergic and GABAergic dysfunction have been hypothesized and identified [8–10]. For example, alcohol withdrawal syndrome (AWS) has been postulated to result from the removal of exogenous alcohol on a chronically imbalanced ratio of glutamatergic/GABAergic neurotransmission, which increases the risk for withdrawal seizures due to excessive excitatory neurotransmission [11, 12].

Many non-benzodiazepine anticonvulsant (NBAC) medications have effects on glutamatergic and GABAergic neurotransmission; these medications, therefore, may have a broad capacity for treatment of alcohol dependence in both withdrawal and relapse prevention via stabilizing effects in the brain in the setting of an allostatic set-point [13]. As a class, NBACs are neuroinhibitory through GABAergic or glutamatergic mechanisms or effects on other classes of ion channels [14]. Individually, however, NBACs vary widely by mechanism of action. This expert narrative review summarizes the scientific evidence for the use of NBACs for the treatment of the AWS and AUD.

1.1 The Role of Pharmacotherapy in the Treatment of Alcohol Use Disorder (AUD)

Benzodiazepines are the treatment of choice for alcohol withdrawal, their use being supported by a strong evidence base demonstrating a reduction in complications [seizures, delirium tremens (DTs)] as well as symptoms [15]. While behavioral and psychosocial interventions remain the mainstay of treatment for AUD, relapse rates remain high without medication treatment [16]. Pharmacotherapies are gaining traction as treatments for use in relapse prevention, by reducing craving and drinking [6]. To date, three medications have been approved by the US FDA for the treatment of alcohol dependence: disulfiram, acamprosate, and naltrexone. Nalmefene has been approved for treatment of alcohol

dependence in Europe. None of these medications has been demonstrated to ameliorate alcohol withdrawal symptoms. Therefore, a treatment gap exists between detoxification and long-term treatment for harm reduction and/or relapse prevention. While AWS and long-term AUD represent a clinical ‘continuum’, they are traditionally treated separately in different clinical contexts with divergent pharmacologic and behavioral management approaches; as expected, attrition is high during these transitions [6]. Developing treatments effective for both AWS and long-term AUDs may enhance treatment adherence/retention, and, thereby, reduce morbidity and mortality.

2 Methods

We conducted a series of English-language medical literature searches using the PubMed, Cochrane Library, and PsycINFO databases using the search terms “medication”, “pharmacotherapy”, “psychopharmacology”, “alcohol abuse”, “alcohol dependence”, “alcohol use disorder”, “alcohol withdrawal syndrome”, “alcohol withdrawal”, “non-benzodiazepine anticonvulsants”, “anticonvulsants”, and the specific medications: “carbamazepine”, “oxcarbazepine”, “valproic acid”, “divalproex”, “gabapentin”, “pregabalin”, “levetiracetam”, “tiagabine”, “lamotrigine”, “topiramate”, and “zonisamide”. We used search terms for alcohol related disorders using diagnostic categories from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (alcohol abuse and dependence diagnoses) [121] and the fifth edition of the DSM (DSM-5) (alcohol use disorder) [122] as many of the studies reviewed predated the release of DSM-5 in 2013. Studies included in the review were cited with reference to the inclusionary criteria and edition of the DSM manual used. We manually searched reference lists of pertinent original research articles, review articles, and textbooks for relevant citations that our searches missed. Articles were selected if they involved human subjects and included original clinical data on pharmacotherapies targeting drinking behaviors, AUDs, or AWS. We also included pharmacotherapy trials targeting co-morbid/co-occurring psychiatric disorders and AUDs if they reported on alcohol-related health outcomes. These trials included double-blind randomized clinical trials (RCTs) comparing one medication with placebo or another medication, non-randomized open-label trials, and prospective cohort studies if they reported on alcohol-related health outcomes.

3 Non-Benzodiazepine Anticonvulsants (NBACs) for the Treatment of Alcohol Withdrawal Syndrome (AWS)

Among patients with moderate-to-severe AUD, abrupt alcohol discontinuation is associated with CNS and autonomic hyper-excitability, leading to associated signs and symptoms (e.g., tremulousness, tachycardia, confusion, seizures) that can be used (along with the patient's detoxification history and medical status) to stratify patients into mild, moderate, or severe AWS severity and risk categories [17]. Subjects with histories of complications (i.e., seizures, DTs) during withdrawal are known to be at higher risk for developing them again, a phenomenon often referred to as the ‘kindling’ phenomenon in alcohol withdrawal [18].

Minozzi et al. [19] recently completed a Cochrane review of NBACs for the treatment of AWS including 56 studies and a total of 4076 participants. While examining only

randomized controlled trials, the authors had difficulty quantifying trial differences due to heterogeneity in study design and outcomes. Comparing anticonvulsants to placebo and comparing different anticonvulsants head-to-head, the authors found no statistically significant differences in alcohol withdrawal symptoms measured by a psychometrically validated and commonly used instrument, the Clinical Institute Assessment of Alcohol Scale-revised (CIWA-Ar), or on outcomes of alcohol withdrawal seizures, DTs, adverse events, or attrition. Comparing different NBACs to benzodiazepines, the authors found that only carbamazepine was associated with a significant reduction in alcohol withdrawal symptoms (CIWA-Ar mean difference = –1.04, 95 % CI –1.89 to –0.20) when compared with the benzodiazepines lorazepam and oxazepam. The authors concluded that there was insufficient data to favor the use of NBACs over benzodiazepines for treatment of AWS.

The results from the Minozzi et al. [19] review underscore the difficulty in developing and conducting well-designed studies to examine AWS. As there is strong evidence to support that benzodiazepines reduce alcohol withdrawal seizures and delirium, there are ethical issues related to use of placebo-controlled designs, leaving the literature with limited data comparing anticonvulsants to placebo for the treatment of AWS. Most studies examining NBACs for the treatment of AWS have either used the study drug as an adjunctive treatment to benzodiazepines to examine alcohol withdrawal symptoms as an outcome measure or compared the study drug to placebo or another drug to examine the amount of symptom-triggered benzodiazepine that is required for safe detoxification as an outcome measure. Symptom-triggered dosing refers to the treatment of AWS by monitoring for withdrawal symptoms at specific time intervals and providing intermittent doses of a benzodiazepine to treat those remaining symptoms after their intensity is determined.

For severe AWS, a meta-analysis of randomized placebo-controlled studies provides clear evidence that benzodiazepines reduce the incidence of alcohol withdrawal seizures (–7.7 seizures per 100 patients) and alcohol withdrawal delirium (–4.9 cases per 100 patients) [15]. It is unclear if NBACs provide the same degree of protection from seizures and DTs and most studies are under-powered to detect differences in seizure and DT rates between groups. Phenytoin has been shown to be ineffective at preventing alcohol withdrawal seizures [20, 21].

3.1 Carbamazepine/Oxcarbazepine

Carbamazepine and its derivative oxcarbazepine inhibit voltage-gated sodium channels and potentiate GABAergic neurotransmission [22, 23]. In addition to the above-mentioned Cochrane review showing some evidence in support of carbamazepine for treating withdrawal, perhaps with some advantages over benzodiazepines, Barrons and Roberts [24] recently completed a systematic review of carbamazepine and oxcarbazepine for the treatment of AWS which also lends support. Across seven studies encompassing five inpatient and two outpatient studies with 612 patients, carbamazepine was associated with a significant reduction in alcohol withdrawal symptoms as measured by CIWA-Ar [25–32]. Carbamazepine was found to be safe and tolerable when administered at daily doses of 800 mg (fixed or tapered over 5–9 days). Four (one out-patient and three inpatient) studies compared carbamazepine to benzodiazepines for the treatment of AWS [25, 27, 29, 30]. No

significant differences were found on seizure incidence and DTs, although there was significant heterogeneity, and as most of the studies were designed to examine withdrawal symptoms (i.e., CIWA-Ar scores), they were underpowered to assess carbamazepine's role in the reduction of seizures and DTs [22]. One of the more promising studies of carbamazepine treatment of AWS was performed by Malcolm et al. [27]; it showed equal effectiveness in detoxification along with some distinct advantages over lorazepam in the early post-detoxification period (described in more detail in Sect. 4).

Two studies have examined the effects of oxcarbazepine on AWS. Koeth et al. [33] completed a double-blind placebo-controlled study of oxcarbazepine for inpatient AWS treatment in 50 subjects with a DSMIV diagnosis of alcohol dependence and a history of severe AWS, with the primary outcome being the number of symptom-triggered clomethiazole capsules. No differences were found between oxcarbazepine and placebo on any of the outcome measures. A 7-day single-blind pilot study by Schik and colleagues [34] compared oxcarbazepine and carbamazepine for the in-patient treatment of alcohol withdrawal in 28 subjects and found that oxcarbazepine but not carbamazepine was associated with a significant reduction in CIWA-Ar scores from baseline; however, this result was driven primarily by the difference in day 1 withdrawal symptoms. No oxcarbazepine and carbamazepine group differences were noted in average CIWA-Ar scores across the completed study period.

3.2 Valproic Acid/Divalproex

Valproic acid's mechanism of action in neuropsychiatric disorders, while not fully understood, is likely related to reduction in phosphatidylinositol 3,4,5-triphosphate, blockade of voltage-gated sodium channels, and increased GABAergic neurotransmission [35]. A systematic review including six studies and 281 subjects examined the efficacy and safety of valproic acid for the treatment of AWS [36]. Many of the studies were methodologically flawed, did not use validated measures of withdrawal symptoms, and were underpowered to examine seizures and DTs as outcomes. Two studies revealed statistically significant effects favoring valproic acid. Of the six studies, only two were prospective placebo-controlled, randomized, double-blind trials. Reoux et al. [37] completed a small study of divalproex sodium (500 mg three times per day) for the inpatient treatment of moderate AWS in 36 adults who met DSM-IV criteria for alcohol dependence. The primary outcome measure from this study was the amount of symptom-triggered oxazepam, and secondary outcome measures included progression of alcohol withdrawal symptoms as detected by CIWA-Ar. Divalproex sodium use was associated with significantly less symptom-triggered oxazepam and attenuated progression of withdrawal symptoms compared with placebo. Hillbom and colleagues [31] compared valproic acid, carbamazepine, and placebo with regards to the incidence of seizures and DTs in 138 alcohol-dependent inpatients treated for AWS. While p values were not reported, seizures occurred in 2.2 % of patients receiving valproic acid and 4.7 % receiving carbamazepine compared with 6.1 % receiving placebo. More patients treated with valproic acid (4.4 %) than with carbamazepine (0 %) and placebo (2 %) experienced DTs.

3.3 Gabapentin and Pregabalin

Gabapentin and the second-generation agent pregabalin are of theoretical interest in AWS due to their GABAergic properties and inhibitory effect on voltage-gated calcium channels containing the α-2δ-1 subunits [38]. Gabapentin has been examined for the treatment of mild-to-moderate and severe AWS in two inpatient and two outpatient randomized controlled studies and for severe AWS in one open-label inpatient study.

In a two-center randomized placebo-controlled trial by Bonnet et al. [39], gabapentin was tested as an adjunctive medication to symptom-triggered clomethiazole for 61 inpatients with alcohol dependence and moderate-to-severe AWS. Gabapentin 400 mg four times a day was compared to placebo in 61 alcohol-withdrawing patients and throughout the 7-day trial was found to have no advantage over placebo in reducing amount of clomethiazole required to decrease symptoms of alcohol withdrawal. Gabapentin was also noted to be safe, well-tolerated, and have a low side effect profile. A randomized, open-label, controlled trial with hospital inpatients compared gabapentin with phenobarbital in the AWS treatment of 27 individuals with alcohol dependence [40]. A 4-day detoxification was offered to both groups with symptom-triggered phenobarbital used for breakthrough withdrawal. Both groups had similar rates of completers and no significant difference in as-needed (PRN) medication requirements. Subjects in each treatment group who required PRN phenobarbital had significantly higher CIWA-Ar scores at baseline. No group differences on alcohol withdrawal, craving, mood, irritability, anxiety, or sleep were observed.

A 2009 double-blinded RCT by Myrick et al. [41] evaluated gabapentin compared with lorazepam in reducing symptoms of alcohol withdrawal in the outpatient setting. One hundred subjects with DSM-IV diagnosis of alcohol dependence and alcohol withdrawal were randomized to receive gabapentin at one of three different fixed-dose taper regimens (600, 900, or 1200 mg/day starting dose) or lorazepam (6 mg/day starting dose) for 4 days with symptom-triggered rescue doses to treat breakthrough withdrawal. Patients were seen daily on days 1–5, 7, and 12. The lowest-dose gabapentin group (600 mg/day) was discontinued after two patients had seizures and one a presyncopal event and their data were not included in the analyses. CIWA-Ar scores decreased over the first 4 days in all treatment groups, but the high-dose gabapentin group (1200 mg/day) had the lowest scores with a continued downward trajectory even after medication discontinuation. Both gabapentin groups had decreased drinking, reduced craving, and decreased anxiety compared with lorazepam during the active treatment days. The high-dose gabapentin group also reported better sleep, less daytime sedation, and better ability to work during follow-up than the lorazepam group. No subjects developed DTs.

Stock and colleagues completed a randomized, double-blind controlled study in an outpatient setting where gabapentin was compared with chlordiazepoxide in 26 veterans (25 males and one female) with mild-to-moderate AWS [42]. Gabapentin (1200 mg/day starting dose) and chlordiazepoxide (100 mg/day starting dose) were administered according to a fixed-dose taper schedule over 6 days and outcome measures included sleepiness, alcohol craving, and ataxia in addition to CIWA-Ar scores. There were no significant differences in AWS symptoms by medication; however, those in the gabapentin group reported decreased daytime sleepiness compared with those who received chlordiazepoxide.

In a 2010 open-label study by Bonnet and colleagues, a higher gabapentin loading dose was studied in patients with more severe alcohol withdrawal symptoms (CIWA-Ar > 15) [43]. A loading dose of gabapentin 800 mg was administered and patients were then monitored and stratified into ‘early responders’ or ‘non-responders’ groups based upon CIWA-Ar score triggering. If withdrawal symptoms decreased over the next 2 h, these subjects were termed ‘early responders’ (27 patients) and administered gabapentin 600 mg four times/day for the next 24 h with tapering over the next several days. For the patients who did not respond within the first 2 h (ten patients), gabapentin was switched to clomethiazole or clonazepam. While 73 % of patients responded to gabapentin 800 mg initially, there were increasing AWS in one subject and two subjects had a seizure in the following 36 h. Non-responders generally had more severe symptoms of alcohol withdrawal—including autonomic hyperarousal—and greater depression and anxiety. While this study was open-label, it does suggest that gabapentin is likely not an effective stand-alone medication in severe AWS.

In summary, gabapentin may be an effective pharmacotherapy in the treatment of mild-to-moderate but not severe AWS symptoms. Due to its limited abuse potential, decreased sedation compared to benzodiazepine-based detoxification, relative safety when combined with alcohol, and, as described in Sect. 4, its potential for relapse prevention and/or reducing harmful drinking, gabapentin appears to be a useful pharmacotherapy for alcohol-dependent individuals with mild-to-moderate AWS, and may be particularly useful in outpatient treatment settings.

Two outpatient studies have examined the efficacy of pregabalin for mild-to-moderate AWS. First, Di Nicola and colleagues conducted an open-label prospective study of pregabalin (flexible dosing regimen between 200 and 450 mg/day) for the outpatient treatment of mild-to-moderate AWS in 40 DSM-IV-diagnosed alcohol-dependent subjects [44]. Pregabalin was safe and tolerable and associated with a significant reduction in CIWA-Ar scores and alcohol craving. Second, pregabalin, tiapride, and lorazepam were compared head-to-head for the outpatient treatment of AWS in 111 subjects with DSM-IV-TR [123] diagnoses of alcohol dependence [45]. All medications significantly reduced AWS, with pregabalin demonstrating significantly better treatment for ‘headache’ and ‘orientation’ withdrawal symptoms. A recent prospective randomized, double-blind, placebo-controlled study has examined the efficacy and safety of pregabalin for treatment of AWS in 42 alcohol-dependent subjects in an in-patient setting using the total amount of symptom-triggered diazepam as the primary outcome measure and reduction in the CIWA-Ar score as a secondary outcome [46, 47]. In this study, pregabalin was equally safe and tolerable but there were no significant between-group differences in the amount of symptom-triggered diazepam or CIWA-Ar scores compared to placebo. These studies provide preliminary evidence that there may be a role for stand-alone pregabalin in the treatment of mild-to-moderate AWS.

3.4 Levetiracetam

The mechanism of levetiracetam for treatment of neuropsychiatric disorders is thought to be related to neuroinhibitory effects produced by inhibition of presynaptic calcium channels and its binding to synaptic vesicle glycoprotein SV2A [48]. There has only been one study

to date that has examined the efficacy of levetiracetam for AWS [47]. In this multicenter, randomized, double-blind placebo-controlled trial, 116 patients were randomized to fixed-dose levetiracetam (starting dose 2000 mg with standardized taper over 6 days) or placebo and symptom-triggered diazepam. While levetiracetam was safe and well-tolerated, no between-group differences were observed for the total diazepam required and CIWA-Ar scores.

3.5 Topiramate and Zonisamide

Topiramate and zonisamide are anticonvulsants approved for the treatment of seizure disorders and migraines and for the adjunctive treatment of partial seizures, respectively. Zonisamide has a unique and multifaceted pharmacological profile; like topiramate, it blocks voltage-dependent sodium channels and inhibits carbonic anhydrase [49, 50]. Zonisamide's effects on GABA and glutamate neurotransmission, however, are less clear; zonisamide may indirectly facilitate GABA and reduce glutamate transmission as opposed to topiramate's direct effects on $GABA_A$ and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors [51, 52]. Topiramate is thought to block L-type calcium channels, but zonisamide appears to be a T-type calcium channel antagonist [49]. Zonisamide may also have direct and biphasic effects on the neuronal release of both dopamine and serotonin [53, 54].

Recently, zonisamide was shown to be an effective adjunct therapy for Parkinson disease, an observation attributed to increased dopamine production in the striatum. This response may include a reversible monoamine oxidase (MAO)-B inhibitory effect, and, consequently, a neuro-protective effect against metabolic stressors [55, 56]. Reversible[1] MAO inhibitors (e.g., moclobemide and zonisamide) are not associated with the adverse effects attributed to traditional MAO inhibitors (e.g., phenelzine, tranylcypramine), which are non-selective and irreversibly bind MAO. As a result, hypertensive crises or dietary restrictions are non-issues. Reversible MAO-B inhibition may also help to explain the beneficial effects of zonisamide on mood and anxiety. Zonisamide is a GABA transporter 1 (GAT1) reuptake inhibitor. In the rat hippocampus and frontal cortex, zonisamide also upregulated and enhanced the function of the glutamate transporter EAAT3 (excitatory amino-acid transporter 3)/EAAC1 (excitatory amino-acid carrier 1) and downregulated the GAT1 [52]. By this mechanism, zonisamide may increase glutamate clearance and potentiate GABAergic neuro-transmission with implications in the treatment of AUDs.

Preliminary studies have suggested that the newer anticonvulsants topiramate and zonisamide may treat AWS. One randomized single-blind placebo-controlled trial compared multiple glutamatergic modifying agents (topiramate, lamotrigine, memantine, and diazepam) on observer-rated (CIWA-Ar) and self-reported [Alcohol Withdrawal Symptom Checklist (AWSC)] AWS in 127 alcohol-dependent males [57]. Topiramate was administered in a fixed dose of 25 mg every 6 h (100 mg/day), and symptom-triggered diazepam was provided for rescue if study medications failed to suppress acute withdrawal symptoms. All active study medication arms—topiramate, lamotrigine, memantine, and diazepam—significantly reduced observer-rated and self-reported AWS when compared to

placebo, but no between-drug differences were observed on these measures or symptom-triggered benzodiazepine administration.

Choi et al. [58] compared topiramate with lorazepam for treating AWS in a randomized, open-label study of 52 hospitalized patients. Both medications treated AWS well and there were no differences in outcomes. A small (n = 12) open-label trial of topiramate in outpatients with AWS suggested that it was safe and well-tolerated and showed promise for the treatment of withdrawal symptoms [59].

A 3-week randomized flexible-dose pilot study was completed comparing zonisamide with diazepam for the treatment of AWS in 40 alcohol-dependent subjects [60]. Zonisamide was started at a dose range of 400–600 mg/day and tapered over the remaining 3 weeks to 100–300 mg/day. AWS decreased significantly in both the zonisamide and diazepam groups with a more marked reduction in the zonisamide group. However, the zonisamide group received more symptom-triggered diazepam for rescue of breakthrough symptoms, a potential confound. At endpoint, the zonisamide group had lower CIWA-Ar, craving, and anxiety scores than the diazepam group. While promising, there are insufficient data to support the use of topiramate or zonisamide for the treatment of AWS at this time.

3.6 Summary of Evidence and Recommendations for AWS

Table 1 shows a summary of the evidence for the use of NBACs for AWS. Carbamazepine and gabapentin have the most evidence suggesting usefulness in treating the AWS; however, the evidence base is not robust. Findings suggest that they likely can be used as an adjunct therapy for AWS treatment, regardless of severity and risk level at presentation. Both are potential monotherapy agents for patients with mild-to-moderate AWS symptoms that are also at low risk for progressing to severe alcohol withdrawal symptoms or complications. The current literature does not support the use of valproic acid/divalproex as a stand-alone treatment for AWS, though it may have some use as an adjunct.

4 Anticonvulsants for the Treatment of Harmful Drinking Patterns in AUDs

With long-term heavy drinking, alcoholic patients develop a ‘protracted abstinence syndrome’ in which they need at least some alcohol to attempt to feel a ‘normal’ mood, reward, and stress response [5]. These deleterious effects of alcohol on the brain may take considerable time, likely on the scale of months to years, of continued sobriety to reverse. It is hypothesized that NBACs are well-suited for managing the symptoms of altered hedonic function, stress reactivity, and craving/urge to drink that are part of the protracted abstinence syndrome in alcoholism.

NBAC effects on glutamatergic and GABAergic neurotransmission may help combat the symptoms of the protracted abstinence syndrome by restoring proper neurotransmission in the ventral striatum and its neurocircuitry. Anticonvulsants may facilitate homeostasis and restorative changes once a subject has obtained sobriety. Glutamate and dopamine interactions are likely necessary components of addiction maintenance [61]. Glutamatergic efferents from the prefrontal cortex, amygdala, and hippocampus innervate the cell bodies of

neurons in the ventral tegmental area and the shell of the nucleus accumbens, facilitating dopaminergic neurotransmission in these key circuits of the ‘reward pathway’ [61].

The hypothesis that anticonvulsants have beneficial effects in patients with AUDs by reversing or compensating for allostatic neuroplasticity in long-term heavy drinkers is further supported by two studies demonstrating that carbamazepine and gabapentin initiation in the AWS may lead to better clinical results post-detoxification. Thus, we may be able to parlay the effects of anticonvulsant treatment of AWS into improved adherence and long-term outcomes in the long-term treatment of AUDs. To test this hypothesis, Malcolm et al. [27] compared carbamazepine and lorazepam treatment in 136 alcoholics in moderate withdrawal and followed drinking patterns in the immediate post-detoxification period (up to 12 days). Carbamazepine and lorazepam were equally effective in treating acute withdrawal symptoms, but carbamazepine-treated subjects drank significantly less in the subsequent treatment phase. For subjects with a history of more than one previous detoxification, the difference in drinking in the post-detoxification period was even more pronounced, with lorazepam-treated subjects averaging about 5 drinks per day and carbamazepine-treated subjects averaging less than 1 drink per day, a statistically and likely clinically significant difference.

Next, Myrick et al. [41] compared two doses of gabapentin with lorazepam for outpatient detoxification and followed drinking patterns in the immediate post-detoxification period (again, up to 12 days). As above, the medications were equivalent in their treatment of the AWS. Subjects randomized to gabapentin drank less during both the detoxification and post-detoxification periods, and experienced less sedation and craving than subjects randomized to lorazepam. Taken together, the results of these two studies support the hypothesis that anticonvulsants redress the underlying neuroplastic changes responsible for both AWS and ongoing heavy drinking, and suggest a potential advantage for their use over benzodiazepines when used as a bridge between AWS and post-detoxification treatment.

4.1 Valproic Acid/Divalproex

Due to its hypothesized ability to increase GABAergic tone and efficacy as a mood stabilizer, divalproex has been studied for alcoholism treatment [62, 63]. A 12-week, double-blind, placebo-controlled pilot study including 39 subjects (31 men and 8 women) with DSM-IV-diagnosed alcohol dependence by Brady et al. [64] showed that divalproex reduced both irritability and the risk of relapse to heavy drinking when compared with placebo. However, the effect on heavy drinking was small (estimated Cohen's $d = 0.10$), and the finding was nominally significant. Both groups experienced substantial improvement on other drinking measures and alcohol intake biomarkers, but divalproex alone reduced irritability.

Next, in a 24-week, double-blind randomized trial of divalproex or placebo added on to lithium monotherapy in 59 subjects with co-morbid bipolar I disorder (all phases of illness) and alcohol dependence, after controlling for medication adherence, divalproex augmentation resulted in fewer heavy drinking days (HDDs), fewer number of drinks/drinking day, and decreased γ-glutamyltranspeptidase (GGT) levels at the end of 6 months. Higher valproate levels also conferred a greater advantage on drinking-related outcomes.

Adjunctive divalproex did not improve bipolar disorder (both manic and/or depressive) symptoms [65]; however, this study was specifically powered for drinking-related measures. To redress mood symptoms in this co-morbid population, Kemp et al. [66] performed an analogous study of 149 rapid-cycling bipolar I patients with co-morbid substance use disorders (alcohol, cannabis, and/or cocaine) comparing lithium monotherapy with combined lithium and divalproex in a 6-month, double-blind, parallel-arm, randomized controlled study. Most patients discontinued participation and, of those that completed therapy, divalproex was not superior to lithium alone on both mood and substance-related outcomes.

4.2 Carbamazepine/Oxcarbazepine

Mueller et al. [67] first reported on carbamazepine maintenance in alcohol dependence. In a 12-month randomized, double-blind, placebo-controlled trial, 29 alcohol-dependent subjects were followed bimonthly with drinking and mood metrics. Although there was significant attrition in this already small sample, carbamazepine outperformed placebo by reducing the number of drinks/drinking day, maximum number of drinks/drinking day at 2 and 4 months, and delay to first HDD. There was no observed benefit on mood. Oxcarbazepine, which, when compared with carbamazepine, has a less severe side effect profile and does not require blood monitoring, has been trialed head-to-head with approved medications for the treatment of alcohol dependence. In a 24-week randomized, open-label trial of oxcarbazepine versus acamprosate in 30 recently detoxified alcohol-dependent patients, oxcarbazepine had similar effects on relapse-related parameters—time to first drink and time to severe relapse—and was equally well-tolerated [68]. In another open-label trial with 84 alcohol-dependent patients, two dose ranges of oxcarbazepine—low (600–900 mg/day) and high (1500–1800 mg/day)—were compared with low-dose naltrexone (50 mg/day) for relapse prevention for up to 90 days post-detoxification [69]. In this study, high-dose oxcarbazepine delayed time to relapse (58.6 % at the end of trial) to a greater degree than both low-dose oxcarbazepine (42.8 %) and naltrexone (40.7 %). High-dose oxcarbazepine also decreased the hostility–aggression subscore on the revised version of the 90-item Symptom Checklist relative to the two other groups. Although these open-label results are promising, as of March 2015, there are no active trials of oxcarbazepine in the treatment of alcohol dependence with or without other common psychiatric co-morbidity listed on ClinicalTrials.gov.

4.3 Lamotrigine

Lamotrigine has demonstrated preliminary efficacy in the treatment of co-occurring psychiatric disorders with alcohol dependence. First, in three patients with co-morbid treatment-resistant schizophrenia and alcohol dependence, open-label lamotrigine augmentation decreased alcohol consumption and craving when added on to clozapine [70]. In another co-morbidity study, add-on open-label lamotrigine (up to 300 mg/day) was administered to 28 bipolar I/II disorder and alcohol-dependent patients for 12 weeks and improved both mood and alcohol-related measures [including craving and carbohydrate-deficient transferrin (CDT)]. Unlike the carbamazepine trials discussed above in Sect. 4.2, there was no attrition, likely due to lamotrigine's less severe side effect profile. There have

been no reported randomized double-blind placebo-controlled trials of lamotrigine in alcohol dependence.

4.4 Tiagabine

Tiagabine, a GAT1 inhibitor, is an anticonvulsant with potential efficacy in generalized anxiety disorder [71]. Due to its GABAergic effects, it has also been a compound of interest in alcohol dependence for relapse prevention/harm reduction. In a 6-month open-label pilot study of 120 recently detoxified alcohol-dependent patients block randomized to either tiagabine ($n = 60$) or non-medication control ($n = 60$), tiagabine improved drinking, mood, and general functioning outcomes with only minor attrition [72]. Interestingly, in an experimental medicine study of tiagabine in non-addicted healthy volunteers, tiagabine did not reduce acute reward-related signaling in response to intravenous alcohol, which suggests that GAT1 reuptake inhibition may not affect mesolimbic reward circuitry in healthy individuals, though it may in patients with alcohol-related GABAergic dysfunction from long-term consumption [73].

4.5 Levetiracetam

The efficacy data for levetiracetam in AUD treatment has been mixed. An initial 10-week open-label pilot study ($n = 20$) revealed that escalating doses of levetiracetam (maximal dose of 2000 mg/day) decreased alcohol consumption from 5.4 to 1.7 standard drinks/day [74]. There is also preclinical evidence that levetiracetam reduces alcohol consumption by altering β-endorphin release in alcohol-preferring rats [75]. Levetiracetam may also have efficacy in alcohol-dependent subjects with co-occurring psychiatric disorders; in three patients with co-morbid alcohol dependence and anxiety disorder(s), 8 weeks of levetiracetam (up to 3000 mg/day) decreased both alcohol consumption and anxiety [76].

Levetiracetam has also been studied in three randomized controlled trials for the long-term treatment of AUD. First, in a multi-site 16-week randomized, placebo-controlled trial of 120 heavy drinking alcohol-dependent patients, although well-tolerated, levetiracetam did not outperform placebo on all drinking-related outcomes, including the primary outcomes of percentage of HDDs and percentage of subjects with no HDD, except for alcohol-related consequences [77]. Next, in a 42-day randomized, crossover, placebo-controlled trial in 46 non-treatment-seeking moderate-to-heavy drinkers, levetiracetam did not improve treatment outcomes relative to placebo [78]. In fact, a median split into low- and high-level drinkers revealed that levetiracetam increased alcohol consumption in the lower half relative to placebo. Finally, in a multi-site randomized, placebo-controlled trial of levetiracetamin 16 weeks post-detoxification, levetiracetam did not have better efficacy than placebo on the primary outcome measures—the percentage and time to relapse of heavy drinking [79]. These results suggest that levetiracetam likely lacks efficacy in the treatment of alcohol dependence [80]. A recent small placebo-controlled trial comparing the effects of topiramate, zonisamide, and levetiracetam showed a benefit of the medication on drinking outcomes versus placebo (described in more detail in Sect. 4.7) [81].

4.6 Gabapentin/Pregabalin

As in AWS, gabapentin and pregabalin have been studied for relapse prevention/harm reduction in AUDs. Gabapentin was initially studied for the treatment of insomnia in adults with AUDs during protracted abstinence and was associated with a reduction in alcohol consumption in all study participants, suggesting a potential efficacy for drinking behavior which lead to subsequent randomized studies [82]. In this initial open-label protocol, gabapentin outperformed trazodone [83], albeit a subsequent randomized, placebo-controlled trial suggested no between-group differences [84]. After several laboratory challenge paradigms revealed that gabapentin was safe and tolerable but did not reduce symptoms of intoxication [85, 86], the first randomized double-blind placebo-controlled study of 60 male Brazilian alcoholic outpatients revealed that, over a 28-day treatment period, low-dose gabapentin (600 mg/day) decreased both alcohol ingestion and craving [87]. After these initial studies, the largest randomized controlled trial of gabapentin in the treatment of alcohol dependence has recently been published [88]. In this 12-week, randomized, double-blind, placebo-controlled trial of two doses of gabapentin (900 or 1800 mg/day) in 150 alcohol-dependent patients, higher-dose gabapentin improved abstinence rates [number needed to treat (NNT) = 8] and delayed relapse to heavy drinking (NNT = 5). There was also a dose-dependent improvement in mood, insomnia, and craving. Gabapentin was well-tolerated, and, although attrition was moderate (85 of 150 patients did not complete the study), it did not differ among treatment arms.

There also appears to be an interactive effect of alcohol withdrawal intensity on gabapentin-induced relapse prevention. Anton et al. [89] studied 60 alcohol-dependent patients who received 2 days of intravenous flumazenil (2 mg incremental bolus × 20 min) to ensure complete withdrawal followed by gabapentin (up to 1200 mg at bedtime for 39 days) or intravenous/oral placebos. The low-alcohol withdrawing group had an increased percentage of drinking days and hastened time to first HDD when randomized to the active medication while the high-alcohol withdrawing subjects displayed the reverse profile. These findings suggest that the intensity of alcohol withdrawal should be co-varied in alcohol dependence trials, and, in clinical settings, considered on selection among pharmacological treatment options. Gabapentin also had preliminary efficacy as an add-on to naltrexone; in a trial of 150 alcohol-dependent subjects randomized to naltrexone (50 mg/day, $n = 50$) alone, naltrexone and gabapentin (up to 1,200 mg/day, $n = 50$) or double placebo ($n = 50$), the combined naltrexone/gabapentin group delayed the time to first HDD and decreased the number of HDDs and drinks/drinking day during the first 6 weeks of the trial [90]. After these first 6 weeks, gabapentin was discontinued in the patients receiving the add-on therapy, and the above-cited differences dissipated for the remainder of the protocol.

Pregabalin, an anticonvulsant that has been approved in Europe for treatment of generalized anxiety disorder, has also been studied for relapse prevention/harm reduction in AUDs. In an initial open-label 16-week trial of pregabalin (150–450 mg/day), ten of 20 patients receiving pregabalin remained alcohol-free at the end of the study—five relapsed, four dropped out, and one discontinued due to adverse effects. Pregabalin has also been compared head-to-head with naltrexone, which revealed similar efficacy on drinking-related outcomes in 71 recently detoxified alcohol-dependent subjects [91]. Unlike naltrexone, pregabalin improved

anxiety, hostility, and psychoticism in vulnerable alcohol-dependent subjects, which suggests that pregabalin may be particularly helpful in select dual diagnosis patients.

4.7 Topiramate

Topiramate may be the most promising medication for reducing and eliminating harmful drinking patterns in AUDs. Johnson et al. [92] first reported topiramate's efficacy in a double-blind, randomized, placebo-controlled trial of 150 alcohol-dependent patients ($n = 75$ in each arm). In this study, topiramate was not only effective in decreasing alcohol-related measures but also improved overall well-being/quality of life, reduced deleterious psychosocial consequences [93], and decreased smoking [94]. In a larger ($n = 371$), multicenter, randomized, placebo-controlled trial, topiramate was again superior to placebo on relapse prevention/harm reduction [95]. Topiramate had a moderate effect size (Cohen's $d = 0.52$) on reducing the percentage of HDDs for treatment-seeking alcoholics who received 14 weeks of flexibledosing (up to 300 mg/day) with concomitant brief behavioral compliance-focused therapy. Topiramate also improved medical (likely stemming from a reduction in body mass index) and psychosocial parameters in this larger trial [96]. However, there was significant attrition in the topiramate arm, and a more conservative analysis (assuming drop-outs returned to baseline drinking levels) reduced efficacy by half, i.e., a mean difference of –16.19 to –8.44 % reduction in the conservative analysis. High-dose topiramate was associated with numerous adverse effects—paresthesia, taste disturbances, anorexia, and cognitive adverse effects—that may ultimately limit its widespread clinical use.

Topiramate has also been studied in longer prospective designs [94] and, in comparison to other medications approved for alcohol dependence including disulfiram [97] and naltrexone, topiramate demonstrated non-inferiority and even superiority in selected studies [98–100]. Due to topiramate's high side effect burden at higher doses, it is critical to determine the optimal dose range for balancing relapse prevention/harm reduction with decreased risk for adverse effects [101]. Hence, in a 16-week post-detoxification protocol of 90 alcohol-dependent patients who received either low-dose topiramate (up to 75 mg/day) with psychotherapy or psychotherapy alone ($n = 60$), topiramate decreased relapse rates and delayed time to relapse relative to psychotherapy alone and also improved alcohol craving and mood [102]. Unfortunately, this study did not have a high-dose topiramate arm, so the full dose range has yet to be compared.

Topiramate's mechanism of change in the treatment of alcohol dependence remains unclear. Neurobiologically, topiramate acts by facilitation of GABAergic neurotransmission and/or inhibition of glutamatergic signaling in corticomesolimbic pathways. Some studies suggest that topiramate may decrease craving for alcohol, which may contribute to its effects on drinking in humans [81, 103–105]. Topiramate was found to have no effect on cue-induced reactivity in an laboratory challenge paradigm in 61 heavy drinkers pre-treated with topiramate or placebo; instead, it altered the subjective experience of intoxication [105]. Another 12-week, double-blind placebo-controlled study revealed that, in addition to reducing drinking and craving, topiramate improved performance in impulsivity paradigms [106]. Even though cognitive complaints are common, cognitive improvement (likely due to

abstinence or decreased drinking outweighing topiramate's cognitive adverse effects) was observed at the end of an 85-day trial of flexible-dose topiramate (50–300 mg/day) [107].

A study of topiramate's effects on drinking, alcohol's reinforcing effects, and craving in non-treatment-seeking heavy drinkers revealed reduced drinking and attenuated reinforcing effects of alcohol, but no effect on craving [105]. A recent pharmacogenetic analysis in a 90 % European American sample revealed that an intronic single nucleotide polymorphism (SNP) in an ionontropic kainate (glutamatergic) receptor subunit gene (*GRIK1*, which encodes the GluR5 subunit protein) was associated with higher serum topiramate concentrations, and the C-allele homozygotes had fewer adverse effects [108]. This SNP (rs2832407), a C-to-A non-coding substitution, has been associated in another European American sample with increased risk for developing alcohol dependence [109]. Due to the combination of moderate effect on relapse prevention/harm-reduced drinking with limiting adverse events, pre-treatment genetic stratification may be a reasonable.

In order to investigate moderate-dose topiramate in heavy drinkers who desired to reduce drinking (but not to quit), and to study the interaction of rs2832407, Kranzler et al. [110] performed a 12-week placebo-controlled trial at a target dose of 200 mg/day in 138 heavy-drinking individuals (>90 % with alcohol dependence). All subjects received brief behavioral therapy aimed at enhancing medication adherence with the goal of non-hazardous drinking. In this study, treatment adherence and study completion were high in both groups, with >80 % of subjects in both groups completing the 12-week trial. Topiramate was superior to placebo on the primary outcomes of reduced HDDs and increased abstinent days per week. It was hypothesized that rs2832407 would predict differential response to topiramate, and, indeed, a pharmacogenetic effect was found in the subset of European Americans ($n = 122$). CC homozygotes but not A-allele carriers, had an excellent response to topiramate, with a statistically significant reduction in HDDs per week ($p = 0.004$). In this study, rs2832407 was not associated with greater side effect burden, suggesting that this SNP may predict efficacy but not tolerability. Recent analyses suggest that the *GRIK1* SNP moderates topiramate's effect on alcohol consumption by altering alcohol expectancies and subjective response to alcohol, an effect that is mediated by self-efficacy for reducing heavy drinking in C-allele but not A-allele carriers [111, 112]. While these pharmacogenetic findings certainly require replication, it may soon be possible to personalize topiramate treatment.

There is only one negative published placebo-controlled trial of topiramate in AUDs ($n =$ 106 alcohol-dependent subjects), and this trial had a ~50 % drop-out rate and other confounding factors that threaten the validity of its findings [113]. Another study of 170 subjects with co-morbid AUD and cocaine dependence showed no effect of topiramate on drinking behaviors versus placebo, suggesting cocaine use may nullify the effects of topiramate on drinking [114]. The use of moderate-dose topiramate is also supported by an active-control effectiveness study ($n = 182$ alcohol-dependent subjects) that demonstrated a clinical benefit at 200 mg/day compared with naltrexone 50 mg/day [100].

An open-label study of 30 subjects who received low-dose topiramate with counseling versus 60 subjects who received counseling alone ($n = 60$) showed preliminary safety and

tolerability of the lower dose with added benefits in the topiramate-treated group [102]. This open-label study has been followed by a 6-week randomized placebo-controlled trial of low-dose topiramate (300 mg/day) for relapse prevention in 52 subjects with alcohol dependence post-detoxification [104]. Martinotti and colleagues [104] found that after 6 weeks of treatment, compared to placebo, those who received low-dose topiramate had fewer drinking days, less alcohol consumption, more days in treatment, reduced alcohol withdrawal and alcohol cravings, and reductions in mood and anxiety symptoms.

A recent meta-analysis of topiramate's effect on drinking showed significant effects for the medication versus placebo on measures of abstinence and heavy drinking, with estimated medium effect sizes ($g = 0.468$, $p = 0.02$, and $g = 0.406$, $p = 0.01$, respectively) [115]. Topiramate has also proven efficacious when examining the FDA-preferred outcome "number of subjects with no heavy drinking days" [110, 116].

In summary, although promising, topiramate's efficacy must be closely balanced with its potential adverse effects. Despite the fact that it remains an off-label treatment, topiramate should be considered as a first-line option for the treatment of AUDs, though it may be preferential to start with a medication such as acamprosate or naltrexone, owing to their more favorable side effect profile. Nonetheless, topiramate's proven efficacy and robust effect on reducing drinking make it an excellent choice for treating AUDs.

4.8 Zonisamide

An alcohol self-administration laboratory study of zonisamide (100 mg) versus placebo in at-risk drinkers ($n = 10$) demonstrated decreased alcohol cravings and consumption by approximately 50 % with zonisamide [117]. This was shortly followed by several clinical trials. First, a 13-week open-label trial of zonisamide (400 mg/day) in alcohol-dependent subjects ($n = 16$) illustrated that zonisamide was well-tolerated and reduced the number of drinks/day at trial endpoint [118]. Another open-label study in 22 alcohol-dependent outpatients treated with either zonisamide (maximum dose of 300 mg/day) or placebo for 12 weeks reported decreased cravings and alcohol consumption, as validated by decreased GGT in the zonisamide group [119].

Our group has reported the first randomized, double-blind, placebo-controlled trial of zonisamide in alcohol dependence [120]. In this 12-week study, zonisamide—titrated up to a maximum dose of 500 mg/day over 8 weeks—decreased HDDs, total drinks/week, and craving at a faster rate than placebo in 40 alcohol-dependent subjects, but had no significant effects on abstinence. Both randomization arms also received seven sessions of cognitive behavioral therapy and had substantial improvement in drinking compared to baseline. There was a significant medication-by-time interaction for drinks/week ($p = 0.004$) (a decrease of 2.2 drinks/week in the zonisamide group vs. 1.4 drinks/week for placebo), at a moderate effect size (Cohen's $d = 0.44$). There was also a significant medication-by-time interaction effect favoring zonisamide for HDD/week ($p = 0.012$) (a small reduction of 0.3 HDD/week in the zonisamide group vs. 0.2 HDD/ week for placebo; Cohen's $d = 0.27$). There was a significant decrease in urge to drink with zonisamide ($p = 0.006$) (1.4 points on the Alcohol Urge Questionnaire/week for zonisamide vs. a 0.6-point reduction for placebo). Additionally, GGT levels showed a trend for greater decrease in the zonisamide group, but

this was not statistically significant. Zonisamide was also well-tolerated, and no serious adverse effects were observed. We found a significant interaction between the age of onset of AUD, medication group, and time. Specifically, zonisamide reduced HDDs per week in early-onset alcoholism (EOA) versus late-onset alcoholism (LOA) by a difference of 0.23 HDD/week ($p = 0.01$). This translates to a greater reduction of about 3 HDD/week by the end of the study for subjects with EOA, which is clinically significant.

Knapp and colleagues (2015) recently published a double-blind, randomized, placebo-controlled study comparing zonisamide (400 mg/day), topiramate (300 mg/day), and levetiracetam (200 mg/day) in 85 participants meeting criteria for DSM-IV diagnosis of alcohol dependence [81]. Study medications were administered for 14 weeks and the study examined treatment outcomes of alcohol consumption as well as self-reported neurocognitive adverse effects and neuropsychological testing. Compared with placebo, zonisamide, topiramate, and levetiracetam all significantly decreased percentage HDDs, and zonisamide and topiramate both significantly decreased drinks per day and percentage of drinking days. Topiramate but not zonisamide or levetiracetam was associated with significantly lower GGT levels at the end of the study period. With regard to neurocognitive effects, treatment with zonisamide and topiramate were both associated with impairments in verbal fluency and working memory on neuropsychological tests, but only topiramate was associated with self-reported mental slowing.

4.9 Summary of NBACs to Reduce Harmful Drinking Patterns

Table 2 gives a summary of the findings for treating alcoholism with NBACs in terms of reducing harmful drinking patterns. Topiramate has substantial evidence of efficacy for treating alcoholism in this setting as a mono-therapy. Gabapentin and other NBACs have less evidence supporting their use but have shown potential efficacy. Gabapentin is usually easier to titrate clinically and has a more benign side effect profile than topiramate.

5 Limitations

There are a number of limitations of this review. Few high-quality controlled studies have examined NBAC pharmacotherapies for AWS and AUD to date. Many of the reviewed studies are underpowered or open-label pilot studies, making interpretations of the potential efficacy of these pharmacotherapies difficult. Early studies of NBAC for AWS predate the use of validated alcohol withdrawal symptom measurements (CIWA-Ar scores) and were underpowered to examine outcomes that occur with relatively low frequency such as seizures and DTs. As benzodiazepines have become the consensus ‘gold standard’ for treatment of moderate-to-severe AWS, bioethical issues complicate the use of placebo-controlled study designs to study severe AWS and moderate AWS with psychiatric and medical co-morbidities in inpatient settings. As such, many recent studies examining NBAC for treatment of moderate-to-severe AWS use add-on and open-label study designs that don’t allow for examination of the isolated effects of NBACs on AWS treatment outcomes. With the exception of some naturalistic studies of topira-mate, most studies were of short duration and few followed patients after the active medication period, limiting our knowledge of the long-term effectiveness of these interventions. This literature review was subject to

publication bias as positive studies are more likely to be published than negative studies. The authors attempted to control for publication bias by also examining and reporting on current studies on clinicaltrials.gov. Future randomized controlled studies are needed to expand on the promising findings from the many open-label reports and to better understand the real-world efficacy of these pharmacotherapies.

6 Conclusions

We have presented preliminary but potentially compelling evidence in support of NBAC medications for both the treatment of AWS and for reducing harmful drinking patterns in AUDs, with the latter indication having the most supporting evidence. NBACs are unlikely to replace benzodiazepines for AWS, but may serve a helpful adjunct role, and may be useful as a monotherapy for milder cases with less risk of complications. Topiramate has proven efficacy in reducing the harmful drinking patterns of AUDs, suggesting it is on par with or perhaps superior to FDA-approved medications for the condition. Finally, anticonvulsants such as carbamazepine, gabapentin, and perhaps others, may be initiated with therapeutic effect during AWS and then continued long-term for relapse prevention/harm reduction, and, at present, there are no FDA-approved pharmacological treatments for AUDs that offer this benefit. The finding that NBACs, when used during withdrawal, might reduce drinking in the early post-withdrawal stages of treatment compared with benzodiazepines is an intriguing and promising finding supporting the usefulness of these medications. Additionally, positive findings from studies with medications such as topiramate and zonisamide showing substantially reduced drinking even in actively heavy drinking subjects that don’t want to be totally abstinent, is also promising. Further research with the NBACs for treating AUDs is warranted.

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Key Points

Alcohol use disorders (AUDs) are associated with harmful allostatic neuroplastic changes in glutamatergic and GABAergic function, leading to an acute alcohol withdrawal syndrome (AWS) and in some cases prolonged/protracted withdrawal symptoms that contribute to the risk for relapse to heavy drinking.

Drugs that target this neural excitatory–inhibitory imbalance through modulation of glutamatergic or GABAergic systems may have a role as pharmacotherapies for AWS and AUDs, and recent randomized clinical trials suggest that non-benzodiazepine anticonvulsants (NBACs) may be effective for the treatment of mild-to-moderate AWS and as agents to reduce heavy drinking in AUDs.

Gabapentin and carbamazepine appear to be the most promising NBAC agents for treating AWS, primarily as an adjunctive treatment to traditional benzodiazepines and/or in mild-to-moderate withdrawal of low-risk patients in outpatient settings. The evidence for use of NBACs to target heavy drinking in outpatient settings is stronger than the evidence for AWS, with most evidence being in support of topiramate and gabapentin.

Table 1

Non-benzodiazepine anticonvulsants for alcohol withdrawal syndrome

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of evidence[a]
Carbamazepine	Inpatient, outpatient, severe AWS	SR Randomized double-blind comparison with benzodiazepines Randomized, double-blind, placebo-controlled study Randomized, open-label pilot study comparison with benzodiazepines and tiapride	Carbamazepine fixed dose starting at 800 mg/day tapered over 4, 7, 9, or 12 days; symptom-triggered dosing (≤1200 mg/day)	Reduction in observer-rated AWS symptoms, episodes of AW seizures, AW delirium (DT), treatment dropout	Grade B (level 2 evidence) for AWS
Oxcarbazepine	Inpatient, severe AWS	Randomized, single-blind pilot study comparison with carbamazepine Randomized, double-blind, placebo-controlled adjunct to benzodiazepines	Oxcarbazepine fixed dose starting at 900 mg/day and tapered over 5-6 days	Amount of symptom-triggered benzodiazepine for safe detoxification, reduction in observer-rated AWS symptoms, AW seizures, AW delirium	Grade C (level 3 evidence) for AWS
Valproic acid/divalproex	Inpatient	SR Randomized, double-blind, placebo-controlled study	Divalproex sodium 500 mg 3 times per day	Amount of symptom-triggered benzodiazepine for safe detoxification, reduction in observer-rated AWS symptoms, AW seizures, AW delirium	Grade B (level 2 evidence) for AWS
Gabapentin	Inpatient, outpatient, moderate AWS, severe AWS	Open-label pilot study Randomized, placebo-controlled adjunct to benzodiazepines Randomized, open-label comparison with phenobarbital with benzodiazepines Randomized, double-blind comparison with benzodiazepines (lorazepam and chlordiazepoxide) Open-label gabapentin dose challenge followed by stratification to gabapentin or benzodiazepines based upon initial response	Gabapentin fixed-taper dosing (starting dose ranging from 600 to 1600 mg/day)	Amount of symptom-triggered benzodiazepine for safe detoxification, reduction in observer-rated AWS symptoms	Grade B (level 2 evidence) for AWS
Pregabalin	Inpatient, outpatient, mild-to-moderate AWS	Open-label study Randomized comparison with tiapride and lorazepam Randomized, double-blind, placebo-controlled trial	Pregabalin flexible dosing between 200 and 450 mg/day	Amount of symptom-triggered benzodiazepine for safe detoxification, reduction in observer-rated AWS symptoms	Grade C (level 3 evidence) for AWS
Levetiracetam	Inpatient	Randomized, double-blind, placebo-controlled adjunct to benzodiazepines	Levetiracetam fixed dose starting at 2000 mg/day tapered over 6 days	Amount of symptom-triggered benzodiazepine for safe detoxification (primary), reduction in AWS symptoms (secondary)	Grade C (level 3 evidence) for AWS
Topiramate	Inpatient, male	Randomized, single-blind, placebo-controlled comparison with benzodiazepines (diazepam), lamotrigine, and memantine with	Topiramate 25 mg fixed dose every 6 h (100 mg/day) over 7 days	Reduction in observer-rated and self-reported AWS symptoms, severity and episodes of AW seizures	Grade C (level 3 evidence) for AWS

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of evidence[a]
		symptom-triggered rescue benzodiazepine [46] Open-label pilot studies			
Zonisamide	Combined inpatient (2 weeks) and outpatient (1 week)	Randomized, open-label pilot study comparison with benzodiazepines (diazepam) with symptom-triggered rescue benzodiazepines	Zonisamide flexible dosing starting at 400–600 mg/day and tapered over 21 days to 100–300 mg/day	Reduction in observer-rated AWS symptoms, reduction in alcohol craving	Grade C (level 3 evidence) for AWS

AW alcohol withdrawal, AWS alcohol withdrawal syndrome, DT delirium tremens, SR systematic review

[a]Levels of evidence presented are based upon the US Preventive Services Task Force (USPSTF) Strength of Recommendation Taxonomy (SORT) approach to grading evidence in medical literature [124]. Levels of evidence include: Level 1: good-quality, patient-oriented evidence including SRs, meta-analyses, and well-designed randomized controlled trials with consistent findings. Level 2: limited-quality, patient-oriented evidence including lower-quality/less consistent SRs, meta-analyses, or clinical trials as well as cohort and case-control studies. Level 3: other evidence in the form of consensus guidelines, disease-oriented evidence, and case series. These levels of evidence are used to determine a strength of recommendation grades, which include A (good-quality patient-oriented evidence); B (limited-quality, patient-oriented evidence); C (other evidence); and no recommendation

Table 2

Non-benzodiazepine anticonvulsants for alcohol use disorders

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of evidence[a]
Carbamazepine	Post-detoxification alcohol dependence	12-month randomized, double-blind, placebo-controlled trial	Carbamazepine fixed dose starting at 800 mg/day	Time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD	Grade B (level 2 evidence) for AUD
Oxcarbazepine	Post-detoxification alcohol dependence	24-week randomized, open-label trial comparison with acamprosate 90-day randomized, open-label trial comparison with naltrexone	Oxcarbazepine fixed dose of 600-900 mg/day (low dose) or 1500-1800 mg/day (high dose)	Time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD	Grade C (level 3 evidence) for AUD
Valproic acid/divalproex	Alcohol dependence, co-morbid alcohol dependence and bipolar disorder, co-morbid substance use disorder (alcohol, cannabis, or cocaine) and rapid cycling bipolar	12-week double-blind, placebo-controlled pilot 24-week double-blind, placebo-controlled add-on study to lithium 6-month randomized, double-blind comparison study of valproate + lithium with lithium	Divalproex sodium 500 mg 3 times day	Relapse to heavy drinking (days), number of HDDs, number of drinks/HDD, GGT, mood	Grade B (level 2 evidence) for AUD
Gabapentin	Alcoholic outpatients, post-detoxification alcohol dependence	28-day randomized, double-blind, placebo-controlled study 12-week randomized, double-blind, placebo-controlled comparison of 2 doses 6-week randomized, double-blind, placebo-controlled add-on to naltrexone	Gabapentin fixed dose of 600, 900, or 1800 mg/day	Abstinence rate, time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD	Grade B (level 2 evidence) for AUD
Pregabalin	Post-detoxification alcohol dependence	16-week open-label, pilot study RCT comparing pregabalin with naltrexone	Pregabalin 150-450 mg/day	Time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD, mood	Grade C (level 3 evidence) for AUD
Lamotrigine	Co-morbid alcohol dependence and bipolar disorder	Randomized, open-label, placebo-controlled add-on study	Lamotrigine fixed dose up to 300 mg/day	Alcohol use, alcohol cravings, mood, CDT	Grade C (level 3 evidence) for AUD
Tiagabine	Post-detoxification alcohol dependence	Randomized, open-label pilot study with non-medication control	Tiagabine	Alcohol use, alcohol cravings, mood	Grade C (level 3 evidence) for AUD
Levetiracetam	Post-detoxification alcohol dependence, co-morbid alcohol dependence and anxiety disorders, non-treatment-seeking moderate-to-heavy drinkers	10-week open-label pilot 16-week multisite, randomized, placebo-controlled study	Levetiracetam fixed dose, titrated to 2000-3000 mg/day	Time to relapse of heavy drinking, standard drinks/day, HDDs, percentage of subjects with no HDDs	Grade C (level 3 evidence) for AUD

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of evidence[a]
		42-day randomized, placebo-controlled crossover study			
Topiramate	Alcohol dependence, post-detoxification alcohol dependence, alcohol-dependent subjects with and without SNP in ionotropic kainite (glutamatergic) receptor subunit gene *(GRIK1)*	Double-blind, randomized, placebo-controlled trials Multicenter, randomized, double-blind, placebo-controlled trial Non-inferiority study comparing topiramate with naltrexone and disulfiram 12-week randomized, placebo-controlled pharmacogenetic study	Topirmate with flexible dosing between 75 (low dose) and 300 mg/day (high dose)	Abstinence rate, time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD, mood, impulsivity (laboratory paradigm)	Grade A (level 1 evidence) for AUD
Zonisamide	Alcohol dependence, at-risk drinkers	Randomized, placebo-controlled, alcohol self-administration laboratory paradigm 13-week open-label pilot study 12-week randomized, double-blind, placebo-controlled study	Zonisamide flexible dosing titrated to a maximum dose of 100-500 mg/day	Abstinence rate, time to first drink, time to first HDD, time to severe relapse, number of HDDs, number of drinks/HDD, mood, alcohol self-administration laboratory paradigm, alcohol craving, alcohol urge, GGT	Grade B (level 2 evidence) for AUD

AUD alcohol use disorder, *CDT* carbohydrate deficient transferrin, *GGT* γ-glutamyltranspeptidase, *HDD* heavy drinking day, *RCT* randomized controlled trial, *SNP* single nucleotide polymorphism, *SR* systematic review

[a]Levels of evidence presented are based upon the US Preventive Services Task Force (USPSTF) Strength of Recommendation Taxonomy (SORT) approach to grading evidence in medical literature [124]. Levels of evidence include: Level 1: good-quality, patient-oriented evidence including SRs, meta-analyses, and well-designed RCTs with consistent findings. Level 2: limited-quality, patient-oriented evidence including lower-quality/less consistent SRs, meta-analyses, or clinical trials as well as cohort and case-control studies. Level 3: other evidence in the form of consensus guidelines, disease-oriented evidence, and case series. These levels of evidence are used to determine a strength of recommendation grades, which include A (good-quality patient-oriented evidence); B (limited-quality, patient-oriented evidence); C (other evidence); and no recommendation