

Review of Topiramate: An Antiepileptic for the Treatment of Alcohol Dependence

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Abstract: Despite the availability of currently approved medications and various psychosocial therapies, alcohol abuse and dependence are increasingly prevalent in the United States, and carry a significant socioeconomic burden. Recently, the novel anti-epileptic topiramate has shown great promise as a new treatment for this disorder. The objective of this review is to discuss the limitations of the currently available options for treating alcohol dependence, to review the results of clinical trials assessing the efficacy of topiramate in treating alcohol dependence, and to describe the pharmacological characteristics and mechanisms of action of topiramate as related to this indication. We systematically reviewed Medline, EMBASE, Cochran Reviews and PsycINFO search terms included combinations of the terms “pharmacotherapy” “topiramate”, “alcoholism” and “alcohol dependence.” Searches were last updated 24 October 2008. Currently approved treatments include disulfiram, naltrexone tablets and injection, and acamprosate. Of these, naltrexone has shown the most benefit, however the effect size is small and may reach its most promising potential when combined with medical management. Alternatively, through multiple mechanisms of action, topiramate in clinical trials has demonstrated safety and efficacy in decreasing both craving and withdrawal symptoms and increasing quality of life measures among alcohol-dependent individuals. The findings of this review suggest that topiramate is a promising new option for the treatment of alcohol dependence, and may offer substantial benefits over currently approved medications. While the manufacturer will not pursue approval of an indication for the treatment of alcohol dependence, the drug will soon be available generically, making it more affordable for a greater proportion of the public.

Keywords: Alcohol dependence, pharmacotherapy, topiramate, disulfiram, naltrexone, acamprosate.

1. BACKGROUND

Alcohol Use Disorder (AUD), is the clinically diagnostic term for alcohol abuse and dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (Text Revision) (DSM-IV-TR) [1]. Alcohol abuse is a maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period: recurrent alcohol use resulting in failure to fulfill major role obligations at work, school, or home; alcohol use in situations in which it is physically hazardous; alcohol-related legal problems; or continued alcohol use despite persistent or recurrent social or interpersonal problems; and that these symptoms must never have met the criteria for alcohol dependence [1].

Alcohol dependence, also called alcoholism, is a chronically relapsing disease characterized by at least three of the following within the past 12-month period: tolerance; withdrawal; alcohol is often taken in larger amounts or over a longer period than was intended; a persistent desire or unsuccessful efforts to cut down or control alcohol use; a great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects; important social,

occupational, or recreational activities are given up or reduced because of alcohol use; or alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol [1]. Successful treatment for alcohol dependence typically consists of detoxification from alcohol followed by rehabilitation and long-term follow-up. Pharmacologic approaches can be integrated into therapy, but psychosocial treatments (e.g. residential programs, individual and group therapy, 12-step programs) have historically been the mainstay [2]. Psychosocial therapy effectively decreases drinking and promotes short-term abstinence however, 40 to 70% of patients typically resume alcohol use within one year post-treatment [3].

Even in today's society, there seems to be a general misconception that alcohol dependence affects only the poor, the homeless or the severely depressed. In fact, it is important to realize just how widespread this disease has become. Alcohol abuse and dependence can affect anyone regardless of age, gender, income, socioeconomic status, or mental state. In the United States (US) alone, the 12-month prevalence of alcohol abuse and alcohol dependence in 2001 and 2002 was 4.65% and 3.81% respectively [4]. The combined 12-month prevalence in the US increased from 7.41% (13.8 million) in 1991-92, to 8.46% (17.6 million) in 2001-2 [4]. This widespread disease carries a significant socioeconomic burden, as the total cost of alcoholism in 1998 was \$184.6 billion [5] and about 10% of Americans will suffer from alcohol de-

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pendence at some point in their lifetime [6]. Despite various treatment modalities, alcohol abuse and dependence are increasingly prevalent in this country and more efficacious options are needed to improve treatment outcomes [2].

2. PATHOPHYSIOLOGY

The search for an ideal treatment is made more difficult by the complexity of the biological pathways involved in the pathophysiology of alcoholism. Drugs of abuse, including alcohol, stimulate the mesolimbic dopaminergic pathway emanating from the ventral tegmental area (VTA). This facilitates the release of dopamine to the nucleus accumbens, the reward center of the brain. The increased extracellular dopamine levels seen in the midbrain with repeated use causes sensitization of the area to behavioral stimuli, such as the anticipation of alcohol, contributing to craving and preoccupation associated with dependence [4, 7, 8].

Though dopamine modulation is typically a prime target for drug development in this field, many other neurotransmitters and their receptors, including serotonin, β -endorphin, glutamate, γ -aminobutyric acid (GABA), cannabinoids and neuropeptide Y are all intricately involved in the development of alcohol dependence [4, 7, 8].

More specifically, extracellular dopamine levels in the nucleus accumbens are controlled by inhibitory GABA transmission and excitatory glutamatergic activity [7, 9]. Acute alcohol intake decreases the activity of GABAergic neurons in the VTA, disinhibits the GABA-mediated dopaminergic afferents to the nucleus accumbens and therefore, increases dopamine levels [7, 9]. The initially stimulating response is associated with the pleasurable effects of and craving for alcohol [8].

The chronic consumption of alcohol produces neuroadaptations of glutamate and GABA receptors [8]. Chronic drinkers develop significantly increased glutamatergic transmission to the nucleus accumbens compared to acute drinkers, caused by long-term glutamate neuronal stimulation and upregulation with an increase of N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainate-sensitive glutamate receptors in the hippocampus [7]. Also contributing, is the repeated alcohol-induced suppression of GABA neurons in the VTA causing a rebound hyperexcitable state, most likely due to decreased GABA-facilitated inhibition from the nucleus accumbens [7, 9]. The resulting chronic extracellular dopamine increase in the nucleus accumbens is probably responsible for the impulse to drink in order to normalize levels of dopamine [7]. In fact, though dopamine D2 receptor availability has recently been linked to a predisposition to, or protection from, the development of alcoholism [10], much more research is needed to clarify the exact nature of dopamine's contribution to drug dependence.

3. CURRENT MEDICATION OPTIONS

Currently, four medications are approved in the US for the treatment of alcohol dependence: disulfiram, naltrexone tablets and injectable, and acamprosate. While the combination of psychosocial with drug therapy provides the best treatment outcome, the clinical use of approved medications is low [11]. Contributing factors include ambiguity of diagnosis and etiology of alcoholism [11, 12] resulting in treat-

ment failure due to using an improperly matched medication for specific subtypes of alcoholism [13, 14] lack of physician knowledge of medication efficacy outside of specialized treatment centers, lack of patient adherence, and the cost of the medications, particularly given that many with this disease don't have healthcare insurance [11].

Disulfiram, the first drug to obtain an indication for treatment of alcohol dependence, was approved over 50 years ago, and its physiological effect provides a psychological deterrent for drinking [4]. Disulfiram inhibits aldehyde dehydrogenase, an enzyme involved in the metabolism of alcohol. Ingestion of alcohol while taking the medication causes an increased concentration of acetaldehyde leading to a toxic reaction that includes flushing, headache, dyspnea, tachycardia, hypotension, nausea and vomiting. Unfortunately, as disulfiram does not directly address physiologic dependence, its clinical efficacy is limited [4, 12]. Moreover, as patient adherence is essential to successful treatment, disulfiram seems to be most useful in highly motivated patients under supervised administration [4, 12].

Naltrexone, a β -endorphin opioid antagonist, has been used for the treatment of alcoholism for the past 20 years [4, 12]. As previously described, alcohol ingestion stimulates neuronal release of β -endorphins, leading to increased release of dopamine in the nucleus accumbens facilitating positive reinforcement [4]. When patients drink alcohol, naltrexone blocks β -endorphin uptake and subsequent downstream dopamine release, thereby limiting the rewarding effect of alcohol [4]. A 2005 Cochrane Review of naltrexone cited efficacy for short-term treatment (3 months or less) of alcohol dependence (naltrexone reduced the chance of a relapse or return to heavy drinking by 28% compared to 43% for controls), but no consistent evidence for benefit after 3 months of pharmacotherapy [15]. Studies to optimize treatment are currently being conducted, hoping to identify patients with certain characteristics, e.g. genotyping associated with familial risk [12], in which naltrexone may be moderated by variations in the mu-opioid receptor gene (OPRM1) [4, 16].

Vivitrol[®], a long-acting intramuscular formulation of naltrexone, may offer some benefit due to more consistent plasma levels (thereby decreasing adverse effects) as well as increased adherence to therapy [17, 18]. In a 6-month, randomized, double-blind, placebo-controlled trial (RDBPCT), 624 alcohol-dependent adults received either 380 or 190 mg of Vivitrol, or placebo, combined with psychosocial intervention [17]. Results showed a significant decrease in the event rate of heavy drinking days (25% decrease with 380mg and 17% decrease with 190 mg) as compared to placebo, particularly in men ($p < 0.001$) but not women (not statistically significant) [17]. Other depot formulations being studied include Naltrel[®] and Depotrex[®], however further trials are needed to establish their safety and efficacy [18].

Used for alcohol dependence in Europe over the past 20 years, the NMDA partial agonist acamprosate was approved in the US (July 2004) for the promotion of alcohol abstinence [4]. Though the exact mechanism is unknown, acamprosate is thought to regulate the increased glutamate activity on cerebral NMDA receptors, mediated through m-glu-R5 receptors [12, 19]. Multiple European studies have shown significant reductions in number of drinking days and higher

abstinence rates at 6 months compared to placebo [4, 12]. By contrast however, American trials could not replicate these results [19, 20]. For example, a RDBPCT by Mason and colleagues reported no significant benefit with acamprosate for the maintenance of abstinence [19].

Multiple concurrent treatment approaches have also been explored. As already noted, the complex pathophysiology of alcohol dependence alters many neurotransmitters and neuronal pathways with two principal outcomes; the positive reinforcement of the pleasurable desire to drink and the negative reinforcement of the withdrawal syndrome [7, 12]. Naltrexone is hypothesized to reduce the positive effects associated with the urge to drink, while acamprosate attempts to stabilize the hyperactivation associated with withdrawal [7]. In theory, a combination of the two that can effectively reduce both effects of alcohol consumption would be an extremely useful pharmacotherapy for alcohol dependence.

The COMBINE study [20], a multi-center RDBPCT, studied the effects of treatment with naltrexone and acamprosate both alone and combined on 1383 recently abstinent, alcohol-dependent patients [20]. These four groups (naltrexone, acamprosate, combination of both, and placebo) were then further divided to receive an intervention called Medical Management (MM), consisting of brief counseling sessions with an emphasis on the importance of medication adherence to achieve abstinence, with or without a longer, more complex psychosocial therapy called Combined Behavioral Intervention (CBI). A ninth group received CBI alone without any medication or MM [20]. Patients receiving MM with naltrexone reported a greater percent of days abstinent and a lower risk of a heavy drinking day, whereas patients receiving acamprosate alone or combined with naltrexone demonstrated no evidence of efficacy, with or without MM or CBI [20]. The results therefore suggest that pharmacotherapy with naltrexone combined with MM for alcohol-dependent patients in a primary health care setting is a viable option that could greatly impact patient access to treatments [20].

There are several potential hypotheses noted for differential results of acamprosate in European versus American trials [18-20]. For example, Jonas and Chabac [21] point out that the intense medical management and rigorous retention strategy employed limited generalizability by providing an idealistic patient population with a higher placebo response rate. Kiefer and Mann [22] also comment that prior to enrollment, 92% of patients achieved abstinence without inpatient detoxification, therefore it is possible that the study targeted a select subpopulation of patients with a low need for relapse prevention treatment, a theory supported by empirically derived subtypes in a nationally representative sample [23].

4. TOPIRAMATE FOR THE TREATMENT OF ALCOHOL DEPENDENCE

Anti-epileptic drugs (AEDs) such as topiramate are occasionally used to treat withdrawal of alcohol dependence by mimicking the presence of alcohol to inhibit excess neuronal excitation [24]. Through multiple mechanisms of action, topiramate may modulate the craving associated with alcoholism in addition to its effects on chronic alcoholism withdrawal [7, 24]. More recent evidence contradicts topi-

ramates' attenuation of craving, but may instead alter the subjective effects of alcohol [25]. Regardless of mechanism, these properties would suggest topiramate therapy for the entire spectrum of withdrawal, abstinence, and relapse prevention, providing a potential off-label treatment option for clinicians in the treatment of alcohol dependence [26, 27].

4.1. Chemistry and Pharmacology

Topiramate is a sulfamate-substituted fructose-1,6-diphosphate analog [7] with a molecular weight of 339.37 daltons [26]. The molecular formula is $C_{12}H_{21}NO_8S$ and the full chemical name is 2,3: 4,5-Di-*O*-isopropylidene- β -D-fructopyranose sulfamate [26]. Originally studied as an anti-diabetic agent, topiramate's structural similarity to acetazolamide, led to its initial approved indication [7, 27]. Topiramate has potent anticonvulsant properties, similar to phenytoin and carbamazepine, though its mechanism of action appears to be dissimilar [27]. Topiramate's unique neurochemical properties prompted the hypothesis [14] that topiramate may be effective for the treatment of alcohol dependence [24].

Topiramate increases GABA_A-facilitated neuronal activity and simultaneously antagonizes AMPA and kainate glutamate receptors [26, 27] which may decrease the alcohol-induced dopamine release in the nucleus accumbens [7, 24]. Theoretically, increased GABA inhibition of dopaminergic neurons in the nucleus accumbens would disrupt the increased excitatory glutamatergic agonism characteristic of chronic alcoholism and attenuate mesolimbic dopaminergic activity [7]. This would temper the acute rewarding effects of alcohol intake in the midbrain and also provide neuroprotective stabilization of the increased glutamatergic activity caused by chronic alcohol intake at the glutamate receptors [24].

In addition to alcohol dependence, topiramate may also be useful in treating alcohol withdrawal [24]. Like other anticonvulsants, topiramate inhibits excess sympathetic nervous system agitation and neuronal hyperexcitability, features of early alcohol withdrawal [24]. In addition to decreased glutamatergic activity and increased GABA_A inhibition, topiramate also modulates ionotropic channels [24]. Specifically, it inhibits L-type calcium channels, limits the activity of voltage-dependent sodium channels and facilitates potassium conductance, all of which contribute to the hyperactivity and resulting anxiety of withdrawal [7]. Studies are currently being conducted to establish the efficacy of topiramate for alcohol withdrawal [7]. Another mechanism of action for topiramate is weak inhibition of the carbonic anhydrase isoenzymes, CA-II and CA-IV, in the brain and in the kidney [7, 28]. In the CNS, carbonic anhydrase is the enzyme responsible for the conversion of carbon dioxide to carbonic acid, the chemical thought to be responsible for the satisfying taste of carbonated beverages [29]. Carbonic anhydrase inhibitors, such as acetazolamide, are known to cause taste perversion of beer and other carbonated drinks, making them undesirable [30]. It is therefore not unreasonable to attempt to assess the extent of the taste perversion effect of topiramate [26] and any association with decreased beer consumption in particular, due to the medication's inhibitory effect on carbonic anhydrase [29].

Although long-term efficacy for the treatment of alcohol dependence has not been studied, the neuroprotective qualities of the drug suggest that it may be useful for extended treatment [7]. Recovering alcoholics have a high relapse rate, but treatment with topiramate putatively stabilizes the excessive neuronal stimulation of chronic alcoholism, and the drug may help to prevent recurrent binge drinking episodes [7].

4.2. Pharmacokinetics

Topiramate follows linear pharmacokinetics over the therapeutic dose range of 200 to 800 mg per day [27]. Oral absorption is rapid and nearly complete with peak plasma concentrations occurring within 2 hours of administration [27]. The relative bioavailability is 80% and is not affected by food [27]. About 15% of topiramate is bound to plasma proteins [27]. The drug is not widely metabolized *in vivo* and is predominantly eliminated (70%) unchanged in the urine [27]. The average elimination half-life approximates 21 hours with steady-state achieved in about 4 days for patients with normal renal function [26, 27]. Rat studies have shown evidence of renal tubular reabsorption of topiramate, but clinical significance has not been evaluated [27].

4.3. Efficacy of Topiramate for Alcohol Dependence

The efficacy of topiramate in reducing alcohol dependence and promoting abstinence was studied in a 12-week RDBPCT conducted in 150 patients between December, 1998 and April, 2001 [9]. Half of the participants received topiramate, 25 mg per day initially, titrated up to 300 mg per day over 6 weeks, and the other half received placebo. Both treatment groups received adjunctive Brief Behavioral Compliance Enhancement Treatment (BBCET) as a non-psychotherapeutic minimal intervention [9].

In this pilot trial, topiramate was found to be significantly more effective than placebo in reducing drinks per day (OR = -2.88 [95% CI, -4.50 to -1.27], $P=0.0006$), drinks per drinking day (average of the weekly ratios of drinks consumed divided by number of drinking days) (OR = -3.10 [95% CI, -4.88 to -1.31], $P=0.0009$), percentage of heavy drinking days (days with consumption of ≥ 5 drinks for men or ≥ 4 drinks for women, divided by the number of study days) (OR = -27.61 [95% CI, -42.20 to -13.02], $P=0.0003$), and log plasma γ -glutamyl transferase (GGT) ratio, an objective indicator of drinking (OR = -0.07 [95% CI, -0.11 to -0.02], $P=0.0046$), and in increasing the percentage of days abstinent (number of non-drinking days divided by number of study days) (OR = 26.21 [95% CI, 12.43 to 39.98], $P=0.0003$) [9]. An additional outcome measure included was the 14-item Obsessive Compulsive Drinking Scale (OCDS) [31] which assesses craving/obsession for alcohol. Topiramate was shown to be effective for reducing obsessive thoughts about alcohol, automaticity of drinking, and interference due to drinking [9]. No serious adverse events were reported during the trial [9].

Results reported by Johnson *et al.* [9] were supported as well by an open-label pilot study performed in Spain with 24 patients that found topiramate to be safe and well tolerated [32]. Based on these results a larger 14-week RDBPCT of 371 alcohol-dependent patients at 17 US sites between January, 2004 and August, 2006 [33]. Similar to the previous

trial, inclusion criteria were patients between 18 and 65 years old with a DSM-IV diagnosis of alcohol dependence; a score of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT) [34]; an average weekly number of standard drinks during the previous 4 weeks of at least 28 for women and 35 for men (one standard drink = 0.5 oz absolute alcohol); a body mass index (BMI) higher than 18; and a negative urine screen for narcotics, amphetamines, antidepressants, propoxyphenes and barbiturates at the time of randomization and at the beginning of the double-blind period [33].

Exclusion criteria included a concurrent axis I psychiatric diagnosis besides alcohol, nicotine, or caffeine dependence; a score of 10 or higher on the CIWA-Ar; a history in the last 6 months of substance abuse or dependence excluding alcohol, nicotine or caffeine; having made more than 4 unsuccessful inpatient treatment attempts; having received formal psychotherapy for a psychiatric disorder other than alcohol dependence within the last 3 months; use of antipsychotics, antiepileptics, mood stabilizers, carbonic anhydrase inhibitors, opioid analgesics, or systemic steroids at enrollment; clinically significant depression; suicidal ideation or attempt in the last month; concurrent treatment other than Alcoholics Anonymous; clinically significant medical conditions (on physical exam, EKG, hematological assessment, biochemistry including bilirubin count, or urinalysis); history of or current renal disease or kidney stones, seizures, or uncontrolled hypertension; a significant neurodegenerative or neurological disorder including seizures; pregnancy or lactation; concurrent use of medications that could potentially affect alcohol intake, or a carbonic anhydrase inhibitor; participants seeking treatment to avoid imprisonment or job loss; and those living in the same household as another participant [33].

Efficacy was evaluated weekly (including baseline), and data were analyzed using two approaches. The first involved imputing baseline values for all missing/dropout data [33]. Using this approach, topiramate recipients showed a significantly greater lowering of percentage of heavy drinking days (mean difference, 8.44% [95% CI, 3.07 to 13.80], $P=0.002$) and drinks per drinking day (mean difference, 0.88 [95% CI, 0.25 to 1.51], $P=0.006$), a higher percentage of days abstinent (mean difference, -7.68% [95% CI, -12.49 to -2.87], $P=0.002$), and reduced plasma GGT (mean difference for log GGT ratio, 0.03 [95% CI, 0.01 to 0.04], $P<0.001$) [33]. The second approach used a repeated-measures mixed model. Topiramate showed even greater efficacy over placebo, with mean differences of 16.19% [95% CI, 10.79 to 21.60] of heavy drinking days, 1.77 [95% CI, 1.19 to 2.36] drinks per drinking day, -13.39% [95% CI, -18.65 to -8.14] of days abstinent, and 0.05 [95% CI, 0.03 to 0.07] for log GGT ratio ($P<0.001$ for all four outcomes) [33].

Adding to these results, Johnson and colleagues using the data from the same trial, analyzed the effects of topiramate on physical health, alcohol craving, and psychosocial well-being [35]. Outcome measures of physical health included liver function tests (plasma aspartate aminotransferase, alanine aminotransferase, and γ -glutamyl transferase), hematological and biochemical measures (plasma cholesterol and bicarbonate and urine pH level), vital signs (blood pressure, pulse, and temperature), and BMI. Outcome measures of psychosocial function included craving/obsession for alcohol (as self-

reported on the OCDS), overall clinical improvement (determined by Clinical Global Impression scales of Improvement (CGI-I) and Severity (CGI-S) [36], harmful consequences of drinking (reported on the Drinker Inventory of Consequences scale (DrInC-2R) [37], quality of life (measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [38], general mood (determined by Profile Of Mood States (POMS) [39], and sleep quality (as gauged by the Medical Outcomes Study (MOS) sleep scale [40].

Topiramate was found to be superior to placebo at improving physical health outcomes [35]. A significant decrease was seen in all liver function test values, including plasma GGT. Plasma cholesterol was also reduced significantly, with a mean difference of 13.3 mg/dL [95%CI, 5.09 to 21.44], ($P=0.0016$) as compared to placebo. In addition, systolic and diastolic blood pressure and BMI were significantly lower in the topiramate group. Plasma bicarbonate levels were also significantly lower, however this did not require any medical intervention. All other physical health measures did not differ significantly between the two groups [35].

Topiramate was also shown to improve measures of psychosocial functioning. Specifically, a reduction in alcohol craving and obsessive drinking behavior was demonstrated by significantly lower scores on all four OCDS subscales [35]. Additionally, topiramate was associated with greater overall clinical improvement (mean differences of 0.67 [95% CI, 0.63 to 0.71], $P=0.0004$ for CGI-I and 0.73 [95% CI, 0.68 to 0.77], $P=0.002$ for CGI-S), greater quality of life (improvement at the 90th percentile on Q-LES-Q subscales of general activities (odds ratio [OR]=1.86, $P=0.037$), leisure time activities (OR=1.94, $P=0.028$), and household duties (OR=1.78, $P=0.024$)), and fewer harmful consequences of drinking (mean difference of 10.08 [95% CI, 5.86 to 14.30], $P<0.001$ on DrInC-2R) [35]. The two groups did not differ significantly in general mood assessed by the POMS. Although topiramate compared with placebo showed a trend for reducing sleep disturbance, this did not reach significance until week 14 (mean difference, 6.37 [95% CI, 2.10 to 10.64], $P=0.004$) [35]. These results confirm those found previously in a similar study using the pilot trial population [41]. Taken together, these results suggest that topiramate has greater efficacy than placebo to improve the quality of life, decrease the severity of alcohol dependence, and reduce the detrimental consequences associated with heavy drinking. Therefore, topiramate may be useful as a "harm-reduction strategy" in alcohol dependent patients who cannot attain the goal of abstinence [41].

Trials have recently compared the efficacy of topiramate to other medications to treat alcohol dependence. For example, in an open trial comparing topiramate to disulfiram in 100 alcohol dependent patients were randomized for 9 months of treatment encouraged to remain abstinent by family members [42]. Of 92 patients completing the study, relapse occurred at a mean of 133 days for patients receiving disulfiram compared to 79 days for those who received topiramate [42]. An open-label naturalistic study randomized 102 patients to either naltrexone or topiramate. The 6-month study demonstrated that both drugs showed a reduction in drinking, however there was a trend favoring topiramate to reduce drinking [43]. Recently a DBPCT evaluated the efficacy of topiramate (induction to 300mg/day) compared to naltrexone (50mg/day) in 155 alcohol dependent patients. Topiramate was statistically sig-

nificant compared to placebo on a number of outcomes. There were no significant differences between naltrexone compared to placebo or topiramate, however topiramate suggested superior outcome trends compared to naltrexone [44]. Finally, topiramate has also been used as an adjunct treatment in addition to other medications for alcohol dependence [45].

4.4. Adverse Events

In these trials, the most common adverse events (reported in 10% or more of participants) were paresthesia, headache, taste perversion, fatigue, anorexia, insomnia, difficulty with concentration or attention, nervousness, difficulty with memory, somnolence, diarrhea, dizziness, pruritis, nausea, dyspepsia, influenza-like symptoms, sinusitis, myalgia, and injury [33]. All except headache, nausea, dyspepsia, influenza-like symptoms, sinusitis, myalgia and injury were more frequent in the topiramate group compared with placebo [33]. Serious adverse events included myopia, cholelithiasis, and convulsions with loss of consciousness (not attributed to the medication) in the topiramate group, and tibial fracture, abnormally elevated serum liver enzymes, diverticulitis, and death due to cardiac arrest with gastrointestinal bleeding and seizures in the placebo group [33].

Other adverse events seen in earlier trials of topiramate as an AED included anxiety, ataxia, psychomotor slowing, and diplopia [27]. Most adverse events appeared to be dose related. About 85% of side effects occurred during the titration period and 85% of those tended to resolve with continued treatment [41]. Also, the largest number of patients who discontinued topiramate treatment because of side effects did so within the first 12 weeks of treatment which suggests that early tolerability may indicate longer term treatment success [46]. Central nervous system (CNS) related side effects were the most disturbing to patients, with cognitive slowing (27.6%) and dysphasia (16%) being the main reasons for medication discontinuation as reported previously [47]. Interestingly, Lee *et al.* [48] determined that the presence of paresthesia, a troublesome side effect caused by carbonic anhydrase inhibition, actually correlated with a more favorable therapeutic response in the prevention of migraine headaches [48]. To our knowledge similar analyses have not been performed or reported for the treatment of alcohol dependence with topiramate.

4.5. Drug Interactions

Although not extensively metabolized (70% renally eliminated), topiramate may be a potential substrate for CYP2C9, an inducer of CYP3A4, and a weak inhibitor of CYP2C19 [49]. Topiramate plasma concentrations are therefore increased by concurrent use of 2C9 inhibitors such as sorafenib, imatinib, and delavirdine, and reduced by concurrent use of 2C9 inducers including bosentan, other antiepileptics (eg. phenytoin, carbamazepine, valproic acid), and barbiturates [49]. Significant changes in phenytoin and valproate plasma concentrations have also occurred with topiramate administration [26]. In addition, concomitant use of topiramate and valproic acid has been associated with the development of hyperammonemia with or without encephalopathy [49]. For these reasons, topiramate use is discouraged in combination with other antiepileptic medications [27].

Coadministration of topiramate with barbiturates or other CNS depressants such as benzodiazepines, opiates, tramadol

or alcohol may result in additive sedation or other CNS depression [49]. During the trials, patients were encouraged to take the medication regardless of whether or not they had been drinking (preferably before starting) but were reminded not to drive or perform any dangerous tasks. In addition, tramadol taken with topiramate may decrease the seizure threshold in some patients [49]. Concurrent use of other carbonic anhydrase inhibitors, such as acetazolamide and dichlorphenamide, should also be avoided, as the increased renal effect of carbonic anhydrase inhibition may potentiate the development of kidney stones [27, 49]. Other significant interactions include an increased clearance of estrogens and progestins (decreasing the efficacy of oral contraceptives or hormone replacement therapy), reductions in pioglitazone (and metabolite) concentrations, increased renal clearance of topiramate with probenecid, reduced absorption with sevelamer, and an increase in concentration when coadministered with hydrochlorothiazide [49].

4.6. Precautions Using Topiramate

Dose related hyperchloremic, non-ion gap, metabolic acidosis is a rare but serious adverse event seen in topiramate post-marketing studies. This condition is caused by a renal decrease of bicarbonate levels secondary to carbonic anhydrase inhibition. Baseline and routine levels of serum bicarbonate should be monitored with topiramate treatment. Dose reduction or discontinuation should be considered with the development of metabolic acidosis [27].

In pre-clinical trials, about 1.5% of subjects developed kidney stones. This may be due to topiramate's inhibition of renal carbonic anhydrase which promotes stone formation by decreasing urinary citrate excretion and increasing urinary pH. Patients using topiramate should drink plenty of water to inhibit new stones from forming by increasing urinary outflow [27].

Topiramate should be used with caution in patients with renal impairment. Patients with moderately impaired kidney function (creatinine clearance 30 to 69 mL/min/1.73m²) had a 42% decrease in topiramate clearance so the dose may need to be reduced. Also, the medication is highly cleared during hemodialysis (120 mL/min as opposed to the normal 20 to 30 mL/min) and this patient population may need supplemental dosing [27].

4.7. Dosing Topiramate for Treatment of Alcohol Dependence

Topiramate is available as an oral tablet (25, 100 and 200 mg) or capsule (15 or 25 mg) that may be taken without regard to meals and is usually dosed twice daily [27]. The clinical trials using topiramate as a treatment for alcohol dependence have established an effective dose of up to 300 mg per day. The drug should be slowly titrated in order to minimize adverse events [27]. A study by Alapati, 1999 [50], recommended a starting dose of 25 mg/day with 25 mg/week dose increments [50]. The problem with this schedule is that it takes 12 weeks to reach a dose of 300mg. However, this titration schedule decreased the frequency of neurocognitive side effects and the rate of discontinuation as compared to patients receiving a 50 mg/day initial dose with subsequent dose increases of 50 mg/week [50]. Withdrawal of the drug must also

be achieved slowly, as seizures have been reported in patients without a history of seizures [27]. Recent evidence suggests the topiramate dose should be decreased by 25% every 4 days for 16 days. The improved tolerability of topiramate with titration is analogous to that of other anticonvulsants [41].

In patients with a creatinine clearance of less than 70 mL/min/1.73m², the dose of topiramate should be reduced by 50% of the recommended dose since topiramate's clearance is reduced. Since hemodialysis clears topiramate 4 to 6 times faster than patients with normal renal function, hemodialysis patients may need a supplemental dose of the medication to avoid rapid decreases of topiramate concentration [27].

5. CONCLUSIONS

While there are many potential candidate medications being investigated, very few have shown a clear and substantial benefit in the treatment of alcohol dependence. Disulfiram use is limited to the extremely motivated and/or supervised patient, as those who wish to drink can simply stop the medication. Naltrexone has shown some utility, however the effect size is small and seems to wear off after only a few months. Despite its success in European trials, acamprosate has not been proven efficacious in US studies, even in combination with naltrexone and psychosocial intervention. Given the current lack of outstanding medications, topiramate shows great promise as a treatment for alcohol dependence. Its therapeutic effect size is in the moderate range, and the benefits appear to increase over time [18]. Clinical trials have demonstrated topiramate's efficacy in improving all measures of self-reported drinking (effect size =.52) and increasing the quality of life among alcohol-dependent individuals. Topiramate has a favorable adverse event profile, especially when titrated slowly to a maximum of 300 mg/day. In addition, preclinical studies and knowledge of the drug's unique mechanisms of action support the notion that topiramate can also reduce withdrawal symptoms, prevent relapse, and promote long-term abstinence. More information is needed however, as to whether the reduced alcohol consumption associated with topiramate in the trials is more related to the length of time on the medication demonstrated after 5 weeks of treatment rather than the 300mg dose achieved. Therefore it is possible that lower doses may be clinically effective. Finally, healthcare professionals should be aware that although topiramate appears to be an effective treatment for alcohol dependence, the manufacturer will not pursue an approval for this indication, as the medication will soon be available generically.

Key Learning Objectives:

- The aim of this review is to provide clinicians with the available data required to make a decision whether or not topiramate would be an appropriate pharmacotherapeutic choice for patients with alcohol dependence.
- Topiramate 300mg per day has been demonstrated to significantly reduce drinks per drinking day in alcohol dependent patients.
- Clinicians should be aware of adverse events associated with topiramate such as word finding difficulties, drowsiness, paresthesias and changes in affect.
- Even though patients may not have a history of seizures, reports suggest that topiramate, an antiepileptic, may somehow induce seizure suddenly stopped, and should be slowly titrated down.

Future Research Questions:

- Are lower doses than 300mg per day just as effective to reduce alcohol consumption?
- What is the appropriate length of treatment with topiramate?
- Why does suddenly halting topiramate potentially cause seizures in some patients?

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