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TOPIRAMATE IN THE NEW GENERATION OF DRUGS: EFFICACY IN THE TREATMENT OF ALCOHOLIC PATIENTS

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Abstract

Predicated upon a neuropharmacological conceptual model, there is now solid clinical evidence to support the efficacy of topiramate for the treatment of alcohol dependence. Topiramate treatment can be initiated whilst the alcohol-dependent individual is still drinking — just when crisis intervention is most likely to be needed by a patient with or without his or her family asking the health practitioner for assistance. Because topiramate can be paired with a brief intervention, there is now the exciting possibility of treating most alcohol-dependent individuals in office-based practice or generic treatment settings. Topiramate's additional effects on other impulse-dyscontrol disorders make it a particularly interesting compound for the treatment of other comorbid drug or psychiatric disorders. Additionally, future studies should explore whether topiramate can be combined with other putative therapeutic agents to increase its efficacy. One notable clinical challenge in the development of topiramate as a pharmacotherapy to treat alcohol dependence is the determination of the smallest dose that can result in efficacy, thereby achieving the optimum balance between therapeutic benefit and adverse event profile. Animal data do provide support for topiramate's general anti-drinking effects but also indicate that its mechanisms of action might rely on several complex pharmacobehavioral changes. Additional preclinical studies are needed to elucidate more clearly the basic mechanistic processes that underlie topiramate's efficacy as a treatment for alcohol dependence. Preclinical information that topiramate may have differential effects based on genetic vulnerability opens up the possibility of future methods to optimize treatment.

Keywords

Topiramate; Alcohol; Treatment; Glutamate; Gamma-aminobutyric acid; Craving; Impulsivity; Relapse

Introduction

Renewed interest in medications to treat alcohol dependence has been spurred by the drive to find more efficacious compounds than those currently approved for use in the U.S. and in most parts of Europe. Scientific advances also show that new molecular targets can be

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Conflict of Interest Statement

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harnessed in medications development. Of this new generation of medications, the anti-seizure medication topiramate appears particularly promising based on the robust results from recent clinical trials. This overview shall provide a brief background and conceptualization of the neuropharmacological effects of topiramate, the results of recent studies of topiramate in the field of alcohol dependence, and a perspective pertaining to its use and further studies that need to be done.

Chemical Description and General Mechanisms of Action

Topiramate is a sulfamate-substituted analog of fructose-1,6-diphosphate. Topiramate is identified chemically as 2,3:4,5-Di-*O*-isopropylidene-beta-D-fructopyranose sulfamate and has structural similarity to acetazolamide, which has anticonvulsant effects [1]. Topiramate is a potent anti-epileptic [2-8] with strong neuroprotective properties [9-14].

Topiramate has at least six important mechanisms of action. These include: 1) facilitation of inhibitory gamma-aminobutyric acid-A ($GABA_A$)-mediated currents at non-benzodiazepine sites on the $GABA_A$ receptor [15,16]; 2) antagonism of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate glutamate receptors [17-19]; 3) inhibition of L-type calcium channels and limitation of calcium-dependent second messenger systems [20]; 4) limitation of activity-dependent depolarization and excitability of voltage-dependent sodium channels [21]; 5) activation of potassium conductance [22], and 6) weak inhibition of carbonic anhydrase isoenzymes — CA-II and CA-IV [23], which are found in both neuronal and peripheral tissues. In renal tubules, carbonic anhydrase isoenzyme inhibition decreases hydrogen ion secretion and increases secretion of Na^+, K^+, HCO_3^-, and water, thereby enhancing the likelihood of acidosis and renal stone formation [23,24].

Pharmacokinetics

Topiramate has a linear profile across a wide range of doses with a bioavailability of at least 80% [24-26]. Topiramate reaches its maximum concentration between 1.3 and 1.7 hours post-ingestion and has a half-life of 19 to 23 hours. Steady-state plasma concentration is reached in about 4 days. Topiramate has low binding potential to protein (~15%), and less than 20% of it undergoes metabolism to inactive metabolites. Most (i.e., up to 80%) of ingested topiramate is excreted unchanged in the urine. Topiramate has no established therapeutic range, and dosing is based upon clinical judgment of the balance between therapeutic response and adverse event profile.

Topiramate has little interaction with other psychotropic drugs, although it might cause additive sedation or other central nervous system depression when taken together with barbiturates, benzodiazepines, opiates, tramadol, or alcohol [27].

There are, however, some important interactions between topiramate and other anticonvulsants. For example, plasma levels of topiramate are reduced 17% when co-administered with sodium valproate; in turn, sodium valproate concentration is decreased 11% in the presence of topiramate [28]. Phenytoin and carbamazepine can decrease the level of topiramate by about 50% [29] and 40% [30], respectively. No significant pharmacokinetic interactions between topiramate (up to 400 mg/day) and lamotrigine (up to 600 mg/day) have been reported [31].

Topiramate can raise plasma levels of metformin by about 18% and reduce plasma levels of digoxin by about 12% [26]. Topiramate doses of up to 200 mg/day [32] have no significant effect on the plasma concentrations of oral contraceptives. In contrast, topiramate doses of 200 to 800 mg/day can be associated with dose-related reductions in the estrogenic

component of oral contraceptives but not of the progestogen moiety [33]; these effects are smaller than those observed with enzyme-inducing anticonvulsant drugs.

Topiramate has no significant effect on plasma levels of either amitriptyline or risperidone [34]. Topiramate administration can increase plasma levels of haloperidol modestly [35]; there is, however, no concomitant effect of haloperidol to alter topiramate concentration. Topiramate can decrease plasma levels of lithium by about 12% [36].

Approved and Other Potential Uses

The Food and Drug Administration (FDA) in the U.S. has approved topiramate for the adjunctive treatment of epilepsy, including partial-onset seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome [37]. The FDA also has approved topiramate for the treatment of migraine [38].

Topiramate is being investigated as a potential treatment for a variety of other disorders, including: metabolic disorders such as diabetes mellitus and obesity; anxiety-related disorders such as post-traumatic stress disorder, and impulse dyscontrol-related disorders such as binge eating, pathological gambling, and substance abuse disorders [39-44].

Safety and Tolerability

Topiramate has a favorable adverse event profile, with most reported symptoms being classified as either mild or moderate [45]. The most common adverse events are paresthesia (which is typically transient in nature), anorexia, difficulty with memory or concentration, and taste perversion. The development of cognitive impairment with topiramate includes word-naming memory difficulties and decreased attention and concentration [34]. Topiramate-induced adverse events increase if a high initial dose is given or there is a rapid titration to a ceiling dose; hence, these dosing strategies should be avoided. Slow titration to the usual ceiling dose of 300 mg/day should be done over a period of at least 6 weeks, and preferably 8 weeks, to minimize adverse events and improve tolerability; however, about 10% of individuals taking topiramate may experience some cognitive difficulty irrespective of the dose titration schedule [46].

Topiramate use has been linked with acute but rare visual adverse events. As of October 2002, 86 cases of acute secondary angle-closure glaucoma had been reported in patients taking topiramate [47]. More broadly, as of January 2005, there had been 371 spontaneous reports of myopia, angle-closure glaucoma, or increased intraocular pressure, for a rate of 12.7 reports per 100,000 patient-years exposure. Usually, the syndrome of acute bilateral myopia associated with secondary angle-closure glaucoma presents as the acute onset of visual blurring, ocular pain, or both. Associated bilateral ophthalmologic findings can include myopia, shallowing of the anterior chamber, conjunctival hyperemia, and raised intraocular pressure. This syndrome resolves within a few days of discontinuing topiramate administration [45]. Even though there have been a few case reports in recent years [48-52], there is no evidence from controlled studies that there has been a change in the frequency or severity of ocular side effects from what had been reported previously.

Topiramate administration is associated with weak inhibition of carbonic anhydrase isoenzymes CA-II and CA-IV, and the resultant renal bicarbonate loss, typically about 4 mEq/L, can lead to metabolic acidosis. As of July 2003, the incidence of metabolic acidosis in topiramate recipients in clinical trials was about 0.3% [34]. Bicarbonate monitoring should be considered in individuals with conditions that may exacerbate this condition, such as renal disease, being on a ketogenic diet, and the use of other carbonic anhydrase-inhibiting drugs. Tapering or stopping topiramate administration results in a rapid return to

normative bicarbonate values. Due to topiramate's tendency to increase the secretion of sodium and potassium ions, bicarbonate, and water and to cause acidosis, there is an increased likelihood of the formation of renal stones [24,53]. The incidence of renal stones associated with topiramate administration is about 1.5%. The likelihood of developing renal stones can be reduced by ensuring that individuals taking topiramate remain well hydrated [34]. Furthermore, because topiramate is excreted mostly unchanged in the urine, it should be used with caution among those with significant renal insufficiency; in contrast, because topiramate clearance is increased during hemodialysis, additional doses might be needed to maintain equivalent dosing [54].

An additional serious, but rare, adverse event associated with topiramate administration is oligohydrosis (decreased sweating) accompanied by hyperthermia [55]. This adverse event is typically seen in children, particularly those who are exposed to high temperature, vigorous physical activity, or both. As of July 2003, the incidence of oligohydrosis in individuals treated with topiramate in clinical trials was about 0.25%. It is recommended that individuals, especially children, receiving topiramate in hot climates or those predisposed to hyperthermic disorders should be checked routinely for symptoms of oligohydrosis [34].

Overall, topiramate is safe and well tolerated, and tolerability to its associated adverse event profile can be improved by decreasing the dose or slowing the drug titration schedule [46,56].

Mechanisms of Action in Treating Alcohol Dependence: Development of a Hypothesis

Johnson [34,57] proposed a neuropharmacological model by which topiramate can decrease alcohol reinforcement and the propensity to drink. This model laid out a hypothesis by which topiramate would be expected to suppress both acute and chronic ethanol consumption. Notably, this model was developed prior to any focused animal experiments or clinical studies in alcohol- or drug-dependent individuals. Therefore, the clinical work that was done subsequent to this hypothesis represents a leap from a concept to a proof-of-concept demonstration of topiramate's efficacy.

Hypothesized effects of topiramate on acute alcohol consumption

The conceptual framework of the hypothesis is that topiramate would be a promising medication for the treatment of alcohol dependence because its dual action to facilitate $GABA_A$-mediated inhibitory impulses, and at the same time antagonize AMPA and kainate glutamate receptors, would suppress ethanol-induced nucleus accumbens (NAcc) dopamine (DA) release, thereby inhibiting the reinforcing effects of alcohol associated with its abuse liability.

Basically, in the non-alcohol-dependent individual, extracellular DA release is inhibited by the activity of gamma-aminobutyric acid (GABA) neurons in both the ventral tegmental area (VTA) and NAcc [57]. Acute drinking decreases the firing rate of these GABA neurons, thereby producing an increase in neuronal activity and release of DA in these limbic structures. Topiramate would be expected to suppress extracellular DA release, particularly in the NAcc, because it would facilitate the inhibitory effects of GABA on DA neurons and block the excitatory effects of glutamatergic activity on DA neurons. Combined, these effects should lead to the profound suppression of DA activity across the cortico-mesolimbic axis [57] (see the upper right panel of Fig. (**1**)).

Hypothesized effects of topiramate on chronic alcohol consumption or alcohol withdrawal

In the chronic drinker or alcohol-dependent individual, the VTA-GABA neurons are in a hyperexcitable state due to decreased inhibition from NAcc GABA neurons, “rebound” excitation following repeated acute suppression of firing by alcohol, and increased glutamatergic tone from other limbic structures. Indeed, critical to the development of this state of sensitization is the recruitment of previously quiescent glutamate receptor type 1 AMPA receptors due to the enhancement of long-term potentiation from repeated glutamatergic neuronal stimulation and activation of L-type calcium channel currents [58]. Thus, chronic alcoholics have a state of VTA-GABA hyperexcitability and VTA-DA hypofunction. This sets up a vicious behavioral cycle. To normalize VTA-DA hypofunction and indeed to obtain levels of reinforcement similar to that of an acute drinker, the chronic drinker would have to drink more severely. On the other hand, if the chronic drinker decided to stop abruptly, the “rebound” in dopaminergic neuronal activity that resulted could be a trigger to reinstate drinking.

Hypothetically, topiramate should have utility in helping the chronic drinker withdraw slowly from alcohol and eventually stop. That is, topiramate would be expected to decrease VTA-GABA neuronal hyperexcitability due to increased GABA tone from NAcc GABA afferents and VTA-GABA interneurons and decreased neuronal sensitization through the blockade of AMPA receptors and L-type calcium channel currents. Hence, topiramate would be expected to “restore” or “normalize” VTA-GABA neuronal activity; yet NAcc DA release would be suppressed because topiramate would attenuate the enhanced glutamatergic excitatory input and facilitate the inhibitory input of GABA to the NAcc [57] (see the lower right panel of Fig. (**1**)). Further, it is plausible that other as yet poorly understood mechanisms, such as topiramate's ability to inhibit carbonic anhydrase, might help to reduce VTA-GABA hyperexcitability during withdrawal states [59].

Indeed, it would be tempting to hypothesize further that topiramate might have utility as a medication for the treatment of alcohol withdrawal symptoms. Apart from topiramate's effects to reduce VTA-GABA neuronal sensitization, its administration would further stabilize neuronal hyperexcitability by its ability to block sodium channels [14] and facilitate potassium conductance [22]. Further, alcohol withdrawal also is associated with hypersensitivity of the locus coeruleus and the liberation of norepinephrine (NE) [60,61] — an effect associated with increased symptoms of anxiety during alcohol withdrawal [62]. The locus coeruleus receives its primary excitatory input from both NMDA and non-NMDA glutamatergic afferents through the nucleus paragigantocellularis [63] and its inhibitory input through $GABA_A$ afferents from the nucleus prepositus hypoglossi [64]; thus the locus coeruleus is under dual excitatory and inhibitory control [65,66]. Topiramate, therefore, by blocking glutamatergic input and facilitating $GABA_A$ currents, might serve to diminish locus coeruleus-associated excitability and the rise in NE release during alcohol withdrawal. Indeed, there is some evidence for this premise as it has been shown in animals that AMPA receptor antagonism can reduce morphine-withdrawal-associated activation of the locus coeruleus [67]. Additionally, topiramate also has been shown to suppress mesolimbic release of monoamines including NE in animals pretreated with nicotine for 14 days [68]. Further, the marked increase in extracellular GABA levels along with $GABA_A$ receptor potentiation should afford added symptomatic relief of anxiety during withdrawal.

Consistent with this premise, topiramate has been shown to reduce anxiety preferentially in the elevated plus-maze paradigm in chronic intermittent ethanol-administered versus control rats [69]. Further, topiramate attenuates withdrawal signs in the kindling model of ethanol dependence by increasing the seizure threshold of the convulsant drug, pentylenetetrazol, in chronic intermittent ethanol-administered versus control rats [69]. Other mechanisms also have been postulated but not yet elucidated clearly. For instance, topiramate's ability to alter

the phosphorylation state of $GABA_A$ [69] and glutamate [70] receptors has been suggested as being important for these anti-seizure effects. Even these hypotheses may not entirely explain topiramate's anti-withdrawal and anti-seizure effects among alcohol-dependent individuals. Notably, there are evidently other important neurochemical interactions between the extended amygdala [71] and cortico-mesolimbic dopaminergic neurons, as well as associated allostatic responses through neuropeptides such as neuropeptide Y. Hence, it is plausible that other mechanistic processes may explain topiramate's therapeutic effects in treating alcohol dependence and withdrawal.

Nevertheless, irrespective of mechanistic considerations, it is of scientific interest that in an open-label human study, topiramate was shown to have utility in treating tonic-clonic seizures associated with alcohol withdrawal [72]. Also, in another pilot study of 30 alcohol-dependent inpatients, topiramate was shown to be as effective as diazepam, and both were significantly more effective than placebo, at reducing alcohol withdrawal symptoms [73].

In sum, topiramate is a complex compound with multiple actions on various neurotransmitter systems and ion channels. Topiramate's mechanisms of action also make it a promising therapeutic tool for the treatment of alcohol dependence and withdrawal. Obviously, it is plausible that the effects of topiramate may be additive in terms of decreasing alcohol reinforcement and, at the same time, being able to prevent withdrawal symptoms.

Animal Studies

Few studies on the effects of topiramate on ethanol consumption in animals have been published. An initial animal study had shown complex effects of topiramate on ethanol drinking in C57BL/6 mice. In that study, high-dose topiramate (50 mg/kg) but not low-dose topiramate (1, 5, and 10 mg/kg) suppressed ethanol intake 2 hours after it was injected into the animal. Topiramate also decreased saccharin preference, but its ability to suppress ethanol preference was associated with some increase in water intake [74]. Notably, in an elegant, recent animal study, Nguyen et al. [75] demonstrated that topiramate can suppress ethanol drinking in C57BL/6 mice; additionally, in contrast with the effects of naltrexone and tiagabine in the same animals, the mice treated with topiramate did not develop any tolerance to its anti-drinking effects. Also in C57BL/6 mice, topiramate can reduce stress-induced increases in alcohol consumption [76]. Further, topiramate also has been shown to suppress alcohol drinking moderately in alcohol-preferring (P) but not Wistar rats [77]. Additional to its ethanol-suppressing effects, there is evidence that topiramate can reduce alcohol withdrawal symptoms in a model of handling-induced convulsions [78]. Hence, the preponderance of the animal literature does support topiramate's anti-drinking effects, particularly among those with genetic vulnerability or where alcohol consumption has been induced by stress, and can ameliorate the symptoms of withdrawal. Interestingly, however, topiramate's effect on ethanol drinking in animals appears to be less striking than that on drinking outcomes in humans. This challenges the notion that animal models can predict directly treatment response in humans, especially when a variety of models have not been used or been available to characterize or “fingerprint” response [79]. The results of additional animal experiments that are examining topiramate's mechanistic effects on ethanol consumption or related behaviors in animals are, therefore, awaited eagerly.

Human Laboratory Study

In an experimental study of 61 male and female heavy drinkers who were not seeking treatment, Miranda et al. [80] showed that both low- and high-dose topiramate — 200 mg/day and 300 mg/day, respectively, titrated over 39 days followed by a week of dose

reduction — were significantly better than placebo at decreasing the percentage of heavy drinking days. The results of additional human laboratory studies are awaited eagerly.

Clinical Efficacy of Topiramate for the Treatment of Alcohol Dependence

Single-site study

Predicated on the hypothesis described above that topiramate would reduce the reinforcing effects of alcohol and aid an alcohol-dependent individual in withdrawing from alcohol, Johnson et al. [39] did a proof-of-concept clinical trial. In this randomized, double-blind, placebo-controlled, 12-week clinical trial, they determined the efficacy of topiramate in reducing drinking and craving and promoting abstinence among alcohol-dependent individuals.

The authors enrolled 150 individuals, 21 to 65 years old, diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [81], who reported drinking at least 21 standard drinks per week for women and at least 35 drinks per week for men, for the 90 days prior to enrollment. All subjects were current drinkers at enrollment. Of these 150 alcohol-dependent individuals, 75 were assigned to receive topiramate (escalating dose of 25 mg/day to 300 mg/day) and 75 had placebo as an adjunct to medication compliance enhancement treatment — brief behavioral compliance enhancement treatment (BBCET) [82]. BBCET is based on the medication compliance treatment used in the National Institute of Mental Health collaborative depression study [83] and can be described as a minimal intervention. Minimal interventions such as the brief advice of Edwards and colleagues [84] have been shown to be effective behavioral management in alcohol dependence.

Over the course of treatment, topiramate was significantly more effective than placebo with regard to all self-reported drinking outcomes, including the objective biochemical measure of drinking, serum gamma-glutamyl transferase (GGT) level [85]. At study end, topiramate recipients compared with placebo recipients had reduced their drinks per day by 2.88 (95% confidence interval [CI] −4.50 to −1.27) more drinks per day ($p = 0.0006$), reduced their drinks per drinking day by 3.10 (95% CI −4.88 to −1.31) more drinks per drinking day ($p = 0.0009$), reduced their heavy drinking days by 27.6% more heavy drinking days ($p = 0.0003$), increased their days abstinent by 26.2% more days abstinent ($p = 0.0003$), and experienced a 0.07 (95% CI −0.11 to −0.02) greater reduction in serum GGT ratio ($p = 0.0046$) than placebo recipients. The therapeutic effect size for the primary efficacy variable — percentage of heavy drinking days — was 0.63. Topiramate also was significantly more effective than placebo at reducing craving for alcohol, measured using the obsessive-compulsive drinking scale (OCDS) [86,87]. Compared with placebo, it reduced all craving factors on the OCDS ($p \leq 0.001$ for each) [39].

For illustrative purposes, it can be seen that the maximum relative probability between topiramate and placebo for achieving continuous abstinence (i.e., the magnitude of the treatment response) was 8.86 at 24 days. Additionally, the maximum relative probability between topiramate and placebo for achieving non-heavy drinking was 5.13 at 18 days [39].

Adverse events due to medication throughout the trial were, typically, of mild to moderate intensity, and none of these adverse events required medical intervention. The adverse events reported more frequently in the topiramate group than in the placebo group included dizziness (28.0% vs. 10.7%, $p = 0.007$), paresthesia (57.3% vs. 18.7%, $p < 0.0001$), psychomotor slowing (26.7% vs. 12.0%, $p = 0.023$), memory or concentration impairment (18.7% vs. 5.3%, $p = 0.012$), and weight loss (54.7% vs. 26.7%, $p = 0.001$). Attrition due to

adverse events did not differ significantly between the two groups, being 4% (3/75) in the topiramate group and 7% (5/75) in the placebo group [39].

The authors concluded that topiramate (up to 300 mg/day) is more efficacious than placebo as an adjunct to BBCET in the treatment of alcohol dependence. Topiramate was safe and well tolerated by this cohort of alcohol-dependent individuals [39].

From the same trial, three elements of psychosocial functioning were measured: clinical ratings of overall well-being and alcohol-dependence severity, quality of life, and harmful drinking consequences [88]. Overall well-being and dependence severity and quality of life were analyzed as binary responses with a generalized estimating equation approach; harmful drinking consequences were analyzed as a continuous response using a mixed-effects, repeated-measures model. Averaged over the course of double-blind treatment, topiramate, compared with placebo, improved the odds of overall well-being (odds ratio [OR] = 2.17; 95% CI 1.16–2.60; p = 0.01); reported abstinence and not seeking alcohol (OR = 2.63; 95% CI 1.52–4.53; p = 0.001); overall life satisfaction (OR = 2.28; 95% CI 1.21–4.29; p = 0.01), and reduced harmful drinking consequences (OR = −0.07; 95% CI −0.12 to −0.02, p = 0.01). There was a significant shift from higher to lower drinking quartiles on percentage of heavy drinking days, which was associated with improvements on all measures of psychosocial functioning. As an adjunct to medication compliance enhancement treatment, topiramate (up to 300 mg/day) was superior to placebo at not only improving drinking outcomes but increasing overall well-being and quality of life and lessening dependence severity and its harmful consequences [88].

In a secondary analysis of data from the single-site trial, Ma et al. [89] investigated whether topiramate also promoted “safe” levels of drinking — ≤1 and ≤2 standard drinks/day for women and men, respectively — among alcohol-dependent individuals. The authors calculated, based on self-reports, specific intervals of up to 30 days of continuous “safe” drinking for each subject. The average longest “safe” drinking period was 16.7 days for topiramate recipients versus 8.9 days for placebo recipients. By day 50 of treatment, 44% versus 26.4% had achieved ≥7 and 30.8% versus 10% had achieved ≥14 continuous “safe” drinking days. Similarly, topiramate increased the relative likelihood of continuous “safe” drinking from 77% for ≥7 days [relative risk (RR) for achieving continuous “safe” drinking = 1.77] to threefold for ≥14 days (RR = 3.37) and fourfold for ≥28 days (RR = 4.07). Thus, participants who received topiramate were more likely to achieve longer periods of “safe” drinking compared with those who received placebo. For alcohol-dependent individuals who drank within an abstinence-oriented treatment program, topiramate promoted “safe” drinking, thereby suggesting the potential of topiramate (up to 300 mg/day) to decrease the public health consequences of hazardous drinking [89].

Multi-site study

In a subsequent 14-week, double-blind, controlled, 17-site clinical trial, Johnson et al. [90] compared the efficacy of topiramate (up to 300 mg/day) versus placebo at improving drinking outcomes in 371 males and females between the ages of 18 years and 65 years who were diagnosed with alcohol-dependence according to the DSM-IV [81] using the Structured Clinical Interview for DSM-IV [91]. All subjects received weekly BBCET [82] as their psychosocial adjunct to treatment.

For the primary analysis of percentage of heavy drinking days, when imputing data for all dropouts as relapse to baseline measure, topiramate compared with placebo recipients showed greater lowering of percentage of heavy drinking days from baseline to week 14 (i.e., from 81.91 ± SD 20.04 to 43.81 ± 40.43 vs. 81.97 ± 19.92 to 51.76 ± 37.43) — mean difference = 8.44, 95% CI 3.07–13.80 (p = 0.002). The between-groups difference occurred

in week 4. Also, on the secondary measures of self-reported drinking and the laboratory marker of drinking, using the primary analytic method of imputing all dropouts as relapse to baseline, topiramate was superior to placebo [90].

For the pre-specified analysis of percentage of heavy drinking days, without imputing missing data for dropouts, topiramate was superior to placebo at improving percentage of heavy drinking days — mean difference = 16.19, 95% CI 10.79–21.60 ($p < 0.0001$). The between-groups difference occurred in week 2. Also, on the secondary measures of self-reported drinking and the laboratory marker of drinking, using the pre-specified analysis, topiramate was superior to placebo [90].

Topiramate versus placebo recipients experienced significant reductions not only in self-reported drinking but also on the laboratory marker of drinking — plasma GGT ($p < 0.0001$ for all comparisons) [90].

Using the primary analytic approach of imputing missing data with the baseline value, topiramate compared with placebo treatment was associated with a significantly higher rate of achieving ≥28 days of continuous non-heavy drinking and ≥28 days of continuous abstinence — hazard ratio 2.28 (95% CI 1.44–3.59; $p = 0.0004$) and 5.03 (95% CI 2.07–12.20; $p = 0.0003$), respectively [90].

Using the pre-specified approach of not imputing missing data, topiramate compared with placebo treatment was associated with a significantly higher rate of achieving ≥28 days of continuous non-heavy drinking and ≥28 days of continuous abstinence — hazard ratio 2.79 (95% CI 1.76–4.42; $p < 0.0001$) and 5.96 (95% CI 2.46–14.46; $p < 0.0001$), respectively [90].

With the primary analytic model and pre-specified model, the topiramate group reached ≥28 days of continuous abstinence significantly faster than did the placebo group ($p < 0.0001$ and $p < 0.0001$, respectively; log-rank test), and the topiramate group reached ≥28 days of continuous non-heavy drinking significantly faster than did the placebo group ($p = 0.0004$ and $p < 0.0001$, respectively; log-rank test) [90].

At study end, on the safety measures, the topiramate group versus the placebo group was associated with reduced liver enzymes — aspartate aminotransferase and alanine aminotransferase — mean difference = 4.7, 95% CI 1.86–7.54, and mean difference = 6.74, 95% CI 2.99–10.49, respectively. Although plasma bicarbonate levels were significantly lower for the topiramate group than for the placebo group (mean difference = 2.50 mmol/L; 95% CI 1.89–3.11; $p < 0.001$), this did not require any medical intervention. Plasma pH level did not differ significantly between the topiramate and placebo groups. No other hematological or biochemical tests differed between the two groups. The two groups did not differ on depressed mood (mean difference = 0.57; 95% CI −0.13 to 1.26) or general mood (mean difference = 0.8; 95% CI −2.52 to 4.12) [90].

Adverse events that were reported to occur in 10% or more of participants included paresthesia, headache, taste perversion, fatigue, anorexia, nausea, insomnia, difficulty with concentration and attention, nervousness, difficulty with memory, somnolence, diarrhea, sinusitis, dyspepsia, injury, dizziness, influenza-like symptoms, pruritus, and myalgia; all except headache, nausea, sinusitis, dyspepsia, injury, influenza-like symptoms, and myalgia were more frequent for topiramate than for placebo recipients. Four participants in each treatment group experienced a serious adverse event. In the topiramate group, one participant had myopia and another had cholelithiasis. Also, one participant had convulsions and loss of consciousness; however, these could not be attributed to the study medication. In contrast, in the placebo group, one participant died following a cardiac arrest associated with

a gastrointestinal bleed and seizures. The precipitating incident could not be determined. Also, three separate individuals had a tibial plateau fracture, abnormally elevated serum liver enzymes, and diverticulitis, respectively.

Alcohol-withdrawal scores assessed on the revised Clinical Institute Withdrawal Assessment for Alcohol scale [92] were exceedingly low and did not differ between the topiramate and placebo groups (mean difference = 0.01; 95% CI −0.31 to 0.33). Few participants reported attending Alcoholics Anonymous — 5.0% and 2.7% for the topiramate and placebo groups, respectively. Rates of concomitant medication use for the topiramate and placebo groups were 88% and 95.7%, respectively. The following percentages of participants received these topiramate doses or equivalent placebo doses, respectively: 0–25 mg (3.8%, 1.6%), 25–50 mg (8.2%, 0.5%), 50–100 mg (12%, 3.2%), 100–150 mg (10.4%, 6.9%), 150–200 mg (13.7%, 10.1%), and 200–300 mg (50.8%, 77.7%) [90].

The rates for compliance with taking topiramate or placebo were similar at 91.46 ± SD 14.96% versus 90.09 ± SD 13.12%, respectively. Means and standard deviations of the topiramate dose and serum level were 171.4 ± 107.6 mg and 4.8 ± 3.7 μg/ml, respectively. There was a predictable and significant relationship between the topiramate dose administered and the serum concentration achieved ($r = 0.71$; $p < 0.0001$). There was, however, no significant correlation between the serum topiramate level and the percentage of heavy drinking days among those who completed week 14 ($r = 0.04$). Different time sampling in obtaining the weekly serum topiramate levels might, however, have contributed to some variability in the results. No numerical difference existed between the topiramate and placebo groups in mean breath alcohol concentration; the average reading was 0.002%. Retention rates at study end among those randomized were 61.2% (112 of 183) and 76.6% (144 of 188) ($p < 0.001$) for the topiramate and placebo groups, respectively, and attrition rates due to adverse events were 18.6% (34 of 183) and 4.3% (8 of 188) ($p < 0.001$), respectively [90].

In a subsequent publication from the multi-site study, Johnson et al. [93] also compared the effects of topiramate (up to 300 mg/day) versus placebo on physical health, obsessional thoughts and compulsions about using alcohol, and psychosocial well-being. Topiramate was more efficacious than placebo in reducing body mass index (calculated as weight in kilograms divided by height in meters squared) (mean difference, 1.08; 95% CI 0.81–1.34; $p < 0.001$), plasma cholesterol level (mean difference, 13.30 mg/dl; 95% CI 5.09–21.44 mg/dl; $p = 0.002$), and systolic (mean difference, 9.70 mm Hg; 95% CI 6.81–12.60 mm Hg; $p < 0.001$) and diastolic (mean difference, 6.74 mm Hg; 95% CI 4.57–8.90 mm Hg; $p < 0.001$) blood pressure to about pre-hypertension levels — effects that might lower the risk of fatty liver degeneration and cirrhosis as well as cardiovascular disease. Topiramate compared with placebo significantly ($p < 0.05$ for all comparisons) decreased obsessional thoughts and compulsions about using alcohol, increased subjects' psychosocial well-being, and improved some aspects of quality of life, thereby diminishing the risk of relapse and longer-term negative outcomes.

In sum, topiramate was significantly more efficacious than placebo at reducing percentage of heavy drinking days, improving all other self-reported drinking outcomes, and reducing plasma GGT in a heterogeneous and geographically diverse population of alcohol-dependent individuals receiving weekly BBCET for 14 weeks [90]. The robustness of topiramate's therapeutic effect was evidenced by the demonstration of clinical efficacy over placebo using different inferential methods. Topiramate's therapeutic effect size for the reduction in percentage of heavy drinking days was 0.52, and the number needed to treat was 3.4 [94]. Topiramate also was efficacious at improving the physical and psychosocial consequences of excessive alcohol consumption and improving general well-being in alcohol-dependent

individuals [93]. Since topiramate's therapeutic effect emerged as early as the 4th week of treatment, it would be important to do studies that determine its smallest therapeutic dose, thereby diminishing the potential for adverse events. An important lesson from this trial is that a slower titration schedule to topiramate's ceiling dose of 300 mg/day — that is, over 8 weeks rather than 6 weeks — might have been associated with greater medication compliance and a milder adverse event profile.

Other Clinical Studies

Additional clinical studies have been done that corroborate and extend the findings of the initial studies by Johnson and colleagues [39,90] by using other paradigms (e.g., relapse prevention) and different outcome measures. To date, no negative studies have been reported.

Baltieri and colleagues [95] compared the efficacy of topiramate (up to 300 mg/day) and naltrexone (50 mg/day) versus placebo in a double-blind, controlled clinical trial that enrolled 155 alcohol-dependent individuals. In that study, topiramate was more efficacious than placebo on a number of measures including time to first relapse (7.8 weeks vs. 5.0 weeks), cumulative abstinence duration (8.2 weeks vs. 5.6 weeks), weeks of heavy drinking (3.4 weeks vs. 5.9 weeks), and percentage of subjects abstinent at 4 weeks (67.3 vs. 42.6) and 8 weeks (61.5 vs. 31.5), but not 12 weeks (46.2 vs. 27.8). The greater efficacy of topiramate compared with placebo remained significant after controlling for Alcoholics Anonymous attendance, which was higher in the topiramate group than in the other groups. There were no significant differences between the naltrexone and placebo groups or between the naltrexone and topiramate groups, and naltrexone showed trends toward inferior outcomes when compared with topiramate. These data support the efficacy of topiramate as a relapse prevention agent and suggest that topiramate might be more efficacious than naltrexone.

In a 6-month, open-label, naturalistic study of 102 alcohol-dependent individuals, topiramate's (up to 400 mg/day) versus naltrexone's (50 mg/day) effects on drinking outcomes were compared [96]. At the end of 6 months, both topiramate and naltrexone were considered efficacious based on clinically defined criteria of percentage of individuals with complete abstinence (47.05% vs. 45.09%) or moderate drinking without problems (25.49% vs. 9.8%). Additionally, subjects who took naltrexone compared with topiramate were more likely to report nicotine addiction (4.2 vs. 2.23; $p = 0.016$) on the Fagerström test for nicotine dependence [97] and greater overall craving on the OCDS [86,87] (1.64 vs. 0.55; $p = 0.021$). Taken together, these data provide general support for topiramate as a treatment for alcohol dependence and again suggest that it might be more efficacious than naltrexone. Due to the open-label nature of this study, considerable care must, however, be taken in interpreting the results of this clinical trial.

Despite the initial evidence from both of these studies [95,96] that topiramate is more efficacious than naltrexone, definitive controlled studies are needed to establish this impression. Furthermore, no study that compares the relative efficacies of topiramate and acamprosate— or the relative efficacies of topiramate and the combination of naltrexone and acamprosate — has been published.

In a recent open, randomized, 9-month trial, De Sousa et al. [98] compared the efficacy of disulfiram versus topiramate at preventing relapse among 100 alcohol-dependent men whose family members had agreed to encourage medical compliance. Alcohol consumption and craving were recorded weekly for 3 months and then biweekly. Among the 92 patients who completed the trial, relapse occurred at a mean of 133 days for those who received disulfiram versus 79 days for those who received topiramate. At 9 months, 90% of

disulfiram recipients and 56% of topiramate recipients remained abstinent. Importantly, however, the topiramate recipients showed less craving than did the disulfiram recipients. Nevertheless, these data must be treated with caution due to the relatively small sample size and open-label design. Indeed, a double-blind, randomized controlled trial would be necessary to provide any definitive comparison between the relative efficacies of topiramate and disulfiram.

In a 12-week, double-blind, randomized controlled trial done in 63 alcohol-dependent men, topiramate compared with placebo was associated with a lower number of drinks per drinking day (6.45 vs. 8.75; $p = 0.04$), a lower percentage of heavy drinking days (33.33 vs. 50.91; $p = 0.001$), and a higher percentage of days abstinent (52.00 vs. 37.14; $p = 0.001$) [99]. Topiramate also was superior to placebo at increasing performance on the stop-signal task [100], which suggests a decrease in impulsivity. Interestingly, topiramate compared with placebo was associated with better performance on the continuous performance test [101]. Plausibly, topiramate's ability to reduce impulsivity might explain why it can improve performance on a task like the continuous performance test that requires both attention and concentration. In consideration of the reported cognitive deficits that have been linked with topiramate administration, these data also suggest that topiramate's effects on cognitive performance might vary depending upon the task being performed.

Recently, data have been presented that suggest that a single nucleotide polymorphism in intron 9 of the GRIK1 gene (rs2832407) was associated with the severity of topiramate-induced side effects and with serum levels of topiramate [102]. Additional studies are, however, needed to substantiate these results. Nonetheless, it is possible that genetic studies might enable the identification of individuals with the greatest likelihood of having significant adverse events from taking topiramate prior to them receiving it.

In sum, these data provide strong and continuing support for topiramate as an efficacious treatment for alcohol dependence.

Discussion

Predicated upon a neuropharmacological conceptual model, there is now solid clinical evidence to support the efficacy of topiramate for the treatment of alcohol dependence. Topiramate's therapeutic effects appear to be robust, with a medium effect size, thereby potentially ushering in a new era of a reliably efficacious medicine for the treatment of alcohol dependence. One notable challenge in the development of topiramate as a pharmacotherapy to treat alcohol dependence is the determination of the smallest dose that can result in efficacy, thereby achieving the optimum balance between therapeutic benefit and adverse event profile.

Importantly, topiramate treatment can be initiated whilst the alcohol-dependent individual is still drinking — just when crisis intervention is most likely to be needed by a patient with or without his or her family asking the health practitioner for assistance. This property of topiramate, along with its ability to be used with a minimal intervention program, augurs well for its widespread use in generic treatment settings. Indeed, the use of topiramate treatment opens up the exciting possibility of office-based treatment for most individuals with alcohol dependence [103,104].

Not all alcohol-dependent individuals who take topiramate stop drinking altogether after a short period of treatment (i.e., 3–6 months) in clinical studies. While some individuals may be considered to be in “partial remission”, they are certainly not “cured” because the risk of relapse remains high. Given that topiramate is neuroprotective and can “normalize” chronic alcohol-induced neuronal sensitization, it would be reasonable to propose that topiramate

may be useful as a long-term treatment for alcohol dependence. That is, the long-term neuroprotective effect of topiramate treatment may afford the recovering alcoholic added time to seek more psychosocial supports that might, eventually, enable the ultimate treatment goal of abstinence to be achieved. At the very least, this strategy might offer some protection against recurrent bingeing episodes.

Of course, it is tempting to consider that the pharmacotherapeutic effects of topiramate might be augmented by the addition of other putative therapeutic agents that have been proposed for treating alcohol dependence. Such combination treatments rely on increasing knowledge about the mechanistic processes associated with alcoholism and conceptual advances to determine which medications would be best to combine with topiramate and at what particular stage of treatment.

Topiramate's additional effects on other impulse-dyscontrol disorders make it a potentially interesting compound for the treatment of other comorbid drug or psychiatric disorders. Indeed, National Institutes of Health studies are currently under way to test topiramate's efficacy as a treatment for alcohol dependence comorbid with nicotine dependence, cocaine dependence, bipolar disorder, and other impulse dyscontrol disorders. Testing the efficacy of topiramate for these comorbid disorders is intriguing as it opens up the possibility that similar or shared underlying mechanistic neuronal processes might be amenable to treatment.

Intriguingly, animal data do provide support for topiramate's general anti-drinking effects but also indicate that its mechanisms of action might rely on several pharmacobehavioral changes. These include topiramate's effect to decrease preference for ethanol, reduce impulsive behaviors, and inhibit stress-induced increases in ethanol consumption. Whilst all of these behaviors appear somewhat analogous to the human condition, additional basic research is needed to characterize fully or “fingerprint” a more complex pattern of response. Such preclinical studies should enable researchers to elucidate more clearly the basic mechanistic processes that underlie topiramate's efficacy as a treatment for alcohol dependence. Preclinical information that topiramate may have differential effects based on genetic vulnerability opens up the possibility of future methods to optimize treatment.

Future research is needed to extend the results of previous clinical trials to specific subpopulations of alcohol-dependent individuals who respond the most, and to see whether the combination of topiramate with other medications could enhance its efficacy.

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Abbreviations used

GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid-A
AMPA	alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
CA	carbonic anhydrase
FDA	Food and Drug Administration

NAcc	nucleus accumbens
DA	dopamine
VTA	ventral tegmental area
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
BBCET	brief behavioral compliance enhancement treatment
GGT	gamma-glutamyl transferase
CI	confidence interval
OCDS	obsessive-compulsive drinking scale
OR	odds ratio
RR	relative risk

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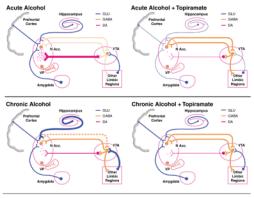

Figure (1).

Schematic illustration of the hypothesized effects of acute and chronic alcohol, both with and without topiramate, on the cortico-mesolimbic dopamine (DA) reward circuit [57]. (Upper left) Acute alcohol suppresses the firing rate of ventral tegmental area (VTA) gamma-aminobutyric acid (GABA) neurons, which leads to less suppression of VTA DA neuronal activity. This disinhibition leads to VTA DA neuronal firing and DA release in the nucleus accumbens (N Acc.) [57]. (Lower left) With chronic drinking, VTA GABA neurons are hyperexcitable, mainly because of increased glutamatergic input, less GABA tone from the N Acc., and rebound firing of GABA neurons because of their long-term suppression from repeated alcohol ingestion. This leads to VTA DA hypofunction and decreased release (compared with the acute condition) of DA in the N Acc. [57]. (Upper right) During acute drinking, the GABAergic influence of topiramate probably predominates, particularly in the N Acc. This leads to greater inhibition of N Acc. DA neurons, and greater GABA tone from the N Acc. to the VTA suppresses VTA DA cell firing. Topiramate concomitantly inhibits the excitatory effects of glutamatergic neurons on DA neurons in the VTA and N Acc. These combined actions of topiramate should lead to profound suppression of DA neuronal activity and DA release in the N Acc. Hence, topiramate reduces the DA-mediated reinforcing effects of acute alcohol [57]. (Lower right) During chronic drinking, the predominant neuronal activity resides with the hyperexcitable state of VTA GABA neurons. Because of GABA-mediated inhibition and glutamatergic blockade of these neurons, topiramate “normalizes” VTA GABA neuronal activity. Although this would, at first, suggest that DA release in the N Acc. would be enhanced, this does not occur, and DA release in the N Acc. is most likely reduced because these N Acc. terminals are contemporaneously inhibited by GABA inhibition and blockade of glutamate (GLU). In the chronic drinker, the anti-glutamatergic and L-type calcium channel effects of topiramate to block sensitization might predominate. Hence, topiramate would make it easier for a chronic alcoholic to withdraw from alcohol because rebound DA release would not occur (if drinking were ceased abruptly), and topiramate would aid in relapse prevention because alcohol's reinforcing effects would be decreased [57]. Line weights represent relative strengths of neuronal activity (heavy, medium, and light). The broken line represents decreased tone. VP, ventral pallidum. Reprinted from Johnson [57] with the permission of John Wiley & Sons, Inc.