Topiramate Pharmacotherapy for Alcohol Use Disorder and Other Addictions: A Narrative Review

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Topiramate is a non-benzodiazepine anticonvulsant medication with multi-faceted pharmacologic action. It has emerged as an efficacious pharmacotherapeutic option for the treatment of addiction, especially alcohol use disorder (AUD). We present a broad narrative review of the putative mechanism of action and clinical utility of topiramate with regard to AUD and other substance use disorders. Collective evidence suggests topiramate is an effective treatment option in AUD, with notable efficacy in reducing harmful drinking patterns in AUD. Though not currently approved by the United States Food and Drug Administration for the indication of AUD, topiramate should be considered as a pharmacological treatment option with high utility among AUD patients. Early pharmacogenetic studies raise the intriguing possibility of identifying patients likely to respond to topiramate using genetic testing, and initial studies show that topiramate may also be useful in treating cocaine use disorder, smoking cessation and behavioral addictions. However, further research is needed in all these areas.

Key Words: alcohol dependence, alcohol use disorder, alcoholism, anticonvulsant, medication treatment, Topiramate

(*J Addict Med* 2018;xx: xxx–xxx)

A lcohol and other substance use disorders (AUD, SUDs) are highly prevalent in the United States and also globally, imposing a tremendous burden on society (Merikangas and McClair, 2012; Sacks et al., 2015; United Nations Office on Drugs and Crime, 2017). AUD is a significant health problem in the United States with a 13.9% 12-month and 29.1% lifetime prevalence (Grant et al., 2015). The 12-month prevalence for AUD reported globally is up to 16% (Rehm and Patra, 2010). SUDs are often chronic diseases with complex neurobiological underpinnings resulting in varied behavioral and psychosocial problems posing significant treatment challenges to clinicians. Investigations into pharmacological treatment of SUDs have not yielded a "magic bullet," but led to the development of multiple pharmacotherapeutic agents, putatively targeting different components of the disease process (ie, craving, euphoria from the substance).

Non-benzodiazepine anticonvulsant medications with their effects on glutamatergic and GABAergic neurotransmission, have broad therapeutic benefits in the treatment of AUD with regard to both withdrawal and relapse prevention, and with varying degrees of effectiveness (Hammond et al., 2015; Pani et al., 2014). Topiramate appears to be an effective treatment option in AUD, and is emerging as a possible option in the management of other SUDs (Johnson and Ait-Daoud, 2010). Here we provide a narrative review of the possible utilities of topiramate in AUD and other SUDs.

SEARCH METHODOLOGY

We conducted a series of English-language medical literature searches using the PubMed, Cochrane Library, and PsycINFO databases using the following search terms: "topiramate," "topiramate + substance abuse/substance use disorder/addiction/withdrawal/side-effects/alcohol/alcohol use disorder/alcohol dependence/cocaine/nicotine/smoking/gambling/eating disorder." Studies involving humans only, published up to September 2017 were included in the review. All study designs, namely meta-analysis, randomized control trials, open trials, case series and case reports were included for review. We manually searched the reference lists of pertinent original research articles, review articles, and textbooks for additional relevant citations.

MECHANISM OF ACTION

Topiramate is a fructose-1,6-diphosphate analogue and was initially developed as an anti-diabetic drug but was later developed as an anti-convulsant due to its similarity with acetazolamide. Topiramate acts as a positive allosteric modulator at $GABA_A$ receptors, which are activated causing increased chloride ion influx into neurons, thus increasing overall GABA mediated inhibition (White, 2003). These activities are probably mediated through non-benzodiazepine binding sites on $GABA_A$ receptors (White et al., 2000). GABA levels in the brain are also increased. Topiramate is a non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate mediated glutamate

receptors causing blockage of glutamate-mediated neuroexcitation, but has no effect on NMDA-sensitive glutamate receptors (Angehagen et al., 2005). In addition, topiramate limits depolarization and excitability at voltage-activated Na^+ channels, causing inhibition of high and repetitive action potential discharges. Topiramate also inhibits L-type Ca^{2+} channels reducing neurotransmitter release and Ca^{2+}-dependent second messenger systems (Zhang et al., 2000). Consistent with its structural similarity to acetazolamide, it also inhibits Types II and IV carbonic anhydrase, leading to inhibition of hydrogen ion secretion by renal tubules, and increasing secretion of Na^+, K^+, HCO_3^-, and water (Dodgson et al., 2000).

The effects of topiramate on pathways involved in addiction have been elucidated to some extent, but hypotheses about how it affects the addicted brain remain largely speculative and have not been fully explored in the context of translational studies (Johnson, 2005; Johnson and Ait-Daoud, 2010; Johnson, 2008). Topiramate is thought to alter the reinforcing properties and subjective experience of drugs and alcohol, and probably helps to normalize and restore balance in the reward circuits of the brain, thus restoring proper hedonic function and stress response among chronically drug or alcohol using persons. Topiramate putatively exerts it effects on midbrain dopaminergic (DA) pathways projecting from ventral tegmental area (VTA) to the nucleus accumbens (NAcc) by enhancing GABAergic neurotransmission and antagonizing glutamatergic neurotransmission, leading to suppression of dopaminergic surges at the NAcc. These proposed effects have not yet been thoroughly investigated in animal studies, although one study found that topiramate treatment reduced the effects of nicotine induced midbrain dopamine release in rats (Schiffer et al., 2001). These actions are thought to decrease the positive reinforcing effects of acute alcohol consumption. The suppression of glutamatergic effects and L-type calcium channel effects caused by topiramate likely suppresses the hyperexcitability of VTA DA neurons associated with chronic drinking, moving them to a more ''normal'' level of excitability. This may help allow a chronic drinker to use less alcohol because of less negative reinforcing drive of rebound glutamatergic tone.

Another possible mechanism of action for topiramate is based on the theoretical framework that addiction is a learned automatic behavior that gets established by forced memorization through neuronal synaptic plasticity involving both long-term potentiation (LTP) and long-term depression (LTD) (Thorens et al., 2011). Topiramate has been suggested to inhibit the expression of addiction-related automatic behavior through glutamatergic receptor inhibition. A dual effect of GABAergic potentiation and AMPA/Kainate mediated glutamatergic suppression has been hypothesized as the potential pathway of topiramate efficacy in AUD as well as other SUDs (Shank and Maryanoff, 2008). Recent small imaging studies have implicated glutamatergic signaling in the process of alcohol craving, thus it is possible that topiramate modulates craving by way of glutamatergic antagonism (Cheng et al., 2018; Frye et al., 2016).

Mechanistic Insights Into Adverse Effects

Topiramate is associated with several adverse effects that can be a nuisance for patients. Paresthesias are a common side effect. Carbonic anhydrase (CA) activity inhibition has been implicated in several of these adverse effects. CA inhibition in the kidneys is the obvious driver of metabolic acidosis associated with topiramate and Type 3 renal tubular acidosis which has also been reported in association with CA inhibition (Garris and Oles, 2005; Sacré et al., 2006). CA inhibition locally and preferentially at sensory neuronal endings leading to acidosis and resulting ectopic activation of sensory neurons has been implicated in parasthesias (unpleasant tingling in extremities) associated with topiramate (Fujii et al., 1993; Spitzer et al., 2002; Swietach et al., 2003). Renal calculi occur at a 2- to 4-fold higher rate among those on topiramate, and are thought to be due to an increase in urinary pH caused by increased excretion of bicarbonates and decreased citrate excretion that promotes precipitation of calcium salts (calcium phosphate) (Welch et al., 2006).

Oligohydrosis is a rare but serious risk of topiramate treatment. Oligohydrosis (insufficient sweating associated with heat or exercise) has been attributed to CA inhibition (Cerminara et al., 2006) and inhibition of aquaporin 5 receptors in sweat glands (Ma et al., 2007). Topiramate is pregnancy category D, and cleft palate can occur with fetal exposure. Due caution should be exercised with topiramate use in women of childbearing potential; a reliable form of birth control should be used as well.

Acute visual disturbance, myopia and acute angle closure glaucoma all occur infrequently among those receiving topiramate, mostly at the beginning of the treatment (Shank and Maryanoff, 2008). Cognitive impairment from topiramate can be significant enough in some patients to cause discontinuation. This seems to be driven by topiramate effect on frontal lobe functions (attention, cognitive speed, verbal fluency, short-term memory, and mental flexibility) (Gomer et al., 2007).

PHARMACOKINETICS, CONTRAINDICATIONS, ADVERSE REACTIONS, AND DRUG-DRUG INTERACTIONS

Bioavailability of topiramate is at least 80%, with linear bioavailability across a wide range of doses (Easterling, 1988). Topiramate achieves peak plasma concentration at 1.3 to 1.7 hours and a steady-state concentration in approximately 4 days. It has a half-life of 19 to 23 hours. It exhibits linear pharmacokinetics and dose-proportional increase in plasma levels. On oral ingestion, only a small percentage is bound to protein (about15%), and converted to inactive metabolites (about 20%). About 50% to 80% of topiramate is excreted unchanged in the urine, and there is no established therapeutic range for this drug. Metabolites have no therapeutic activities and are mostly excreted through urine. Renal impairment decreases topiramate clearance and increases the half-life (Guerrini and Parmeggiani, 2006; Perucca, 2015). A 50% dose reduction is advised in moderate to severe impairment in renal function. No dose reduction is required in hepatic impairment.

Interactions with other drugs including anticonvulsants and psychotropic agents are minimal, but include the risk of hyperammonemia when used in combination with valproic acid (Rosenfeld, 1997). There is some hepatic metabolism

(hydroxylation, hydrolysis, and glucuronidation), and topiramate can induce CYP3A4, and inhibit CYP2C19. Topiramate may decrease the effectiveness of oral contraceptives with ≤35 μg of estrogenic component through a non-CYP3A4 mechanism (Garnett, 2000). Phenytoin and carbamazepine can substantially decrease topiramate concentrations in the blood. Smaller (<20%) variations in topiramate and valproate levels can occur with co-administration, and topiramate can also induce small changes in levels of metformin (increased), digoxin (decreased), and lithium (decreased) (Johnson and Ait-Daoud, 2010). A list of possible serious and common side effects is given in Table 1 (Johnson and Ait-Daoud, 2010; Kenna et al., 2009; Marmura, 2014).

TOPIRAMATE AND ALCOHOL USE DISORDERS

Early Clinical Trials With Placebo Controls and Without Required Pre-Treatment Abstinence

Johnson et al. (2003) performed the first double-blind randomized placebo-controlled trial (DBRPCT) comparing topiramate with placebo among those diagnosed of *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed* Alcohol Dependence (Johnson et al., 2003). It was a 12-week study with 150 participants between the ages of 21 to 65 years and reported drinking of at least 21 standard drinks per week for women and 35 standard drinks per week for men. Abstinence from alcohol was not a criterion for enrollment.

TABLE 1. Adverse Effects, Cautions, and Drug Interactions With Topiramate Treatment

Serious adverse effects (Incidence)
Open angle glaucoma (12.7 per 100,000 patients years exposure)
Symptoms: acute onset of visual blurring, ocular pain or both. Resolves within a few days of discontinuation.
Visual disturbances including palinopsia (after image that persists after the visual stimulus has left) and various visual perception abnormalities have been also reported rarely.
Metabolic acidosis (0.3%)
Tapering or stopping results in resolutions
Renal stones (1.5%)
Prevented by increasing water intake
Oligohydrosis (0.25%)
Decreased sweating, more in children, particularly with high heat exposure
Common adverse effects (seen in >10%)
- Mostly classified as mild or moderate
- Mostly seen in dose titrating phase
- Often resolves with continued treatment
- Almost always resolves with discontinuation.
Paresthesia, anorexia, difficulty in concentration or memory, taste perversion, headache, fatigue, insomnia, somnolence, nausea, dyspepsia, diarrhea, influenza-like symptoms
Pregnancy and lactation:
Pregnancy Category D (increased fetal risk)
10% to 20% of maternal serum levels in breast milk. Limited experience
Drug interaction:
- Phenytoin, carbamazepine, valproic acid and lamotrigine may increase topiramate levels.
- Topiramate may decrease levels of lithium, digoxin, valproic acids, and estrogens, and increase levels of amitryptiline.
- Concomitant valproic acid use may increase risk of hyperammonemia and encephalopathy
- Caution with other carbonic anhydrase inhibitors (zonisamide, acetazolamide) and metformin which can cause metabolic acidosis

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Participants were excluded if they had a co-occurring Axis-I diagnosis, concurrent use of any other substance (confirmed by urine toxicology), significant alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment score >15), were taking any medication which could have an effect on alcohol consumption, were receiving any treatment for alcohol dependence within the last 30 days or any significant medical illness. Seventy-five subjects were randomized to topiramate (started with 25 mg/d, titrated for 8 weeks to goal of 300 mg/d), 75 received placebo, and all received weekly medication compliance management.

At the end of the study, compared to placebo, individuals on topiramate had significant benefits on primary outcomes with 2.88 fewer drinking days (DD; 95% confidence interval [CI] −4.50 to −1.27; $P = 0.0006$), 3.10 fewer drinks per drinking day (DDD; 95% CI −4.88 to −1.31; $P = 0.0009$), 27.61% fewer heavy drinking days (HDD; 95% CI −42.20 to −13.02; $P = 0.0003$), 26.21% more days abstinent (95% CI 12.43 to 39.98; $P = 0.0003$), and a decline in plasma gamma-glutamyl transferase levels (a log plasma gamma-glutamyl transferase [GGT] ratio of 0.07; 95% CI −0.11 to −0.02; $P = 0.0046$). The secondary outcome of craving for alcohol as measured by obsessive compulsive drinking scale also showed significant improvement in the topiramate arm compared to placebo. There was no difference in outcomes based on early onset and late onset alcoholism classification of subjects. No serious side effects were reported, but there was a significantly higher proportion of non-serious adverse effects in the topiramate arm (dizziness, paraesthesia, psychomotor slowing, memory or concentration impairment, and weight loss) with adverse effect related attrition rates of 4% in topiramate arm and 7% in placebo arm. This study established the proof of concept that topiramate is an efficacious treatment for alcohol dependence.

Secondary analysis of the data from Johnson et al. (2003) reported that the improvement in drinking outcomes by topiramate also resulted in the decline in overall clinical severity of alcohol dependence, improvement in quality of life and reduction in harmful consequences of drinking alcohol as measured by Clinical Global Impressions Scale, Quality of Life Enjoyment and Satisfaction Questionnaire, and Drinker Inventory of Consequences scale respectively (Johnson et al., 2004). A further secondary analysis of the data from the first clinical trial revealed that participants who received topiramate were more likely to achieve longer periods of "safe" drinking periods (≤1 and ≤2 standard drinks per day for women and men respectively) with average longest 'safe' drinking period of 16.7 ± 20.9 days for the topiramate group compared with 8.9 ± 15.5 days for the placebo group (Ma et al., 2006).

Based on the results of previous trial (Johnson et al., 2003), Johnson and colleagues performed a 14-week, multi-site, DBRPCT of 371 individuals to determine efficacy and safety of alcohol dependence treatment with topiramate (Johnson et al., 2007). In this study with similar inclusion and exclusion criteria as the previous study, 183 participants were assigned to topiramate up to 300 mg/d rapidly titrated over 5 weeks and 188 participants to matching placebo tablets, with both groups receiving weekly manual guided "Brief Behavioral Compliance

Enhancement Treatment (BBCET)" to promote adherence with the study medication and the treatment regimen. For primary analysis, using a conservative analysis with all dropouts treated as relapse to baseline, the topiramate arm showed a greater decrease in the mean percent of HDD at 14 weeks (81.91% HDD [SD 20.04%] to 43.81% [43.81%]) compared to placebo arm (81.97% [19.92%] to 51.76% [37.43%]). The mean difference in HDD between topiramate and placebo was 8.44% (95% CI: 3.07% to 13.80%; $P = 0.002$), and significant difference was achieved by week 4 (corresponding to a dose of 200 mg daily at week 4). When missing data for dropouts were excluded as per a pre-specified mixed-model analysis plan, the difference in percentage improved to 16.19% (95% CI: 10.79% to 21.60%; $P < 0.001$), and a significant difference was achieved by week 2.

Topiramate was found to be more efficacious than placebo in all the secondary outcomes, percent of days abstinent, DDD and log plasma GGT ratio, both by primary analysis and pre-specified mixed model analysis ($P < 0.001$ for all outcomes). The main limitation of this study was the attrition rate (256 out 371 completed the study), with adverse events being the main reason for dropping out. Attrition rates due to adverse events were higher for the topiramate group (34 of 183) compared to placebo group (8 of 188). Adverse events that were reported to occur in 25% or more of participants were paresthesia, headache, taste perversion, fatigue, anorexia, nausea, insomnia, difficulty with concentration and attention, and nervousness. The higher rate of adverse effects and attrition may have been related to the faster titration schedule. Another limitation of this study was the lack of a follow-up period to determine relapse following medication withdrawal.

In secondary analysis of Johnson et al. (2007), topiramate was found to be more efficacious at reducing physical health measurements including body mass index (mean difference [MD] 1.08; 95% CI 0.81 to 1.34; $P \leq 0.001$), liver enzymes ($P \leq 0.001$), plasma cholesterol (MD 13.30 mg/dl; 95% CI 5.09 to 21.44 mg/dl; $P = 0.002$), systolic blood pressure (MD 9.70 mm Hg; 95% CI 6.81 to 12.60 mm Hg; $P \leq 0.001$), and diastolic blood pressure (MD 6.74 mm Hg; 95% CI 4.57 to 8.90 mm Hg; $P \leq 0.001$). Topiramate was also associated with significant improvement in psychosocial functioning as measured by sub-scales of Obsessive and Compulsive Drinking Scale (OCDS) (Johnson et al., 2008). While it is possible that topiramate induced a decrease in obsessional thoughts and compulsions about alcohol consumption leading to a reduction in alcohol consumption, the opposite may be plausible also; a reduction in drinking causing a decrease in craving. Topiramate also showed improvement in other areas of functioning such as sleep, physical quality of life, leisure time activities, and household duties.

Collectively, the results of the above 2 initial clinical trials established topiramate as a viable and effective treatment for AUD. Over a short-term period (12–14 weeks), topiramate reduced consumption of alcohol and improved adverse physical and psychosocial effects of alcohol consumption among those with AUD. Abstinence was not a requirement for initiation of topiramate treatment in the above 2 trials. Similar effects of reduction in DDD ($P < 0.05$), HDD ($P < 0.001$) and alcohol craving with

topiramate treatment were also demonstrated by Rubio et al. (2009) in a 12-week RDBPCT among 63 patients with DSM-IV alcohol dependence.

Later Placebo-Controlled Studies With Pre-Treatment Abstinence Requirement

Two DBRPCTs of topiramate use in AUD with a requirement for pre-treatment abstinence were not associated with significant therapeutic advantage, but these studies were conducted in populations that were markedly different from earlier clinical trials by Johnson and colleagues.

A 12-week DBRPCT by Likhitsathian and colleagues in 106 patients (topiramate and placebo 53 patients each) with DSM-IV AUD recruited from a residential treatment centers for alcohol detoxification and treatment in Thailand did not show any therapeutic advantage for topiramate (Likhitsathian et al., 2013). Topiramate was started in the post detoxification period and continued in outpatient care with dose escalation similar to Johnson et al. (2007). Twenty-eight participants in the topiramate group (52.8%) and 25 participants in the placebo group (47.2%) completed the study, and mean percentages of HDD and time to first day of heavy drinking did not differ between 2 arms. Two patients in placebo arm dropped out due to severe adverse effects, delirium and cardiac death, and none in topiramate arm. The authors suggested that the more intensive psychotherapy and residential treatment program administered to all participants may have diluted topiramate effect, which is a reasonable assumption. The ~50% drop out rate also limits the interpretation of the study results.

Kampman and colleagues compared topiramate to placebo in a unique set of patients with co-occurring DSM-IV alcohol and cocaine dependence in a 13-week DBRPCT. They could not demonstrate any advantage in alcohol or cocaine related outcomes with topiramate treatment (Kampman et al., 2013). A total of 170 patients were randomized to topiramate titrated up to 300 mg/d for 8 weeks or placebo after an initial period of cocaine and alcohol abstinence with both groups receiving cognitive behavioral therapy for relapse prevention. Although topiramate reduced alcohol craving, it did not show any advantage in preventing alcohol relapse or consumption. Although the overall rates were low, more patients on topiramate achieved a stable period of abstinence (20% vs 7%). The findings of this rigorous study likely reflect the impact of dual-addictive comorbidity on response to medication treatments for SUDs.

Low Dose Topiramate Trials With Pre-Treatment Abstinence

The efficacy of low dose (≤ 100 mg/d) topiramate following a period of abstinence in treating alcohol dependence was demonstrated in 2 clinical trials, 1 open-label study of augmentation of psychotherapy with topiramate (Paparrigopoulos et al., 2011), and a second randomized placebo-controlled study that also included patients with multiple SUDs and dual diagnosis (Martinotti et al., 2014).

In the open-label study, investigators enrolled 90 patients with DSM IV-TR alcohol dependence and no other SUD, and every third patient was assigned to topiramate up to

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75 mg/d (n = 30) in addition to 4 to 6 weeks duration of cognitive behavioral psychotherapy that all received (Paparrigopoulos et al., 2011). Over the 4-month study period those assigned to topiramate had significantly lower relapse rates (*P* = 0.043), longer time to relapse (*P* = 0.008) as well as lesser depression and anxiety symptoms. In the second DBRPCT, 52 patients were assigned to either topiramate titrated up to 100 mg/d or placebo in addition to supportive group therapy held by counselors and psychologists twice a week after a short alcohol detoxification (Martinotti et al., 2014). About 30% patients in both groups had dual diagnosis and multiple SUDs (cannabis, cocaine, and benzodiazepines), reflecting a real-life scenario. The topiramate group had fewer drinking days (*P* < 0.05), lower alcohol consumption, reduced craving, and improvement of anxiety and depression symptoms. These 2 trials support use of a lower dose of topiramate as an effective treatment in typical treatment scenarios in the early part of recovery.

Clinical Trials With Comparison to Other Medications

In these smaller clinical trials, topiramate was initiated after a period of abstinence in various clinical settings and compared with other drugs for treatment of AUD.

Topiramate was compared with Naltrexone and placebo in a 12-week DBRCT reported by Baltieri et al in patients diagnosed with ICD-10 alcohol dependence enrolled after 1-week alcohol detoxification (Baltieri et al., 2008). The study population was composed of males between 18 and 65 years who did not meet the exclusion criteria of current use of any other substances besides alcohol and nicotine, previous treatment with topiramate or naltrexone within 6 months of randomization, co-occurring mental health problem that might require drug treatment and clinical history of intellectual disorder or co-existing serious medical illness. A total of 155 participants were randomly assigned to topiramate started at 25 mg/d and titrated up to 300 mg/d by week 8 (n = 52), naltrexone 50 mg/d (n = 49) or placebo (n = 54). All the participants received relapse prevention counseling and were encouraged to participate in alcohol anonymous groups. The intention-to-treat principle was used for analysis with data from patients who withdrew or missed a visit deemed to be non-abstinent at the time of missed visit. Topiramate was statistically better than placebo on the primary outcomes of time to first relapse (mean of 7.8 weeks, SD—4.9 vs 5.0 weeks, SD—4.8 in placebo group; *P* = 0.01), cumulative abstinence duration (mean of 8.2 weeks, SD—4.5 vs 5.6 weeks, SD—4.8 in placebo group; *P* = 0.02), and heavy drinking weeks (mean of 3.4 weeks, SD—4.5 vs 5.9 weeks, SD 4.8 in placebo group; *P* = 0.02). The effects of naltrexone with respect to these outcomes were not significantly different from that of either topiramate or placebo.

According to authors, the study lacked adequate power to detect the differences between naltrexone with topiramate or placebo. A total of 70 participants dropped-out which was an important limitation of the study, but the lowest drop-out rate was in the topiramate group (placebo 57.4%, naltrexone 40.8%, topiramate 36.4%). Lack of women and fixed dosing of naltrexone were other limitations.

The efficacy of topiramate in preventing relapse over a longer period of 9 months was compared to that of Disulfiram in an open-label randomized study by De Sousa et al, in a sample of 100 men aged 18 to 65 years with DSM-IV alcohol dependence diagnosis undergoing alcohol detoxification in a private psychiatric hospital in India (De Sousa et al., 2008). To be eligible, patients were required to have a family environment that assured treatment adherence and gathering of follow-up information. Subjects were excluded if they were using other substances (except nicotine), had any co-occurring mental health problem, any significant medical condition or previous treatment with either study drug. Patients were then randomized to treatment with Disulfiram 250 mg/d (n = 50) or topiramate 150 mg/d (n = 50) without blinding and followed up for 9 months. At the end of the study only 10% of the disulfiram group had relapsed to a day of heavy drinking (>5 alcoholic drinks/40 g alcohol in 24 hours) compared to 44% in the topiramate group (*P* = 0.0003). Mean time until first relapse was significantly greater with disulfiram compared to topiramate (133 days; SD—21 days, and 79 days; SD—18 days, respectively; *P* = 0.0001). Craving scores were better in the topiramate group. This study highlights the effectiveness of disulfiram when adherence through strong family support is ensured. The main limitations are lack of placebo and blind.

Topiramate (50–400 mg, with a dose escalation every 4 days) was compared to naltrexone 50 mg/d in combination with as needed disulfiram (250–500 mg) augmentation of pharmacotherapy in case of treatment failure, in a 6-month naturalistic randomized open-label trial (Flórez et al., 2008). They enrolled men and women (15%) between ages of 18 to 65 years who had been actively drinking (>210 g/wk alcohol for men, >140 g/wk for women), undergone alcohol detoxification and seeking treatment for alcohol use disorder as defined by ICD-10 criteria. Exclusion criteria were similar to prior studies. The enrolled 102 individuals were randomized to receive Naltrexone (n = 51) or topiramate (mean dose 212.77 mg/d, n = 51). Data were analyzed on an intention-to-treat basis with drop-outs assumed to have resumed heavy drinking on the day after last contact. Both groups had similar efficacy in maintaining abstinence at 3 and 6 months, but topiramate was more efficacious in decreasing alcohol craving, maintenance of moderate drinking, and decreasing nicotine consumption. This study was underpowered for the wide range of outcomes they measured and lacked placebo control. In a subsequent larger similar follow-up study, Florez and colleagues demonstrated that topiramate at a mean dose of 200 mg/d was superior to naltrexone regarding improvement on multiple measures of alcohol dependence and consumption at 6 months (all significant *P* < 0.04) (Flórez et al., 2011).

Topiramate Trials Targeting Reduction in Drinking (As Opposed to Abstinence) Among Heavy Drinkers With and Without Alcohol Dependence

The proven efficacy of topiramate in substantially reducing heavy drinking in clinical trials of those without a goal of abstinence makes it an ideal agent to help heavy drinkers reduce their drinking to safe or moderate levels when

that is their explicit goal, as opposed to total abstinence. Furthermore, since it was safe and effective in initial trials when titrated while patients were regularly heavy drinking, it would seem to be a potentially desirable treatment for regular heavy drinkers that are on the milder end of the AUD spectrum (ie, problem drinkers, but not those that would have been alcohol dependent by DSM-IV criteria). Two studies support the efficacy of topiramate in reducing drinking among heavy drinkers with and without current alcohol dependence, and without a goal of abstinence.

In the first of these studies, Miranda et al. (2008) in a non-treatment RDBPC laboratory study compared the effects of topiramate 200 mg/d, topiramate 300 mg/d and placebo on alcohol consumption and exposure to alcohol and alcohol cues in the lab among 61 non-treatment seeking heavy drinkers with and without DSM-IV alcohol dependence (Miranda et al., 2008). While the primary goal of the study was to administer the drug to subjects and then measure its effects on craving and the response to alcohol in the laboratory, their drinking behavior was also monitored during the course of participation. Compared to placebo, both doses of topiramate reduced drinks per week and percentage of HDD ($P < 0.05$). However, this reduction was not thought to be due to reduction in craving as hypothesized by the authors, as cue-induced craving was not reduced in the laboratory. However, at the 200 mg/dose, topiramate showed a reduction in the positive reinforcing effects of alcohol administration. A subsequent follow-up study in a similar population by (Miranda et al., 2016) using ecological momentary assessment found a similar reduction in drinking and determined that topiramate reduced craving after an initial drink of alcohol, suggesting that reduction in craving after a drinking episode begins is at least part of its mechanism of action.

In the second and more recent trial, Kranzler et al. (2014b) recruited 138 regularly heavy drinking subjects, most of whom also had a DSM-IV alcohol dependence diagnosis (>90%) though it was not required for study entry, for a 12-week RDBPCT comparing topiramate (200 mg/d max dose) to placebo in addition to brief counseling (Kranzler et al., 2014b). A pre-treatment abstinence period was not required, and this was the first treatment trial in subjects with a goal of cutting down their drinking to safe levels as opposed to abstinence. Those receiving topiramate had significantly reduced HDD ($P < 0.001$), increased abstinent days ($P = 0.03$), lower liver enzymes (GGT), and alcohol-related problems compared to placebo. A major focus of this study was to explore the role of genetic markers in predicting who would respond well to topiramate in the European American subsample. Topiramate was most effective in reducing HDD in patients with CC genotype of rs2832407, a single-nucleotide polymorphism of the *GRIK1* gene, and not in A-allele carriers. *GRIK1* encodes the GluK1 subunit, 1 of the 2 subunits of potent glutamate receptors to which topiramate selectively binds (Kranzler et al., 2009). These pharmacogenetic results should be interpreted cautiously though due to the relatively small sample size of the CC group (n = 51, only 20 of which received topiramate), and require replication. An earlier smaller trial by Ray and colleagues had also suggested a role for the *GRIK1* gene in stratifying patients on possibility

of adverse effects with topiramate treatment in heavy drinkers (Ray et al., 2009). No difference was observed for adverse events with topiramate based on variation in genotype in the Kranzler study. The C allele is the major allele but is also the AUD risk associated allele, and the minor allele frequency for rs2832407 in European Americans is estimated to be about .385, making the CC genotype fairly common. It is not yet known whether this polymorphism is functional or not. Together these studies suggest that topiramate is efficacious in reducing alcohol consumption to moderate and safe levels among heavy drinkers with and without AUD diagnosis.

A 3 and 6-month follow-up after completion of the genotype study by Kranzler et al showed persistent topiramate associated benefits regarding alcohol related problems in the overall sample and HDD in *GRIK1* rs2832407 C-allele homozygotes (Kranzler et al., 2014c). A unique strength and noteworthy facet of this study was the use of a daily telephonic data collection method via an automated system which allowed for a micro-longitudinal analysis of daily psychological processes related to drinking behavior. Genotype (CC) moderated the effects of topiramate on craving, positive alcohol expectancies, and self-efficacy, but only changes in self-efficacy (ie, belief in the ability to resist heavy drinking) mediated treatment response. Thus, the relationship of genotype and self-efficacy in terms of the topiramate treatment effect on heavy drinking is one of moderated mediation (Kranzler et al., 2014a). Topiramate use in general improved self-efficacy measures. Though craving moderated response to topiramate, it did not mediate it. This is in contrast to at least 1 analysis of naltrexone treatment response in AUD showing partial mediation by reduction in craving, such that about half of the treatment response is derived from that reduction (Subbaraman et al., 2013).

Also, of note in the trial by Kranzler et al. (2014b), the 200 mg dose was well tolerated with high retention in the study, and though side effects were more frequent in the topiramate group, there was no significant difference in retention or dropouts due to side effects between the placebo and topiramate groups. To further explore the clinical benefit of topiramate in that trial, Feinn et al. (2016) examined the data and calculated a number needed to treat (NNT), and also calculated conservative adjusted rates of those measures assuming "harm" with either moderate or severe adverse events and reducing the NNT by those adverse event rates (Feinn et al., 2016). They calculated an NNT of 5.29 for absence of heavy drinking in the last 4 weeks of treatment, and adjusting for adverse events the NNT ranges between 6.12–7.52), which compares favorably to recent estimates of the NNT for acamprosate and oral naltrexone (both with NNT in the range of ~9 to 12, although a direct comparison is difficult to make because of somewhat different outcomes used in those calculations).

A recent 14-week, small, double-blind, randomized trial of topiramate, zonisamide, levitiracetam, and placebo (~20 heavy drinking subjects with a goal of abstinence or safe drinking, in each group), with a minimal behavioral intervention platform (BBCET), confirmed results of other trials (Knapp et al., 2015). Topiramate was titrated over 7 weeks to a target dose of 300 mg daily and was fairly well tolerated.

Topiramate reduced drinking significantly more than placebo on measures of heavy drinking ($P < 0.0001$) and overall drinking, with a significant reduction in GGT levels and craving.

Meta-Analyses

A meta-analysis using data from the core placebo-controlled studies showed that topiramate treatment was associated with a significant decrease in HDD, more abstinent days (2.9 days), and decreased GGT levels compared to placebo with no significant heterogeneity in effect between trials conducted among those with DSM-IV alcohol dependence and heavy drinkers (Arbaizar et al., 2010). Side effects, especially paraesthesia, were more common in topiramate group, with heterogeneity between trials. In a more recent meta-analysis extracting data from 7 RCTs, topiramate treatment in patients with AUD was associated with a significantly favorable effect of moderate size on abstinence ($P < 0.01$) and heavy drinking compared to placebo ($P = 0.02$), a smaller favorable effect on GGT outcomes, and a small, marginally significant effect on craving (Blodgett et al., 2014). Another recent meta-analysis also found evidence to support topiramate's efficacy but found no increased risk of harm from side effects (Jonas et al., 2014).

TOPIRAMATE TREATMENT OF THE ALCOHOL WITHDRAWAL SYNDROME

Non-benzodiazepine anticonvulsants are increasingly being used for alcohol withdrawal syndrome (AWS) management, and are then often continued for ongoing outpatient treatment of AUD as with gabapentin (Hammond et al., 2015; Leggio et al., 2008). Carbamazepine and gabapentin appear to be the most promising, and they may be useful as monotherapy for the treatment of mild-to-moderate low-risk patients with the AWS. A few studies have examined a role for topiramate in treating AWS and found some evidence of potential efficacy, but these findings need further confirmation (Leggio et al., 2008; Hammond et al., 2015). Similar to gabapentin, topiramate is also a promising drug with its dual role of treating AWS and then preventing relapse on continued use. With further evidence to support its use in treating AWS, it may be possible to initiate topiramate for AWS treatment and then continue it for relapse prevention.

CLINICAL SUMMARY OF AUD TRIALS

Among those with AUD and heavy drinking, topiramate treatment resulted in substantially reduced consumption of alcohol (DD, DDD, and percentage of HDD) and increased abstinence rates and increased abstinent days. Topiramate treatment lasted 3 to 4 months, and was supplemented by psychotherapy or adherence therapy, at least on a weekly basis. Although some studies required some level of abstinence prior to topiramate initiation, topiramate use was also associated with decreased alcohol consumption among those who continued drinking through the time of study entry. This is very important clinically as many patients are unwilling or unable to achieve 4 to 7 days of abstinence prior to initiation of medication treatment, or to check themselves in for residential rehabilitation. Topiramate effects on drinking, unlike acamprosate and naltrexone, do not appear to be substantially affected by pre-treatment abstinence or detoxification (Maisel et al., 2013). Topiramate also reduced alcohol craving and obsession in clinical trials, although with a smaller effect size. In addition, topiramate improved overall well-being and life satisfaction, reduced consequences of harmful drinking consequences, and in general improved measures of physical health (GGT, plasma cholesterol, systolic and diastolic blood pressure and BMI) (Tables 2–4).

Adverse effects, especially parasthesias, appear to impact treatment retention, but not necessarily in an overwhelming way. Low doses of topiramate (≤ 100 mg/d) with lower side effect rates also seem to be associated with significant benefits related to alcohol consumption reduction. Despite these impressive short-term effects, the clinicians are cautioned that long-term studies are yet to be done. The best balance of efficacy and tolerability may be at the 200 mg daily dose range, as demonstrated in the medium size trial by Kranzler et al. (2014b), in which completion rates were high and did not differ between placebo and topiramate groups. We include further discussion on topiramate side effects and their practical clinical management in the case series article that accompanies this review in this volume of the journal.

TOPIRAMATE FOR COCAINE USE DISORDER

Although the mechanisms of action of topiramate strongly suggest its utility in Cocaine use disorder, the early clinical trials have not shown the level of efficacy seen with AUD (Minozzi et al., 2015; Siniscalchi et al., 2015). A small initial pilot study enrolling DSM-IV Cocaine dependence patients without other SUD and high chances of clinical success, could not demonstrate any significant benefits with topiramate treatment (Kampman et al., 2004). In a subsequent larger RDBPCT among those with DSM-IV cocaine dependence and comorbid alcohol dependence, Kampman et al could not again demonstrate any significant benefits with topiramate treatment (Kampman et al., 2013). Johnson and colleagues, in a RDBPCT among DSM-IV cocaine dependence patients, showed that topiramate treatment compared to placebo resulted in significantly lower weekly proportion of cocaine use days (13.3% vs 5.3%) and higher likelihood of urinary cocaine free weeks (16.6% vs 5.8%) (Johnson et al., 2013). They also reported decreased cocaine craving and observer rated improvement in global functioning. Observing high treatment drop-out rates in previous trials, Nuijten et al. (2014) conducted an open-label study looking at the effectiveness of augmenting cognitive behavior therapy with topiramate treatment among those with cocaine use disorder with regards to treatment retention or cocaine use (Nuijten et al., 2014). The treatment retention in the topiramate arm was low, and no benefits with cocaine or other substance use were demonstrated. Another DBRPCT comparing a combination of extended release mixed amphetamine salts and topiramate and placebo among those with cocaine dependence showed that proportion of those achieving 3-week cocaine abstinence was substantially higher in the treatment arm (33% vs 16.7%), especially among heavy cocaine users (Mariani et al., 2012).

TABLE 2. Studies of Topiramate for Alcohol Use Disorder

Year, Author, and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Johnson et al. (2003); DBRPCT	n = 150; TOP: 75; PLC: 75; patients were non-abstinent at start	12 weeks; Started with 25 mg/d, titrated to 300 mg/d by week 8 and maintained	1°—Drinking days (DD), drinks per DD, HDD, Abstinence, GGT levels; 2°—craving	TOP was significantly better than PLC in all 1° outcomes. TOP had greater effect on craving than PLC	Medium size study
Johnson et al. (2004); DBRPCT secondary analysis of above	n = 150; TOP: 75; PLC: 75; patients were non-abstinent at start	12 weeks; Started with 25 mg/d, titrated to 300 mg/d by week 8 and maintained	Overall well-being and alcohol dependence severity, quality of life (QOL), harmful drinking consequences	TOP improved the odds of overall well-being, reported abstinence, QOL and harmful drinking	
Ma et al. (2006); DBRPCT secondary analysis of above	n = 150; TOP: 75; PLC: 75; patients were non-abstinent at start	12 weeks; Started with 25 mg/d, titrated to 300 mg/d by week 8 and maintained	TOP's ability to promote 'safe' drinking; ($\leq$1 and $\leq$2 standard drinks per day for women and men, respectively	TOP increased the relative likelihood of continuous 'safe' drinking compared to PLC	
Fernandez-Miranda et al. (2007); Open-label trial of TOP as adjunctive therapy	n = 64; patients with poor previous outcomes to standard treatment for alcohol dependence	12 months; Variable dose of 50–400 mg/d	Retention rate, drinking days/month, SDU/day, ADIS, craving and priming scale,	Significant improvement in all measured outcomes including decrease in MCV and GGT	High drop-out rate, intention-to-treat analysis was not used, lack of placebo
Johnson et al. (2007); Multi-site DBRPCT; (both groups received weekly adherence enhancement therapy)	n = 371; TOP: 183; PLC: 188; patients were non-abstinent at start	14 weeks; Started with 25 mg/d, titrated to 300 mg/d by week 8 and maintained	1°—self-reported % of HDD; 2°—self-reported, % of abstinent days and drinks per DD and GGT levels	TOP was more efficacious at reducing %HDD (baseline data of drop-outs was used for their missing data); Significant improvement in secondary outcomes.	High rate of medication discontinuation in the TOP group
Johnson et al. (2008); Secondary analysis of 2007 study	n = 371; TOP: 183; PLC: 188; patients were non-abstinent at start	14 weeks; Started with 25 mg/d, titrated to 300 mg/d by week 8 and maintained	TOP's effect on physical health, obsessional thoughts and compulsions about using alcohol and psychosocial well being	TOP more efficacious in reducing; BMI, liver enzymes, cholesterol, systolic and diastolic BP and other outcomes	
De Sousa et al. (2008); Randomized open-label trial comparing TOP and Disulfiram	n = 100 (all men); TOP: 50; DIS: 50; patients were detoxified prior to start	9 months; TOP: 150 mg/d; DIS: 250 mg/d	Comparing the efficacy of TOP and DIS for preventing alcohol relapse	Mean number of days for relapse –; DIS: 133; TOP: 79; % patients abstinent at 9 months; DIS: 90%; TOP: 56%	TOP dose was perhaps not optimized (low), however DIS was superior. No placebo, no women.
Florez et al. (2008); Randomized open-label trial comparing TOP and Naltrexone	n = 102; TOP: 51; NAL: 51; Patients were detoxified prior to start	6 months; TOP: 200–400 mg/d (avg dose 212.77 mg/d); NAL: 50 mg/d	Comparing the efficacy of TOP and NAL for treatment of alcohol dependence	No statistically significant differences noted between both groups, TOP was found superior in reducing cravings, more relapse in NAL group	Absence of placebo group, rigid dose for NAL (50 mg) compared to flexible dosing range for TOP
Miranda et al. (2008); DBRPC laboratory study (NOT A TREATMENT TRIAL) in non-treatment-seeking heavy drinkers	n = 61; TOP (200 mg/d): 20; TOP (300 mg/d): 21; PLC: 20	5 weeks; TOP: 200 mg/d and 300 mg/d target dose titrated over 32 days and maintained for 7 days before testing	To study dose dependent effects of TOP on cue-elicited craving and subjective response to alcohol. Secondary also included comparison of heavy drinking between groups	Both doses of TOP reduced frequency of HDD. TOP did not affect craving for alcohol during titration or during cue-reactivity or in response to alcohol challenge. At 200 mg/d, TOP reduced stimulating effects of alcohol.	Not a treatment trial, these subjects were not trying to quit drinking yet they still reduced.

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TABLE 2 (Continued)

Year, Author, and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Baltieri et al. (2008); DBRPCT comparing TOP and NAL	n = 155 (all men); TOP: 52; NAL: 49; PLC: 54; Patients were detoxified prior to start	12 weeks; TOP: titrated from 25 mg/d to 300 mg/d by week 8; NAL: 50 mg/d	Time to first relapse (consuming >60g ethyl alcohol, cumulative abstinence duration, weeks of heavy drinking	Intention to treat analysis was done.; TOP statistically superior to PLC in multiple outcome measures.; TOP showed trends towards better efficacy than NAL	High drop-out rates, no women
Rubio et al. (2009); DBRPCT, examining effects on impulsivity and drinking	n = 63; TOP: 31; PLC: 32	12-week study with TOP titrated up to 400 mg daily	Drinks per drinking day, number of heavy drinking days, impulsivity measures, craving	TOP group drank less on drinks per drinking day ($P < 0.05$) and the number of heavy drinking days ($P < 0.001$). TOP reduced impulsive measures, and less impulsivity was associated with less drinking. TOP reduced craving	Small study
Paparrigopoulos et al. (2011); Open-label trial comparing TOP + Psychotherapy (PTH) with PTH alone	n = 90; TOP + PTH: 30; PTH: 60; Patients were detoxified prior to start	4–6 weeks inpatient followed by 4 months of out-patient follow-up; TOP: 75 mg/d titrated over 3 weeks	To assess efficacy and tolerability of low-dose TOP as adjunctive treatment in alcohol dependence	Both groups did well.; Individuals in TOP fared better during inpatient treatment.; During follow-up; relapse rate was lower and time to relapse was longer with low dose TOP	Small sample size, open-label trial
Florez et al. (2011); Randomized open-label trial comparing TOP and NAL	n = 182; TOP: 91; NAL: 91; Patients were detoxified prior to start	6 months; TOP: 200 mg/d (titrated over 4 weeks); NAL: 50 mg/d	Comparing the efficacy of TOP and NAL for treatment of alcohol dependence	Patients on TOP did significantly better at reducing alcohol intake and cravings	Lack of placebo control
Likhitsathian et al. (2013); DBRPCT	n = 106; TOP: 53; PLC: 53; patients were detoxified prior to start	12 weeks; TOP: 100–300 mg/d	1°—% of HDD, time to first day of heavy drinking; 2°—craving, quality of life	No significant differences between the mean % of HDD or time to first day of heavy drinking between both groups.	
Kampman et al. (2013); RDBPCT in comorbid cocaine and alcohol dependence	n = 170; TOP:83; PLC:87	13 weeks; TOP: 300mg/d	Primary outcome measures: self-reported alcohol and cocaine use, and thrice weekly urine drug screens. Secondary outcome measures: cocaine and alcohol craving, Addiction Severity Index results, cocaine withdrawal symptoms, and clinical global improvement ratings	Increased retention with TOP, but TOP did not reduce alcohol use compared to PLC	Co-occurring cocaine and alcohol dependence population
Martinotti et al. (2014); SBRPCT; Both groups received rehabilitation	n = 52; TOP: 26; PLC: 26; patients were detoxified prior to start	6 weeks; TOP: 100 mg/d, titrated over 2 weeks	Assess efficacy and tolerability of low-dose TOP for relapse prevention	Individuals on TOP had: fewer DD, less daily alcohol consumption, more days of treatment, reduced craving and withdrawal, improvement of anxiety, depression and OC symptoms.	Small study

DBRPCT, double blind randomized placebo-controlled trial; TOP, topiramate; PLC, placebo.

TABLE 3. Topiramate for Smoking Cessation

Year, Study and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Johnson et al. (2005); DBRPCT (Sub-group analysis of 2003 study)	n=94; TOP: 45; PLC: 49	12 weeks; TOP: titrated from 25 mg/d to 300 mg/d	Smoking cessation by self-report and serum cotinine level	TOP recipients: more likely to abstain from smoking, higher cessation rates, lower serum cotinine level	Checked for smoking in alcohol-dependent individuals thus limiting generalizability
Sofuoglu et al. (2006); Double blind PLC-controlled crossover study	n=12;	One adaption and 3 experimental sessions.; Individuals received TOP (25 mg or 50 mg) or PLC	To determine effect of TOP on subjective and physiological effects of intravenous nicotine	TOP enhanced subjective effects from nicotine compared to PLC. TOP attenuated increase in HR by Nicotine	Only a single small dose of TOP was given, IV nicotine may produce effects different than inhaled, long-term effects are unknown
Khazaal et al. (2006); Case series	n=13; (individuals presently smoking)	TOP initiated with 25 mg/d increased until smoking reduction of >50% was observed; Range: 50–800 mg/d (average dose: 185 mg/d)	Potential efficacy of TOP in smoking cessation	6 out of 13 individuals were abstinent after 2 months, 2 more reduced smoking by >50%.; 3 subject had to interrupt due to intolerable side-effects	Small sample, open design, lack of control
Reid et al. (2007); DBRPCT	n=40 (15 females)	9 days; TOP: titrated up to 75 mg/d over 7 days	Effect of TOP on: abstinence related nicotine withdrawal, cue induced cigarette craving, acute effects of smoking	TOP enhanced withdrawal and smoking reward.; Other objective findings suggestive of needing less smoke for desired effects	Low dose of TOP, brief study duration,
Arbaizar et al. (2008); Case report	n=1	TOP: 200 mg/d; Aripiprazole: 15 mg/d	Evidence of potential efficacy	Reduction in number of cigarettes smoked per day	
Anthenelli et al. (2008); DBRPCT	n=87 (49 females); TOP: 43; PLC: 44	11 weeks; TOP: titrated from 25 mg/d to 200 mg/d by week 6	1°—CO confirmed abstinence of 4 weeks from 8–11 week; 2°—withdrawal, body weight, safety	Overall no significant difference in abstinence. Men treated with TOP more likely achieve prolonged abstinence than women treated with TOP	Small sample size, assessment of smoking by CO levels only, results lack generalizability
Weinberger et al. (2008); Secondary data analysis of a trial for Schizoaffective disorder	n=24 (50% of the full sample); TOP: 13; PLC: 11	8 weeks; TOP: 100–400 mg/d	Effect of TOP on smoking	No differences between the treatment groups were seen.	Study not aimed at reducing smoking, it was an alcohol trial
Balieri et al. (2009); DBRPCT (Sub-group analysis of 2008 alcohol trial)	n=155 male alcohol-dependent outpatients (52 non-smokers and 103 smokers)		Comparing smoking and non-smoking alcoholics in treatment outcomes; Verifying efficacy of TOP and NAL to decrease smoking	Intention-to-treat analysis revealed smoking status increased odds of relapsing into drinking.; TOP showed effectiveness to reduce smoking when compared to PLC in those that adhered to medication	
Oncken et al. (2014); DBRPCT; Comparing TOP, TOP + nicotine patch and PLC	n=57; TOP: 19; TOP/NIC: 19; PLC: 19	10 weeks; TOP: titrated from 25 mg/d to 200 mg/d by week 5; NIC: 21 mg/d patch started on quit date (2 weeks after medication)	1° Does TOP increase quit rates compared with PLC?; 2° Does NIC add to quit rates observed with TOP alone?	TOP alone or in combination with NIC showed higher quit rate than PLC and reduced weight	Small sample size, open-label of the nicotine patch, lack of NIC only group

TABLE 3 (Continued)

Year, Study and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Anthenelli et al. (2017); DBRPCT	n=129; TOP: 63; PLC: 66; All abstinent alcohol dependent males wanting to quit smoking, ~60% military veterans, ~45% with drug use disorders	12 weeks; TOP: titrated from 25mg/d to 200mg/d over 6 weeks	1° endpoint was 4 week confirmed abstinence rates; 2° endpoint relapse to alcohol	No significant differences found in smoking quit rates, nor in relapses to alcohol or drugs	Only males, high rates of comorbid addictive disorder

DBRPCT, double blind randomized placebo controlled trial; TOP, topiramate; PLC, placebo; NIC, nicotine replacement.

Together these data suggest that topiramate may have some beneficial effect in cocaine use disorder, but the clinical utility is still marginal. However, it has been suggested that topiramate offers better therapeutic benefit than the other meager pharmacotherapeutic choices in the treatment of cocaine use disorder (Johnson et al., 2013). The utility of topiramate in methamphetamine dependence has been tested in 1 exploratory study. Elkashef and colleagues examine 200 mg daily topiramate in a 13-week RDBPCT of methamphetamine dependence (Elkashef et al., 2012). There were no significant differences in abstinence rates in the last 6 weeks of the study. A secondary analysis of this data showed significant modulation of expression of specific genes among those treated with topiramate, suggesting potential mechanistic pathways (Li et al., 2014).

TOPIRAMATE IN CIGARETTE SMOKING CESSATION

Secondary analyses of 2 clinical trials of topiramate efficacy in alcohol dependence showed that smoking cessation rates were very low in this population of smokers, but topiramate treatment was associated with tobacco use related clinical benefits (Baltieri et al., 2009; Johnson et al., 2005). In a secondary analysis of data from 94 patients who were smoking cigarettes enrolled in the initial proof of concept DBRPCT of topiramate efficacy in alcohol dependence, smoking cessation outcomes in 45 patients in the topiramate arm and 49 patients in the placebo arm were compared (Johnson et al., 2005). Although overall smoking cessation rates were low at 9 and 12 weeks, the rates were substantially higher in topiramate arm compared to placebo arm. Another secondary analysis of a DBRPCT of topiramate and naltrexone efficacy in alcohol dependence showed that the number of cigarettes smoked were lower in smokers on topiramate whereas no significant reduction was seen in the naltrexone or placebo arms (Baltieri et al., 2009). However, in a secondary analysis of DBRPCT of topiramate efficacy in schizoaffective disorders, there was no substantial difference in tobacco related outcomes in the topiramate arm compared to placebo (Weinberger et al., 2008).

In a double-blind placebo controlled crossover study among 12 patients to determine the effect of topiramate on acute physiological and subjective responses to intravenous nicotine, topiramate enhanced the pleasurable, but not aversive effects of nicotine (Sofuoglu et al., 2006). In another DBRPCT, after a 9-day period of treatment with 100 mg target dose of topiramate compared to placebo, those on topiramate treatment experienced more symptoms of nicotine withdrawal during periods of brief cigarette abstinence, and enhanced rewarding effects of a smoked cigarette even with a low nicotine intake compared to placebo (Reid et al., 2007). Authors concluded that their data did not support the assumption that topiramate treatment was an effective treatment for smoking cessation, and may in fact increase the likelihood of full relapse in abstinent smokers.

In an 11-week smoking cessation DBRPCT with 6-week titration of topiramate to a 200-mg daily dose, overall tobacco cessation rates were similar among both arms from 8 to 11 weeks. However, a gender specific effect was seen with

TABLE 4. Studies of Topiramate for Cocaine Use Disorder

Year, Author and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Kampman et al. (2004); DBRPCT; Both groups received CBT	n = 40; TOP: 20; PLC: 20	13 weeks; TOP: 200 mg/d, titrated over 8 weeks and maintained	Abstinence to cocaine verified by twice weekly urine benzoylecgonine test	Both groups did well.; TOP group did significantly better than PLC group to be abstinent	Small sample size, only participants with moderate dependence and low withdrawal were enrolled, only 1 female participant
Reis et al. (2008); Open-label trial	n = 28 (all males)	12 weeks; TOP: 25–300 mg/d (mean: 127 mg/d)	To assess action of TOP on craving, cocaine use, and tolerability	Significant changes in craving measures, but not overall reduction in cocaine use	Open-label design, lack of a control group, small study
Mariani et al. (2012); DBRPCT; Comparing MAS-ER + TOP with PLC	n = 81; MAS-ER + TOP: 39; PLC: 42	12 weeks; MAS-ER: 60 mg/d (titrated over 2 weeks); TOP: 300 mg/d (initiated at 25 mg/d titrated over 6 weeks)	1° proportion of individuals who achieved 3 consecutive weeks of abstinence	MAS-ER + TOP group had a larger proportion of 3 consecutive weeks of abstinence.	Does not address whether both medications are necessary for efficacy
Johnson et al. (2013); DBRPCT	n = 142; TOP: 71; PLC: 71	12 weeks; TOP: 300 mg/d (started with 50 mg/d titrated over 6 weeks)	1° difference in proportion of cocaine non-use days from baseline; 2° cocaine-free weeks, craving, global functioning	Intention to treat analysis.; TOP more efficacious in increasing cocaine non use days.; More likelihood of urinary cocaine free weeks, decrease in craving and increase global functioning	
Nuijten et al. (2014); Open-label trial; Both groups received CBT	n = 74	12 weeks; TOP: 200 mg/d	Acceptance and effectiveness of TOP as an adjunctive to CBT in crack cocaine dependence	Intention to treat analysis. TOP neither improved treatment retention nor reduced cocaine use	
Kampman et al. (2013); DBRPCT in comorbid cocaine and alcohol dependence	n = 170; TOP:83; PLC:87	13 weeks; TOP: 300mg/d	Primary outcome measures: self-reported alcohol and cocaine use, and thrice weekly urine drug screens. Secondary outcome measures: cocaine and alcohol craving, Addiction Severity Index results, cocaine withdrawal symptoms, and clinical global improvement ratings	Increased retention with TOP, TOP group had greater abstinence in last 3 weeks of trial, worse withdrawal symptoms associated with better cocaine outcomes for TOP group	

MAS-ER, mixed amphetamine salts extended release; DBRPCT, double blind randomized placebo controlled trial; TOP, topiramate; PLC, placebo.

men on topiramate having higher quit rate compared to placebo (37.5% vs 3.7%), whereas women on topiramate had lower quit rates compared to placebo (Anthenelli et al., 2008). In a recent 10-week DBRPCT, Oncken and colleagues reported that topiramate (target 200 mg/d) combined with nicotine transdermal patch was more efficacious than placebo in achieving abstinence in the last 4 weeks of the trial (37% vs 5%) (Oncken et al., 2014). Although the smoking cessation rate was higher in topiramate alone (26%) compared to placebo, it was not statistically significant. Both topiramate groups performed significantly better than placebo on weekly abstinence rates (7 day point prevalence). Topiramate groups on average lost weight, whereas the placebo group gained weight. In this study, topiramate appeared to reduce the rewarding effects of nicotine over time, reduce some nicotine withdrawal symptoms over time, reduce smoking, and decrease weight, all of which are clinically important outcomes.

Despite those positive initial findings, a more recent fairly large (N = 129) DBRPCT of topiramate (without concomitant nicotine replacement) in abstinent alcoholic men that wanted to quit smoking found no advantage to the medication (Anthenelli et al., 2017). In this twelve-week study of all males, about 60% of which were military veterans, and all had AUD (albeit in remission), with many also having another SUD, subjects received a 6-week titration of topiramate up to a dose of 200 mg daily (or placebo). The primary endpoint was carbon monoxide confirmed 4-week continuous abstinence rates, and the secondary endpoint was any relapse to drugs or alcohol in that time period. All subjects received brief therapy to help with quitting and with medication adherence. Quit rates were fairly low in both groups (~11% or less) and there was no significant difference. About 30% of subjects in both groups relapsed to alcohol or drugs, a nonsignificant difference. A secondary analysis of this study found that subjects classified as Babor type B alcoholics had diminished smoking levels in the follow-up phase when treated with topiramate versus placebo ($P < 0.001$, cigarettes per day), an effect that was mediated by reduced intent to smoke and reduced craving to relieve negative affect (Isgro et al., 2017).

Together these studies suggest topiramate may have some use in tobacco cessation, especially when combined with nicotine replacement therapy, or in patients that fail other medications for smoking cessation. However, more studies of longer duration, and probably with concomitant nicotine replacement are needed. Since gaining weight is a major concern and deterrent to smoking cessation in patients, topiramate may be useful in addressing this concern and helping to motivate patients into the action phase of treatment.

TOPIRAMATE AND PATHOLOGICAL GAMBLING

Gambling disorders have a spectrum of psychopathology including impulsive, compulsive, and addictive behaviors. Various groups of drugs have been studied selectively targeting these components including anti-depressants and mood stabilizers targeting compulsive component and opioid antagonist targeting addictive or reward seeking component (Dannon et al., 2005; Lupi et al., 2014). Therapeutic possibilities of pharmacological manipulation of the glutamatergic system targeting impulsive component are also being explored more recently (Pettorruso et al., 2014). Topiramate, with its activity on glutamatergic and reward systems appears to be an attractive option. Dannon et al. (2005) performed a 12-week study that randomized 31 patients with pathological gambling to topiramate or fluvoxamine, and was blinded to the rater who administered various psychometric instruments, but not to the clinicians and patients. Patients on topiramate showed significant improvement from baseline (60% remission), whereas fluvoxamine patients showed only modest improvement ((38%) that was not statistically significant.

A study of 42 patients in a 14-week DBRPCT testing efficacy of topiramate in treatment of pathological gambling showed no significant treatment effect of topiramate (Berlin et al., 2013). In a 12-month follow-up of patients who achieved remission from pathological gambling from various 12-week trials who were continued on the respective medications for 3 more months in an open-labeled fashion and stopped, most patients on topiramate (6 out of 9) were able to maintain full response in the subsequent medication free 6-month period (Dannon et al., 2007). In another naturalistic study of patients who received 4 different medications for 2-year period and followed up for another 2-year medication free period, 10 of 17 topiramate subjects dropped out. However, those patients remaining on the medication showed significant improvement in depression and anxiety scores, which was maintained at the end of 48-month follow-up (Rosenberg et al., 2013). In summary although conceptually promising, topiramate remains an experimental treatment option in pathological gambling.

TOPIRAMATE AND BINGE EATING DISORDERS

Binge eating disorder (BED) is a behavior pattern of consumption of a large amount of food within a discrete amount of time, and there is a sense of loss of control. BED is potentially driven by dysfunction of brain impulse control, reward and mood regulation systems involving dopaminergic mechanisms (Brownley et al., 2015; McElroy et al., 2015). Topiramate with its effect on reward systems, mood regulation and appetitive/weight loss effects has emerged as an efficacious pharmacological treatment option in BED. In a 14-week DBRPCT, McElroy et al. (2003) compared topiramate to placebo in treatment of BED and reported that topiramate treatment (25–600 mg/d) resulted in substantial reduction of binging, global severity of illness, obsessive compulsive features of BED weight and body mass index, even after accounting for increased adverse effects in topiramate group. These findings were replicated in a multi-center 16-week DBRPCT with a lower dose and slower dose escalation of topiramate to limit adverse effects, and not including those with bipolar disorder as a previous study did (McElroy et al., 2007). The benefits of topiramate treatment with regards to BED and weight loss were accompanied by lower discontinuation rates due to adverse effects in this study (29% Vs. 43% in the earlier study). In a small randomized control study by Brambilla et al. (2009), addition of topiramate as a part of multi-modal therapy (calorie restriction, cognitive behavior

therapy and sertraline) resulted in improved BED symptoms. Although long-term studies are unavailable, an open-label follow-up of the patients enrolled in the first study showed that the topiramate benefits in BED and weight loss in the first 14 weeks were maintained at 42 weeks (McElroy et al., 2004). Although not FDA approved, topiramate is an effective treatment option for BED, especially if there is comorbid SUD. However, high adverse effect rates, especially cognitive effects, limit its use in the BED population.

CONCLUSIONS

Topiramate, with its multi-faceted pharmacologic action has emerged as an efficacious pharmacotherapeutic option for the treatment of the alcohol use disorder, a chronic disease with complex mechanisms. Topiramate appears to have robust anti-drinking effects that, in our opinion, would position it as an effective pharmacological therapy for AUD. Topiramate appears to be the most efficacious drug in reducing harmful drinking patterns, though further study may be needed to confirm that impression based on meta-analyses. Topiramate has been generic for many years now and thus probably will never be FDA approved for AUD treatment, but prescribers should not let its regulatory status deter them from prescribing it for AUD. Recent studies focused on the pharmacogenetic moderation of topiramate effects and its risk-to-benefit ratio based on adjusted NNT address the early worries regarding the limitation of its use due to serious side effects that are infrequent, but often impose a burden on patients. Additionally, prescribers should keep in mind that severity and occurrence of side effects appear to be dose related, as well as related to the rapidity of titration. Patients may benefit from a thorough discussion of the risks and benefits prior to starting treatment, along with an emphasis on educating them about the potential side effects and adverse reactions, especially cognitive side effects, which often are a transient phenomenon noted in the titration phase.

The promise of wide spread use of topiramate in other SUDs, due to its unique multi-dimensional pharmacodynamic profile, may be slowly being realized as evidence is accumulating recently. But it is too early to firmly recommend its use in non-alcohol related addictive disorders. Future investigations should fully explore these therapeutic possibilities in addiction, an area that desperately needs new therapeutic options.

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