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Topiramate in the treatment of substance related disorders: a critical review of the literature

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Abstract

Objective—To critically review the literature on topiramate in the treatment of substance related disorders.

Data Sources—A PubMed search of human studies published in English through January 2009.

Study Selection—26 articles were identified and reviewed; these studies examined topiramate in disorders related to alcohol, nicotine, cocaine, methamphetamine, opioids, ecstasy, and benzodiazepines.

Data Extraction—Study design, sample size, topiramate dose and duration, and study outcomes were reviewed.

Data Synthesis—There is compelling evidence for the efficacy of topiramate in the treatment of alcohol dependence. Two trials show trends for topiramate's superiority over oral naltrexone in alcohol dependence, while one trial suggests topiramate is inferior to disulfiram. Despite suggestive animal models, evidence for topiramate in treating alcohol withdrawal in humans is slim. Studies of topiramate in nicotine dependence show mixed results. Human laboratory studies that used acute topiramate dosing show that topiramate actually enhances the pleasurable effects of both nicotine and methamphetamine. Evidence for topiramate in the treatment of cocaine dependence is promising, but limited by small sample size. The data on opioids, benzodiazepines, and ecstasy are sparse.

Conclusion—Topiramate is efficacious for the treatment of alcohol dependence, but side effects may limit widespread use. While topiramate's unique pharmacodynamic profile offers a promising theoretical rationale for use across multiple substance related disorders, heterogeneity both across and within these disorders limits topiramate's broad applicability in treating substance related disorders. Recommendations for future research include exploration of genetic variants for more targeted pharmacotherapies.

Keywords

Topiramate; substance abuse; substance related disorders; critical review

Introduction

Substance related disorders are a significant source of morbidity and mortality, and pose substantial cost to society. Yet there are limited pharmacological agents that effectively treat these disorders. US Food and Drug Administration (FDA)-approved pharmacological treatment options for alcohol dependence include three agents with very different mechanisms of action: naltrexone (an opioid antagonist), acamprosate (a putative NMDA

glutamate receptor antagonist), and disulfiram (an acetaldehyde dehydrogenase antagonist that deters alcohol use by producing an aversive reaction when alcohol is consumed). Though many patients have benefited from these agents, their effects are moderate, and some individuals with alcohol dependence fail to respond to them.¹ Furthermore, these agents are for use primarily in individuals who have already initiated abstinence rather than in individuals who continue to drink. Current treatment of nicotine dependence includes use of nicotine replacement, bupropion (a partial dopamine agonist), and more recently varenicline (a partial agonist of the nicotine acetylcholine receptor). Methadone (a long-acting opioid), and buprenorphine (a partial agonist of the mu-opioid receptor) have been effective for treatment of opiate dependence in some patients, but their use is limited by their abuse potential and access limitations. While some studies indicate efficacy of disulfiram,²⁻⁸ baclofen,⁹ modafinil,¹⁰ and bupropion¹¹ for cocaine dependence, no pharmacological agent for the treatment of cocaine or methamphetamine dependence has been approved.

Substance related disorders are heterogeneous, and the underlying neurobiology of each disorder is complex. Though the dopamine hypothesis is an oversimplification and does not fully explain the neurobiology of all substance related disorders, abnormalities of the dopamine reward pathway that projects from the ventral tegmental area (VTA) to the nucleus accumbens is hypothesized to be involved as the final common pathway in many addictive disorders. An agent, such as topiramate, that targets this reward pathway may be of promise in the treatment of a number of substance related disorders.

Topiramate is a sulfamate-substituted fructopyranose derivative with a unique pharmacodynamic profile. To start, it facilitates gamma-aminobutyric acid (GABA) transmission by binding to a non-benzodiazepine site on GABA-A receptors, and inhibits glutamatergic transmission at ionotropic AMPA/kainate receptors, which mediate voltage-dependent sodium and L-type calcium currents. The secondary effects of these actions are hypothesized to include neurostabilization and downstream reduction of dopamine release in the corticomesolimbic system, which is known to be involved in mechanisms of reward and reinforcement. Indeed, topiramate has been shown to attenuate nicotine-induced mesolimbic dopamine release in rats.¹² Secondly, topiramate's blockade of AMPA-type glutamate receptors in the nucleus paragigantocellularis appears to inhibit noradrenergic neurons in the locus coeruleus, the activation of which is thought to play a role in producing the autonomic symptoms of withdrawal states. Finally, it is a weak inhibitor of carbonic anhydrase, which may contribute to its anticonvulsant effects, a potentially important property in the treatment of withdrawal.

Topiramate was first approved for epilepsy and for migraine prophylaxis. Off-label use of topiramate includes adjunctive treatment of bipolar disorder,¹³⁻²³ post-traumatic stress disorder,²⁴⁻²⁶ bulimia nervosa,²⁷⁻²⁹ binge-eating disorder,³⁰⁻³³ and obesity.³⁴⁻³⁹ Topiramate has also shown benefit in reducing weight gain associated with atypical antipsychotics.^{29, 40, 41} There is now a growing body of literature examining the efficacy of topiramate in many different substance related disorders, including alcohol dependence and withdrawal, nicotine dependence, cocaine dependence, benzodiazepine dependence and withdrawal, and ecstasy abuse. This paper will critically review the existing literature and provide directions for future research.

Search Method

Using the Medline database, we searched for English language articles using the following search terms: topiramate and substance abuse, topiramate and substance dependence, topiramate and withdrawal, topiramate and alcohol, topiramate and nicotine, topiramate and

cocaine, topiramate and opiates, and topiramate and benzodiazepines. Studies in humans published through January 2009 were included. All study designs, including randomized control trials (RCTs), open trials, case series, and case reports, were included for review. We also reviewed the reference lists of these articles to search for any publications that may not have appeared in the Medline search.

Results

Our search identified 26 articles for review. Twelve studies were relevant for alcohol, six for nicotine, two for cocaine, one for methamphetamine, two for opioids, two for benzodiazepines, one for ecstasy. The results of these studies are presented in Table 1 and critically reviewed below.

The Use of Topiramate in Alcohol-Related Disorders

Alcohol Dependence—There is compelling evidence for the use of topiramate in the treatment of alcohol dependence. The literature contains one case series, one chart review, four open trials, three RCTs, and one human laboratory study. Among these are included three studies comparing topiramate to approved medications naltrexone and disulfiram.

Huguelet et al⁴² describe two cases in which adjunctive treatment with topiramate was associated with reductions in alcohol consumption in alcohol dependent patients with co-occurring schizophrenia or bipolar disorder. Topiramate was well-tolerated; side effects included only moderate sedation and weight loss.

Chiu et al⁴³ performed a retrospective chart review of psychiatric patients at a university medical center who received topiramate for any reason in the previous two years. Forty-six individuals were identified as having received topiramate during the study period. Nineteen patients took topiramate for one or more months, 12 of them for substance use disorders (alcohol, n = 9; heroin and amphetamine, n = 1; meperidine, n = 1; nicotine, n = 1; average dose 112.5 mg/day). According to the authors, 6 of the 9 individuals who received topiramate for alcohol dependence or abuse achieved full or partial remission. The study is limited by the lack of control cases, the lumping together of heterogeneous substance use disorders, incomplete information regarding patterns and severity of substance abuse and remission, and limited descriptions of the 27 patients excluded from the study.

Rubio et al⁴⁴ conducted a 12-week open-label study of topiramate as an adjunctive therapy in 24 patients with alcohol dependence and co-occurring psychiatric disorders (borderline personality, bipolar, and eating disorders). At baseline, participants drank an average of 39 drinks per week for mean duration 8.6 years. Topiramate (50 mg/day titrated up to 400 mg/day; mean final dose 261 mg/day) was given as an adjunct to selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, lithium, and anti-craving drugs (e.g., naltrexone, acamprosate). All participants improved on measures of craving, weekly drink consumption, and serum concentrations of carbohydrate deficient transferrin (CDT), an objective measure of alcohol consumption. Limitations of the study include small sample size, lack of a control group, and the possible confounding effects of other psychotropic drugs, especially acamprosate and naltrexone, on outcome.

Fernandez Miranda et al⁴⁵ also performed an open-label study of topiramate, this time as adjunctive therapy in alcohol dependent patients who had failed other treatments. Participants were 64 individuals (54 men, 10 women) with mean alcohol abuse duration of 16.8 years. Many had co-occurring psychiatric disorders (personality, affective, and psychotic disorders) and were on concomitant psychotropic medications (34% on antidepressants, 25% anxiolytics, 23% neuroleptics, 22% opiate agonists/antagonists, and

11% unspecified “drugs with anti-abuse effects”). The observation period was 12 months, longer than in most studies. The addition of topiramate 50–400 mg/day improved all outcome measures with statistical significance. Number of drinking days per month decreased from 23.6 days at baseline to 4.8 days at 12 months; standard drinks per day decreased from 16 to 2; and self-report scales of craving, priming (loss of control after starting to drink), and alcohol dependence showed significant reductions over the 12 month period. Significant decreases were also observed for mean corpuscular volume (MCV) and gamma glutamyl transferase (GGT). The study was limited by lack of placebo, non-standardized titration schedules, and a high dropout rate. Only 40 patients remained at 6 months, and 22 patients by 12 months; the causes for drop-out were largely undescribed. Intention-to-treat analysis was not used, so only data from the 22 patients who completed the study appear to have been presented, a major limitation.

The first RCT of topiramate for the treatment of alcohol dependence was performed in 2003 by Johnson et al.⁴⁶ This was a 12-week randomized double-blind, placebo-controlled trial in 150 participants, ages 21–65, with alcohol dependence, who reported drinking at least 21 standard drinks per week (women) and 35 drinks per week (men). Participants were not required to initiate abstinence prior to entry. Participants were excluded if they had a co-occurring axis I psychiatric disorder, a urine toxicology screen positive for any other substances, significant alcohol withdrawal symptoms with a Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale > 15, were on medications with a potential effect on alcohol consumption, or if they had received treatment for alcohol dependence in the month prior to enrollment. Participants in the treatment group started topiramate 25 mg with a weekly titration to 300 mg by week 8. Compared to those receiving placebo, topiramate recipients had 2.9 fewer average drinks per day, 3.1 fewer drinks per drinking day, 27.6% fewer heavy drinking days (5 drinks per day for men and 4 per day for women), and 26.2% more days abstinent. Plasma GGT levels, ratings of drinking obsessions, automaticity of drinking, and interference due to drinking were significantly lower with topiramate than placebo. Of interest, in all measures, there were increasing differences compared with placebo as the study progressed, with differences becoming statistically significant at week 8. Secondary analyses revealed improved overall well-being and life satisfaction, and reduced harmful drinking consequences in alcohol-dependent individuals treated with topiramate.⁴⁷ Further post-hoc analyses revealed that topiramate increases the chances of achieving “safe” drinking levels⁴⁸ defined as 1 standard drink per day for women, and 2 standard drinks for men, based on National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines. Participants in the topiramate group could sustain longer periods of safe drinking (16.7 mean days with topiramate, 8.9 mean days with placebo). Dizziness, paresthesias, psychomotor slowing, memory or concentration impairment, and weight loss were more commonly reported in the topiramate group.

The most impressive data demonstrating the benefits of topiramate in the treatment of alcohol dependence are from a subsequent study by Johnson et al⁴⁹ who performed a 14-week multi-site, randomized, double-blind, placebo-controlled trial of 371 men and women aged 18 to 65 with alcohol dependence. Compared to their original study,⁴⁶ this was a larger, longer, multicenter study (17 sites) with a more rapid titration of medication (300 mg at week 5 rather than week 8). Furthermore, in analyzing the results, missing data for drop-outs was replaced with the participants’ baseline data so that the most conservative possible estimates could be calculated. Topiramate was more efficacious than placebo at reducing the percentage of heavy drinking days from baseline to the end of the study. The mean difference between the two groups from baseline to week 14 was 8.4%, with statistical significance reached by week 4. Using less stringent statistical techniques to account for dropouts, the difference increased to 16.2% at week 14, and statistical significance was reached by week 2. Participants receiving topiramate showed statistically significant

improvements in the secondary outcome measures of percent of abstinent days, drinks per drinking day, and serum GGT. Of interest, there was a higher attrition rate related to adverse events in the topiramate group. The topiramate group reported significantly higher rates of paresthesias (51% vs. 11%), taste perversion (23% vs. 5%), anorexia (20% vs. 7%), difficulty with concentration/attention (15% vs. 3%), nervousness (14% vs. 8%), dizziness (12% vs. 5%), and pruritus (10% vs. 1%). The higher rate of adverse effects in this study compared to the prior study by Johnson⁴⁶ may have been related to the faster titration schedule.

Since the demonstration of topiramate's efficacy in the treatment of alcohol dependence, efforts have been made to compare topiramate with approved medications. There is one study comparing topiramate to disulfiram⁵⁰ and two studies comparing topiramate to oral naltrexone,^{51, 52} which are described below. There are no studies to date comparing topiramate with acamprosate, the medication with the mechanism of action most similar to topiramate.

De Sousa et al⁵⁰ performed an open-label trial comparing topiramate to disulfiram. Participants were 100 purely alcohol-dependent men undergoing inpatient detoxification in a large city in India. Inclusion criteria required that family members (wife or parents) could ensure treatment compliance and provide regular follow-up information. Participants were excluded for other substance use disorders except nicotine dependence, co-occurring psychiatric disorders, or previous treatment with either study drug. Patients were randomized to disulfiram 250 mg daily (n = 50) or topiramate 50 mg three times daily (n = 50), without blinding. Relapse was defined as the consumption of more than 5 alcoholic drinks in 24 hours. Follow-up was weekly or bi-weekly for 9 months. At the endpoint, only 10% of the disulfiram group had relapsed compared to 44% in the topiramate group (p=0.0001). Mean time to relapse was also significantly shorter in the topiramate group (76 days) compared to the disulfiram group (133 days). The results of this study suggest that disulfiram is superior to topiramate in preventing alcohol relapse. However, the study design favors disulfiram to some degree. The topiramate dose of 150 mg/day was low, and potentially inadequate. Only relapse was measured; less binary outcomes, like number of drinks per week, were not evaluated. Moreover, medication non-adherence is a common reason for treatment failure with disulfiram; and non-adherence was minimized by excluding participants without strong family support. There was no placebo arm and no blinding. Greater familiarity with disulfiram (a medication well-established for alcohol dependence), especially its potential to produce a noxious reaction with even slight alcohol intake, might lead clinicians to more strongly encourage abstinence in patients on disulfiram.

Florez et al⁵¹ performed a head-to-head trial of topiramate and naltrexone for the treatment of alcohol dependent patients. This was a 6-month naturalistic, randomized, open-label trial taking place in an outpatient alcohol clinic in Spain. Participants were 102 alcohol-dependent patients (ICD 10 criteria) who had been drinking heavily during the past month (>210 grams per week for men, >140 grams per week for women) and who sought treatment at the clinic. Exclusion criteria included additional substance use disorders except nicotine dependence, co-occurring axis I psychiatric disorders, and lack of a reliable family member able to provide information to the investigators. Participants were randomized to oral naltrexone 50 mg once daily with no further dose escalation, or topiramate 50 mg daily increased by 50 mg every 4 days until 200 mg/day was reached. Patients in the topiramate arm reporting persistent cravings or alcohol intake had topiramate doses further increased up to 400 mg/day. If alcohol intake or cravings were not controlled with naltrexone or topiramate, the medication was considered a treatment failure, and disulfiram 250–500 mg was added. Participants were evaluated at enrollment and at 3 and 6 months on measures of alcohol intake, consequences related to drinking, alcohol cravings, medication tolerability,

and medication compliance. Initial assessments also included biological markers of alcohol consumption, including serum GGT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and MCV. In addition, a composite outcome measure was determined for each individual, and patients were categorized into groups according to whether they met criteria for abstinence, moderate drinking with or without problems, or heavy drinking with or without problems. The average topiramate dose by 6 months was 212.77 mg/day. Both groups showed substantial reduction in their drinking. By 6 months, 45% of the naltrexone group and 47% of the topiramate group were abstinent. While there were no statistically significant differences between the two groups with respect to progress on the composite measure, more patients in the naltrexone group compared to the topiramate group relapsed (45% naltrexone vs. 27% topiramate at 6 months). Topiramate was superior to naltrexone in reducing alcohol-related cravings, as assessed by the Obsessive Compulsive Drinking Scale (OCDS) at both 3 and 6 months. There was a trend for topiramate patients to improve more than naltrexone patients on measures of alcohol dependence-related disability, quality of life, nicotine dependence, GGT, and MCV. A greater percentage of patients taking topiramate reported adverse effects at 3 months (details not presented by the authors), but by 6 months, the differences in adverse effects between the two groups reportedly disappeared. There was no difference between groups in drop-out rates, number of patients requiring disulfiram, or medication adherence. Study limitations include small sample size, absence of a placebo group, and lack of blinding. Furthermore, it may be inequitable to compare topiramate's flexible dosing range with naltrexone's single dose of 50 mg.

Baltieri et al⁵² conducted a more methodologically rigorous head-to-head double-blind RCT comparing topiramate, oral naltrexone, and placebo over 12-weeks. Participants were males 18–60 years, meeting ICD-10 diagnosis for alcohol dependence, enrolled in an outpatient substance abuse treatment program in Sao Paulo, Brazil. Participants' average daily alcohol use was 301 grams, suggesting moderate to severe alcohol dependence. Exclusion criteria included current abuse or dependence of other substances except nicotine, treatment with either study medication within six months, serious medical illness, and co-occurring psychiatric disorders requiring drug treatment. All enrolled patients (n = 155) underwent one week of outpatient detoxification before randomization to topiramate 300 mg/day (n = 52), naltrexone 50 mg/day (n = 49), or placebo (n = 54). Topiramate was titrated from 25 mg/day to 300 mg/day by week 8. Capsules were identical in appearance, quantity, and dosing schedule across conditions. Primary outcome variables were time to first relapse (consumption of > 60 grams of alcohol), cumulative abstinence duration, number of weeks of heavy alcohol consumption (> 90 grams of alcohol), and subjective reports of side effects. Patients were assessed eight times over the 12 week study, and kept daily alcohol monitoring cards. Family members were interviewed to obtain collateral report. The authors performed intention-to-treat analyses. Consistent with prior RCT results,^{46, 49} topiramate was statistically superior to placebo on a number of outcome measures, with longer time to first relapse (7.8 weeks vs. 5.0 weeks, p = 0.01), higher cumulative abstinence duration (8.2 weeks vs. 5.6 weeks, p = 0.02), and fewer weeks of heavy drinking (3.4 weeks vs. 5.9 weeks, p = 0.02) than placebo. There were no statistically significant differences between naltrexone and placebo or between naltrexone and topiramate. Based on a power analysis, the authors report that their sample size of 155 was inadequate and could achieve only 75% power to detect differences between the medication groups. While comparisons between topiramate and naltrexone yielded no statistically significant results, there were trends suggesting that topiramate was more efficacious than naltrexone on almost all outcome measures. Drop-out rates were high, but lowest in the topiramate group (57% in placebo, 41% naltrexone, 36% topiramate). Though the topiramate group had slightly higher rate of paresthesias, there were no statistically significant differences in side effects between the three groups. The main shortcomings of this study include limited ability to generalize the findings to women and inadequate power to detect differences between topiramate and

naltrexone, the primary comparison of interest. Overall, however, this was an elegant and thoughtfully designed study.

The studies described above demonstrate the clinical efficacy of topiramate in reducing rates of alcohol consumption compared to placebo and may suggest superiority of topiramate over oral naltrexone, but the specific mechanism by which topiramate reduces alcohol intake is unclear. Miranda et al⁵³ performed a double-blind, randomized control human laboratory study to examine the hypothesis that topiramate reduces alcohol intake by reducing alcohol craving. Participants were 61 non-treatment seeking heavy drinkers (consuming in the previous 90 days 18–60 drinks per week if male, 14–53 drinks per week if female) recruited from community advertisements. Exclusion criteria included the use of medications that could affect mood or drinking. Participants were randomized to topiramate 200 mg/day, topiramate 300 mg/day, or placebo. Capsules were identical in appearance and quantity across groups. The authors tested two doses of topiramate because the 2003 Johnson et al⁴⁶ study found significant reductions in alcohol intake at the dose of 200 mg/day even though target dose had been 300 mg/day. Medication was titrated over 32 days, followed by up to 7 days at the target dose, during which the laboratory session occurred. During the titration period, participants were followed once weekly to assess alcohol use, craving, and side effects. Mean medication compliance was 96.5%, as assessed by electronic bottle caps and blood samples. After reaching target dosing, participants underwent a laboratory assessment of alcohol cue reactivity, including exposure to a glass of the participant's preferred alcohol and the commercially labeled alcohol bottle, and an alcohol challenge in which they drank beer until blood-alcohol level was 0.06%. Topiramate reduced drinking as dose increased. At week 3, the 300 mg topiramate group reported significantly fewer drinks per week than the other groups. Furthermore, both topiramate groups showed reductions in the percent heavy drinking days at weeks 3 and 4. Surprisingly, changes in drinking were not accompanied by changes in weekly reports of craving for alcohol. Consistent with these results, in the laboratory, topiramate neither affected the subjective or physiological responses to alcohol cues nor urge to drink alcohol during administration. These results suggest that topiramate likely reduces alcohol intake through a mechanism that does not involve changes in craving.

Alcohol Withdrawal—Topiramate has shown promise in animal models of alcohol withdrawal. In rodent and mouse models of alcohol withdrawal, topiramate has been associated with improved maze performance, decreased anxiety-related behaviors, and increased seizure threshold.^{54, 55} The use of topiramate in the treatment of alcohol withdrawal has been less studied in humans. The literature contains only one open study and one RCT of antiglutamatergic medications including topiramate.

Rustembegovic et al⁵⁶ performed an open-label trial of topiramate 50 mg twice daily for 30 days in 12 patients with alcohol dependence who had at least 1–2 tonic-clonic seizures per year. The authors reported positive results, as all participants were observed to be free from tonic-clonic seizures. However, this study contained multiple methodologic limitations, including lack of a comparison group, inadequate description of study participants, lack of definition and duration of alcohol dependence, and absence of data regarding possible comorbid seizure disorders.

In a single-blind RCT, Krupitsky et al⁵⁷ randomized 127 alcohol dependent males to receive placebo, the benzodiazepine diazepam 10mg every 8 hours, or one of three antiglutamatergic agents (lamotrigine 25mg every 6 hours, memantine 10mg every 8 hours, or topiramate 25mg every 6 hours) for 3 days to treat alcohol withdrawal. If CIWA was >10, participants were treated with “rescue” diazepam (10mg every 4 hours in addition to study medication). Topiramate was more efficacious than placebo in reducing symptoms of alcohol withdrawal on days 2 and 3, as evidenced by both lower observer and self-rated

alcohol withdrawal severity scores. However, no statistically significant differences were seen between diazepam and the antiglutaminergic medications. Though topiramate was slightly more efficacious than memantine at treating alcohol withdrawal symptoms, it was less efficacious than lamotrigine, the only antiglutamatergic agent that was superior to placebo averaged over time (topiramate and memantine were superior to placebo only on days 2–3). There were no statistically significant differences between the active agents in the need for rescue diazepam. However, non-statistically significant differences did exist, with the topiramate group requiring the highest percentage of rescue dosing (diazepam 12%, lamotrigine 20%, memantine 27%, topiramate 38%, placebo 88%). The authors appear to have carefully selected dosage to compromise between efficacy and anticipated side effects; nonetheless, higher or more frequent dosing of topiramate might have shown more robust effects in treating alcohol withdrawal. While the study is informative, shortcomings include the relatively small sample size, the all-male sample, and the single-blinding.

The Use of Topiramate for Nicotine Dependence

In animals, acute pretreatment with topiramate inhibited nicotine-induced increases in release of dopamine and norepinephrine.¹² In humans, the results on the effects of topiramate for the treatment of nicotine dependence are inconsistent, with a case report⁵⁸ and two studies showing positive results,^{59, 60} two studies showing that topiramate actually increases cravings and the subjective pleasure of nicotine,^{61, 62} and an RCT showing that the effects of topiramate may be modulated by gender.⁶³

Arbaizar et al⁵⁸ describe a 34 year old man with cocaine and alcohol dependence and diabetic complications whose compulsively smoking decreased (from 80–100 to 40–60 cigarettes/day within 2 months) when topiramate 200 mg/day and aripiprazole 15 mg/day were added.

Khazaal et al⁵⁹ performed a non-randomized, uncontrolled flexible-dose pilot study of topiramate for smoking cessation. Participants were 13 smokers (7 men, 6 women), who smoked at least one pack per day, had a Fagerstrom score >5, and failed to maintain abstinence for more than 8 weeks in at least one previous cessation attempt with nicotine replacement or bupropion. Ten (77%) sought medical assistance for smoking cessation, and three (23%) were receiving topiramate for other reasons, including bipolar disorder and cocaine and heroin detoxification. Two participants had bipolar disorder; no others had concomitant psychopharmacological treatment. A flexible dosing strategy was employed with initial dose of 25 mg/day increased by 25 mg each week until week 4, then by 50mg each week until smoking reduction > 50% was observed, after which the dose was maintained for 3 weeks. Maximum doses ranged from 50–800 mg/day, with an average of 185 mg/day. Six of the 13 smokers were abstinent two months after the start of topiramate, and two more participants reduced their cigarette consumption by > 50%. Three subjects interrupted treatment with topiramate due to intolerable side effects (slurred speech, word finding difficulties, psychomotor slowing, depressive symptoms, and fatigue). Study limitations included its open design, absence of a control group, small sample size, and heterogeneous sample.

Johnson et al⁶⁰ performed a subgroup analysis of smokers in their single-site RCT of topiramate for alcohol dependence⁴⁶ showing topiramate as a promising medication for the treatment of cigarette smoking in alcohol dependence.⁶⁰ Of the 150 randomized alcohol-dependent individuals, 94 were self-reported current smokers, 49 in the placebo group and 45 in the topiramate group. The odds ratio for participants in the topiramate group achieving self-reported abstinence from smoking was 4.46 (95% CI 1.08–18.39; p=0.04) compared to placebo, as demonstrated by a serum cotinine level < 28 ng/ml. The main limitation of this study was that it was a subgroup analysis of a larger study, so the sample consisted of

nicotine dependence among a sample of alcohol dependent individuals, potentially limiting its generalizability.

Contrary to the results above, two human laboratory studies employing exposure paradigms found that topiramate actually increased nicotine craving, reward, and withdrawal. Sofuoglu et al⁶¹ examined topiramate's effects on acute physiological and subjective responses to intravenous nicotine in 12 overnight abstinent smokers (7 male, 5 female) using a double-blind, placebo-controlled, cross-over study design. They investigated the effect of a single dose of topiramate (25 mg or 50 mg) or placebo on the experience of nicotine administered intravenously in three study sessions, separated by 3–9 days to minimize medication carryover effects. Participants smoked an average of 18.7 cigarettes/day, had a Fagerstrom score of 7.1, and were not dependent on substances other than nicotine. Abstinance for at least 8 hours before each study session was verified by breath carbon monoxide levels and baseline plasma nicotine and cotinine concentrations. Two hours following the single dose study medication, participants received intravenous nicotine barbiturate. Ratings of "drug strength," "good effects," and "drug liking" were greater for both the 50 mg and 25 mg doses of topiramate than for placebo, and the rating of "head rush" was greater for the 50 mg dose of topiramate compared to placebo. Topiramate did not affect subjective response to saline. Topiramate had no effect on mood ratings, suggesting that the enhancement of pleasurable effects of nicotine could not be attributed to nonspecific mood changes by topiramate. The study has some limitations. First, intravenous nicotine may produce a very different experience than nicotine inhaled in cigarette smoke. Second, the authors provided only a single small dose of topiramate. Though the acute effect of topiramate was to enhance the rewarding properties of nicotine in this study, the more chronic, longer term effects are unknown.

Consistent with the findings of Sofuoglu et al,⁶¹ Reid et al⁶² showed that topiramate enhanced the rewarding effects of nicotine and increased the symptoms of nicotine withdrawal. The authors studied cue-elicited craving and withdrawal in 40 smokers (>15 cigarettes/day) in a 9-day double-blind, RCT. Participants were assessed at baseline and after completion of the 9-day treatment. Topiramate was titrated to 75 mg over 7 days. On day 9, after three hours of smoking abstinence, participants were tested in two sessions, one in which they were exposed to cigarette cues (e.g., lighter, ashtray, cigarettes, cigarette smoke, and video clips of people smoking), and another in which they were exposed to neutral cues (e.g., seashells, string, cinnamon scent, and a video of people in an office), with the sequence of cue sessions presented in random order. After the two sessions, participants smoked a single cigarette using a controlled puff volume apparatus to assess nicotine's pharmacokinetic, physiological, and subjective effects. Number of puffs and volume per puff were measured. Participants in the topiramate group experienced more withdrawal symptoms, had higher withdrawal ratings regardless of cue type (neutral or smoking-related), and experienced more smoking reward on day 9. Puff volume, total volume smoked, and plasma nicotine levels were lower in the topiramate group compared to placebo, suggesting that participants treated with topiramate needed less smoke to achieve their desired level of satisfaction. The authors concluded that, contrary to prior results,^{59, 60} topiramate is not an effective treatment for managing cigarette craving and withdrawal during brief smoking cessation. Though topiramate doses were higher in this study than in the previous study by Sofuoglu et al,⁶¹ 75 mg/day is significantly lower than the doses used in the two studies with positive results,^{59, 60} highlighting the question of differential effects depending on dose. Similarly, participants in this study received topiramate for nine days, longer than the single dose administered in the study by Sofuoglu et al,⁶¹ but brief compared to most studies.

Anthenelli et al⁶³ conducted the first double-blind RCT of topiramate as an aid to smoking cessation. Eighty-seven adult smokers (>10 cigarettes/day), ages 18–65 years, who were motivated to quit smoking were recruited from the community via advertisements. Exclusion criteria included a serious quit attempt using formal treatments in the 90 days prior, an axis I psychiatric disorder within the past year, a positive urine toxicology screen for anything other than cannabis, and current use of psychotropic medications. Participants received topiramate up to 200 mg/day (n = 44) or placebo (n = 43) over 11 weeks. Topiramate was started at 25 mg daily and titrated to the target of 200 mg/day by week 6. Individuals who could not tolerate the target dose were permitted to take doses as low as 50 mg/day. The target quit date was set for day 42, one week after participants were expected to have achieved steady state levels of topiramate 200 mg/day. The primary outcome measure was a minimum of 4 weeks of carbon monoxide-confirmed abstinence. Overall, there was no significant difference in prolonged abstinence between the topiramate (7 of 43 participants) and placebo groups (7 of 44 participants). However, exploratory analysis revealed differences by gender. Topiramate-treated men were nearly 16 times more likely to achieve prolonged smoking abstinence compared to topiramate-treated women (37.5% vs. 3.7%). Of interest, women receiving placebo showed a trend toward prolonged abstinence with roughly 4–5 times higher rates than those receiving topiramate. On the other hand, topiramate-treated men showed a trend toward prolonged abstinence, with 4 times higher rates than placebo-treated men. According to the authors, though the study was not powered adequately to test for gender effects, results suggest potential male-specific effects for topiramate as an aid to smoking cessation, with topiramate possibly unmasking neurochemical differences in the brains of male and female smokers (e.g. in GABA levels). An alternative explanation is that randomization did not eliminate group differences by gender. The authors note that on average, men taking topiramate had more previous quit attempts compared with topiramate treated women.

The Use of Topiramate for Cocaine Dependence

The literature on topiramate and cocaine dependence consists primarily of a 13-week double-blind, RCT by Kampman et al.⁶⁴ Participants were 40 treatment-seeking cocaine-dependent individuals 18–60 years old, without other substance dependence except nicotine, taking no other psychotropic medications, and using at least \$100 of cocaine in the prior month. The starting dose of topiramate 25 mg was increased by 25 mg each week to 200 mg/day at week 8. In addition, participants received twice weekly individual manualized cognitive behavioral relapse prevention therapy. The study groups were comparable except that the topiramate group had, on average, a significantly higher Addiction Severity Index composite score and a higher Hamilton Depression Rating Scale score. Despite the relative higher severity of addiction in the topiramate-treated group, topiramate recipients were more likely to be cocaine-abstinent after week 8 compared to placebo recipients, as assessed by twice weekly qualitative urine benzoylcegonine tests (UBT's). There was no difference between groups during the 8-week medication titration period. However, a significant difference between groups emerged during the full-dose period. The Addiction Severity Index composite score declined significantly in both groups over the course of the study, but there was a significant group effect, with lower scores in the topiramate group. Cocaine craving declined over the trial in both groups, but there was a trend toward average craving scores declining more in the topiramate group. Adverse events were evenly distributed between the topiramate and placebo groups. Study limitations were its small sample size and the enrollment of only one female participant. Moreover, the study may have selected for participants with only moderate severity of cocaine dependence, as only participants with relatively low cocaine withdrawal symptom severity at intake were enrolled. Finally, the topiramate dose was relatively low, and perhaps a higher dose might have yielded even better outcomes.

Reis et al⁶⁵ subsequently investigated the effect of topiramate 25–300 mg/day (mean dose 127 mg/day) for 12 weeks in an open-label, uncontrolled trial of 28 cocaine dependent males in an outpatient clinic in Brazil. Participants were 18–55 years of age, intranasal cocaine users, without other serious mental disorders, on no psychotropic medications, and without exposure to pharmacologic treatments for cocaine dependence in the preceding 12 months. Biweekly follow-up included qualitative urine benzoylecgonine tests (which detect cocaine 24–60 hours after last use) and the first three items on the Minnesota Cocaine Craving Scale (intensity, frequency, and duration of craving). The authors report that significant reduction in craving intensity and duration was observed in 25% of the sample. The average rate of abstinence (the number of negative urine tests divided by the total number of urine tests during the study) was 25.4%. There were no severe side effects. This study had significant limitations including small sample size, open-label design, and lack of clarity in data presentation, making the results difficult to interpret.

The Use of Topiramate for Methamphetamine Dependence

In a mouse model, treatment with a single dose of topiramate had no effect on methamphetamine-induced behavior (e.g., expression and frequency of stereotypy) or in modulating the rewarding properties of methamphetamine, as measured by conditioned place preference.⁶⁶ In humans, the literature consists of only a laboratory RCT, which suggests that topiramate may be ineffective for the treatment of methamphetamine dependence and may enhance the reinforcing properties of methamphetamine. Johnson et al⁶⁷ performed a human laboratory study, using a double-blind, placebo-controlled, cross-over design. Participants were 10 recently abstinent methamphetamine-dependent individuals, ages 31 to 44 years, with no other axis I psychiatric disorder except nicotine dependence, recruited through community advertisements. Oral doses of topiramate (0, 100, and 200 mg) were administered in two divided doses as a pretreatment before intravenous methamphetamine (0, 15, and 30 mg). Participants stayed in the hospital for 27 days and underwent a sequence of 9 treatments, with sessions every 2–3 days. Methamphetamine produced predictable increases in euphoria, stimulation, and craving. Topiramate administered alone was associated with mild reductions in positive subjective mood, but pretreatment with topiramate enhanced the effects of methamphetamine. On the Multiple-Choice Questionnaire (MCQ), assessing an individual's preference for drug over monetary award, there was a trend toward topiramate increasing the value of methamphetamine over money. On the End-of-Day questionnaire (EDQ), given 6 hours after methamphetamine administration, higher methamphetamine and topiramate doses were associated with greater propensity to want to use again, and there was an interaction such that topiramate significantly enhanced the methamphetamine effect. With the Visual Analogue Scale of Methamphetamine Effects (VAS-M), in which subjects mark a 100 mm line labeled left to right from “not at all” to “extremely” for various measures, topiramate increased “stimulate” statistically significantly, and showed a trend toward increasing “euphoria” but not “craving” levels in participants receiving methamphetamine. On the Global Rating of Stimulation (GRS), assessing effects on overall mood, topiramate alone trended towards decreasing GRS scores, but significantly accentuated the positive effect of methamphetamine. The authors propose that pretreatment with topiramate may produce a mild negative mood that subjectively accentuates the positive experience of methamphetamine by comparison, or that topiramate may pharmacokinetically increase plasma methamphetamine levels through alkalization of urine. Limitations of this study include small study size, its artificial laboratory setting, which may limit generalizability to clinical situations, the potential for tolerance to methamphetamine over the study, and the acute dosing schedule of topiramate, which could overestimate adverse effects and underestimate efficacy. In a separate analysis, Johnson et al⁶⁸ investigated topiramate's effects on cognitive function in methamphetamine-dependent individuals and found mixed

effects; topiramate improved reaction time in a test of attention and concentration, and impaired performance on a test of perceptual motor ability.

The Use of Topiramate for Opioids

Zullino et al⁶⁹ describe three cases of topiramate used as an alternative to clonidine for the treatment of opioid withdrawal. All were individuals in their twenties and early thirties, dependent on opioids for 7–8 years, with previous detoxification admissions, and also using other substances. The patients received variable dosing of topiramate for detoxification, with maximum doses of 500 mg/day. All three cases received other psychotropic medications, including mirtazapine, zolpidem, methadone, olanzapine, and tolperisone (a centrally-acting muscle relaxant). The authors detected no significant withdrawal symptoms except myalgia in two cases. Other than fatigue in one patient, there were no adverse effects from topiramate. The authors propose that topiramate might have more efficacy and fewer side effects than clonidine for opiate withdrawal. However, the data are from case reports, and are thus very limited.

Zullino et al⁷⁰ performed a retrospective study comparing topiramate with clonidine and carbamazepine/mianserin in opioid detoxification, and found that topiramate was the best tolerated and most efficacious of the three. Ten consecutively admitted patients treated with topiramate were compared with 10 consecutively admitted patients treated with clonidine and 10 consecutively admitted patients treated with a carbamazepine/mianserin combination. Patients with alcohol or benzodiazepine dependence were excluded, but those with concomitant use of antidepressants or antipsychotics, and those with stimulant or cannabis dependence were not excluded. The topiramate detoxification protocol entailed 500 mg for the first 3 days, followed by a taper of 50–100 mg/day for 6 days. The clonidine protocol was a 7 day taper from 600 µg/day. The third detoxification protocol involved carbamazepine 600 mg and mianserin 60 mg for 7 days, followed by a 3 day taper of carbamazepine alone. During the detoxification period, patients could additionally receive rescue medications for myorelaxation (tizanidine, tolperisone), insomnia (zolpidem, zopiclone, trimipramine), pain (ibuprofen, piroxicam), nausea (metoclopramide or ondansetron), and anxiety (olanzapine, promazine) as needed. The primary outcome measures were dose adjustments due to side effects and the use of rescue medications. The authors found that significantly more patients in the clonidine and carbamazepine/mianserin groups required reductions in daily doses due to intolerable side effects (including hypotension for clonidine and nausea for carbamazepine). While the use of hypnotics, anxiolytics, antidiarrheals, and anti-emetics was comparable between the three groups, topiramate treatment was associated with less use of analgesics and myorelaxants. Study limitations were its relatively small sample size, lack of standard outcome measures like withdrawal severity and craving, and lack of randomization and blinding. In addition, the differences observed could be attributable to the particular dosing strategies selected by the investigators.

There are no published studies to date on topiramate for opioid dependence.

The Use of Topiramate for Benzodiazepine-Related Disorders

Only two published case reports of topiramate treatment of benzodiazepine dependence and withdrawal exist in the literature. Cheseaux et al⁷¹ describe a 41 year old man with severe benzodiazepine dependence (intranasal midazolam up to 90 mg/day for 7 years), who was rapidly detoxified using topiramate (300 mg on day 1, 500 mg on days 2–3, with a taper until day 9). His only withdrawal symptoms were insomnia and nausea. Michopoulos et al⁷² describe a 44 year old woman with alprazolam dependence (using 5–6mg/day for 7 years, with multiple failed trials of long-acting benzodiazepines, lamotrigine, and SSRI's), co-

occurring depression, anxiety, and histrionic traits who was able to reduce alprazolam use with topiramate. Every 10 days, 25 mg/day of topiramate was added while alprazolam was simultaneously reduced by 0.5 mg/day. As single case reports, these data may be of interest as starting points for further investigation. On the other hand, the possibility that topiramate may confer no additional benefit over anticonvulsants like valproate and carbamazepine⁷³ in the treatment of benzodiazepine dependence must also be considered.

The Use of Topiramate for 3,4-methylenedioxy-N-methylamphetamine (MDMA) Use Disorders

The literature on the use of topiramate for the treatment of MDMA (ecstasy) use disorders is even more limited. There is a single case study by Akhondzadeh and Hampa⁷⁴ who report that topiramate 200 mg/day for 3 months in a 24 year old man with ecstasy abuse (2–4 times a week for 3 years) was associated with decreased ecstasy consumption and attenuated ecstasy-induced euphoria.

Discussion

As a GABA agonist and non-NMDA glutamate antagonist that stabilizes neurons and decreases mesocorticolimbic dopamine release, topiramate is a pharmacological agent with strong theoretical benefits in the treatment of substance related disorders. Based on the mechanisms involving attenuation of downstream midbrain dopamine release, topiramate would be expected to attenuate the reinforcing and rewarding properties of substances of abuse. Furthermore, topiramate's blockade of AMPA receptors, which are believed to play a more important role than NMDA receptors in the withdrawal-induced activation of noradrenergic neurons in the locus coeruleus⁷¹ would predict that topiramate might be particularly effective in the treatment of alcohol and benzodiazepine withdrawal. Moreover, topiramate, which is a non-addictive agent, may serve as a more desirable alternative to other agents with abuse liability. Topiramate is increasingly being studied and considered for use in a variety of impulsive-compulsive spectrum disorders, including obsessive-compulsive disorder, trichotillomania, bulimia nervosa, binge-eating disorder, and pathologic gambling. These disorders and substance related disorders have in common repetitive behaviors that persist with apparently minimal self-control despite significant negative consequences. It is feasible that topiramate may work in all of these conditions by attenuating the reinforcing properties of these compulsive behaviors.

Since the year 2002, there has been a growing body of literature on the use of topiramate for substance related disorders. There is a convergence of evidence for the efficacy of topiramate in alcohol dependence, with the strongest support provided by a multi-site RCT showing a significant positive effect.⁴⁹ In addition, two studies,^{51, 52} though underpowered, suggest that topiramate may be more effective than standard doses of oral naltrexone, an FDA approved medication, for the treatment of alcohol dependence. Topiramate was not shown to be more efficacious than disulfiram; however, the study was an open trial using relatively low doses of topiramate. While topiramate is hypothesized to work by reducing craving for alcohol, according to one human laboratory study, topiramate reduced drinking measures without any effect on craving, suggesting that topiramate may be working through a mechanism independent of craving.

Despite topiramate's efficacy in the treatment of alcohol dependence, topiramate's side effect profile may limit its use. In the 2007 alcohol dependence multi-site RCT by Johnson et al,⁴⁹ there was a significantly higher drop-out rate in the topiramate group compared to placebo. Paresthesias and cognitive dulling appear to be among the most common and problematic side effects associated with topiramate. Lainez et al⁷⁵ examined the time course of adverse events associated with topiramate using pooled data from three 26-week double-

blind, placebo controlled multi-center studies of topiramate for the prevention of migraines at a dose of 100mg/day, titrated over 4 weeks and maintained for 22 weeks. Adverse effects led to treatment discontinuation in 24.9% of patients receiving topiramate compared to only 11.0% of patients receiving placebo. The overall incidence of paresthesias was quite high, at 50.5%; 90% of individuals who experienced paresthesias experienced them by day 31. The overall incidence of any cognitive symptom was 21.2%; 90% of individuals experiencing this adverse effect had it by day 45. The incidence of fatigue was 15.0%; 90% of those reporting fatigue experienced it by day 39. The overall incidence of loss of appetite was 14.5%. Future research should be directed toward determining optimal dosing strategies to minimize adverse effects while maximizing benefit.

While the evidence for the use of topiramate in treating alcohol dependence is robust, the evidence for the use of topiramate in treating other substance related disorders is characterized by limited data or mixed findings. For alcohol withdrawal, though animal models suggest that topiramate may decrease the seizure risk associated with chronic intermittent alcohol use, an RCT in humans comparing three antiepileptic agents suggests that topiramate is not superior to existing treatments (e.g., diazepam), and may be less effective than other anticonvulsants like lamotrigine. Studies examining topiramate in the treatment of opioid, benzodiazepine, and MDMA (ecstasy) are extremely limited, consisting mostly of case reports. In cocaine dependence, one pilot RCT and one open-label trial are promising but limited, and larger RCT's are needed. The data for topiramate use in nicotine dependence is mixed, with a subgroup analysis and an open trial showing reduction in nicotine dependence, but two human laboratory studies demonstrating enhancement of nicotine effects. A human laboratory study on methamphetamine dependence similarly shows that topiramate accentuates the rewarding effects of methamphetamine. Thus, for some substances, topiramate may act in a direction that is opposite of the anticipated effect.

It is possible that the findings demonstrating accentuation of rewarding drug effects by topiramate are attributable to differences in dosing and treatment duration. The studies in which topiramate was found to enhance the rewarding effects of nicotine^{61, 62} and methamphetamine⁶⁷ were human laboratory studies in which topiramate was administered acutely, between 1–9 days prior to the experiment. The human laboratory results showing that topiramate enhances the positive effects of methamphetamine are surprising, given that topiramate was shown to reduce the use of cocaine, another dopamine agonist, in a 13 week RCT.⁶⁴ It is possible that an individual may experience more adverse than beneficial effects with an acute dose of topiramate, and that the substance of abuse overcomes this dysphoric effect. Alternatively, it is possible that the therapeutic effects of topiramate, like those of serotonin selective reuptake inhibitors (SSRI's), may not be detectable for several weeks, possibly reflecting the time it takes for compensatory neuroplastic changes to occur. A human laboratory study done in alcohol dependence⁵³ did not show a similar pattern of reward enhancement with topiramate; however, patients were treated with topiramate for a longer duration (4 weeks). These findings suggest that treatment duration may be an important consideration when using topiramate for substance related disorders.

Alternatively, the findings that topiramate may reduce craving and reinforcement in alcohol dependence but enhance the rewarding effects of nicotine and methamphetamine may simply reflect the complexity and heterogeneity of different substance related disorders. It is unlikely that one medication can treat multiple heterogeneous substance related disorders, each of which is characterized by complex neurobiology. Alcohol causes intoxication through effects on diverse ion channels and neurotransmitter receptors, including GABA_A receptors, particularly those containing δ subunits which mediate tonic inhibition of neurons by ambient GABA.⁷⁶ Alcohol dependence results from compensatory changes that occur after prolonged alcohol exposure, including internalization of GABA_A receptors, which

allows adaptation to the effects of alcohol.⁷⁶ While the unique downstream dopamine effects have been emphasized, topiramate may be particularly efficacious for the treatment of alcohol dependence because of its direct effects on the GABA_A system. Topiramate, like the glutamate antagonist acamprosate, may act to rebalance the inhibitory and excitatory inputs exerted by GABA and glutamate, respectively. If this is the case, then further investigation of topiramate for the treatment of benzodiazepine dependence, another substance related disorder primarily mediated by GABA, may be worthwhile. Given that the dopamine effects of topiramate are relatively indirect, topiramate may be less effective in modulating more robust releases of dopamine associated with highly potent dopamine agonists like methamphetamine and cocaine.

Beyond the heterogeneity across different substance related disorders, there is significant variation in clinical course and outcome even among individuals with the same substance disorder. For example, in the RCT by Anthenelli et al,⁶³ topiramate-treated men were nearly 16 times more likely to achieve prolonged smoking abstinence than topiramate-treated women. It is clear that some individuals respond to topiramate more than others. A multitude of factors, such as gender, genetic polymorphisms, co-morbidities, and psychosocial factors, may influence whether an individual successfully responds to a particular medication. Genetic variants associated with more specific subgroups of substance dependent individuals are starting to be identified. A recent study suggests that patients with alcoholism who carry the *Asp40* allele of the μ -opioid receptor gene (*OPRM1*) are more likely to respond to treatment with naltrexone.⁷⁷ Similarly, a recent genome wide association study identified multiple single nucleotide polymorphisms that were associated with the ability to successfully quit smoking using agents like bupropion and nicotine replacement therapy.⁷⁸ Future directions for research should be aimed at increased integration of pharmacogenetic approaches to link genotype with both phenotypes and endophenotypes, with the goal of identifying targeted therapies for specific patient subgroups. Given that the most compelling evidence for topiramate exists for the treatment of alcohol dependence, an exploration of candidate genes that predict response to topiramate in alcohol dependence would be valuable. GABA_A receptors containing the δ subunit, in particular the $\alpha 4\beta 2\delta$ and $\alpha 6\beta 2\delta$ receptors, are exceptionally sensitive to alcohol.⁷⁶ Potential genes of interest may include genes that code for the δ subunit of GABA_A and the μ -opioid receptor gene, among others. Optimally, a blinded head-to-head RCT comparing topiramate to the three FDA-approved medications for alcohol dependence (naltrexone, acamprosate, disulfiram) and placebo, including factor analysis of genetic variants associated with response to these pharmacotherapies, would provide tremendous insight into the complexity and heterogeneity that is characteristic of alcohol dependence and other substance related disorders.

In sum, there is compelling evidence for the use of topiramate for the treatment of alcohol dependence. However, topiramate's side effect profile may limit its widespread use. While the data are limited, the existing literature suggests that despite the neurobiological rationale for potential use in a variety of addictive and compulsive spectrum disorders, topiramate is unlikely to bear out as a pharmacologic panacea to be broadly applied across all substance related disorders, with some studies related to nicotine and methamphetamine dependence actually showing that topiramate may enhance the pleasurable effects of the substance. While there is strong evidence supporting the efficacy of topiramate in alcohol dependence, more direct comparisons with already existing approved medications for alcohol dependence are needed. Furthermore, factors analyses, including analysis of genetic variants associated with response to topiramate, would be a valuable next step in research.

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Table 1

Human studies on topiramate for the treatment of substance related disorders.

| Alcohol Dependence | | | | | | |
|----------------------|-------------------------------|--|---|---|--|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results | |
| Johnson et al, 2003 | RCT, double blind | n=75 topiramate (23 female), n=75 placebo (20 female) | 300mg/day×12 wks | Self-reported drinking. | Topiramate group had 2.88 fewer average drinks/d, 3.10 fewer drinks per drinking day, 27.6% fewer heavy drinking days, and 26.2% more days abstinent from alcohol. | |
| Rubio et al, 2004 | Open trial | n=24 adults (11 female) with alcohol dependence and co-morbid psychiatric disorders for which the use of topiramate was indicated. No placebo group. | Average 262mg/day (range 200–400mg)×12 weeks | Weekly drink consumption, craving, and CDT. | Improvements in craving scores ($p<0.001$), weekly drinks ($p<0.001$), CDT ($p<0.05$). | |
| Huguelet et al, 2005 | Case series | n=2 males with co-occurring psychiatric disorders (schizophrenia, bipolar disorder) | Case 1: 150mg/day×4 months. Case 2: 300mg/day for unknown duration. | Alcohol consumption. | Case 1: abstinence. Case 2: reduction in alcohol consumption from 3L/d to 3dL/d. | |
| Chiu et al, 2007 | Retrospective chart review | n=9 adults (2 female) with alcohol abuse or dependence and co-occurring psychiatric disorders | Variable; average dose 112.5mg/day over an unknown time period. | Partial or complete remission in alcohol consumption. | 6/9 patients achieved full or partial remission from alcohol use disorders | |
| Miranda et al, 2007 | Open trial | n=64 (10 female) with co-occurring psychiatric disorders | Average 196mg/day (range 50–400mg)×12 months | Number of drinking days per month, number of drinks per day. | Decrease from 23.6 to 4.8 drinking days per month. Decrease from 16 to 2 drinks per day. | |
| Johnson et al, 2007 | RCT, double blind, multi-site | n=183 topiramate (46% female), n=188 placebo (52% female) | 300mg/day×14 wks | Self-reported percentage of heavy drinking days. | Mean difference 8.44% (95%CI 3.07–13.80%) | |
| De Sousa et al, 2008 | Randomized open label trial | n=50 topiramate, n=50 disulfiram. All males with stable family supports/supervision. | Topiramate 50mg TID vs. disulfiram 250mg/day×9 months | Relapse rates, time to relapse. | Lower relapse rates in disulfiram (10%) vs. topiramate (44%). Shorter mean time to relapse in topiramate (76 days) vs. disulfiram (133 days). | |
| Florez et al, 2008 | Randomized, open label trial | n=51 topiramate (8 female), n=51 naltrexone (7 female) | Topiramate 200mg–400mg/day vs. naltrexone 50mg PO daily×6 months | Alcohol intake, craving, disability, quality of life, GGT, MCV. | No significant differences between groups in abstinence (47% in topiramate group vs. 45% in naltrexone group). Less severe cravings in topiramate group compared to naltrexone group. Trend for greater improvement in alcohol-related disability, quality of life, GGT, MCV in topiramate compared to naltrexone. | |
| Baltieri et al, 2008 | RCT, double blind | n=52 topiramate, n=49 naltrexone, n=54 placebo. All males. | Topiramate 300mg/day vs. naltrexone 50mg/day PO vs. placebo×12 weeks. | Time to first relapse, cumulative abstinence duration, weeks of heavy drinking. | Topiramate superior to placebo on all 3 outcome measures (7.8 vs. 5.0 weeks to first relapse; 8.2 vs. 5.6 weeks of cumulative abstinence; 3.4 vs. 5.9 weeks of | |

| Alcohol Dependence | | | | | |
|---------------------|---|---|--|--|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Miranda et al, 2008 | Randomized, double-blind human laboratory study | n=20 topiramate 200mg/day (30% female), n=21 topiramate 300mg/day (38% female), n=20 placebo (40% female). All non-treatment seeking. | Topiramate 200mg/day vs. topiramate 300mg/day vs. placebo×4 weeks. | Weekly assessments of alcohol intake and craving during medication titration. Laboratory assessment of alcohol cue reactivity. Laboratory assessment of alcohol effects after alcohol challenge. | Topiramate significantly reduced drinking (fewer drinks per week and percent of heavy drinking days) compared to placebo as dose increased, but no effect on craving. No effect of topiramate on urge to drink when presented with cues. No effect of topiramate on urge to drink during alcohol administration. |

| Alcohol Withdrawal | | | | | |
|---------------------------|-------------------|--|---|--|---|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Rustembegovic et al, 2002 | Open trial | n=12 patients with alcoholism who have 1–2 tonic clonic seizures a year. | 50mg BID×30 days | Number of seizures during study. | No seizures observed. |
| Krupitsky et al, 2007 | RCT, single blind | n=26 topiramate, n=25 lamotrigine, n=26 memantine, n=25 diazepam, n=25 placebo. All males. | Topiramate 25mg every 6 hrs; lamotrigine 25mg every 6 hrs; memantine 10mg every 8 hrs; diazepam 10mg every 8 hrs, all for 7 days. | Self-rated and observer-rated withdrawal scores. | Topiramate was superior to placebo, did not differ significantly from diazepam, and was slightly less effective than lamotrigine. |

| Nicotine Dependence | | | | | |
|----------------------|------------------------------|---|---|--|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Johnson et al, 2005 | RCT, subgroup analysis | n=45 topiramate (11 female), n=49 placebo (13 female) | 300mg/day×12 weeks | Smoking abstinence | OR 4.46 (95%CI 1.08–18.39) |
| Khazaal et al, 2006 | Open trial | n=13 smokers (6 female) with 1 failed quit attempts | Flexible dosing strategy (Range 50–800mg/day) | Smoking abstinence at 2mths | 6/13 abstinent and 2/13 decreased smoking by >50% |
| Sofuoglu et al, 2006 | Cross-over laboratory design | n= 12 (5 female) smokers | Single doses of 25mg, 50mg, and placebo before administration of nicotine 0.5mg and 1mg IV. | Subjective ratings of nicotine effects (DEQ) and nicotine withdrawal | “Drug strength,” “good effects,” and “drug liking” greater for 25mg and 50mg topiramate vs placebo (p<0.05). “Head rush” greater for 50mg topiramate vs. placebo (p<0.05). |
| Reid et al, 2007 | RCT, double blind | n=19 topiramate (5 female), n=21 placebo (10 female) | 75mg/day×9 days | Subjective ratings of nicotine craving and withdrawal | Topiramate enhanced subjective ratings of withdrawal after the 3hr abstinence period, and increased the rewarding effects of a smoked cigarette. |

| Nicotine Dependence | | | | | |
|------------------------|-------------------|---|---|---|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Arbaizar et al, 2008 | Case report | n=1 (34yo male with polysubstance dependence, diabetes, and metabolic encephalopathy) | Topiramate 200mg/day and aripiprazole 15mg/day×2 months | ---- | Reduction in smoking from 80–100 cigarettes/day to 40–60 cigarettes/day. |
| Anthenelli et al, 2008 | RCT, double blind | N=43 topiramate (27 female), n=44 placebo (22 female) | 200mg/day×11 weeks | Prolonged abstinence (minimum of 4 weeks of carbon-monoxide confirmed smoking abstinence) | No difference between topiramate (7/43) and placebo (7/44). But exploratory analysis showed that topiramate-treated men (37.5%) are more likely to achieve prolonged abstinence compared to topiramate-treated women (3.7%). |

| Cocaine Dependence | | | | | |
|---------------------|-------------------|---|--|---|---|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Kampman et al, 2004 | RCT, double blind | n=20 topiramate (5% female), n=20 placebo (0% female) | 200mg×13 weeks | Cocaine use, measured by urine benzoyllecgonine test (UBT) | Topiramate group was more likely to be abstinent compared to placebo group after week 8 ($Z=2.67$, $p=0.01$). |
| Reis et al, 2008 | Open trial | n=28 intranasal cocaine dependent males | Average dose 127mg/day (range 25–300mg/day)×12 weeks | Abstinence rate (number of negative UBT's divided by total number of UBT's). Intensity, frequency, and duration of cocaine craving. | Average rate of abstinence was 25%. Intensity and duration of cocaine craving was reduced in 25% of sample. No decrease in craving frequency. |

| Methamphetamine Dependence | | | | | |
|----------------------------|------------------------------|---|--|---|---|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Johnson et al, 2007 | Cross-over laboratory design | n=10 (3 females) non-treatment seeking methamphetamine-dependent adults | 100mg or 200mg in divided doses (on the evening before and on the morning of study) prior to administration of IV methamphetamine 15mg and 30mg. | Multiple choice questionnaire (MCQ), End-of-Day questionnaire (EDQ), Visual analogue scale for methamphetamine effects (VAS-M), Global Rating of Stimulation (GRS). | MCQ: topiramate had trend of accentuating effect of methamphetamine to increase value of drug over money. EDQ: topiramate significantly enhanced effect of methamphetamine in increasing desire to use again. VAS-M: topiramate increased the stimulating and euphoric effects of methamphetamine. GRS: topiramate alone had trend of decreasing effect on mood, but significantly accentuated the positive effect of methamphetamine on mood. |

| Opioid Withdrawal | | | | | |
|---------------------|-------------|---|---|--|---|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Zullino et al, 2002 | Case series | n=3 (2 female) | Variable; max dose 500mg with taper | ---- | No significant withdrawal symptoms, and minimal adverse effects. |
| Zullino et al, 2004 | Open trial | n=10 topiramate (4 female), n=10 clonidine (4 female), n=10 | Topiramate 500mg×3 days with taper down by 100mg/day×2days then by 50mg/day×4 days; clonidine 600µg×3 days with taper×4 days; | Dose adjustments and use of other p.r.n. medications | 7/10 receiving clonidine and 9/10 receiving carbamazepine/mianserin required dose reductions due to side effects, compared to |

| Opioid Withdrawal | | | | | |
|-------------------|--------|------------------------------------|--|-------------------------|---|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| | | carbamazepine/mianserin (3 female) | carbamazepine 600mg and mianserin 60mg×7 days with carbamazepine taper×3 days. | | 2/10 in topiramate group. Topiramate group required less analgesics (p<0.05) and myorelaxants (p<0.001) compared to other groups. |

| Benzodiazepine Dependence and/or Withdrawal | | | | | |
|---|-------------|---|-------------------------|-------------------------|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Cheseaux et al, 2003 | Case report | n=1 (41yo male with intranasal midazolam use up to 90mg/day×7yrs) | 500mg with taper×9 days | ---- | Rapid detoxification from benzodiazepines, with minimal withdrawal symptoms. |
| Michopoulos et al, 2006 | Case report | n=1 (44yo female with depression, subthreshold anxiety, and alprazolam addiction 5–6mg/day) | 200mg×6mths | ---- | Reduced alprazolam intake to 1.5mg at 6mths without withdrawal symptoms. |

| 3,4-methylenedioxy-N-methylamphetamine (MDMA or Ecstasy) Dependence | | | | | |
|---|-------------|-----------------|-------------------|-------------------------|--|
| Study | Design | Sample | Dose and Duration | Primary Outcome Measure | Results |
| Akhondzadeh and Hampa, 2005 | Case report | n=1 (24yo male) | 200mg×3 mths | ---- | Decreased consumption. Attenuated sense of euphoria. |