Topiramate in the Treatment of Substance-Related Disorders: A Critical Review of the Literature

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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 was conducted 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*.

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 1 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.

Conclusions: 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.

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Substance-related disorders are a significant source of morbidity and mortality and pose substantial cost to society. Yet there are limited pharmacologic agents that effectively treat these disorders. US Food and Drug Administration (FDA)–approved pharmacologic treatment options for alcohol dependence include 3 agents with very different mechanisms of action: naltrexone (an opioid antagonist), acamprosate (a putative *N*-methyl-D-aspartate [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 μ-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 bupropion[11] for cocaine dependence, no pharmacologic 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 to the nucleus accumbens are 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 γ-aminobutyric acid (GABA) transmission by binding to a nonbenzodiazepine site on $GABA_A$ receptors, and inhibits glutamatergic transmission at ionotropic α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (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 ceruleus, 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] posttraumatic 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.[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 article will critically review the existing literature and provide directions for future research.

DATA SOURCES AND SELECTION

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, 6 for nicotine, 2 for cocaine, 1 for methamphetamine, 2 for opioids, 2 for benzodiazepines, and 1 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 1 case series, 1 chart review, 4 open trials, 3 RCTs, and 1 human laboratory study. Among these are included 3 studies comparing topiramate to approved medications naltrexone and disulfiram.

Huguelet et al[42] describe 2 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 al[43] performed a retrospective chart review of psychiatric patients at a university medical center who received topiramate for any reason in the previous 2 years. Forty-six individuals were identified as having received topiramate during the study period. Nineteen patients took topiramate for 1 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/d). 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 al[44] 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/d titrated up to 400 mg/d; mean final dose, 261 mg/d) was given as an adjunct to selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, lithium, and anticraving drugs (eg, 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 al[45] 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/d improved all outcome measures with statistical significance. The number of drinking days per month decreased from 23.6 days at baseline to

Table 1. Human Studies on Topiramate for the Treatment of Substance-Related Disorders

Study	Design	Sample	Dose and Duration	Primary Outcome Measure	Results
Alcohol dependence					
Johnson et al,[46] 2003	RCT, double blind	n = 75 topiramate (23 female), n = 75 placebo (20 female)	300 mg/d × 12 wk	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,[44] 2004	Open trial`	n = 24 adults (11 female) with alcohol dependence and comorbid psychiatric disorders for which the use of topiramate was indicated. No placebo group	Average 262 mg/d (range, 200–400 mg) × 12 wk	Weekly drink consumption, craving, and CDT	Improvements in craving scores ($P < .001$), weekly drinks ($P < .001$), CDT ($P < .05$)
Huguelet et al,[42] 2005	Case series	n = 2 males with co-occurring psychiatric disorders (schizophrenia, bipolar disorder)	Case 1: 150 mg/d × 4 mo. Case 2: 300 mg/d for unknown duration	Alcohol consumption	Case 1: abstinence. Case 2: reduction in alcohol consumption from 3 L/d to 3 dL/d
Chiu et al,[43] 2007	Retrospective chart review	n = 9 adults (2 female) with alcohol abuse or dependence and co-occurring psychiatric disorders	Variable; average dose 112.5 mg/d over an unknown time period	Partial or complete remission in alcohol consumption	6/9 patients achieved full or partial remission from alcohol use disorders
Fernandez Miranda et al,[45] 2007	Open trial	n = 64 (10 female) with co-occurring psychiatric disorders	Average 196 mg/d (range, 50–400 mg) × 12 mo	No. of drinking days per mo, no. of drinks per d	Decrease from 23.6 to 4.8 drinking days per mo. Decrease from 16 to 2 drinks per d
Johnson et al,[49] 2007	RCT, double blind, multi-site	n = 183 topiramate (46% female), n=188 placebo (52% female)	300 mg/d × 14 wk	Self-reported percentage of heavy drinking days	Mean difference, 8.44% (95% CI, 3.07–13.80)
De Sousa et al,[50] 2008	Randomized open-label trial	n = 50 topiramate, n = 50 disulfiram. All males with stable family supports/ supervision	Topiramate 50 mg tid vs disulfiram 250 mg/d × 9 mo	Relapse rates, time to relapse	Lower relapse rates in disulfiram (10%) vs. topiramate (44%). Shorter mean time to relapse in topiramate (76 d) vs disulfiram (133 d)
Florez et al,[51] 2008	Randomized open-label trial	n = 51 topiramate (8 female), n = 51 naltrexone (7 female)	Topiramate 200–400 mg/d vs naltrexone 50 mg po daily × 6 mo	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,[52] 2008	RCT, double blind	n = 2 topiramate, n = 49 naltrexone, n = 54 placebo. All males	Topiramate 300 mg/d vs naltrexone 50 mg/d po vs placebo × 12 wk	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 wk to first relapse; 8.2 vs 5.6 wk of cumulative abstinence; 3.4 vs 5.9 wk of heavy drinking). No statistically significant difference between topiramate and naltrexone, but trends toward superior outcomes in topiramate group. No statistically significant difference between naltrexone and placebo

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Table 1 (continued). Human Studies on Topiramate for the Treatment of Substance-Related Disorders

Study	Design	Sample	Dose and Duration	Primary Outcome Measure	Results
Alcohol dependence (continued)					
Miranda et al,[53] 2008	Randomized, double-blind human laboratory study	n = 20 topiramate 200 mg/d (30% female), n = 21 topiramate 300 mg/d (38% female), n = 20 placebo (40% female). All non–treatment seeking	Topiramate 200 mg/d vs topiramate 300 mg/d vs placebo × 4 wk	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 wk 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					
Rustembegovic et al,[56] 2002	Open trial	n = 12 patients with alcoholism who have 1–2 tonic clonic seizures a year	50 mg bid × 30 d	No. of seizures during study	No seizures observed
Krupitsky et al,[57] 2007	RCT, single blind	n = 26 topiramate, n = 25 lamotrigine, n = 26 memantine, n = 25 diazepam, n = 25 placebo. All males	Topiramate 25 mg every 6 hr; lamotrigine 25 mg every 6 hr; memantine 10 mg every 8 hr; diazepam 10 mg every 8 hr; all for 7 d	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					
Johnson et al,[60] 2005	RCT, subgroup analysis	n = 45 topiramate (11 female), n = 49 placebo (13 female)	300 mg/d × 12 wk	Smoking abstinence	OR 4.46 (95% CI, 1.08–18.39)
Khazaal et al,[59] 2006	Open trial	n = 13 smokers (6 female) with ≥ 1 failed quit attempts	Flexible dosing strategy (range, 50–800 mg/d)	Smoking abstinence at 2 mo	6/13 abstinent and 2/13 decreased smoking by > 50%
Sofuoglu et al,[61] 2006	Crossover laboratory design	n = 12 (5 female) smokers	Single doses of 25 mg, 50 mg, and placebo before administration of nicotine 0.5 mg and 1 mg IV	Subjective ratings of nicotine effects (DEQ) and nicotine withdrawal	"Drug strength," "good effects," and "drug liking" greater for 25 mg and 50 mg topiramate vs placebo ($P < .05$). "Head rush" greater for 50 mg topiramate vs placebo ($P < .05$)
Reid et al,[62] 2007	RCT, double blind	n = 19 topiramate (5 female), n = 21 placebo (10 female)	75 mg/d × 9 d	Subjective ratings of nicotine craving and withdrawal	Topiramate enhanced subjective ratings of withdrawal after the 3-h abstinence period, and increased the rewarding effects of a smoked cigarette
Arbaizar et al,[58] 2008	Case report	n = 1 (34-year-old male with polysubstance dependence, diabetes, and metabolic encephalopathy)	Topiramate 200 mg/d and aripiprazole 15 mg/d × 2 mo	NA	Reduction in smoking from 80–100 cigarettes/d to 40–60 cigarettes/d
Anthenelli et al,[63] 2008	RCT, double blind	n = 43 topiramate (27 female), n = 44 placebo (22 female)	200 mg/d × 11 wk	Prolonged abstinence (minimum of 4 wk 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					
Kampman et al,[64] 2004	RCT, double blind	n = 20 topiramate (5% female), n = 20 placebo (0% female)	200 mg × 13 wk	Cocaine use, measured by urine benzoylecgonine test (UBT)	Topiramate group was more likely to be abstinent compared to placebo group after week 8 ($Z = 2.67$, $P = .01$)
Reis et al,[65] 2008	Open trial	n = 28 intranasal cocaine-dependent males	Average dose, 127 mg/day (range, 25–300 mg/d) × 12 wk	Abstinence rate (number of negative UBTs divided by total number of UBTs). 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

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Table 1 (continued). Human Studies on Topiramate for the Treatment of Substance-Related Disorders

Study	Design	Sample	Dose and Duration	Primary Outcome Measure	Results
Methamphetamine dependence					
Johnson et al,[67] 2007	Crossover laboratory design	n = 10 (3 females) non–treatment seeking methamphetamine-dependent adults	100 mg or 200 mg in divided doses (on the evening before and on the morning of study) prior to administration of IV methamphetamine 15 mg and 30 mg	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					
Zullino et al,[69] 2002	Case series	n = 3 (2 female)	Variable; max dose 500 mg with taper	NA	No significant withdrawal symptoms, and minimal adverse effects
Zullino et al,[70] 2004	Open trial	n = 10 topiramate (4 female), n = 10 clonidine (4 female), n = 10 carbamazepine/ mianserin (3 female)	Topiramate 500 mg × 3 d with taper down by 100 mg/d × 2 d then by 50 mg/d × 4 d; clonidine 600 μg × 3 d with taper × 4 d; carbamazepine 600 mg and mianserin 60 mg × 7 d with carbamazepine taper × 3 d	Dose adjustments and use of other prn medications	7/10 receiving clonidine and 9/10 receiving carbamazepine/mianserin required dose reductions due to side effects, compared to 2/10 in topiramate group. Topiramate group required less analgesics ($P < .05$) and myorelaxants ($P < .001$) compared to other groups
Benzodiazepine dependence and/or withdrawal					
Cheseaux et al,[71] 2003	Case report	n = 1 (41-year-old male with intranasal midazolam use up to 90 mg/d × 7 y)	500 mg with taper × 9 d	NA	Rapid detoxification from benzodiazepines, with minimal withdrawal symptoms
Michopoulos et al,[72] 2006	Case report	n = 1 (44-year-old female with depression, subthreshold anxiety, and alprazolam addiction 5–6 mg/d)	200 mg × 6 mo	NA	Reduced alprazolam intake to 1.5 mg at 6 mo without withdrawal symptoms
3,4-methylenedioxymethylamphetamine (MDMA or Ecstasy) dependence					
Akhondzadeh and Hampa,[74] 2005	Case report	n = 1 (24-year-old male)	200 mg × 3 mo	NA	Decreased consumption. Attenuated sense of euphoria

Abbreviations: bid = twice a day, CDT = carbohydrate deficient transferrin, DEQ = Drug Effects Questionnaire, GGT = γ glutamyl transferase, IV = intravenous, MCV = mean corpuscular volume, NA = not applicable, po = by mouth, prn = as needed, RCT = randomized controlled trial, tid = three times a day.

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 γ glutamyl transferase (GGT). The study was limited by lack of placebo, nonstandardized titration schedules, and a high dropout rate. Only 40 patients remained at 6 months, and 22 patients by 12 months; the causes for dropout 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 years, 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 score >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 levels,[48] defined as ≤1 standard drink per day for women, and ≤2 standard drinks for men, based on National Institute on Alcohol Abuse and Alcoholism 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 al[49] who performed a 14-week multisite, randomized, double-blind, placebo-controlled trial of 371 men and women aged 18 to 65 years 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 dropouts were 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 2 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 Johnson[46] 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 1 study comparing topiramate to disulfiram[50] and 2 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 al[50] 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 randomly assigned to disulfiram 250 mg daily (n=50) or topiramate 50 mg 3 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 biweekly for 9 months. At the endpoint, only 10% of the disulfiram group had relapsed compared to 44% in the topiramate group ($P=.0001$). 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/d was low, and potentially inadequate. Only relapse was measured; less binary outcomes, like number of drinks per week, were not evaluated. Moreover, medication nonadherence is a common reason for treatment failure with disulfiram; and nonadherence 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 al[51] performed a head-to-head trial of topiramate and naltrexone for the treatment of alcohol dependence. 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 g per week for men, >140 g 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/d was reached. Patients in the topiramate arm reporting persistent cravings or alcohol intake had doses further increased up to 400 mg/d. 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 biologic markers of alcohol consumption, including serum GGT, aspartate aminotransferase, alanine aminotransferase, 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/d. 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 2 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 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 (specific details not presented); but by 6 months, the differences in adverse effects between the 2 groups reportedly disappeared. There was no difference between groups in the rates of dropout, disulfiram use, 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 al[52] conducted a more methodologically rigorous head-to-head double-blind RCT comparing topiramate, oral naltrexone, and placebo over 12-weeks. Participants were males aged 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 g, suggesting moderate to severe alcohol dependence. Exclusion criteria included current abuse or dependence of other substances except nicotine, treatment with either study medication within 6 months, serious medical illness, and co-occurring psychiatric disorders requiring drug treatment. All enrolled patients (n = 155) underwent 1 week of outpatient detoxification before randomization to topiramate 300 mg/d (n = 52), naltrexone 50 mg/d (n = 49), or placebo (n = 54). Topiramate was titrated from 25 mg/d to 300 mg/d 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 g of alcohol), cumulative abstinence duration, number of weeks of heavy alcohol consumption (> 90 g of alcohol), and subjective reports of side effects. 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, $P = .01$), higher cumulative abstinence duration (8.2 weeks vs 5.6 weeks, $P = .02$), and fewer weeks of heavy drinking (3.4 weeks vs 5.9 weeks, $P = .02$) 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. Attrition was high in all groups, but lowest in topiramate (57% in placebo, 41% naltrexone, 36% topiramate). Though the topiramate group reported more paresthesias, there were no statistically significant differences in side effects between

the 3 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 al[53] 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 randomly assigned to topiramate 200 mg/d, topiramate 300 mg/d, or placebo. The authors tested 2 different doses of topiramate because the 2003 Johnson et al[46] study found reductions in alcohol intake with 200 mg/d even though study target dose was 300 mg/d. Medication was titrated over 32 days, followed by up to 7 days at the target dose. Participants were followed once weekly. Mean medication compliance was 96.5%, as assessed by electronic bottle caps and blood samples. 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 percentage of heavy drinking days at weeks 3 and 4. Surprisingly, changes in drinking were not accompanied by changes in weekly reports of craving for alcohol. After reaching target dose, 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 neither affected the subjective or physiologic responses to alcohol cues nor urge to drink during alcohol 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 1 open study and 1 RCT of antiglutamatergic medications including topiramate.

Rustembegovic et al[56] 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 methodological 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 al[57] randomly assigned 127 alcohol-dependent males to receive placebo, the benzodiazepine diazepam 10 mg every 8 hours, or 1 of 3 antiglutamatergic agents (lamotrigine 25 mg every 6 hours, memantine 10 mg every 8 hours, or topiramate 25 mg every 6 hours) for 3 days to treat alcohol withdrawal. If CIWA score was >10, participants were treated with "rescue" diazepam (10 mg 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, nonstatistically 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 report[58] and 2 studies showing positive results,[59,60] 2 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 al[58] describe a 34-year-old man with cocaine and alcohol dependence and diabetic complications whose compulsive smoking decreased (from 80 to 100 to 40–60 cigarettes/d within 2 months) when topiramate 200 mg/d and aripiprazole 15 mg/d were added.

Khazaal et al[59] performed a nonrandomized, uncontrolled flexible-dose pilot study of topiramate for smoking cessation. Participants were 13 smokers (7 men, 6 women), who smoked at least 1 pack per day, had a Fagerstrom score > 5, and failed to maintain abstinence for more than 8 weeks in at least 1 previous cessation attempt with nicotine replacement or bupropion. Ten (77%) sought medical assistance for smoking cessation, and 3 (23%) were receiving topiramate for other reasons, including bipolar disorder and cocaine and heroin detoxification. Two participants had bipolar disorder; no others had concomitant psychopharmacologic treatment. A flexible dosing strategy was employed with initial dose of 25 mg/d increased by 25 mg each week until week 4, then by 50 mg each week until smoking reduction > 50% was observed, after which the dose was maintained for 3 weeks. Maximum doses ranged from 50 to 800 mg/d, with an average of 185 mg/d. Six of the 13 smokers were abstinent 2 months after the start of topiramate, and 2 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 al[60] performed a subgroup analysis of smokers in their single-site RCT of topiramate for alcohol dependence[46] showing topiramate as a promising medication for the treatment of cigarette smoking in alcohol dependence.[60] Of the 150 randomly assigned 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 to 18.39; $P = .04$) 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, 2 human laboratory studies employing exposure paradigms found that topiramate actually increased nicotine craving, reward, and withdrawal. Sofouglu et al[61] examined topiramate's effects on acute physiologic and subjective responses to intravenous nicotine in 12 overnight abstinent smokers (7 male, 5 female) using a double-blind, placebo-controlled, crossover 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 3 study sessions, separated by 3–9 days to minimize medication carryover effects. Participants smoked an average of 18.7 cigarettes/d, had a Fagerstrom score of 7.1, and were not dependent on substances other than nicotine. Abstinence 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 al[62] 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/d) 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 3 hours of smoking abstinence, participants were tested in 2 sessions, 1 in which they were exposed to cigarette cues (eg, lighter, ashtray, cigarettes, cigarette smoke, and video clips of people smoking), and another in which they were exposed to neutral cues (eg, seashells, string, cinnamon scent, and a video of people in an office), with the sequence of cue sessions presented in random order. After the 2 sessions, participants smoked a single cigarette using a controlled puff volume apparatus to assess nicotine's pharmacokinetic, physiologic, 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/d is significantly lower than the doses used in the 2 studies with positive results,[59,60] highlighting the question of differential effects depending on dose. Similarly, participants in this study received topiramate for 9 days, longer than the single dose administered in the study by Sofuoglu et al,[61] but brief compared to most studies.

Anthenelli et al[63] conducted the first double-blind RCT of topiramate as an aid to smoking cessation. Eighty-seven

adult smokers (> 10 cigarettes/d), 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/d (n = 44) or placebo (n = 43) over 11 weeks. Topiramate was started at 25 mg daily and titrated to the target of 200 mg/d by week 6. Individuals who could not tolerate the target dose were permitted to take doses as low as 50 mg/d 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/d. 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 (eg, 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/d 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 benzoylecgonine tests (UBTs). 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 1 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 al[65] subsequently investigated the effect of topiramate 25–300 mg/d (mean dose 127 mg/d) for 12 weeks in an open-label, uncontrolled trial of 28 cocaine-dependent men 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 UBTs (which detect cocaine 24–60 hours after last use) and the first 3 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 (eg, 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 al[67] performed a human laboratory study, using a double-blind, placebo-controlled, crossover 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 2 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, 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, 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 Analog Scale of Methamphetamine Effects, in which subjects mark a 100 mm line labeled left to right from "not at all" to "extremely" for various measures, topiramate increased "stimulate" with statistical significance, and showed a trend toward increasing "euphoria" in participants receiving methamphetamine. On the Global Rating of Stimulation (GRS), assessing effects on overall mood, topiramate alone trended toward 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 alkalinization 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 al[68] 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 al[69] describe 3 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/d. All 3 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 2 cases. Other than fatigue in 1 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 al[70] 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 3. 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/d for 6 days. The clonidine protocol was a 7-day taper from 600 μg/d. 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 odansetron), 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 antiemetics was comparable between the 3 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 2 published case reports of topiramate treatment of benzodiazepine dependence and withdrawal exist in the literature. Cheseaux et al[71] describe a 41-year-old man with severe benzodiazepine dependence (intranasal midalzolam up to 90 mg/d 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 al[72] describe a 44-year-old woman with alprazolam dependence (using 5–6 mg/d for 7 years, with failed trials of long-acting benzodiazepines, lamotrigine, and SSRIs), co-occurring depression, anxiety, and histrionic traits who was able to reduce alprazolam use with topiramate. Every 10 days, 25 mg/d of topiramate was added while alprazolam was simultaneously reduced by 0.5 mg/d. 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 carbamazepine[73] in the treatment of benzodiazepine dependence must also be considered.

The Use of Topiramate for 3,4-Methylenedioxymethylamphetamine (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 Hampa[74] who report that topiramate 200 mg/d 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 pharmacologic 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 ceruleus,[71] would predict that topiramate might be particularly effective in the treatment of alcohol and benzodiazepine withdrawal. Moreover, topiramate, which is a nonaddictive 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 pathological 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 multisite RCT showing a significant positive effect.[49] In addition, 2 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 1 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 multisite RCT by Johnson et al,[49] there was a significantly higher dropout 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 al[75] examined the time course of adverse events associated with topiramate using pooled data from three 26-week double-blind, placebo-controlled multicenter studies of topiramate for the prevention of migraines at a dose of 100 mg/d, 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 3 antiglutamatergic agents suggests that topiramate is not superior to existing treatments (eg, 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, 1 pilot RCT and 1 open-label trial are promising but limited, and larger RCTs 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 2 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 methamphetamine[67] 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 SSRIs, 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 dependence[53] 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 1 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, comorbidities, 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[77] 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. Similarly, a recent genome-wide association study[78] identified multiple single nucleotide polymorphisms that were associated with the ability to successfully quit smoking using agents like bupropion and nicotine replacement therapy. 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 in 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 α4β2δ and α6β2δ 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 3 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, factor analyses, including analyses of genetic variants associated with response to topiramate, would be a valuable next step in research.

Drug names: acamprosate (Campral), alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), baclofen (Lioresal, Kemstro, and others), buprenorphine (Buprenex, Subutex, and others), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), clonidine (Catapres, Duraclon, and others), diazepam (Diastat, Valium, and others), disulfiram (Antabuse), ibuprofen (Caldolor, Ibu-tab, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), memantine (Namenda), methadone (Methadose, Dolophine, and others), methamphetamine (Desoxyn), metoclopramide (Reglan, Metozolv, and others), mirtazapine (Remeron and others), modafinil (Provigil), naltrexone (Vivitrol, ReVia, and others), olanzapine (Zyprexa), ondansetron (Zofran and others), piroxicam (Feldene and others), tizanidine (Zanaflex and others), topiramate (Topamax and others), trimipramine (Surmontil and others), varenicline (Chantix), zolpidem (Zolpimist, Ambien, and others), zopiclone (Lunesta).

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REFERENCES

1. Litten RZ, Fertig J, Mattson M, et al. Development of medications for alcohol use disorders: recent advances and ongoing challenges. *Expert Opin Emerg Drugs*. 2005;10(2):323–343.
2. Carroll KM, Nich C, Ball SA, et al. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*. 1998; 93(5):713–727.
3. Carroll KM, Nich C, Ball SA, et al. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction*. 2000;95(9):1335–1349.
4. George TP, Chawarski MC, Pakes J, et al. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol Psychiatry*. 2000;47(12):1080–1086.
5. Petrakis IL, Carroll KM, Nich C, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction*. 2000;95(2):219–228.
6. Carroll KM, Fenton LR, Ball SA, et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry*. 2004;61(3):264–272.
7. Baker JR, Jatlow P, McCance-Katz EF. Disulfiram effects on responses to intravenous cocaine administration. *Drug Alcohol Depend*. 2007; 87(2–3):202–209.
8. Grassi MC, Cioce AM, Giudici FD, et al. Short-term efficacy of Disulfiram or Naltrexone in reducing positive urinalysis for both cocaine and cocaethylene in cocaine abusers: a pilot study. *Pharmacol Res*. 2007;55(2):117–121.
9. Shoptaw S, Yang X, Rotheram-Fuller EJ, et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry*. 2003;64(12):1440–1448.
10. Dackis CA, Kampman KM, Lynch KG, et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology*. 2005;30(1):205–211.
11. Poling J, Oliveto A, Petry N, et al. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry*. 2006;63(2):219–228.
12. Schiffer WK, Gerasimov MR, Marsteller DA, et al. Topiramate selectively attenuates nicotine-induced increases in monoamine release. *Synapse*. 2001;42(3):196–198.
13. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. *J Affect Disord*. 1998;50(2-3):245–251.
14. Chengappa KN, Rathore D, Levine J, et al. Topiramate as add-on treatment for patients with bipolar mania. *Bipolar Disord*. 1999;1(1):42–53.
15. McElroy SL, Suppes T, Keck PE, et al. Open-label adjunctive topiramate in the treatment of bipolar disorders. *Biol Psychiatry*. 2000;47(12): 1025–1033.
16. Calabrese JR, Keck PE Jr, McElroy SL, et al. A pilot study of topiramate as monotherapy in the treatment of acute mania. *J Clin Psychopharmacol*. 2001;21(3):340–342.
17. Ghaemi SN, Manwani SG, Katzow JJ, et al. Topiramate treatment of bipolar spectrum disorders: a retrospective chart review. *Ann Clin Psychiatry*. 2001;13(4):185–189.
18. Grunze HCR, Normann C, Langosch J, et al. Antimanic efficacy of topiramate in 11 patients in an open trial with an on-off-on design. *J Clin Psychiatry*. 2001;62(6):464–468.
19. Bozikas VP, Petrikis P, Kourtis A, et al. Treatment of acute mania with topiramate in hospitalized patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(6):1203–1206.
20. DelBello MP, Kowatch RA, Warner J, et al. Adjunctive topiramate treatment for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2002;12(4):323–330.
21. McIntyre RS, Mancini DA, McCann S, et al. Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disord*. 2002;4(3):207–213.
22. Saxena S, Fieve R. Adjunctive open label topiramate in bipolar disorder. *Int J Neuropsychopharmacol*. 2002;6:56.
23. Vieta E, Torrent C, Garcia-Ribas G, et al. Use of topiramate in treatment-resistant bipolar spectrum disorders. *J Clin Psychopharmacol*. 2002;22(4):431–435.
24. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 2002;63(1):15–20.
25. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry*. 2004;4(1):24.
26. Tucker P, Trautman RP, Wyatt DB, et al. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(2):201–206.
27. Hoopes SP, Reimherr FW, Hedges DW, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, pt 1: improvement in binge and purge measures. *J Clin Psychiatry*. 2003;64(11):1335–1341.
28. Hedges DW, Reimherr FW, Hoopes SP, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, pt 2: improvement in psychiatric measures. *J Clin Psychiatry*. 2003;64(12):1449–1454.
29. Nickel C, Tritt K, Muehlbacher M, et al. Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord*. 2005;38(4):295–300.
30. Appolinario JC, Fontenelle LF, Papelbaum M, et al. Topiramate use in obese patients with binge eating disorder: an open study. *Can J Psychiatry*. 2002;47(3):271–273.
31. McElroy SL, Arnold LM, Shapira NA, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003;160(2):255–261.
32. McElroy SL, Shapira NA, Arnold LM, et al. Topiramate in the long-term treatment of binge-eating disorder associated with obesity. *J Clin Psychiatry*. 2004;65(11):1463–1469.
33. McElroy SL, Hudson JI, Capece JA, et al.Topiramate Binge Eating

Disorder Research Group. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry*. 2007;61(9):1039–1048.
34. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res*. 2003;11(6):722–733.
35. Astrup A, Caterson I, Zelissen P, et al. Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obesity (Silver Spring)*. 2004;12(10):1658–1669.
36. Wilding J, Van Gaal L, Rissanen A, et al. OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord*. 2004;28(11):1399–1410.
37. Tonstad S, Tykarski A, Weissgarten J, et al. Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Cardiol*. 2005;96(2):243–251.
38. Stenlöf K, Rössner S, Vercruysse F, et al. OBDM-003 Study Group. Topiramate in the treatment of obese subjects with drug-naive type 2 diabetes. *Diabetes Obes Metab*. 2007;9(3):360–368.
39. Toplak H, Hamann A, Moore R, et al. Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes (London)*. 2007;31(1):138–146.
40. Lin YH, Liu CY, Hsiao MC. Management of atypical antipsychotic-induced weight gain in schizophrenic patients with topiramate. *Psychiatry Clin Neurosci*. 2005;59(5):613–615.
41. Kim JH, Yim SJ, Nam JH. A 12-week, randomized, open-label, parallel-group trial of topiramate in limiting weight gain during olanzapine treatment in patients with schizophrenia. *Schizophr Res*. 2006;82(1):115–117.
42. Huguelet P, Morand-Collomb S. Effect of topiramate augmentation on two patients suffering from schizophrenia or bipolar disorder with comorbid alcohol abuse. *Pharmacol Res*. 2005;52(5):392–394.
43. Chiu Y-H, Lee T-H, Shen WW. Use of low-dose topiramate in substance use disorder and bodyweight control. *Psychiatry Clin Neurosci*. 2007;61(6):630–633.
44. Rubio G, Ponce G, Jiménez-Arriero MA, et al. Effects of topiramate in the treatment of alcohol dependence. *Pharmacopsychiatry*. 2004;37(1):37–40.
45. Fernandez Miranda JJ, Marina González PA, Montes Pérez M, et al. Topiramate as add-on therapy in non-respondent alcohol dependant patients: a 12 month follow-up study. *Actas Esp Psiquiatr*. 2007;35(4):236–242.
46. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*. 2003;361(9370):1677–1685.
47. Johnson BA, Ait-Daoud N, Akhtar FZ, et al. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. *Arch Gen Psychiatry*. 2004;61(9):905–912.
48. Ma JZ, Ait-Daoud N, Johnson BA. Topiramate reduces the harm of excessive drinking: implications for public health and primary care. *Addiction*. 2006;101(11):1561–1568.
49. Johnson BA, Rosenthal N, Capece JA, et al.Topiramate for Alcoholism Study Group. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA*. 2007;298(14):1641–1651.
50. De Sousa AA, De Sousa J, Kapoor H. An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *J Subst Abuse Treat*. 2008;34(4):460–463.
51. Flórez G, García-Portilla P, Álvarez S, et al. Using topiramate or naltrexone for the treatment of alcohol-dependent patients. *Alcohol Clin Exp Res*. 2008;32(7):1251–1259.
52. Baltieri DA, Daró FR, Ribeiro PL, et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction*. 2008;103(12):2035–2044.
53. Miranda R Jr, MacKillop J, Monti PM, et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. *Alcohol Clin Exp Res*. 2008;32(3):489–497.
54. Cagetti E, Baicy KJ, Olsen RW. Topiramate attenuates withdrawal signs after chronic intermittent ethanol in rats. *Neuroreport*. 2004;15(1):207–210.
55. Farook JM, Morrell DJ, Lewis B, et al. Topiramate (Topamax) reduces conditioned abstinence behaviours and handling-induced convulsions (HIC) after chronic administration of alcohol in Swiss-Webster mice. *Alcohol Alcohol*. 2007;42(4):296–300.
56. Rustembegovic A, Sofic E, Kroyer G. A pilot study of Topiramate (Topamax) in the treatment of tonic-clonic seizures of alcohol withdrawal syndromes. *Med Arh*. 2002;56(4):211–212.
57. Krupitsky EM, Rudenko AA, Burakov AM, et al. Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. *Alcohol Clin Exp Res*. 2007;31(4):604–611.
58. Arbaizar B, Gómez-Acebo I, Llorca J. Decrease in tobacco consumption after treatment with topiramate and aripiprazole: a case report. *J Med Case Reports*. 2008;2(1):198.
59. Khazaal Y, Cornuz J, Bilancioni R, et al. Topiramate for smoking cessation. *Psychiatry Clin Neurosci*. 2006;60(3):384–388.
60. Johnson BA, Ait-Daoud N, Akhtar FZ, et al. Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial. *Arch Intern Med*. 2005;165(14):1600–1605.
61. Sofuoglu M, Poling J, Mouratidis M, et al. Effects of topiramate in combination with intravenous nicotine in overnight abstinent smokers. *Psychopharmacology (Berl)*. 2006;184(3–4):645–651.
62. Reid MS, Palamar J, Raghavan S, et al. Effects of topiramate on cue-induced cigarette craving and the response to a smoked cigarette in briefly abstinent smokers. *Psychopharmacology (Berl)*. 2007;192(1):147–158.
63. Anthenelli RM, Blom TJ, McElroy SL, et al. Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation. *Addiction*. 2008;103(4):687–694.
64. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2004;75(3):233–240.
65. Reis AD, Castro LA, Faria R, et al. Craving decrease with topiramate in outpatient treatment for cocaine dependence: an open label trial. *Rev Bras Psiquiatr*. 2008;30(2):132–135.
66. Tatsuta T, Kitanaka N, Kitanaka J, et al. Lack of effect of anticonvulsant topiramate on methamphetamine-induced stereotypy and rewarding property in mice. *Pharmacol Biochem Behav*. 2007;87(1):48–55.
67. Johnson BA, Roache JD, Ait-Daoud N, et al. Effects of acute topiramate dosing on methamphetamine-induced subjective mood. *Int J Neuropsychopharmacol*. 2007;10(1):85–98.
68. Johnson BA, Roache JD, Ait-Daoud N, et al. Effects of topiramate on methamphetamine-induced changes in attentional and perceptual-motor skills of cognition in recently abstinent methamphetamine-dependent individuals. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(1):123–130.
69. Zullino DF, Cottier A-C, Besson J. Topiramate in opiate withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(6):1221–1223.
70. Zullino DF, Krenz S, Zimmerman G, et al. Topiramate in opiate withdrawal-comparison with clonidine and with carbamazepine/mianserin. *Subst Abus*. 2004;25(4):27–33.
71. Cheseaux M, Monnat M, Zullino DF. Topiramate in benzodiazepine withdrawal. *Human Psychopharmacology: Clinical & Experimental*. 2003;18(5):375–377.
72. Michopoulos I, Douzenis A, Christodoulou C, et al. Topiramate use in alprazolam addiction. *World J Biol Psychiatry*. 2006;7(4):265–267.
73. Pages KP, Ries RK. Use of anticonvulsants in benzodiazepine withdrawal. *Am J Addict*. 1998;7(3):198–204.
74. Akhondzadeh S, Hampa AD. Topiramate prevents ecstasy consumption: a case report. *Fundam Clin Pharmacol*. 2005;19(5):601–602.
75. Láinez MJA, Freitag FG, Pfeil J, et al. Time course of adverse events most commonly associated with topiramate for migraine prevention. *Eur J Neurol*. 2007;14(8):900–906.
76. Rogawski MA. Update on the neurobiology of alcohol withdrawal seizures. *Epilepsy Curr*. 2005;5(6):225–230.
77. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch Gen Psychiatry*. 2008;65(2):135–144.
78. Uhl GR, Liu Q-R, Drgon T, et al. Molecular genetics of successful smoking cessation: convergent genome-wide association study results. *Arch Gen Psychiatry*. 2008;65(6):683–693.

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