

Topiramate for Alcohol Dependence

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Request

Is topiramate effective for the treatment of alcohol dependence?

Response

BACKGROUND

Alcohol dependence is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition–text revision, (DSM-IV-TR) as a condition in which at least 3 of the following 7 criteria are present within a 12-month time period: tolerance to alcohol effects, withdrawal symptoms upon stopping alcohol consumption, impaired control, drinking more or longer than intended, neglect of activities, increased time spent drinking or recovering from drinking, or continued use despite recurrent psychological or physical problems.¹ Worldwide, more than 76 million people suffer from alcohol dependence; nearly 8 million of these persons are Americans.² Alcohol dependence is reported to be the third leading preventable cause of death in the US, which results in significant morbidity and approximately 85,000 deaths annually.^{3–6} Because of inadequate screen-

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OBJECTIVE: To evaluate the evidence for the use of topiramate for alcohol dependence.

DATA SOURCES: MEDLINE (1966–June 2008) and Cochrane Database (2008, Issue 1) searches were conducted using the search terms alcohol dependence and topiramate. Bibliographies of selected articles were examined for additional data sources.

STUDY SELECTION AND DATA EXTRACTION: English-language, randomized, controlled trials evaluating topiramate for treatment of alcohol dependence in humans were selected for review. Three randomized controlled trials and 2 re-analyses were identified. Findings pertaining to efficacy and safety were extracted.

DATA SYNTHESIS: Evidence suggests that topiramate antagonizes excitatory glutamate receptors, inhibits dopamine release, and enhances inhibitory γ -aminobutyric acid function. These mechanisms may be significant in the treatment of alcohol dependence. Controlled trials have described the use of topiramate, titrated up to 300 mg daily, for alcohol dependence, and have reported decreases in drinking behavior and improvements in quality of life. Adverse effects associated with topiramate included abnormal skin sensation, dizziness, taste perversion, anorexia, pruritus, and difficulty with memory and concentration. In one of the reviewed trials, adverse effects did not account for an increased withdrawal rate. However, in another, when topiramate was titrated over a shortened time period, an increased withdrawal rate was seen. Recently, topiramate has been reported to increase suicide risk, primarily in patients with epilepsy. No cases of suicide were recorded in the alcohol dependence trials.

CONCLUSIONS: Results of published trials are promising, showing efficacy for drinking outcomes and quality of life as well as general safety. However, additional larger, longer-term trials are needed to establish the optimal patient type that would benefit most from topiramate treatment in addition to dosing, duration of treatment, and tolerability of topiramate for alcohol dependence. At this time, data are insufficient to support using topiramate in conjunction with brief weekly compliance counseling as a first-line agent for alcohol dependence.

KEY WORDS: alcohol dependence, topiramate.

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ing and discrepancies in self-reported use, alcohol dependence is often underdiagnosed and untreated. In 2004, the Substance Abuse and Mental Health Services Administration reported that only 30% of affected individuals receive treatment for alcohol dependence.⁷

It has been suggested that alcohol dependence is caused by alcohol's effects on inhibitory and excitatory neuronal pathways including γ -aminobutyric acid (GABA) and glutamate, respectively.^{8,9} Over time, alcohol alters pathway receptor expression, leading to tolerance and potential central nervous system injury.⁸ Additionally, endogenous dopamine mediates craving and reward in alcoholics; therefore, drugs targeting this neurotransmitter have been investigated to decrease alcohol dependence.¹⁰

Although abstinence is the ultimate outcome when treating alcohol dependence, goals such as decreasing the incidence, shortening the course, reducing episode severity, and preventing relapse are essential. Recently, reduction in the frequency of heavy drinking was recognized as the major factor for lessening disease burden and improving quality of life.¹¹ Traditionally, the most recognized strategy in the US for treating alcohol dependence consists of specialty treatment programs using psychosocial therapy.¹² Over the past decade, the treatment of alcohol dependence has seen the integration of medications and treatment in primary care settings.¹³

Medications currently approved by the Food and Drug Administration for alcohol dependence include disulfiram (aldehyde dehydrogenase blocker), naltrexone (opioid antagonist), and acamprosate (functional glutamate antagonist).¹⁴⁻¹⁶ With different mechanisms of action, each drug may benefit different subgroups of patients.^{17,18} While these agents are effective in a heterogeneous alcohol-dependent population, limited efficacy has been reported. A meta-analysis of disulfiram revealed limited and largely negative documentation for its efficacy in treating alcohol dependence, with no effect on alcohol craving.¹⁹

Naltrexone and acamprosate have shown efficacy in several trials and meta-analyses in improving rates of continuous abstinence and preventing relapse to heavy drinking; however, conflicting data and a small effect size exist for both agents.¹⁹⁻²³ The effectiveness of these medications may be limited by decreased adherence due to poor tolerability of adverse effects (ie, fatigue, impotence, headache, nausea, vomiting, liver enzyme abnormalities, diarrhea, insomnia, anxiety, psychotic reactions, depression, suicide) and frequent dosing regimens. Variable adherence rates for disulfiram (18.2–61%),^{14,24} oral naltrexone (24–95%),^{25,26} and acamprosate (30–84.2%)^{27,28} have been reported. Together, these limitations often translate into treatment failure and poor outcomes; therefore, other medications for alcohol dependence are needed.

Data²⁹⁻³³ suggest that topiramate, an anticonvulsant also approved for migraine prevention,³⁴ may be effective for

treating alcohol dependence. Proposed mechanisms for its effectiveness involve the dopamine pathways that are responsible for the rewarding and craving components of alcohol dependence.^{35,36} These mechanisms include antagonizing excitatory glutamate receptors and inhibiting dopamine release within the mesocorticolimbic system while enhancing inhibitory GABA.³⁶

LITERATURE REVIEW

Researchers have evaluated the efficacy of topiramate for alcohol dependence in randomized controlled trials. MEDLINE (1966–June 2008) and Cochrane Database (2008, Issue 1) searches were conducted, with English language and human studies as set limits. Search terms included alcohol dependence and topiramate. Bibliographies of selected articles were examined for additional sources. Three randomized controlled trials and 2 reanalyses were identified and are summarized below.

Johnson et al.²⁹ published the first double-blind, randomized, controlled 12-week trial evaluating topiramate for alcohol dependence. Enrolled individuals ($n = 150$) with DSM-IV–diagnosed alcohol dependence had self-reported drinking behavior that consisted of drinking a mean of at least 35 and 21 standardized drinks weekly for men and women, respectively. Abstinence was not required at enrollment. Participants received twice-daily doses of topiramate (titrated upwards to 300 mg daily, reached at week 8) or placebo and weekly brief standardized medication adherence management (a standard minimum psychosocial adherence enhancement emphasizing medication adherence as key to changing drinking behavior). Primary endpoints were self-reported drinking that included drinks per day, drinks per drinking day, percentage of heavy drinking days (defined as ≥ 5 drinks daily for men and ≥ 4 drinks daily for women), percentage of days abstinent, and plasma γ -glutamyl transferase levels (an objective index for true alcohol consumption) measured at weeks 3, 6, 9, and 12. The secondary outcome was self-reported craving.

At week 12, topiramate-treated individuals had consumed 2.88 fewer drinks per day (95% CI -4.50 to -1.27 ; $p = 0.0006$) and 3.10 fewer drinks per drinking day (95% CI -4.88 to -1.31 ; $p = 0.0009$), as well as a 27.6% reduction in heavy drinking days ($p = 0.0003$), a 26.2% increase in abstinent days ($p = 0.0003$), and a reduction in log plasma γ -glutamyl transferase ratio (0.07 reduction, 95% CI -0.11 to -0.02 ; $p = 0.0046$) compared with placebo. Self-reported craving decreased in topiramate-treated individuals and was highly correlated with primary endpoint findings. Adverse effects reported with greater frequency with topiramate versus placebo included dizziness (28.0% vs 10.7%; $p = 0.007$), abnormal skin sensations (57.3% vs 18.7%; $p < 0.0001$), psychomotor slowing (26.7% vs 12.0%; $p = 0.023$), memory or concentration impairment

(18.7% vs 5.3%; $p = 0.012$), and weight loss (54.7% vs 26.7%; $p = 0.001$); however, the withdrawal rate was similar between groups. A medication adherence rate of 80% or more was reported for both groups. These results suggest that topiramate, when used with standardized medication adherence management, has a positive effect on drinking outcomes. Although not detailed for individual subjects, the impact of the raw number for reductions in drinking measure outcomes suggest clinical implications, as men and women had consumed at least a mean of 35 and 21 standard drinks per week, respectively. Additionally, almost a 30% reduction in the number of heavy drinking days was realized. The study duration was only 12 weeks; however, topiramate's efficacy steadily increased to study end. Unfortunately, follow-up to determine whether a plateau or reduction in efficacy occurs with time was not performed. Recruitment by newspaper or radio advertisements and exclusion of those with a current Axis I psychiatric diagnosis (other than alcohol or nicotine dependence) suggest that subjects may have been relatively healthy, thus limiting external validity. Other limitations include a modest sample size, pill count adherence assessment, and use of self-reported drinking endpoints; however, plasma γ -glutamyl transferase level was a confirmatory endpoint.²⁹

Investigators from the initial trial used exactly the same methods and subjects enrolled in the initial trial to further evaluate topiramate's efficacy for alcohol dependence.³⁰ Primary outcomes, measured by validated scales, included overall well-being and severity of alcohol-dependence, quality of life, and harmful drinking consequences. When topiramate-treated individuals were compared with those receiving placebo, improvements in overall well-being (OR 2.17; 95% CI 1.16 to 2.60; $p = 0.01$), abstinence and nonseeking behavior (OR 2.63; 95% CI 1.52 to 4.53; $p = 0.001$), and increased quality of life (OR 2.28; 95% CI 1.21 to 4.29; $p = 0.01$) were reported. Additionally, reductions in harmful drinking consequences were reported in topiramate-treated subjects (OR -0.07; 95% CI -0.12 to -0.02; $p = 0.01$). These findings indicate that topiramate, when used with additional medication adherence enhancement, improved drinking outcomes as well as psychosocial elements. Since the same methods and group of subjects were used in this trial, many of the limitations are the same as in the previous trial. Posttreatment follow-up was not provided; thus, it is unknown whether psychosocial improvements are sustained. In this study, a correlation between psychosocial functioning and heavy drinking was not examined; therefore, it is not possible to predict whether the relationship between these 2 factors is one of cause and effect. Additionally, because an optimal control group (ie, those who would have received adherence enhancement interventions without adjunctive placebo) was not used, it is difficult to isolate effects of topiramate alone.

Not all alcohol-dependent patients achieve abstinence; thus, it is important to know whether "safe" drinking levels can be realized. Johnson et al. performed a secondary analysis of their initial data^{29,30} to determine whether self-reported continuous safe levels of drinking (defined as ≤ 2 standard drinks daily for men or ≤ 1 for women) could be achieved.³¹ The mean longest safe drinking time period reported for topiramate-treated and placebo-treated individuals was 16.7 and 8.9 days, respectively. Additionally, by day 50, periods of 1 week or more and 2 weeks or more of continuous safe drinking were achieved more often by topiramate-treated subjects than by those receiving placebo (1 wk: 44% vs 26.4%; 2 wk: 30.8% vs 10%, respectively). It was concluded that topiramate, when coupled with an abstinence-oriented treatment program, promotes safe drinking in alcohol-dependent individuals. The safe drinking definition used in this study was established by the National Institute on Alcohol Abuse and Alcoholism,³⁷ although this definition can vary between authorities and countries. As this was a secondary analysis of previously conducted trials, results should be interpreted with caution.

In response to earlier data, Johnson et al.³² conducted a multicenter, double-blind, placebo-controlled, 14-week trial to evaluate the efficacy of topiramate in 371 DSM-IV diagnosed alcohol-dependent individuals who drank 35 or more drinks/week (men) and 28 or more drinks/week (women). Although all participants were drinking at study entry, they had to convey an interest in decreasing alcohol consumption in order to be enrolled. Subjects received escalating doses of topiramate (≤ 300 mg/day, reached by week 6) or placebo and weekly manual-guided brief behavioral adherence enhancement treatment. The primary endpoint was self-reported percentage of heavy drinking days (the number of days that ≥ 5 standard drinks/day for men and ≥ 4 standard drinks/day for women were consumed, divided by the number of study days). Other outcomes included percentage of abstinent days, drinks per drinking day, and plasma γ -glutamyl transferase levels.

A reduction in the percentage of heavy drinking days from baseline was found at week 14 when topiramate-treated subjects were compared with those receiving placebo (mean difference 8.44%; 95% CI 3.07% to 13.8%; $p = 0.022$). Moreover, differences in secondary outcomes were detected when topiramate-treated subjects were compared with those receiving placebo ($p < 0.001$ for all comparisons). Adverse events more common with topiramate than placebo included abnormal skin sensation (50.8% vs 10.6%; $p < 0.001$), taste perversion (23.0% vs 4.8%; $p < 0.001$), anorexia (19.7% vs 6.9%; $p < 0.001$), pruritus (10.4% vs 1.1%; $p < 0.001$), and difficulty concentrating (14.8% vs 3.2%; $p < 0.001$). The withdrawal rate attributed to adverse events was significantly greater for topiramate-treated participants than for those receiving placebo

(18.6% vs 4.3%, respectively; $p < 0.001$). Medication adherence rates were high and similar between groups (mean \pm SD $91.46 \pm 14.96\%$ for topiramate, $90.09 \pm 13.12\%$ for placebo). Limitations of this trial include short-term duration without a follow-up period, relatively healthy participants, and an increased incidence of topiramate adverse effects, possibly from a shorter titration period.³²

A secondary analysis of the previously described study evaluated topiramate's effects on physical and psychosocial health.³³ Physical health was gauged by the following primary outcomes: liver function test results, plasma cholesterol levels, plasma bicarbonate levels, urine pH levels, blood pressure, heart rate, temperature, and body mass index. Validated scoring systems were used to define outcomes of psychosocial health, including thoughts of obsession and compulsions, overall clinical improvement, harmful consequences of drinking, quality of life, general mood, and sleep quality. Overall, topiramate had predominantly positive effects on physical health, including a significant decrease in plasma aspartate aminotransferase ($p = 0.001$), alanine aminotransferase ($p < 0.001$), plasma γ -glutamyl transferase ratio ($p < 0.001$), bicarbonate ($p < 0.001$), total cholesterol ($p = 0.002$), and urine pH ($p = 0.01$). Notably, both diastolic and systolic blood pressure were significantly decreased ($p < 0.001$). It may be theorized that these positive effects decrease the progression of cirrhosis and cardiovascular disease.

While general mood and alcohol withdrawal symptoms were not significantly improved ($p = 0.63$ and $p = 0.94$, respectively), topiramate led to multiple psychosocial improvements, including decreases in obsessional thoughts ($p < 0.001$) and harmful consequences of drinking ($p < 0.001$), along with overall clinical improvement ($p < 0.001$). Additionally, improvements in quality of life ($p = 0.04$), leisure time activities ($p = 0.03$), and household duties ($p = 0.02$) were reported. Sleep disturbances were not significantly decreased until week 14 ($p = 0.004$). Because the same methods and group of subjects were used in this trial as in the previously described trial, the limitations are similar. Also, because this is a secondary analysis, these results should be interpreted carefully.³³

Discussion

Alcohol dependence is a heterogeneous, complex disorder; therefore, multiple treatment approaches are needed.^{1,8,9} Topiramate's mechanism appears to involve dopamine pathways that are responsible for reward and craving, which is a different mechanism of action from those of medications currently approved for alcohol dependence.¹⁴⁻¹⁶ Although results of the summarized studies²⁹⁻³³ demonstrate topiramate's efficacy for treatment of alcohol dependence, several questions remain unanswered. Due to exclusion criteria and recruitment strategies, evaluated

subjects may have been healthier and more homogenous than the general alcohol-dependent population. Unlike the topiramate trials discussed, most other trials evaluating medications for alcohol dependence required initial abstinence so that the medications' effectiveness to prevent relapse could be measured.³⁸ The lack of need for initial abstinence in topiramate trials could become an important factor in primary care settings, since it suggests that topiramate could be offered earlier than other medications for alcohol abstinence. Trial endpoints, although self-reported, did have an objective confirmatory measure (plasma γ -glutamyl transferase levels) and consisted of clinical outcomes and goals that are considered measures for lessening disease burden and improving quality of life.¹² Medication adherence rates for the topiramate studies were approximately 80–91%, which are higher than those reported with disulfiram^{14,24} but similar to those reported in trials for oral naltrexone and acamprosate.²⁵⁻²⁸ The summarized trials²⁹⁻³³ were short-term (12–14 wk) without follow-up; therefore, long-term efficacy (eg, 1-y relapse rates) is unknown. It has been reported that approximately 70% of alcohol-dependent individuals will relapse within one year without a medication adjunct to psychosocial therapy.³⁹ Recently, topiramate—similar to naltrexone and acamprosate—has been reported to increase suicide risk, primarily in patients with epilepsy³⁴; however, no cases of suicide were recorded in the trials summarized in this article. In the multicenter trial,³² subjects attempting suicide or with suicidal ideation 30 days before week 0 were excluded. A meta-analysis of the data evaluating topiramate for alcohol dependence has not been conducted, nor has topiramate been compared with other medications approved for alcohol dependence; thus, conclusions cannot be drawn regarding effectiveness between agents. Nonetheless, it has been suggested that topiramate has a medium therapeutic effect size compared with oral naltrexone and acamprosate, which have reported small effect sizes.¹⁹ Collectively, possible benefits of topiramate over the other agents include multiple effects (ie, psychosocial, drinking outcomes, cravings), with a medium effect size and early therapy initiation.

Summary

Currently, evidence to support the use of topiramate in conjunction with brief weekly adherence counseling as first-line treatment for alcohol dependence is insufficient. Results of published trials are promising, showing efficacy for drinking outcomes and quality of life as well as general safety, but larger, longer-term trials are needed to establish the optimal patient type that would benefit most from topiramate treatment in addition to dosing, duration of treatment, and tolerability of topiramate for alcohol dependence.

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Topiramato en la Dependencia Alcohólica

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EXTRACTO

OBJETIVO: Evaluar la evidencia sobre el uso de topiramato en el tratamiento de la dependencia alcohólica.

FUENTES DE DATOS: Se realizaron búsquedas en MEDLINE (1966–junio 2008) y la base de datos Cochrane (2008, Número 1) con los términos de búsqueda “alcohol dependence” y “topiramate”. Para localizar fuentes de datos adicionales se examinaron las bibliografías de los artículos seleccionados.

SELECCIÓN DE LOS ESTUDIOS Y EXTRACCIÓN DE DATOS: Se seleccionaron para revisión los ensayos clínicos controlados, aleatorios, publicados en inglés, que evaluaban el uso de topiramato en dependencia alcohólica. Se identificaron 3 ensayos clínicos controlados aleatorios y se extrajeron los datos sobre eficacia y seguridad.

SÍNTESIS DE DATOS: La evidencia sugiere que el topiramato antagoniza los receptores de glutamato, inhibe la liberación de dopamina, y aumenta la función inhibitoria del ácido gamma-amino-butírico. Estos mecanismos pueden estar implicados en el tratamiento de la dependencia alcohólica. Se han realizado ensayos clínicos controlados sobre el uso de topiramato (hasta 300 mg/día) en la dependencia alcohólica que han presentado disminuciones en la ingesta de alcohol y mejoras en la calidad de vida (QOL). Los efectos adversos asociados con topiramato incluyen: sensaciones cutáneas anormales, mareos, alteraciones del gusto, anorexia, prurito, y dificultades de memoria y concentración. En 3 de los 4 ensayos estos efectos no influyeron en las tasas de abandono de los sujetos. Sin embargo, en un ensayo se detectó un incremento de la tasa de abandono cuando el topiramato se administró durante un período de tiempo reducido. Se ha notificado recientemente que el topiramato aumenta el riesgo de suicidio en pacientes con epilepsia. No se detectaron casos de suicidio en los ensayos realizados sobre su uso en dependencia alcohólica.

CONCLUSIONES: Los resultados de los ensayos publicados son prometedores y muestran eficacia en el consumo de alcohol y en QOL, así como bastante seguridad en su uso, pero se precisan ensayos más amplios y prolongados para establecer el paciente tipo, la dosificación y duración de tratamiento óptimos y la tolerabilidad del topiramato en el tratamiento de la dependencia alcohólica. Por el momento los datos que respaldan su uso, en combinación con orientaciones semanales breves sobre la adherencia, como tratamiento de primera línea en la dependencia alcohólica son insuficientes.

Traducido por Juan del Arco

Le Topiramate est-il Efficace pour Traiter la Dépendance à l’Alcool?

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RÉSUMÉ

OBJECTIF: Évaluer les évidences reliées à l’utilisation du topiramate dans le traitement de la dépendance à l’alcool.

SOURCES DES DONNÉES: Des recherches des bases de données MEDLINE (1966–juin 2008) et Cochrane (2008, numéro 1) ont été effectuées. Les mots clés utilisés pour la recherche étaient alcohol dependence et topiramate. Les bibliographies des articles retenus ont aussi été consultées pour identifier des sources de données additionnelles.

SÉLECTION DES ÉTUDES ET EXTRACCIÓN DES DONNÉES: Les études, publiées en anglais, randomisées contrôlées et évaluant le topiramate pour traiter la dépendance à l’alcool chez l’humain, ont été retenues pour évaluation. Trois études randomisées contrôlées ainsi que 2 analyses secondaires de ces études ont été retenues pour évaluation. Les données reliées à l’efficacité et l’innocuité ont été extraites de ces études.

SYNTHÈSE DES DONNÉES: Des évidences suggèrent que le topiramate exerce un effet antagoniste au niveau des récepteurs excitateurs du glutamate, inhibe la libération de dopamine et augmente les effets inhibiteurs de l’acide gamma-amino-butyrique. Ces effets pourraient être utiles pour le traitement de la dépendance à l’alcool. Des études contrôlées ont décrit l’utilisation du topiramate (titré jusqu’à 300 mg/jour) pour diminuer les comportements de dépendance à l’alcool et ont rapporté une diminution de la consommation d’alcool ainsi qu’une amélioration de la qualité de vie (QOL). Les effets indésirables associés au topiramate incluaient des sensations cutanées anormales, des étourdissements, une altération du goût, de l’anorexie, du prurit, ainsi que des troubles de concentration, et de mémoire. Dans 3 des 4 études ces effets indésirables n’ont pas été associés avec une augmentation du taux d’abandon de l’étude. Toutefois, une augmentation du taux d’abandon a été observée dans une étude où le topiramate était titré rapidement sur une courte période. Une augmentation du risque suicidaire associée au topiramate, principalement chez les patients épileptiques, a été rapportée récemment. Aucun cas de suicide n’a été observé dans les études du topiramate pour diminuer la dépendance à l’alcool.

CONCLUSIONS: Les résultats des études publiées sont prometteurs. Ces études ont montré l’efficacité du topiramate pour diminuer la consommation d’alcool et améliorer la qualité de vie ainsi que la sécurité de cet anticonvulsivant. Des études de plus grande taille et à plus long terme sont toutefois nécessaires pour définir le type de patient pouvant bénéficier du topiramate ainsi que préciser les doses optimales, la durée de traitement et la tolérabilité du topiramate pour le traitement de la dépendance à l’alcool. Dans l’état actuel des connaissances, les données sont insuffisantes pour supporter l’utilisation du topiramate en association avec un counselling hebdomadaire comme première ligne de traitement de la dépendance à l’alcool.

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