

Topiramate Treatment of Alcohol Use Disorder in Clinical Practice

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Topiramate is an anticonvulsant medication with increasingly strong evidence, supporting its use for treating alcohol use disorder (AUD) based on clinical trials. These clinical cases summarize the initiation and titration of topiramate in AUD treatment. The core issues of patient selection, consideration of comorbid psychiatric and medical conditions, side-effect profile, safety and effectiveness are reviewed. Addiction physicians should take a leading role in using topiramate to treat AUDs, working with patients to balance the benefits of topiramate with the risk.

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

(*J Addict Med* 2018;xx: xxx–xxx)

CASE DESCRIPTIONS

Case 1

Our first case is a 56-year-old African American male with a 35-year history of alcohol use, hypertension, and a recent diagnosis of hepatitis C. He started drinking alcohol at age 21 while serving in the Army. He began with heavy drinking episodes on weekends, but his drinking escalated after discharge from the Army. In his mid to late 20s, he drank up to 1 pint of vodka and 12 beers daily. He had lost many jobs due to excessive absence related to his alcohol use. As part of the antiviral treatment evaluation for hepatitis C, the patient was referred for addiction treatment, and was required to complete 3 months of treatment before beginning antiviral therapy.

Initially, he reported alcohol intake of 12 to 16 beers daily. He described themes of loss of control, cravings, disrupted relationships, and irritable mood related to his alcohol use. He had tried disulfiram in the past, but reported nonadherence after 1 week. Additionally, he had gone through

a 12-week trial of naltrexone (up to 100 mg daily dose) without effect, though with poor adherence. He did not have co-occurring psychiatric conditions.

He was started on a dose of 25 mg topiramate daily which was titrated to twice daily after 1 week. He reported no significant side effects after 2 weeks. He was titrated to 50 mg bid after 4 weeks, and reported some mild cognitive side effects. He reported that his alcohol intake was reduced to 6 to 8 beers daily. Urine ethyl glucuronide testing (EtG) weekly suggested reduced drinking, though it remained indicative of continued alcohol use. Due to cognitive complaints, the dose was held at 50 mg twice daily.

After 4 weeks, his cognitive complaints abated. He continued to drink >8 beers daily. His hepatitis C treatment was delayed due to continued alcohol use. His laboratory studies, including urine EtG and serum gamma glutamyl transferase (GGT), demonstrated continued substantial alcohol intake. At the 4-week mark, we increased the dose to 50 mg in the morning and 75 mg at bedtime for 2 weeks, then increased again to 75 mg twice daily for 2 weeks. No further side effects or complaints were reported. At week 8, he reported a reduction of alcohol intake to 4 beers daily. He had no further cognitive complaints or other side effects. Urine EtGs and blood GGTS were trending down weekly.

At 12 weeks, patient was tolerating 100 mg of topiramate twice daily. He continued to report a lower level of drinking and a reduced craving to drink. His side-effect profile remained low, with little to no complaints of cognitive dulling. Urine EtGs and blood GGT testing within the past 8 weeks demonstrated a reduced amount of alcohol intake. EtG level at week 12 was 980 ng/mL, which reduced from 1290 ng/mL at week 8. Serum GGT was 50 IU/L at week 12 (within normal limits for the assay at the laboratory), and reduced from 195 IU/L at the date of topiramate initiation.

Case 2

A 52-year-old European American military veteran male, with a history of opioid use disorder (OUD), alcohol use disorder (AUD), and major depressive disorder, who was in remission from both substance use disorders after 1.5 years of treatment with buprenorphine and an antidepressant. He had been abstinent on acamprosate for almost a year, but had discontinued it. There was a question of a slight relapse to alcohol after that, though the patient denied it, and increased frequency of monitoring with EtG rapidly returned the measurement to zero levels. After another 5 months of therapy with no relapse to opioids or alcohol, he desired taper and

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Received for publication January 4, 2016; Revised September 8, 2016 accepted September 11, 2016.

The authors disclose no conflicts of interest.

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ISSN: 1932-0620/16/0000-0001

DOI: 10.1097/ADM.0000000000000444

discontinuation from buprenorphine. He then started experiencing alcohol craving while decreasing the dose of buprenorphine gradually. He was restarted on acamprosate 666 mg, 3 times daily, and the tapering dose of buprenorphine was held constant at 8 mg daily. However, the patient continued to have alcohol cravings 1 month after.

As the patient was still requesting a taper off of buprenorphine, topiramate was added to the regimen for eventual cross-taper with acamprosate. Topiramate was titrated to 200 mg daily over about 5 weeks, and the patient reported no side effects. The patient noted elimination of alcohol cravings with titration of the topiramate, had no relapse to alcohol, and was able to resume tapering of buprenorphine. EtGs were negative (at zero), and though there was an elevated GGT and slight elevation of both AST and ALT, this was attributed to his history of fatty liver and overweight, as the EtG and overall clinical picture were consistent with abstinence.

Case 3

A 55-year-old postmenopausal female, college-educated, homemaker, mother of 2 sons (teenager and young adult), had a 20-year history of AUD, generalized anxiety disorder (GAD), and hypothyroidism. The patient had a history of good response to low-dose topiramate (<100 mg daily), initially prescribed about 18 years ago during her first treatment attempts. It is reported by the patient that she then had a 5-year period of sobriety while on topiramate, combined with regular attendance of AA meetings.

The patient has had numerous relapses over the years and had been on topiramate several times. Notably, she reports doing well on the medication, but would often stop taking it and eventually relapse to alcohol. She described marital and family stressors to almost always be the trigger for relapse. She had been to residential rehab facilities and detoxification several times. She had tried naltrexone once for a few weeks, but it made her feel sedated and “clumsy,” so she stopped it. Possibly naltrexone was helpful in treating her alcohol use though as she reports being sober during that time.

The patient was referred to an addiction treatment clinic after a recent 14-day relapse to heavy daily drinking that required detoxification, followed by a 30-day residential rehabilitation program. She presented with a treatment goal of abstinence from alcohol. She was discharged from the rehab program on 380 mg of IM naltrexone every 4 weeks, topiramate 100 mg daily, gabapentin 300 mg 3 times a day, venlafaxine, and weekly sessions of psychotherapy. She was interested in getting back into 12-step programming. Marital and family stressors remained very high.

We continued her on IM naltrexone (with a plan to discontinue after about 9 months), and increased the topiramate to 200 mg daily, discontinuing eventually the gabapentin. With the topiramate at a moderate dose (200 mg daily), she had no side effects and stated she had no alcohol craving, “I don’t even think about alcohol anymore.” She was sober for 8 weeks on that regimen with negative EtG and daily electronic breathalyzer monitoring (via the Soberlink system). Weeks later, family stressors increased abruptly again; however, this time, instead of discontinuing therapy and returning

to drinking, the patient pre-emptively checked herself back into residential substance use rehabilitation for a short stay (2 weeks). She remained sober with confirmed biomarker testing (EtG and GGT) another month later. After several months, the naltrexone was discontinued and she remained sober at 2 months after that while on just the topiramate, which is the last biomarker testing point.

DISCUSSION

Topiramate is an anticonvulsant medication with strong evidence supporting its use for treating AUD based on clinical trials. It is perhaps the most promising medication tested for that purpose to date. Topiramate is known to act via multiple pharmacologic mechanisms including GABA-A receptor modulation and glutamate receptor blockade (Johnson and Ait-Daoud, 2010). Topiramate is hypothesized to reduce drinking by attenuating positive reinforcement from alcohol (Johnson et al., 2007) and possibly also by reducing alcohol craving. In addition, a recent study suggests that the medication works by increasing a person’s self-efficacy for resisting heavy drinking (Kranzler et al., 2014) (see the accompanying review by Manhapra et al. in this issue for additional information on mechanism of action).

In 1 randomized controlled trial, topiramate reduced alcohol intake and cravings, and improved quality of life and health (Johnson et al., 2003; Johnson, 2004). In a subsequent multisite trial, the topiramate group demonstrated reduced obsessional thoughts and compulsions about alcohol, reduced number of heavy drinking days, and reduced risk of relapse (Johnson et al., 2007; Johnson et al., 2008). Furthermore, in a recent meta-analysis (Blodgett et al., 2014), 7 randomized placebo controlled trials (RCTs) were evaluated, and topiramate had a moderate effect size by increasing abstinence and reducing heavy drinking. Feinn et al. estimated the number needed to treat (NNT) for topiramate based on outcomes from a recent trial as (overall NNT is 5.29, and adjusting with adverse events the NNT ranges between 6.12 and 7.52), which are more favorable than recent estimates of the NNT for acamprosate and oral naltrexone (both NNT ~12) (Feinn et al., 2016). The high clinical importance of this estimate is its ability to capture both the clinical benefit and adverse effects of topiramate. The authors calculated the NNT to reduce heavy drinking and adjusted it using 2 levels of adverse event severity. According to Feinn et al., the topiramate treatment effect on heavy drinking appears superior against either naltrexone or acamprosate, before and even after adjusting for adverse events (Feinn et al., 2016). It is important to point out that there are no current comprehensive head-to-head comparison trials of these medications, and these conclusions are not definitive.

Patient Selection Factors in Clinical Practice

The clinical decision to choose a medication for certain patients depends on many factors. A thorough diagnostic assessment that takes into consideration mental health history, medical history, current level of motivation for treatment, severity of alcohol consumption, history of abstinence, adverse effects of withdrawal such as withdrawal seizures or delirium tremens, history of adverse effects to medications,

in addition to a psychosocial assessment, are all needed to personalize the clinical decision of medication-assisted treatment of AUD.

Compared with 3 other evidence-based medication interventions for AUD (naltrexone, acamprosate, disulfiram), topiramate is increasingly becoming a valid treatment option that can be considered a first-line treatment in most patients with AUD, given the above mentioned promising evidence.

It has been suggested that a patient's goal (ie, either abstinence or reduction to nonhazardous drinking levels) may influence response to medications. For example, it was thought that a goal of abstinence was more conducive to successful treatment with acamprosate. This assumption was based upon findings of a greater effect of acamprosate on abstinence, and a greater effect of naltrexone on reducing heavy drinking and craving. Those basic relationships to outcomes have been confirmed in meta-analysis, but a specific goal of abstinence did not significantly influence treatment outcomes. Detoxification before treatment and a longer period of abstinence required before treatment did influence treatment outcomes for both acamprosate and naltrexone (Maisel et al., 2013). Other recent studies have suggested that opioid receptor antagonists like naltrexone can be efficacious regardless of patient goal (see Niciu and Arias, 2013 for a review). In addition, topiramate appears to work well with a patient goal of either abstinence or nonharmful drinking (Kranzler et al., 2014). Moreover, topiramate is likely to be effective across the spectrum of AUD severity, based on the inclusion of regular heavy drinkers regardless of whether they met all *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed* criteria for alcohol dependence in the study by Kranzler et al. (2014).

Unlike other medication options (such as acamprosate, or both PO and IM naltrexone), in which an abstinence period before starting treatment has shown to improve efficacy, topiramate is effective even when started and titrated in currently heavy-drinking patients. Nalmefene, however, a medication similar to naltrexone used in Europe, has proven efficacy in large trials with a small effect size when given to those with AUD that are currently heavy drinking (see Niciu and Arias, 2013 for a review). The condition of abstinence was only met in cases 2 and 3 of this case series. In case 2, naltrexone was not an option as patient was on mu-opioid partial agonist therapy (for OUD), and acamprosate had demonstrated limited benefit in his case. Case 1 was for a heavy drinker with no achieved abstinence period; hence topiramate presented a reasonable evidence-based option.

Dual diagnosis patients with comorbid post-traumatic stress disorder (PTSD) may have an added benefit when treated with topiramate. Open label studies of topiramate have suggested efficacy for PTSD symptoms such as nightmares and insomnia with adjunct topiramate treatment (Berlant, 2000; Berlant and van Kammen, 2002). Randomized controlled trials have demonstrated efficacy as an add-on treatment in treating PTSD symptoms, and also reducing high-risk alcohol intake in combat veterans (Alderman et al., 2009). Additionally, a more recent randomized controlled trial has evaluated topiramate for use with veterans with co-occurring alcohol use and PTSD (Batki et al., 2014). This trial found that topiramate can reduce alcohol use,

cravings, drinking days, and also the amount of alcohol consumed, and also has a beneficial effect on PTSD symptoms, specifically hyperarousal. The authors noted the negative cognitive effects with topiramate (a common side effect), but also found these effects were transient and eventually tolerated. Overall, the limiting factors for topiramate appear to be the side-effect profile, which can involve cognitive impairment, and also risks of metabolic acidosis, acute glaucoma, and others.

Another approach for selecting a particular treatment for substance use patients is by their co-occurring SUDs. While there is some emerging evidence that topiramate can be effective in treating patients with cocaine use disorder (Johnson et al., 2013), there is limited evidence to the efficacy of topiramate in treating co-occurring AUD and cocaine use disorder. This is important as there is a high comorbidity between AUD and cocaine use disorder. In some estimates, 60% to 80% of patients with cocaine use disorder have alcohol dependency (Regier et al., 1990, Carroll et al., 1993). A study published in 2013 reported no effect for topiramate on alcohol use, but was associated with a greater end of study abstinence from cocaine in patients with comorbid AUD and cocaine use disorder (Kampman et al., 2013). While future research is needed, at the clinical level, topiramate may still be a clear option (compared with naltrexone, acamprosate, or disulfiram, which has no evidence in cocaine use disorder) when treating patients with comorbid alcohol and stimulant use. In addition, as seen in case 2, co-occurring AUD and OUD may present a challenge for alcohol treatment when patients are on mu-opioid agonist therapy (such as buprenorphine or methadone) as naltrexone cannot be used in these cases. Hence, topiramate or acamprosate can be chosen for these patients, with evidence suggesting better response to topiramate on AUD compared with acamprosate.

Furthermore, given the emerging evidence in studies looking at certain genotypes (such as rs2832407, a *GRIK1* gene polymorphism) associated with better response to topiramate in patients with AUD, it is possible that in the future case selection can be guided by genotyping in clinical settings (Kranzler et al., 2014).

Finally, from a pharmacokinetic standpoint, topiramate is largely renally cleared (about 70% recovered unchanged in the urine) and dosage adjustment is required in subjects with impaired renal function (creatinine clearance <70 mL/min/1.73 m², see product packaging information). There is some hepatic metabolism (hydroxylation, hydrolysis, and glucuronidation), and topiramate can induce CYP3A4, and inhibit CYP2C19. Consideration should be made for patients on estrogen containing oral contraceptives, as ethinyl estradiol clearance may be increased by about 30% and birth control could theoretically be less effective, though progesterone-based contraceptives are not affected (Rosenfeld et al., 1997). Patients with hepatic impairment may have higher concentrations of the medication.

Side Effects and Tolerability

The patient from case 1 experienced some cognitive side effects, and cognitive dulling, specifically anomia and problems with verbal fluency are commonly reported with topiramate use and the intensity of the side effect is

TABLE 1. Titration Schedule for 300 mg Daily Target Dose

Week	Morning Dose, mg	Night-time Dose, mg	Total Daily Dose, mg
1	—	25	25
2	25	25	50
3	50	50	100
4	75	75	150
5	100	100	200
6	100	200	300

Adapted from Johnson et al., 2007.

dose-dependent. Anecdotally, in our experience, patients who are heavy alcohol users get less cognitive side effects from topiramate compared with other types of patients—an effect likely mediated by the degree of allostatic neuroplastic changes from chronic heavy alcohol exposure. Paresthesia is quite common, and some subjects may also note poor concentration.

Topiramate is generally well-tolerated, but some patients do experience concerning adverse side effects, especially at higher doses and without gradual dose titration (Blodgett et al., 2014). It is very important to have a candid discussion with patients about risk and benefits of this medication, and educate patients about side effects. Most commonly encountered side effects are of paresthesia/numbness, nausea/vomiting, cognitive impairment, headache and dizziness. Often these side effects are transient and occur during the up titration of the medication, though they can be persistent. It is important to prepare the patient by mentioning that topiramate can often have nuisance side effects, but that they often are transient and that they will not harm the patient; they will go away if the medication is stopped. Sometimes, persistent side effects warrant a reduction in dose. In the a multicenter trial of topiramate for treating AUD with a target dose of 300 mg daily, dropouts due to adverse events were significantly more common with topiramate than with placebo (18.6% vs 4.3%, respectively) (Johnson et al., 2007). In a smaller trial using a 200 mg daily target dosage, completion rates did not differ significantly between topiramate and placebo, and the medication was fairly well-tolerated, though there were significantly more adverse events in the topiramate group (Kranzler et al., 2014).

Earlier studies of topiramate showed better tolerability for lower doses (50–100 mg/d). Side effects and adverse reactions, especially central nervous system related, are dose-related (Bray et al., 2003). Side effects are usually reported in the first 8 weeks of treatment, usually during titration phase. According to Bray et al., paresthesia, which is the most commonly reported adverse event, was dose-dependent, and was noted to decrease over time. Cognitive side effects (such as difficulty with memory, difficulty with concentration or attention, psychomotor slowing, and somnolence) are usually reported with higher doses of topiramate. According to Bray et al., these side effects were transient, and abated without dose adjustment (Bray et al., 2003). However, it is the authors' recommendation to reduce the dose should these side effects continue without abatement after a

reasonable period of waiting (ie, 4–6 weeks) as they may limit adherence in AUD patients.

According to the package insert, initiating treatment with topiramate starts with a dose of 25 mg twice daily; however, the majority of the trials have started at 25 mg daily. Dose is usually increased by 25 to 50 mg, divided on 2 doses every week up to 200 mg divided twice daily (ie, 100 mg twice a day) as a target dose. Randomized controlled trials used different titration schedules; however, most studies had a target dose of 200 to 300 mg/d (Blodgett et al., 2014). A titration of the medication over about 5 to 6 weeks is recommended in clinical practice for the treatment of AUD (Tables 1 and 2).

When discontinuing topiramate, a taper of approximately 25 to 50 mg per day is recommended, to avoid the precipitation of seizure, which is a rare event, but possible even in nonepileptic patients. Topiramate can usually be tapered off in an approximately 1-week period (or less) in patients without epilepsy. If a severe side effect is suspected (acute angle closure glaucoma, metabolic acidosis), you could consider immediately stopping the medication. If the myopic syndrome is suspected, the patient should be referred with urgency for measurement of intraocular pressure and ophthalmologic evaluation, and if confirmed, topiramate can be discontinued with rapid taper or abruptly.

In female patients of child-bearing age, it is important to discuss teratogenic risks and recommend use of contraceptives while in treatment with topiramate, as it is pregnancy category D, and there is a 1.4% risk of cleft lip and/or palate if exposure to topiramate happened in the first trimester. This risk is in comparison with 0.38% to 0.55% for other antiepileptic drugs and 0.07% with no antiepileptic exposure (please refer to the North American Antiepileptic Drug Pregnancy Registry). It is possible there are additional risks as yet unknown to the child if exposed in utero, and this should be discussed with the patient in the context of informed consent. Topiramate should be prescribed cautiously to women of child-bearing age, and consideration should be given to tapering and discontinuing topiramate in a woman without a history of seizure disorder that becomes pregnant while on it. The risks of continuing topiramate in pregnancy should include consideration of the risks of continued heavy drinking during pregnancy with a possible outcome of fetal alcohol syndrome. Consultation with an obstetrician should be included as well.

In summary, it may be clinically useful to describe the potential risks and side effects of topiramate to patients as consisting mostly of “nuisance” side effects that may be

TABLE 2. Titration Schedule for 200 mg Daily Target Dose

Week	Morning Dose, mg	Night-time Dose, mg	Total Daily Dose, mg
1	—	25	25
2	25	25	50
3	25	50	75
4	50	50	100
5	50	100	150
6	100	100	200

Adapted from Kranzler et al., 2014.

transient (such as cognitive effects, or paresthesia), and those which are likely attenuated with dose adjustment, and with complete cessation upon withdrawal of the medication. Patients should also be informed of the more serious but much more rare risks such as renal calculi, metabolic acidosis, acute angle-closure glaucoma, and the myopia syndrome. Anecdotally, in our clinical experience, we usually ask patients to increase their liquids consumption (as hydration may reduce the risk of renal calculi), to notify us of persistent visual changes, general malaise not associated to another likely syndrome (ie, not a common cold), and to get immediate medical attention for acute glaucoma symptoms such as abrupt change of vision with pain or redness in 1 or both eyes.

CONCLUSIONS

Topiramate is an anticonvulsant with much evidence supporting its use in the treatment of AUD alone or with some co-occurring conditions like PTSD. It also has some evidence (though mixed) supporting its use in cocaine use disorder. Recent studies show a favorable harm adjusted NNT compared with other AUD evidence-based medication treatments such as naltrexone or acamprosate. Topiramate provides an excellent option to treat patients with AUD, especially those who are heavy drinkers often without the need for detoxification or abstinence. A thorough discussion with patients of the risks and benefits before starting treatment is recommended, along with an emphasis on educating them about the potential side effects and adverse reactions, especially cognitive side effects, which may be a transient phenomenon noted in the titration phase, especially in the first 8 weeks of treatment.

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