High-Dose Baclofen for Treatment-Resistant Alcohol Dependence

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Abstract: Alcohol dependence is associated with a wide array of physical and psychiatric complications and is a major cause of morbidity and mortality worldwide. Recent randomized trials of baclofen, with a total daily dose 30 mg administered in 3 divided doses, have supported its efficacy in reducing craving and promoting abstinence from alcohol. Individual case studies support a possible increased effect at higher doses for treatment-resistant patients. Here, we report on 4 alcohol-dependent patients resistant to standard treatments who responded to higher doses of baclofen ranging from 75 to 125 mg daily. Further research into the use of high-dose baclofen for treatment-resistant alcohol dependence is warranted.

Key Words: baclofen, alcohol dependence treatment, alcohol dependence, high-dose baclofen

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Alcohol consumption is a major cause of preventable morbidity and mortality worldwide, and alcohol dependence is associated with an array of physical and psychiatric complications.[1] Symptomatic treatment of the alcohol withdrawal syndrome followed by ongoing individual or group psychological support has traditionally been the mainstay of treatment for alcohol dependence; however, sustained improvement rates are low and relapses common.[2] Recent advances in our understanding of the neuroscience of addiction have led to the development and use of an increasing range of pharmacotherapeutic agents that promote abstinence with substantially improved outcomes for patients with alcohol dependence.[3,4] Naltrexone, acamprosate, and disulfiram[5–7] are widely used; and a number of other agents including baclofen, topiramate, and ondansetron are accumulating evidence for their clinical effectiveness.[3,4] These agents exert their effects at sites implicated in the etiology of craving and modulate neurotransmitters that include dopamine, γ-aminobutyric acid (GABA), glutamate, and serotonin.

Baclofen, a GABA-B agonist, is widely used for symptomatic relief of muscle spasticity related to multiple sclerosis and spinal conditions, where it is commonly titrated to total daily maintenance doses between 30 and 100 mg administered in 2 to 3 divided doses.[8] Of note, considerably higher doses have also been used with good effect.[8] Recent studies have suggested that baclofen may also assist in the maintenance of abstinence from alcohol through the modulation of GABAergic neurons in the ventral tegmental area and limbic system,[9] stabilizing dopaminergic neurons with a clinical reduction in craving.

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Preclinical data[10] and 2 unblinded open-label trials support the effect of baclofen on reducing heavy drinking.[11,12] Two blinded randomized clinical trials by Addolorato et al[13,14] showed a significant effect of baclofen on reducing craving for alcohol and improving abstinence-related outcomes; however, a trial by Garbutt et al[15] did not show any positive effect on drinking outcomes. These trials have all used a total daily dose of 30 mg, which was chosen based on the open clinical studies and represents the minimum therapeutic dose recommended by the drug manufacturer to avoid adverse effects.[14]

A translational model of treatment of substance dependence based on animal studies using high-dose baclofen to completely suppress craving was proposed by Ameisen[16] in 2005 and was accompanied by a case study using a total daily dose of 270 mg soon reduced to 120 mg.[17] Other single-case studies following this model have also have been published.[18,19] A further study was also published indicating that large doses of alcohol could be taken safely in the presence of up to 80 mg of baclofen.[20] Considering the safe and efficacious use of high doses of baclofen for comfort care of neurological conditions and its safety with concurrent alcohol administration, using high-dose baclofen may have merit in a subgroup of patients with otherwise treatment-resistant alcohol dependence.

We report on the following 4 successful cases (Table 1) on using high-dose baclofen for alcohol dependence in patients who remained treatment resistant to other modalities including a total daily dose of 30 mg of baclofen prescribed in combination with other anticraving medications. With regard to safety, none of the 4 patients reported a history of epilepsy or cardiac disease. A thorough physical examination was performed; and liver function, renal function, and basic hematologic parameters were evaluated at the commencement of treatment before attaining informed consent.

Baclofen was increased from a total daily dose of 30 mg by 12.5 to 25 mg each week as tolerated and until craving was suppressed. Doses were divided twice or 3 times daily depending on patient's preference and compliance. Each patient was medically reviewed with regard to adverse effects at least weekly during the titration phase and fortnightly once stabilized. After a minimum of 3 months of stabilization, baclofen was then reduced to the lowest effective dose to minimize the risk of adverse effects, or a significant withdrawal syndrome should the baclofen be abruptly ceased.[21]

Case 1

A 43-year-old woman, employed, with 4 children, and with a 15-year history of depression and alcohol dependence attended an outpatient clinic. She was taking 150 mg of sertraline and regularly attending Alcoholics Anonymous.

She reported becoming a "heavy drinker" in her 30s with escalating use over the last 4 years after a divorce. At presentation, she reported drinking a bottle of wine daily (80 g alcohol) with the addition of a 750-mL bottle of spirits daily (220 g alcohol) on weekends. She had significant withdrawal symptoms when trying to cease drinking and reported high levels of

TABLE 1. Summary of Cases

	Duration of Alcohol Dependence (y)	Alcohol Consumed Before Treatment	Concomitant Anticraving Agents	Maximum Total Daily Dose of Baclofen (mg)	Adverse Effects
Case 1: 43-year-old woman	4	80 g/d	Naltrexone 100 mg daily	75	Mood lability during dose reduction
Case 2: 31-year-old man	11	160 g/d	Acamprosate 666 mg tds	87.5	Nil
Case 3: 46-year-old man	20	220 g/d	Nil	100	Fatigue, sleeplessness during dose reduction, relapse on dose reduction
Case 4: 36-year-old man	20	360 g once weekly (binge pattern)	Acamprosate 999 mg bd	125	Nil

bd indicates twice daily; tds, three times daily.

craving when not drinking. She had had a single period of sobriety lasting 6 weeks approximately 1 year before presentation, with no other periods of abstinence in the previous 4 years.

She initially received both counseling and pharmacological support with naltrexone and acamprosate but did not tolerate acamprosate owing to persistent diarrhea. After a month of abstinence, she reported daily cravings of severe intensity and 2 episodes of drinking greater than 80 g of alcohol within a 2-hour period. Baclofen, to a total daily dose of 30 mg, was added with no effect on her craving after 3 weeks. The baclofen dose was then titrated over 4 weeks to 75 mg with a dramatic suppression of cravings, and she maintained abstinence from alcohol for the following 3 months. The baclofen dose was then reduced to a total daily dose of 50 mg, and she has achieved more than 9 months of abstinence, no cravings, stable mood, and excellent social functioning.

Case 2

A 31-year-old male factory worker with an 11-year history of alcohol dependence attended outpatients after being diagnosed by his neurologist with an alcohol-related bilateral upper and lower limb peripheral neuropathy. He was drinking 2 bottles of wine daily (160 g alcohol) and had 4 previous charges of driving under influence, been involved in a number of physical fights, had and persistent episodes of absenteeism from work.

He described cravings lasting 30 minutes occurring up to 5 times each day. He was commenced on acamprosate and naltrexone but did not tolerate naltrexone owing to unremitting headaches. Topiramate was then introduced but not tolerated owing to dizziness. He had not found counseling useful in the past but did read a number of motivational self-help books. Six weeks after commencement of treatment, he drank up to 8 bottles of beer (120 g of alcohol) each day for 3 days. Baclofen, up to a total daily dose of 30 mg, was introduced, but cravings persisted 1 month after its introduction.

Over the coming 5 weeks, the baclofen dose was titrated up to 87.5 mg, with a substantial suppression of cravings, and he became abstinent. After 6 months of continuous abstinence, his baclofen was slowly reduced to 50 mg without a reemergence of cravings. He has now completed 9 months without any alcohol intake associated with a stabilization of his peripheral neuropathy.

Case 3

A 46-year-old male baker with type 2 diabetes, dyslipidemia, asthma, depression, and alcohol dependence attended outpatients. He was first diagnosed with alcohol dependence at age 26 and reported drinking a bottle of spirits daily (220 g of alcohol) for the 2 years before presentation. He reported significant cue-induced cravings, being unable to walk past a bottle shop without buying alcohol. He began individual counseling and pharmacotherapy involving naltrexone, acamprosate, and a total daily dose of 30 mg of baclofen. Despite this treatment and his stated aim of being abstinent from alcohol, he continued low-level drinking and complained of ongoing cue-induced cravings.

After 3 months of reduced drinking, he relapsed to his previous heavy daily use for 6 weeks and ceased his medications. After re-presenting, his other anticraving agents were ceased and his baclofen dose was titrated over 6 weeks to 100 mg. A validated measure of alcohol craving, the Obsessive-Compulsive Drinking Scale,[22] had dropped from 39 pretreatment to 9 after stabilization, and he achieved abstinence.

After 7 months of abstinence, the patient's dose of baclofen was gradually reduced. When it reached a total daily dose of 50 mg, he reported an increase in craving and relapsed to daily intake of a bottle of spirits (220 g of alcohol). He was admitted to a residential withdrawal unit, and during his admission, the dose of baclofen was increased to 100 mg.

After the increase in his baclofen dose, the cravings were suppressed, and he maintained abstinence for 5 months. He describes some daytime fatigue but does not wish to reduce his current dose of baclofen.

Case 4

A 36-year-old man with bipolar disorder, managed with olanzapine and citalopram, attended outpatients after a number of minor criminal offences committed when intoxicated. He reported drinking a carton of beer on a single occasion each week (360 g of alcohol) and described feeling anxious and experiencing craving on alcohol-free days. This had been a regular pattern since age 16, and his longest period without alcohol since that time had been 6 weeks.

He had been prescribed naltrexone in the past, with no effect on his drinking, but had some benefit from acamprosate. He was commenced on acamprosate and a total daily dose of 30 mg of baclofen with minimal effect on his binge drinking, which continued to occur on a weekly basis. After a trial of 3 months of treatment, his dose was increased over 6 weeks to 125 mg daily after which he ceased drinking alcohol for 3 months. He relapsed to binge drinking twice weekly for 1 month, which was associated with a depressive episode, which was then followed by a further 7 months of abstinence.

DISCUSSION

The aforementioned case studies demonstrate that high-dose baclofen may benefit patients with alcohol dependence, with all of the patients reporting a sustained period of abstinence after an upward titration of their baclofen. The reported mechanism was a suppression of craving, and the further use of validated clinical tools to measure craving would be valuable in the future to document this effect.

By titrating baclofen slowly, there were few adverse effects, and the drug was generally well tolerated. Transient mild symptoms occurred during dose reductions in 2 of the 4 cases. All the patients have been retained in intensive medical treatment for more than 9 months, with cases 1 and 3 continuing counseling or 12 step-based supports in addition to pharmacotherapy.

After a period of stable abstinence, an attempt was made in cases 1 to 3 to reduce baclofen doses. Two of the patients, cases 1 and 2, had long periods of stability, and a dose reduction to lower maintenance doses was possible. This suggests that in some patients, higher doses of baclofen may only be necessary in the first 3 to 6 months after cessation of alcohol. This partially mitigates against concerns of using high-dose baclofen for long periods. The patient in case 3 had a significant return of cravings and a relapse to heavy drinking when baclofen was reduced, necessitating a reinstatement of higher doses.

Whereas it is impossible to rule out a placebo effect for the aforementioned cases, each had a long history of failed treatments and demonstrated a sustained period of improvement associated with suppression of craving on high-dose baclofen. Because most of the patients continued other anticraving medications, it is unclear whether baclofen may work cumulatively or even synergistically with other medications aimed at cravings or other psychiatric symptoms. The concomitant use of other medications may have also partially concealed the effectiveness of baclofen, and there was no attempt at reducing or ceasing concomitant anticraving medications while on baclofen. It is also unclear from the length of this study whether tolerance to the anticraving effect of baclofen may develop over a longer period of treatment. As with many treatments for addiction, the length of time required for treatment may have considerable interindividual variability.

Although only a small group, there is already considerable heterogeneity with regard to sex, age, motivations, and pattern of drinking. The variety of cases presented argues against easy matching of clinical typologies with baclofen treatment and raises a number of questions regarding optimal dose, delivery of care, and length of treatment.

In summary, these case studies suggest that doses of baclofen greater than a total daily dose of 30 mg may suppress craving in patients with alcohol dependence who have not responded to lower doses or other anticraving medications. Furthermore, high-quality research into the use of high-dose baclofen for alcohol dependence is warranted to confirm these findings.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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