SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 3
Page N. 103-109
Year: 2024

Review Article www.wjahr.com

OFF-LABEL BENEFIT OF BACLOFEN: ALCOHOL USE DISORDER & ALCOHOL WITHDRAWAL SYNDROME

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Article Received date: 26 December 2023 **Article Revised date:** 16 January 2024 **Article Accepted date:** 05 February 2024

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INTRODUCTION

Baclofen, an anti-spasmodic drug developed by Swiss chemist Heinrich Keberle, as an antiepileptic in the year 1962. Although baclofen was found to be ineffective for the treatment of epilepsy, it was found effective in the treatment of spasticity in specific patients, based upon this it was recognized and introduced as anti-spasmodic in the year 1971 and the US Food and Drug Administration (FDA) granted approval in 1977 for the treatment of spasticity associated with multiple sclerosis, spinal cord injuries, and other spinal cord pathologies.[1]

KEYWORDS: baclofen, alcohol use disorder, alcohol withdrawal syndrome, benzodiazepines.

Baclofen is an FDA-approved medication utilized for the treatment of reversible muscle spasticity. It is specifically prescribed to alleviate flexor spasms, clonus, and associated pain, which are frequent complications of spinal cord injuries and multiple sclerosis. Additionally, Baclofen is employed for various FDA approved and off-label purposes.[2]

Some of the FDA approved indications of baclofen.[3]

- Oral baclofen is used for management of reversible spasticity, specifically aiming to alleviate conditions such as flexor spasms, clonus, and associated pain. These symptoms are common consequences of spinal cord lesions and multiple sclerosis.
- The FDA has granted approval for the utilization of intrathecal baclofen administration in the management of spasticity resulting from cerebral causes, such as traumatic brain injury, or severe spasticity originating from the spinal cord that remains unresponsive to maximum doses of oral baclofen, tizanidine, and/or dantrolene. In situations where patients encounter intolerable side effects or exhibit insufficient response to oral therapy, healthcare providers may consider the use of intrathecal baclofen.

Off label indications of baclofen.

- Alcoholic liver disease.
- Decreasing alcohol cravings and alcohol-related anxiety.[4]
- Trigeminal neuralgia, gastroesophageal reflux disease & hiccups.[5]
- Short term treatment for spasticity associated with cerebral palsy.[6]

Mechanism of action- Baclofen acts muscle-relaxant by inhibiting both monosynaptic and polysynaptic reflexes while also suppressing the excitability of gamma motoneurons. Additionally, this medication inhibits reflex collaterals that link the myofibrillary α1 fibers and α-motoneurons within the efferent gamma-loop segment, leading to the deactivation of muscle fibers.[7]

ALCOHOL USE DISORDER (AUD) & ALCOHOL WITHDRAWAL SYNDROME (AWS)

Alcohol use disorders encompass conditions marked by compulsive and excessive alcohol consumption, coupled with an inability to control alcohol intake. Globally, these disorders are highly prevalent, particularly in high-income and upper-middle-income nations, and they contribute significantly to mortality and disease burden, through medical complications like liver cirrhosis or injuries. Despite their widespread occurrence, these

disorders often go undertreated, a phenomenon attributed to both the stigma attached to them and a lack of systematic screening in primary health care. However, it's worth noting that effective and cost-efficient psychosocial and pharmacological interventions are available for addressing alcohol use disorders.[8]

Regardless of geographic location, alcohol use disorder (AUD) is more common in men than women. The estimated lifetime prevalence is 14.8% for men and 3.5% for women in Europe, and 11.5% for men and 5.1% for women in the Americas.[9,10]

Alcohol withdrawal syndrome (AWS) is a clinical condition that may occur 6-24 hours after suddenly stopping or reducing alcohol consumption. It is marked by increased activity in the autonomic nervous system, leading to symptoms such as restlessness, tremors, anxiety, cognitive disturbances, elevated blood pressure, rapid heart rate, and fever.[11]

Symptoms of AWS manifest in over 50% of individuals with alcohol use disorders, requiring varied pharmacological interventions. The syndrome can manifest across a spectrum, ranging from mild to severe forms. Timely identification and proper treatment are crucial, as AWS stands as a significant, foreseeable contributor to both mortality and morbidity in individuals struggling with alcohol-related issues.[12]

Mechanism of Baclofen In AWS: The mesolimbic dopamine pathway, which involves dopamine-producing cells in the ventral tegmental area that extend projections into the nucleus accumbens, plays a vital role in the reward and addictive aspects of drug use.[13] The main way Baclofen addresses alcohol dependence is believed to involve diminishing the rewarding effects of alcohol. This occurs through the suppression of alcohol-induced dopamine release in the mesolimbic dopamine system.[14]

Baclofen exerts agonistic effects on $GABA_B$ receptors situated in various brain regions, including the mesolimbic circuit and the ventral tegmental area. This action inhibits the firing of dopaminergic neurons induced by alcohol and suppresses alcohol-triggered dopamine release in the nucleus accumbens. Therefore, the reinforcing properties of both alcohol and drugs are reduced.[15,16]

In an in-vivo study baclofen did not influence the natural motor activity in rats, its effects were not attributed to the muscle-relaxant or sedative properties of the drug. Instead, these effects were seen as stemming from its capability to diminish the motivational strength of alcohol.[17]

Furthermore, $GABA_B$ receptors, which are abundant in limbic structures associated with anxiety regulation, can be activated to alleviate anxiety. Clinical evidence indicates that baclofen may have an anxiety-reducing effect in individuals with Alcohol Use Disorder (AUD). Post-hoc analyses in a study revealed that baclofen was particularly effective in individuals with both AUD and coexisting anxiety. This finding has been supported by a recent meta-analysis. Therefore, in addition to mitigating the reinforcing aspects of alcohol by suppressing alcohol-induced dopamine release in the mesolimbic dopamine system, baclofen's impact on drinking patterns may also be linked to its ability to address symptoms of anxiety.[18]

CASE STUDIES & SERIES OF BACLOFEN IN AWS

A 31-year-old male factory worker with an 11-year history of alcohol dependence was diagnosed with an alcohol-related bilateral upper and lower limb peripheral neuropathy. It was reported that the patient was drinking 2 bottles of wine daily (160 g alcohol) and had 4 previous charges of drink & drive, and been into various physical fights, and missing work. The patient described cravings lasting 30 minutes occurring up to 5 times each day. He was started with Acamprosate and Naltrexone but was unable to tolerate Naltrexone due to severe headaches. Topiramate was then introduced but not tolerated due to dizziness. 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. The patient has completed 9 months, at the time of reporting without any alcohol intake associated with a stabilization of his peripheral neuropathy.

A 36-year-old male diagnosed with bipolar disorder and currently taking Olanzapine and Citalopram sought outpatient care following a series of minor criminal incidents that occurred during episodes of intoxication. The patient reported consuming a carton of beer weekly (equivalent to 360 g of alcohol) and described feelings of anxiety and cravings on days without alcohol. This pattern of alcohol consumption had persisted since the age of 16, with the longest period of abstinence lasting 6 weeks. Previous treatment with Naltrexone had shown no significant improvement in his drinking behavior, while Acamprosate was reported to have some beneficial effects. The patient was initiated on Acamprosate and a daily total of 30 mg of baclofen, with minimal impact on his weekly binge drinking. After a 3-month trial, the baclofen dose was gradually increased over 6 weeks to reach 125 mg per day, resulting in three months of abstinence. Subsequently, a relapse occurred, marked by twice-weekly binge drinking for one month, accompanied by a depressive episode. Following this relapse, the patient abstained from alcohol for an additional seven months.

A 43-year-old employed woman, mother of four, and with a 15-year history of depression and alcohol dependence sought assistance at an outpatient clinic. She was currently taking 150 mg of Sertraline and actively participating in Alcoholics Anonymous. The patient disclosed that she had developed a pattern of "heavy drinking" in her 30s, with escalating alcohol consumption over the last four years following a divorce. At the time of presentation, she admitted to consuming a daily bottle of wine (80 g alcohol) and a 750-mL bottle of spirits (220 g alcohol) on weekends. She experienced significant withdrawal symptoms when attempting to cease drinking and reported intense cravings during periods of abstinence. Despite attending counseling and receiving pharmacological support with naltrexone and acamprosate, the patient could not tolerate acamprosate due to persistent diarrhea. After achieving one month of abstinence, she faced severe daily cravings and had two episodes of consuming more than 80 g of alcohol within a two-hour period. Baclofen was introduced at a total daily dose of 30 mg initially, but it had no noticeable impact on her cravings after three weeks. Subsequently, the baclofen dose was titrated up over four weeks to 75 mg, resulting in a significant suppression of cravings. The patient-maintained abstinence from alcohol for the subsequent three months. The baclofen dose was then gradually reduced to a total daily dose of 50 mg, and she has sustained over nine months of abstinence, reporting no cravings, stable mood, and excellent social functioning.

A 46-year-old male baker diagnosed with type 2 diabetes, dyslipidemia, asthma, depression, and alcohol dependence sought outpatient care. The onset of alcohol dependence occurred at the age of 26, and he reported consuming a daily bottle of spirits (220 g of alcohol) for the 2 years leading up to his presentation. The patient experienced significant cravings triggered by cues, particularly when passing a bottle shop. Despite engaging in individual counseling and receiving pharmacotherapy, including Naltrexone, Acamprosate, and a total daily dose of 30 mg of Baclofen, he continued to engage in low-level drinking and complained of persistent cue-induced cravings. Following three months of reduced drinking, the patient experienced a relapse to heavy daily alcohol use for a period of six weeks and subsequently discontinued his medications. Upon re-presentation, his other anti-craving medications were discontinued, and the Baclofen dose was gradually increased over six weeks to reach 100 mg. The Obsessive-Compulsive Drinking Scale, a validated measure of alcohol craving, decreased from 39 before treatment to 9 after stabilization, leading to the achievement of abstinence. After maintaining abstinence for 7 months, the patient's Baclofen dose was slowly reduced. However, when the dose reached a total daily dose of 50 mg, he reported an increase in cravings and relapsed to a daily intake of a bottle of spirits (220 g of alcohol). Subsequently, he was admitted to a residential withdrawal unit, and during this admission, the Baclofen dose was increased to 100 mg. Following the dose adjustment, cravings were effectively suppressed, and the patient-maintained abstinence for 5 months. Although he experienced some daytime fatigue, he expressed no desire to reduce his current baclofen dose.[19]

In a comparative study conducted by Addolorato G et al. to compare the efficacy, tolerability and safety of Baclofen v/s Diazepam in treatment of AWS. In this study, 37 patients diagnosed with AWS were included and randomly assigned to two groups. Eighteen patients (15 males, 3 females; median age: 46.5 years) received oral administration of baclofen at a dose of 30 mg per day for 10 consecutive days. The remaining 19 patients (17 males, 2 females; median age: 42.0 years) were orally administered diazepam at a dose of 0.5-0.75 mg/kg per day for 6 consecutive days, with a gradual tapering of the dose by 25% daily from day 7 to day 10. The evaluation of physical symptoms of AWS was conducted using the Clinical Institute Withdrawal Assessment (CIWA-Ar). As per the study, the CIWA-Ar scores were significantly reduced by both baclofen and diazepam treatments, with no notable differences observed between the two interventions. When assessing individual CIWA-Ar subscales for sweating, tremors, anxiety, and agitation, both baclofen and diazepam led to a significant reduction in scores for sweating, tremors, and anxiety, with no significant distinctions between the two drug treatments. Although both treatments lowered the agitation score, diazepam exhibited a slightly faster onset compared to baclofen.

The effectiveness of baclofen in treating uncomplicated alcohol withdrawal syndrome (AWS) is similar to that of the established "gold standard," diazepam. These findings imply that baclofen could be regarded as a potential novel medication for the management of uncomplicated AWS.[20]

CLINICAL TRIALS OF BACLOFEN IN AWS

In a two-year observational study conducted on 100 patients to examine the long-term effects of baclofen in large cohort of alcohol-dependent patients. Patients with alcohol dependance, resistant to normal treatments, were administered with increasing doses of baclofen, their alcohol intake (in grams) and craving for alcohol were assessed at 3, 6, 12, & 24 months respectively before the initiation of treatment.

While all patients were initially assessed as "high risk," approximately half of patients demonstrated a transition to a "low risk" status at 3, 6, 12, and 24 months. The combined percentage of patients categorized as "low risk" & "moderate risk" (considered improved patients) was 84% at 3 months, 70% at 6 months, 63% at 1 year, and 62% at 2 years, indicating a consistent pattern of improvement throughout the two-year period. Notably, the average maximum dose of baclofen administered was 147 mg/day. A high percentage (92%) of patients acknowledged experiencing the craving-suppressing

effects of baclofen. Significant associations were identified between the pre-treatment alcohol consumption in grams and the required maximal dose of baclofen, as well as between the presence of a mental disorder and a diminished effectiveness of baclofen.

According to the study, it was revealed, baclofen, when prescribed without an upper dosage limit induces a seamless reduction or suppression of alcohol craving. Potential constraints on the efficacy of baclofen encompass the presence of a concurrent mental disorder, simultaneous use of other psychotropic medications, insufficient genuine motivation in patients to cease alcohol consumption, and challenges in reaching the optimal baclofen dose due to intolerable side effects, which may occasionally be linked to an excessively rapid protocol of dose escalation.[21]

In a randomized, double-blind controlled study aimed to investigate the effectiveness & safety of baclofen in achieving & maintaining alcohol abstinence in patients with liver cirrhosis. Between October 2003 and November 2006, the Institute of Internal Medicine in Rome, Italy, received 148 referrals of patients with liver cirrhosis and alcohol dependence. In a randomized manner, 84 of these patients were assigned to either oral baclofen or a placebo for a duration of 12 weeks. The primary focus was on determining the proportion of patients who achieved and sustained alcohol abstinence. The assessment of this outcome included measures such as total alcohol abstinence and cumulative abstinence duration, evaluated during outpatient visits. A relapse was defined as the consumption of more than four drinks per day or an overall intake of 14 or more drinks per week persisting for at least 4 weeks. The analysis was conducted based on the intention-to-treat principle. Among the 42 patients who were given with baclofen, 71% (30 patients) achieved and maintained abstinence, whereas only 29% (12 patients) of the 42 individuals assigned to the placebo group achieved this outcome. The rate of dropouts (treatment termination) was similar between the baclofen group (14%) and the placebo group (31%), and this difference was not statistically significant (p=0.12). The cumulative abstinence duration was approximately twofold higher in patients assigned baclofen compared to those given a placebo, with mean values of 62.8 (SE 5.4) days and 30.8 (SE 5.5) days, respectively (p=0.001). Notably, no hepatic side-effects were documented in either group. Baclofen demonstrates effectiveness in promoting alcohol abstinence among individuals with alcohol dependence and liver cirrhosis. The medication is well-tolerated, suggesting a potentially significant role in the treatment of this patient population.[22]

Lyon JE et al. conducted a randomized, double-blind, placebo-controlled trial to determine the $GABA_B$ agonist baclofen on acute symptomatic AWS. Patients admitted to the hospital experiencing symptoms of AWS were administered symptom-triggered benzodiazepine treatment with lorazepam according to a standard protocol. These individuals were randomly assigned to receive either oral Baclofen at a dose of 10 mg three times daily or a placebo. The severity of AWS was evaluated using the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar), while the Lorazepam dosage was closely monitored. A total of seventy-nine participants were enrolled in the study. Among the 44 individuals who exhibited symptoms of AWS, they were randomly assigned to either baclofen or a placebo. Thirty-one subjects, comprising 18 in the baclofen group and 13 in the placebo group, successfully completed the 72-hour assessment period, either entirely as inpatients or with outpatient follow-up. In the baclofen treatment group, the likelihood of requiring high doses of benzodiazepines (20 mg or more of lorazepam over 72 hours) to manage AWS was lower (1 out of 18) compared to the placebo-treated group (7 out of 13) (P = 0.004). The study revealed a noteworthy decrease in the utilization of high doses of benzodiazepine (specifically lorazepam) for addressing symptomatic AWS when baclofen was administered. Further investigation into the application of low-dose baclofen for AWS management is noted to have the potential to enhance patient safety by diminishing reliance on high-dose benzodiazepines.[23]

LITERATURE REVIEWS OF BACLOFEN IN AWS

Baclofen, recognized as a selective $GABA_B$ receptor agonist primarily indicated for central spasticity treatment, has gained approval in France for addressing Alcohol Use Disorder (AUD). Its approval in France is contingent upon previous unsuccessful attempts with alternative medical treatments, with a prescribed dose not exceeding 80 mg/day. Despite this approval, no other countries have sanctioned baclofen for treating AUD. Recent evidence highlights genetic links between diminished expression of the GABA transporter GAT-3 and alcohol-preferring tendencies in rats, as well as alcohol dependency in humans, underscoring the significance of this system in maladaptive alcohol use. While there is some indication that baclofen treatment may be linked to abstinence, consistent evidence for reducing heavy drinking has not been established. Baclofen's predominant renal excretion makes it a potential pharmacotherapy for AUD patients with liver disease. Multiple meta-analyses conducted in 2018 on baclofen's efficacy in AUD treatment yielded mixed results.[24]

Rose et al. analyzed 12 randomized controlled trials (RCTs) focusing on parameters such as heavy drinking days, abstinent days, and abstinence rates. Their findings led them to the conclusion that baclofen resulted in a significant improvement in abstinence rates, with a Number Needed to Treat (NNT) of 8.[25]

Pierce et al. conducted a study incorporating 13 randomized controlled trials (RCTs) that assessed variables such as time to lapse, percentage of days abstinent, and the percentage of patients who achieved

abstinence. They also explored the moderating impact of baclofen dosage (categorized as low dose: 30–60 mg/day and high dose >60 mg/day) and pre-trial drinking levels. The results indicated that baclofen demonstrated superiority in prolonging the time to lapse and increasing the percentage of patients achieving abstinence. The efficacy of baclofen was more pronounced when individuals had higher alcohol consumption levels before trial enrollment. Interestingly, high-dose baclofen did not exhibit greater effectiveness than low-dose baclofen, although it was associated with better tolerability.[26]

The 'Cagliari statement' on the use of baclofen in AUD is a consensus document formulated by an international expert panel comprising physicians, psychologists, researchers, and a consultant nurse. Based on their evaluation of clinical practice and research evidence regarding baclofen in AUD patients, the panel concluded that baclofen continues to show promise as a pharmacotherapy for AUD. However, the consensus acknowledges that clear superiority over a placebo has not been firmly established, and the current strength of evidence supporting its treatment efficacy is considered lower compared to that of medications already approved for treating AUD.[27]

Baclofen is reported to be associated with adverse effects, such as sedation even at low doses (e.g., 30–75 mg/day), and concerns about safety, including the risk of overdose and sedation, have been reported. Individuals with a history of self-harm or unstable mood may be particularly at risk, and caution is advised in prescribing, requiring a careful clinical assessment. It is advisable to avoid prescribing baclofen to those at high risk, and dose adjustments should be made cautiously. Consequently, it is not recommended as the initial or first-line treatment for the condition. The heterogeneity among patients with Alcohol Use Disorder (AUD) may play a significant role in the varying results observed across trials. It is conceivable that individuals with a higher severity of dependence are more likely to respond to baclofen treatment. Additionally, a retrospective analysis of one trial suggested a potential moderation of baclofen's treatment effect by a $GABA_B$ receptor polymorphism. However, the validity of this result needs confirmation through replication with a prospective genotype-stratified trial design. Beyond baclofen itself, recent investigations are exploring the role of $GABA_B$ positive allosteric modulators (PAMs) as potential new pharmacological approaches for AUD.[28]

Baclofen appears to be a well-tolerated medication with minimal adverse effects reported at prescribed doses, and there is no indication of euphoria or other pleasurable effects associated with the drug. While these findings are promising, further studies are necessary to validate the role of baclofen in Alcohol Withdrawal Syndrome (AWS). The demonstrated efficacy of baclofen in preventing alcohol relapse suggests its potential as a promising treatment for both AWS and post-withdrawal. The absence of significant side effects and liver toxicity makes it feasible to consider using this drug in the treatment of individuals with Alcohol Use Disorder (AUD) who also have liver disease.[29,30]

DISCUSSION AND CONCLUSION

Overall, despite weaknesses in study designs, some studies indicate that the use of baclofen at a daily dose of 30 mg, and also to 147mg/day highest as employed in different existing studies, may prove effective in alleviating symptoms of alcohol withdrawal. With a treatment history involving just over 31, 42 and 37 patients for alcohol withdrawal syndrome using baclofen, the studies remain unfavorable to be deemed as confirmed treatment, with less favorable studies possibly remaining unpublished. Furthermore, it remains uncertain whether there would be any advantages in employing symptom-triggered baclofen doses and permitting higher doses. At present, the standard practice does not endorse the routine administration of baclofen at a 30 mg daily dose except within the context of clinical trials. Benzodiazepines are recommended as the primary treatment option. Additionally, it remains uncertain whether baclofen effectively prevents severe alcohol withdrawal symptoms, such as seizures and delirium tremens.

The preferred approach for managing both planned and unplanned alcohol withdrawal syndrome (AWS) involves the use of benzodiazepines, administered through either a fixed dose or a symptom-triggered regimen. Careful titration is recommended to effectively suppress signs and symptoms of AWS. Despite the use of tailored and notably higher doses of baclofen in various trials aimed at maintaining abstinence from alcohol, it is surprising that the exploration of higher (tailored) doses for AWS has not been systematically undertaken. The utilization of higher doses may potentially enhance effectiveness, but the associated risks, including an increased likelihood of adverse events and baclofen discontinuation syndrome, particularly in cases of self-discharge, should be taken into consideration.

Further research is warranted to explore the potential role of baclofen as an adjunct to benzodiazepines in alcohol withdrawal syndrome (AWS). Specifically, investigations should aim to determine whether there are additive or synergistic effects resulting from the combination of these two drugs. This becomes particularly intriguing when contemplating baclofen maintenance for preventing relapse and addressing anxiety or post-withdrawal symptoms.

Considering the favorable safety profile of baclofen in individuals with alcohol-related liver disease, including cirrhosis, and the responsive nature of these patients to low doses, there is a potential role for baclofen in the management of alcohol withdrawal syndrome (AWS) within this patient demographic. Additionally, it is crucial to gain a more in-depth understanding of the

impact of baclofen on various symptoms associated with AWS.

Based on the findings of the review, although there is a close association between baclofen and AWS based on the above case studies & series, clinical trials and literature reviews. Baclofen is found to be effective for patients with AWS, in abstinence and showing anti-cravings effect. Several areas for further research on baclofen in the management of alcohol withdrawal syndrome (AWS) are recommended. This encompasses conducting trials to assess the efficacy of tailored (higher) doses of baclofen in AWS, initiating specific trials in patients with advanced liver disease, and exploring the use of baclofen in individuals experiencing severe delirium unresponsive to conventional benzodiazepine treatment. It is emphasized that these studies should uphold high standards of quality and preferably adopt a multicenter trial approach.

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