5-16-2020

Baclofen Use in Alcohol Withdrawal Patients in Inpatient Settings: A Systematic Review

Mona T. Petal

BACLOFEN USE IN ALCOHOL WITHDRAWAL PATIENTS IN INPATIENT SETTINGS

A SYSTEMATIC REVIEW

By

Mona T. Patel

A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2020

Abstract

Aim: To carry out a systematic review of the available evidence from health decision makers, patients, and therapists regarding the ability of Baclofen use in decreasing alcohol withdrawal symptoms to patients in inpatient settings. acute care setting.

Methodology: Systematic searches were carried out on the following databases: Academic Search Premier, CINAHL, Cochrane and PsycINFO via EBSCO Host, Embase, MEDLINE via PubMed, and Web of Science. The last search date was May 28, 2019. The search was limited to the last 10 years, i.e., from January 1st, 2010.

Findings: Four studies were included in the final review. The total population was 258 patients. The studies did not report any statistically significant difference between Baclofen to placebo during the end of the treatment when it comes to decreasing alcohol withdrawal symptoms and reduction of alcohol intake. There was also not a considerable difference between baclofen and standard care dropout, adverse events, and anxiety. Baclofen also increased the frequency of vertigo, dry mouth, and sleepiness.

Conclusions: It was uncertain whether Baclofen improves withdrawal signs and symptoms and reduces side effects in comparison to placebo or other medicines as the studies reviewed did not point to any statistical significance. It is recommended that future reviews assume the meta-analysis approach that can help in measuring the level of heterogeneity in such studies to effectively examine the extent to which baclofen can be effective.

Keywords: Alcohol Use Disorder, Baclofen, Efficacy, Safety.

Acknowledgements

I would like to begin by thanking my family and relatives for the tremendous love, inspiration, praise, and support that they have given me throughout my entire journey. First, I thank the Lord for giving me blessings and the opportunity to put myself in the arms of the ill. I have come this far with the Lord and without him, I would not be here. Next, from the very beginning, my two amazing parents Bhogilal and Pramila Desai. Dad, you have continuously instilled the best for me and have strived the importance of education no matter what. Mom, I thank you for constantly giving me hope and inspiration on becoming a Nurse Practitioner and ensuring success. You both have believed in me and gave me the opportunity and the perseverance to never give up on my dreams and aspirations. You are backbone to all of my current and future successes. To continue, my husband Tushar Patel. You have unceasingly shown me that the world needs knowledgeable, intellectual, and intelligent medical professionals and I strive to be that. I thank you so much for your love, support, respect, and dignity so that I can provide the best care for those who need it most. I am honored that you have instilled positive values in our family and without you my life would be incomplete. To my beautiful daughters Shreena and Krisha Patel, I hope that you know that nothing comes easy, and everything comes with a passion and a desire. I love you, and I faithfully believe that you both will do great things in the world. This has all been for you. To my extended family, Rohit Patel, my sister Vaishali Patel, Kush, and Anushka Patel, I thank you for your continuous encouragement, well wishes, strength, and support. I have found a passion for nursing and have promised myself that with all the sacrifices and tough times that I have endured, I WILL never give up in what I do best which is being a Nurse. I have promised myself that I will finish what I have started because after all, this is only the beginning.

Table of Contents

Baclofen Use in Alcohol Withdrawal Patients in Inpatient Settings: A Systematic Review

Background/Statement of the Problem

Alcohol use disorder (AUD), or at times referred to as alcoholism, is a pattern of alcohol consumption that is characterized by the following: (1) being preoccupied with alcohol, (2) failing to control the level of alcohol use, (3) having to drink more to get the same effect, (4) continuing to drink even after it leads to problems, and (5) experiencing withdrawal symptoms when a person wants to stop use or reduce the amount of alcohol use (Boels et al., 2017). Unhealthy use of alcohol compromises both the users' safety and health, which also leads to other alcohol-related problems. In some cases, unhealthy use of alcohol has been referred to as 'binge drinking', which is a drinking pattern in which an individual consumes five or more alcoholic beverages in less than two hours (Minozzi et al., 2018). For one to know that they are suffering from AUD, one simply needs to review whether one's alcohol consumption leads to repeated distress and functional problems in his or her life. This can range from mild to severe, but even a mild disorder can lead to serious issues, making it more important than ever to treat such conditions.

Alcohol use disorder is classified as a behavioral disorder represented by dysfunctional patterns of alcohol use that can lead to several psychophysical, affective and cognitive symptoms, as well as serious implications for psychosocial well-being and health (Minozzi et al., 2018). Alcohol use disorder is reported to be one of the most widespread psychiatric disorders (Boels et al., 2017). The World Health Organization (WHO), reported in 2018 that the one-year prevalence of AUDs globally was 4.1%, with

the highest prevalence in European nations and North America at 7.5% and 6%, respectively

Globally, the misuse of alcohol is one of the main health risk factors for such conditions as epilepsy, homicide, liver disease, motor vehicle accidents, esophageal cancer, and other intentional injuries (Minozzi et al., 2018). Boels et al. (2017) and Minozzi et al. (2018) have argued that developing mechanisms for helping AUD patients reduce alcohol cravings may be one way to help reduce the implications of AUD. The prescription medication, Baclofen, has been suggested as one method to help AUD patients in reducing their craving for alcohol (Minozzi et al., 2018 and Boels et al., 2017).

Problem Statement

The treatment of AUD has been dominated by psychological strategies, such as: psychotherapy (individual or group), behavior therapy, cue exposure, contingency management, skills training, cognitive behavioral therapy, family, and couple therapy, etc. Although these methods have been developed as a focused psychological strategy, their effectiveness has been limited. Minozzi et al. (2018) reviewed 12 randomized controlled trials (RCT) involving 1128 outpatients from different hospitals, and concluded that nearly 70% of patients failed to respond to such interventions, and for those who responded to the treatment, only a small number managed to reduce patient craving of alcohol (Minozzi et al., 2018). Baclofen, which is a newer treatment option for AUD, has seen little or no focus in a hospital setting but has received much attention over the past few years in an outpatient setting. Researchers such as Leggio et al. (2015), Ponizovsky et al. (2015) and Morley et al. (2014) have yielded conflicting results in their studies when it comes to Baclofen and its ability to deal with patients' alcohol cravings.

The diversity of these findings has sparked a discussion on the potential moderators of alcohol craving. The purpose of this project is to present a systematic review of the best available evidence regarding the use of Baclofen in the treatment of alcohol withdrawal symptoms for inpatients. The outcomes that will be measured in this research include relapsing, frequency of alcohol use, reduction of amount of alcohol consumption after using Baclofen, occurrence of adverse events after using Baclofen, dropout from treatment, and the possibility of anxiety and depression.

Literature Review

The literature search for this review was performed using the databases Cochrane and MEDLINE via PubMed. The search terms used were: Alcoholism, Alcohol Disorder, Alcohol Dependence, Alcohol Overdose, Baclofen and Alcohol, Baclofen Use, Inpatient Settings, Comorbidity, Randomized Placebo-Controlled Trials, High Dose Baclofen Use, Addictive Behavior, Clinical Institute Withdrawal, Clinical Trial, Craving, Relapse Prevention, and GABAb. The search was limited to studies published within the last 6 years as influenced by the evidence-based practice (EBP) approach of only recommending contemporary interventions.

Alcoholism

Alcoholism refers to a pattern of alcohol consumption, which involves issues managing consumption, and preoccupation with the next alcohol consumption. Even when an individual is aware that consumption is leading to problems, they continue to consume more to achieve the same effect, and experience withdrawal symptoms when they want to stop or reduce drinking alcohol (Boels et al., 2017). Alcoholism is the fourth leading cause of preventable death worldwide, after smoking, high blood pressure, and obesity. A study carried out by the World Health Organization in 2018, revealed that alcoholism resulted in 3 million deaths in 2016, primarily males, which accounted for 5.3% of all deaths the world. The economic implications of alcoholism in 2010 was $249 billion, or $2.05 per drink (Sacks et al., 2015); and as of 2018 the figure has more than doubled to $566 billon, or $5.01 per drink (WHO, 2018). The dependence on and misuse of alcohol has severe health, economic, and social consequences for alcohol abusers, their families, and the society at large (Fogarty International Center, 2016). Alcohol is a psychoactive substance that affects every organ of the body. Literature has linked its

consumption to cancer, injuries, tuberculosis, and hundreds of other persisting conditions (Boels et al., 2017). Crime, violence, unemployment, and absenteeism are also negative consequences related to excessive use of alcohol (Boels et al., 2017). Aside from killing more than 3 million people annually, alcohol consumption is also directly tied to most disabilities among people aged between 15 and 49 years (Fogarty International Center, 2016). This makes it more important than ever to study how to effectively deal with alcohol and its complications.

The ethology of alcoholism is multifactorial, including genetic, social, psychological, and environmental factors (Boels et al., 2017). In recent years, the phenomenon of craving in alcoholism has also received renewed attention. The ethology of alcohol craving, and alcoholism, considers alcohol to be a food and drug. Thus, in essence, the same common appetite mechanism involved in ordinary eating is the same mechanism involved in alcohol ingestion (Ray et al., 2016). While some people can regulate their food intake, others cannot; this is same for alcohol ingestion (Ray et al., 2016). Past studies have suggested at least three likely kinds of alcohol cravings (Jones et al., 2015; Yamini et al., 2014). The first is *unadorned hunger*, which is the desire to drink that is not based on conditioning and cues. For instance, someone who is used to taking more than 5 bottles per drinking session and reduces to less than 2 bottles per drinking session is more likely to revert to consuming 5 bottles per drinking session compared to someone who is used to consuming less than 2 bottles per drinking session (Jones et al., 2015). The second case relates to *cues and conditioning* (Yamini et al., 2014). This concept relates to environmental cues that trigger craving of alcohol or cause discomfort to alcohol consumers who want to withdraw from alcohol consumption (Yamini et al.,

2014). The third concept suggests that drinking is an *automated process*, which makes controlling it very difficult. These concepts will further be discussed in the next section of this literature review with regards to their specific theories.

Boels et al. (2017) suggested that some individuals react differently to alcohol use, which can make some individuals more susceptible to AUD. Some risk factors that cause people to react different include: a family history of abuse, steady alcohol consumption over time, beginning alcohol use at an early age, depression, social and cultural factors, history of Bariatric surgery, and history of trauma (Boels et al., 2017). Because individuals respond differently to alcoholism, diverse treatment methods have also been developed that can be tailored to the patient's needs (Boels et al., 2017). Treatment can include brief intervention, group or individual counseling, an inpatient stay program, or an outpatient program. Some of the interventions include detoxification and withdrawal programs, psychological counseling, oral medication, education, injected medication, constant healthcare support, spiritual practice, etc. (Boels et al., 2017).

According to Hasin et al. (2016), as stress increases during sobriety, craving may also increase. In a national epidemiologic survey on alcohol and related conditions by Hasin et al. (2016), the researchers found that 75% of participants attributed their alcohol cravings to stress. The researchers recruited participants from the NESARC-III target population, which is a non-institutionalized civilian population (18+ years). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) is a nationwide representative survey of more than 46,000 Americans who submitted data on AUDs and their associated disabilities, as well as saliva samples. The aim of this study was to provide further understanding of the risk factors, prevalence, health disparities, and costs

of AUDs. The data, which is available publicly, also includes information on stress and alcohol consumption. Hasin et al. (2016) found that 56% of the participants attributed alcohol consumption to stress-related factors.

Theoretical Models of Alcohol Craving

As discussed, in the previous section, people react differently to alcohol consumption. Accordingly, it is relevant to examine different theoretical models of alcohol craving to better understand the basis behind the different reactions to alcohol consumption. Craving refers to the conscious experience of a desire to consume alcohol (Hasin et al., 2016). Various models explain the basis of craving, which are grouped into the following classes: phenomenological theories, conditioning theories, and cognitive theories. Phenomenological theories of craving are mainly descriptive in nature and are derived from the observations and interviews conducted on clinical addicted patients (Hasin et al., 2016). Phenomenological theories such as the Loss of Control Theory and the Unawareness of Compulsion to Drink Theory, both discussed by Drummond (2001), consider craving to be a symptom of alcoholism where an individual shows signs of alcohol addiction and obsessive use of alcohol. Drummond (2001) defined alcohol addiction and obsessive use of alcohol as the consumption of more than 2 drinks in one hour.

Conditioning theories, on the other hand, include the conditioned withdrawal model, the conditioned process model, the conditioned drug-like model, the two-process theory, the incentive sensitization theory, and the cue-reactivity model (Drobes et al., 2001). These groups of theories differ slightly in terms of the effect of an alcoholic patient's withdrawal from alcohol use.

Conditioning theories are, however, all derived from the belief that neutral stimuli in someone's environment can elicit conditioned responses through a process termed conditioned learning. Neutral stimuli are stimuli that initially produce no specific response other than focusing attention (Drobes et al., 2001). Drobes et al. (2001) proposed that the conditioned responses sparked by such cues, for example an alcohol advertisement, can lead to alcohol craving. According to conditioning theories, alcohol withdrawal is negatively affected by the users' displeasure of the substance used to help in their withdrawal. This may happen if a patient negatively reacts to the drug is introduced to help in the withdrawal, for example an allergic reaction to a medication (Connor et al., 2016). The two-process theory, incentive sensitization theory, and the cue-reactivity model argue that alcohol withdrawal is negatively affected by the same environmental cues, as alcohol advertisements (Drobes et al., 2001). Drobes et al. (2001) points out that when an individual views an alcohol advertisement it may affect the withdrawal process. In other words, it may entice them to want to consume again.

The last group of theories that attempt to describe craving experienced in AUD are known as cognitive theories. Theories in this category include cognitive social learning theory, cognitive labeling model, dual affect model, dynamic regulatory model, and cognitive processing model (Nandrino et al., 2014). Cognitive theories are derived from the belief that in a high-risk situation, e.g., where one of the alcoholic individuals is faced with a choice of consuming a drink or not, the probability of consuming will rely on their expectations. Some of these expectations include efficacy expectations and outcome expectations. Efficacy expectations are the person's confidence in their ability to

resist the temptation to consume alcohol, whereas outcome expectations are the person's beliefs concerning the consequences of consuming a drink or not (Nandrino et al., 2014).

Non-Pharmacological Treatments for Craving

By examining the possible causes of alcohol craving, it becomes evident that health care providers should focus attention on both pharmacological and non-pharmacological methods for craving. A multi-faceted approach in managing AUD, and craving, may provide a more individualized method for successful alcohol withdrawal treatment. Non-pharmacological interventions are important components of alcohol craving that can be applied alone or together with medication. Connor et al. (2016) points out that a combination of both has been found to be more effective in managing AUD compared to pharmacological treatment alone. Some of the non-pharmacological treatments of alcohol craving include psychotherapy (individual or group), behavior therapy, cue exposure, contingency management, skills training, cognitive behavior therapy, family and couple therapy, etc. (Connor et al., 2016). Psychotherapy is the verbal interaction between a patient or a group of patients and a therapist, which is aimed at altering the behavior and feelings of the patients. In AUD, an example of psychotherapy is Alcoholics Anonymous (AA) (Connor et al., 2016). Cue exposure is the act of exposing AUD patients to prevention and coping stimuli each time they see something that relates to alcohol; such stimuli can include pictures of the severe effects of alcoholism on alcohol abusers (Connor et al., 2016).

Very few people with AUD seek treatment on their own. Studies carried out by Hasin et al. (2016) and Grant et al. (2015) had comparable results when they concluded that around 5-15% of people with AUD seek therapeutic interventions voluntarily. Such

persons are usually taken to therapists by friends or family members, and thus may end up being less motivated to go through the therapy sessions. Some of these patients never feel the need of undergoing the therapy sessions, whereas other simply decline.

A review carried out by the Canadian Agency for Drugs and Technologies in Health (2014) examined compliance rate between pharmacological treatments versus non-pharmacological treatments when treating AUD. The review, which included 8 reports, found that in an outpatient population, patients tend to comply more with non-pharmacological treatments versus pharmacological treatments. The agency attributed the low compliance with pharmacological treatments to the decreased supervision granted to outpatients. This is because non-pharmacological treatments, whether in-patient or outpatient, still require patients to be physically present with a therapist in order for the interventions to be administered (Canadian Agency for Drugs and Technologies in Health, 2014). Another conclusion made by the Canadian Agency for Drugs and Technologies in Health (2014) was that there have been no clinical trials focusing on the effectiveness of non-pharmacological interventions alone. Currently the literature only provides evidence of the studies that have compared pharmacological versus non-pharmacological interventions.

Pharmacological Treatments for Craving

Though non-pharmacological treatments have demonstrated effectiveness, pharmacological interventions offer alternative methods for patients who suffer from alcohol craving (Hasin et al., 2016). Pharmacological treatments for craving argue that the same person may experience different types of cravings depending on the rewards they get or the coping issues they experience (Grant et al., 2015). Expanding on this

notion, Saha et al. (2016) adds that the same individual can experience obsessive rewarding or coping cravings or even a combination of them. Saha et al. (2016) further points out that reward cravings occur when an individual consumes alcohol to gain the perceived rewards. Coping cravings, on the other hand, emerge when one consumes alcohol due to perceived challenges they face while not intoxicated, such as stress (Saha et al., 2016).

Naltrexone. One of the most well-known pharmacological methods for treating craving is the use of Naltrexone, which is sold under the brand name ReVia and Vivitrol (Oslin et al., 2015). Naltrexone helps in reducing alcohol craving within the first three months of use in nearly 36% of the users, which makes it helpful for curbing alcohol use in patients (Oslin et al., 2015; Foa et al., 2013). Nonetheless, some of the drawbacks of naltrexone are that it cannot be used in hepatic disease patients, or in patients with past cases of depression or suicide attempts because depression is one of the side effects of Naltrexone (Oslin et al., 2015). Another medication used for withdrawal is Disulfiram, which works by inhibiting the enzyme acetaldehyde dehydrogenase, thus reducing the after-effects of alcohol consumption. The use of Disulfiram, however, is limited, as this medication is self-administered in the outpatient setting. Compliance has been found to be poor when patients self-administer this medication but is has demonstrated effectiveness when administered in the clinical setting (Oslin et al., 2015). For example, a randomized control trial conducted by Foa et al. (2013), found that Disulfiram helped to reduce alcohol craving in 49% of in-patients, while only reducing alcohol craving in 14% of the out-patients who self-administered the drug. The study included 165 patients (95 in-patients and 70 out-patients) recruited from the University of Pennsylvania and the

Philadelphia Veterans Administration. Foa et al. (2013) noted the challenges with self-administration of this type of medication and claimed that some of the patients at times skipped or completely stopped using the drugs because of the challenges.

Benzodiazepines. Another common pharmacological treatment for craving is the use of benzodiazepines. Benzodiazepines are controlled, schedule IV substances that are only used following a healthcare professional's recommendation for alleviation of AUD withdrawal symptoms (AAC, 2019). Whereas many people diagnosed with AUD never go through severe withdrawal symptoms or complications, benzodiazepines are usually prescribed during the initial phase of detoxification, as they tend to work best during the initial phase when alcohol withdrawal symptoms present most strongly. Dixit et al. (2016) demonstrated this in a review comparing the effectiveness between benzodiazepines and disulfiram. This review, which included 17 clinical trials published between 2011 and 2015 concluded that AUD patients tend to be less responsive to benzodiazepines after three weeks of treatment, and the symptoms are still present. Investigators in this study point out that benzodiazepines are best used to manage withdrawal symptoms during the first week or two of treatment, and if the symptoms do not subside, the intervention should be changed (Dixit et al., 2016).

Alternative Pharmacological AUD Treatment: Baclofen

While the pharmacological and non-pharmacological treatments discussed above have been approved for treating AUD patients, their clinical and non-clinical use is rather limited by different factors. As previously stated, even though disulfiram reduces alcohol craving, its ability to cause depression renders it a dangerous medication for patients with past depression issues (Minozzi et al., 2018). Other substances, such as naltrexone and

benzodiazepines, have been ruled as safe and effective among AUD patients, but the high variation in response to treatment suggests that some patients might not benefit from this intervention (Chaignot et al., 2018). An alternative, such as Baclofen, offers promise in recent research because this medication lacks any of the unwanted adverse effects and addictive properties discussed earlier of such treatments as Benzodiazepines, Disulfiram, and Naltrexone.

Baclofen. Baclofen is an agonist of the γ-aminobutyric acid type B receptor that is sold under the brand names Lioresal and Kemstro. It was originally approved for use in spasticity-related neurological illnesses but has only recently emerged as a treatment option for AUD (Boels et al., 2017). Baclofen has been investigated as an option for treating alcohol craving since the early 2000s after a group of researchers found that baclofen prevented withdrawal symptoms in rats (Minozzi et al., 2018). This seminal work has since led to the investigation, and possible use for this treatment in human beings. For example, a single-patient case report presented by Perogamvros et al. (2015) concluded that the administration of baclofen 10mg every 8 hours improved the patient's Clinical Institute Withdrawal Assessment for Alcohol (CIWA) score. The case report included a 61-year-old patient with AUD who was referred to the sleep laboratory in an unnamed university hospital in Basel after previously incurring three road accidents due to sleepiness.

In a cohort report study consisting of 165,334 patients aged between 18 and 70 years, Chaignot et al. (2018) showed that baclofen was effective in reducing Delirium Tremens (DT) among patients in the ICU. Delirium Tremens is one of the most severe form of alcohol withdrawal, which is manifested by altered mental status and sympathetic

overdrive, which can lead to cardiovascular collapse. The participants were recruited from the French national health insurance information system database (SNIRAM), and had to have an initial diagnosis of AUD, with baclofen as the treatment intervention. The researchers compared DT to a placebo treatment. The number of hospital days was significantly lower among DT patients who were treated with baclofen (*M*=23 days) compared to those treated with a placebo (*M*=39 days). Most notably, the death rate was also significantly lower among the patients who used baclofen (9%) compared to those who received the placebo treatment (15%) (Chaignot et al., 2018).

While several open-label trials, case series, and case reports have shown the effectiveness of Baclofen in AUD patients (Brennan et al., 2013; Reynaud et al., 2017; Rolland et al., 2014), some randomized controlled trials (RCTs) (Farokhnia et al., 2017; Ponizovsky et al., 2015), have shown conflicting findings. For instance, in Farokhnia et al. (2017), 80 AUD patients received 30 mg/day of Baclofen or a placebo for 12 weeks in addition to eight sessions of a comprehensive psychological intervention. Researchers found no difference between baclofen and placebo in the percentage of heavy drinking days, time to lapse, and abstinent days (Farokhnia et al. (2017). Reynaud et al. (2017) also compared the effectiveness of 30 mg/day of baclofen and a placebo in the treatment of AUD for 12 weeks as well. The authors found that baclofen significantly reduced the number of drinks per drinking day.

As noted earlier, researchers have found it difficult to assess the efficacy of interventions such as baclofen in outpatients due to lack of compliance with self-administration (Beraha et al., 2016; Cooney et al., 2019). However, a treatment such as this may still be beneficial if employed in the inpatient setting. Therefore, the purpose of

this review was to systematically review the use of baclofen in the inpatient setting for AUD patients during withdrawal.

Theoretical Framework

This review utilized the PRISMA framework discussed by Stewart et al. (2015). The word PRISMA, which stands for Preferred Reporting Items for Systematic reviews and Meta-Analyses, comprises of a four-phase flow diagram, which guides researchers on how to improve on their reporting of systematic reviews and meta-analyses (Stewart et al., 2015). Even though the checklist recommends that researchers mainly use RCTs when conducting their systematic reviews, the PRISMA framework can also be used in reviewing other types of research methods for evaluation of data reporting. The four-phase flow diagram that was adapted from Stewart et al. (2015) is attached in Figure 1 below.

The procedure for the literature research is illustrated in Fig. 1 below. The process began by searching multiple databases for the necessary literature. In the search results, duplicates were removed, and the titles and abstracts of the remaining studies were reviewed to see if they met the inclusion criteria. Once the studies that did not meet the inclusion criteria based on their titles and abstracts were excluded, the remaining studies were fully reviewed and those that did not meet the inclusion criteria based on their objectives, designs, and findings were also excluded. These steps are illustrated in figure 1 below:

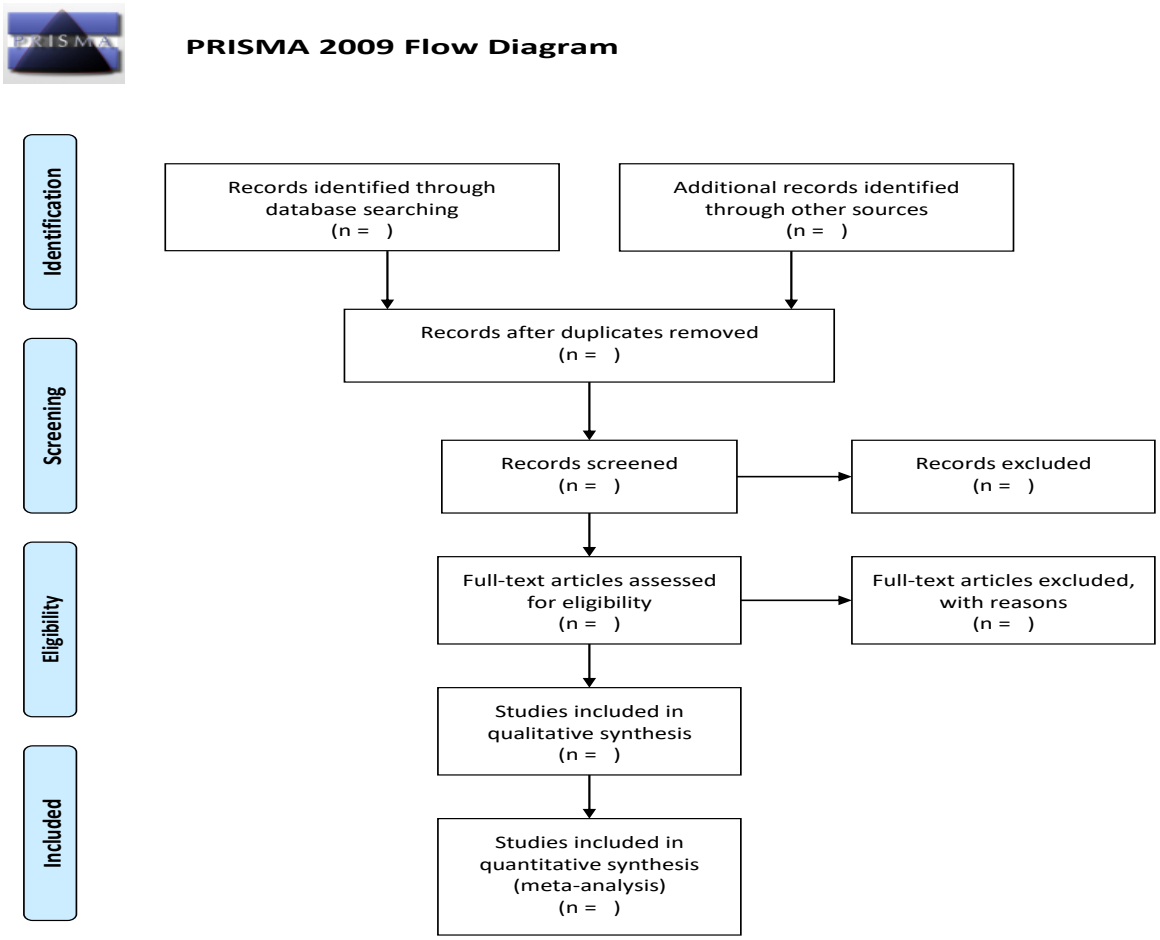

Figure 1. *Four-phase flow diagram for preferred reporting items for systematic reviews and meta-analyses (Liberati et al., 2009)*

Method

Purpose

The purpose of this project was to present a systematic review of the best available evidence regarding the use of baclofen in the plan of care in the treatment of alcohol withdrawal symptoms for patients within an acute care hospital setting.

Inclusion/Exclusion Criteria

The inclusion criteria for studies included was as follows: (a) Alcohol withdrawal; (b) January 1, 2013 onward; (c) English language; (d) Intervention utilizing Baclofen; (e) Inpatients aged > 18 and diagnosed with alcohol withdrawal disorder; and (f) Randomized controlled trials (RCT) studies. The exclusion criteria for the literature search was: (a) Not published in English language; (b) Patients younger than 18 years old; (c) Outpatients; and (d) Non-RCT's.

Search Strategy

The literature search was performed using the databases Cochrane and MEDLINE via PubMed. The search terms used were: Alcoholism, Alcohol Disorder, Alcohol Dependence, Alcohol Overdose, Baclofen and Alcohol, Baclofen Use, Inpatient Settings, Comorbidity, Randomized Placebo-Controlled Trials, High Dose Baclofen Use, Addictive Behavior, Clinical Institute Withdrawal, Clinical Trial, Craving, Relapse Prevention, and GABAb. The search was limited to studies published within the last 6 years as influenced by the evidence-based practice (EBP) approach of only recommending contemporary interventions.

Data Collection

Descriptive data collected from each study was summarized in study description tables (Appendix B), which specifies the researcher names, date of publication, aim(s), design, sample, setting, and methods. Additionally, a second set of tables, labeled 'Outcome Data Collection' (Appendix C) display data collected regarding outcomes under investigation in this review. These include: (1) relapsing, which was measured by the number of patients who returned to drinking during the cause of the study and the follow-up; (2) frequency of alcohol use, which was measured by the percentage of abstinent days at the end of treatment; (3) the amount of alcohol consumption, which was measured by the number of drinks per drinking occasion or drinking day; (4) occurrence of adverse events after implementing the intervention such as fatigue and tiredness, insomnia, pain, vertigo, dizziness, drowsiness, sedation, dry mouth, and constipation; (5) dropout from treatment, and (6) possibility of anxiety and depression.

Critical Appraisal

The assessment of the quality and bias present in all retrieved studies was done using the *Critical Appraisal Skills Program* (CASP) tool (Appendix D). The CASP tool addresses such factors as sequence generation, allocation concealment, participants' blinding, blinding of assessors, incomplete outcome data, and selective reporting (Higgins et al., 2017). The *Critical Appraisal Skills Program* was developed to help researchers judge the quality of randomized controlled trials (RCTs) based on the factors mentioned above (Higgins et al., 2017). These factors are usually judged as either high, low, or unclear depending on how the people who carry out RCTs report on them in their studies. The importance of the tool is that it offers a universally agreed upon method of

judging RCTs to know whether to implement the evidence uncovered (Higgins et al., 2017).

Data Synthesis

All studies included within this systematic review were evaluated to compare the differences and similarities using a narrative approach. A narrative of the findings is presented in the next section to discuss the findings of the data synthesis. The outcomes from each individual trial are combined through a thematic analysis, thus the review was not be able to measure any degree of heterogeneity, which can only be achieved through a meta-analysis. A thematic approach is where one study is the leading themes arising from the outcomes of each trial and reports these themes.

Results

Search Results

The databases search retrieved 199 studies. Upon further assessment, 98 duplicates were removed, leaving a total of 101 studies. Eighty-seven more studies were excluded after a review of their title and abstracts. The full texts of the remaining 14 studies were assessed and an additional ten were excluded due to the following: they are awaiting classification, studies are ongoing, the study objectives do not meet this review's inclusion criteria, the study designs do not meet this review's inclusion criteria. In the end, a total of 4 studies were included in this review. A flow diagram of the procedure that was followed to exclude 195 studies from the review and include the selected four is outlined in Appendix A.

Individual Study Description

The aim of a study conducted by Heppe et al. (2019) (Appendix B-1) was to determine if severity of AWS decreased in hospitalized patients who received baclofen in their care. This study was a double blind, placebo controlled, randomized trial design. The study was carried out at Denver Health, a university-affiliated, urban, public, safety-net hospital. The study involved 101 medical inpatients who were at risk for developing, or presented with, mild AWS. Patients were grouped into two groups who received oral medication of either baclofen 10 mg, (n=50) or placebo (n=51) every eight hours for five days or until hospital discharge. All participants also received symptom driven benzodiazepine as directed by Severity of Ethanol Withdrawal Scale SEWS protocol. The study measurements included: the proportion of patients progressing to moderate or severe AWS, and difference in mean SEWS assessment scores at 24h, 48h, and 72h

between groups; peak and cumulative dosage of benzodiazepines over 72h post-enrollment (Heppe et al., 2019).

The purpose of the study by Lyon et al. (2011) (Appendix B-2) study was to determine the effect of gamma- Aminobutyric acid (GABA)-B agonist baclofen on the course of acute symptomatic AWS. The research assumed a prospective, randomized, double-blind placebo-controlled clinical design. It was carried out in two tertiary-care hospitals in Duluth, Minnesota. The study involved 31 inpatient adults who were admitted for any reason, including AWS, and judged to be at high risk for AWS. Patients were grouped into two groups who received oral medication of either: baclofen 10 mg, (n=18) or placebo (n=13) every eight hours for 72 hours or until hospital discharge. All participants also received symptom driven lorazepam as directed by CIWA-AR protocol. Measurements included: AWS severity was assessed using the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-AR) and Lorazepam dose was monitored every eight hours for 72 hours or until hospital discharge.

The aim of the study by Girish et al. (2016) (Appendix B-3) was to compare the efficacy and tolerability of baclofen with chlordiazepoxide in uncomplicated AWS. The study assumed a randomized, open-label, standard controlled, parallel group study of baclofen, and chlordiazepoxide in AWS design. The study was carried out in a tertiary-care hospital in India. It involved 60 inpatient adults who were admitted for uncomplicated AWS. Patients were grouped into two groups who received oral medication of either baclofen 30 mg, (n=30) or chlordiazepoxide 75 mg (n=30) for 9 days in decremented fixed dosage. Lorazepam was used as a rescue medication. Measurements included: CIWA-AR to assess clinical efficacy and Clinical Global

Impression scores, symptom-free days, and subject satisfaction scores were used as the secondary efficacy parameters.

The purpose of the study by Gulati et al. (2019) (Appendix B-4) was to compare the efficacy of baclofen and benzodiazepine (lorazepam) in reducing symptoms of AWS. The study assumed a single-center, randomized, open-label design. It was carried out in an acute care setting in the Department of Psychiatry, GMCH, Chandigarh, in India. It involved 66 patients with the diagnosis of alcohol dependence as per ICD-10 criteria were enrolled. Patients were grouped into two groups who received oral medication of either: baclofen 10 mg, (n=30) 3 times or lorazepam 8-12 mg (n=30). The patients received B1 (100 mg/day through intramuscular route) and psychotherapeutic interventions. Measurements included: reduced severity of alcohol dependence as measured by the Severity of Alcohol Dependence Questionnaire (SAD-Q) and alcohol withdrawal was measured using the CIWA-AR.

Critical Appraisal

As earlier discussed in the methodology, the risk of bias was assessed using the CASP tool as recommended by Cochrane. For a tabular summary of the bias of the 4 studies, see Appendix D. All studies had low risks when it came to random sequence generation, implying that the sample population was randomized. One of the 4 studies (Heppe et al., 2019) did not report on the group allocation, implying the risk was unclear in that study, while the remaining confirmed to conceal the allocation of groups. All the 4 studies confirmed to blind the participants and assessors to the objective outcomes, implying that the risk was low. Only two did not report blinding of the subjective outcomes, implying that the risk was unclear (Girish et al., 2016; Gulati et al., 2019). The

outcome blinding was thus fairly at low risk. Only one study failed to report on dropouts, missing data, and thus were judged as unclear (Lyon et al., 2011). All the 4 studies reported all outcomes, implying that there was no selective reporting.

Cross Study Analysis

Study Characteristics

The cross-study analysis table (Appendix E) demonstrates the primary and secondary outcomes investigated for each study. This review included four randomized controlled trials (RCTs) with a total of 258 patients. The mean sample size was 64.5 participants, with a range of 31 participants (Lyon et al., 2011) to 101 participants (Heppe et al., 2019). The mean participant age was 42 years across all studies and included a majority of more men when compared to women. All the participants had to have been diagnosed of alcohol use disorder and who were currently drinking. Two of the studies were carried out in university hospitals in the United States (Heppe et al., 2019; Lyon et al., 2011), while the other two were carried out in India (Girish et al., 2016; Gulati et al., 2019). The outcome measures included in the 4 studies were as follows: (1) relapsing, (2) frequency of alcohol use, (3) amount of alcohol consumption, (4) occurrence of adverse events, (5) dropout from treatment, (6) anxiety and depression.

Interventions

All studies used different doses of Baclofen: in Lyon et al. (2011) (between 30 mg and 270 mg per day), in Heppe et al. (2019) (between 30 mg and 60 mg per day), in Girish et al. (2016) (between 30 mg and 150 mg per day), and Gulati et al. (2019) (30 mg per day). The mean duration of intervention was 18.1 weeks, and mean duration for studies was 19.9 weeks.

Major Outcomes

Some of the themes that were extracted from the findings of the 4 studies included: (1) relapsing, (2) frequency of alcohol use, (3) amount of alcohol consumption, (4) occurrence of adverse events, (5) dropout from treatment, (6) anxiety and depression.

Relapsing. Relapsing was measured by the number of patients who returned to drinking during the course of the study and the follow-up (Lyon et al., 2011; Heppe et al., 2019; Girish et al., 2016). These studies, which had a combined total of 192 patients, did not report any difference between the baclofen group and standard care (placebo) group, implying that both baclofen and standard care can influence one's ability of relapsing.

Frequency of Alcohol Use. Frequency of alcohol use was measured by the percentage of abstinent days at the end of treatment. Only 1 of the 4 studies (Lyon et al., 2011) found a statistically significant reduction ($P = 0.002$) in the frequency of use, implying that baclofen can reduce the frequency one's alcohol use. One clinical trial (Heppe et al., 2019) reported the main percentage of days abstinent for each group, but the researchers did not provide the SD values; the mean percentage of days abstinent was 62.6% for the baclofen patients, and 46.1% for the placebo patients. The rest of the studies never found any difference between the baclofen group and placebo group; this means that both baclofen and standard care can influence one's frequency of alcohol use.

Amount of Alcohol Consumption. The amount of alcohol consumption was measured by the number of drinks per drinking occasion or drinking day. Two studies involving 131 participants found that baclofen tends to increase drinks per drinking occasion as compared to the placebo group (Heppe et al., 2019; Lyon et al., 2011). One other study involving 66 participants (Gulati et al., 2019) did not report any difference

between the baclofen group and placebo group, implying that both baclofen and standard care can have an impact on one's amount of alcohol consumption.

Occurrence of Adverse Events. Adverse events were measured by the number of participants with at least one side effect after the end of the treatment. Some of the adverse events measured include: fatigue and tiredness, insomnia, pain, vertigo, dizziness, drowsiness, sedation, and dry mouth (Gulati et al., 2019; Heppe et al., 2019), including constipation as measured in Lyon et al. (2011) and Girish et al. (2016). It is important to remember that the total number of participants accounted for in these studies was 258. There was no difference between the baclofen group and placebo group in the abovementioned adverse events aside from dry mouth, sleepiness, vertigo.

Dropout from Treatment. This measure was present in all the 4 studies; all of them reported no difference between the baclofen group and placebo group when it came to drop out from the treatment. This meant that both baclofen and standard care can equally influence the decision of dropping out from the treatment. Furthermore, there was no statistically significant difference in the number of patients who dropped out of the studies due to adverse events in both the control and intervention groups.

Anxiety and Depression. Two studies with a total of 145 patients used different scales to measure the level of anxiety and depression between the baclofen and placebo groups (Heppe et al., 2019; Lyon et al. 2011). None of the studies reported any difference between the two groups when it comes to anxiety, but Lyon et al. (2011) found that baclofen tends to reduce the level of depression among patients. This is one of the positives of baclofen that was found during the review of the 4 studies.

Summary and Conclusions

The aim of this research was to offer a systematic integration of the available evidence from health decision makers, patients, and therapists regarding the ability of baclofen in decreasing alcohol withdrawal symptoms to AUD patients in an acute care setting. The treatment of AUD was in the past dominated by psychological strategies, and even if methods from different therapeutic and theoretical backgrounds have been developed, the effectiveness of these methods are limited. A high number of patients fail to respond to such interventions, and for those who do, only a small number of them manage to maintain their abstinence (Minozzi et al., 2018). Baclofen as one of the treatment options for AUD has received much attention over the years. Systematic searches were carried out on different databases and four randomized controlled trials on baclofen were retrieved. A summary of the findings from the studies is presented in the next section.

This review included a total of four randomized controlled trials with 258 participants and a minimum study duration of 19.9 weeks. All the four studies compared baclofen to placebo (standard care), but they rarely reported on any statistically significant superiority between baclofen to placebo during the end of the treatment when it comes to reduction of withdrawal symptoms and drinking. Furthermore, this review found no considerable difference between baclofen and standard care dropout, dropout because of adverse events, anxiety, and number of participants with more than one adverse event that was measured.

The current review employed a narrative approach to determine these findings. None of the four studies pointed to a significant difference between baclofen and

standard care. Baclofen was found to be similar to standard care in ensuring continuous abstinence and reducing drinking amount and frequency. The findings of this systematic review did not indicate a conclusive implication when using baclofen to treat alcohol use disorder. Additionally, no support was found for the application of baclofen as a first-line treatment option for AUD patients. It is worth mentioning, however, that baclofen was found to significantly reduce the level of depression among patients compared to the placebo group (Heppe et al., 2019). Unfortunately, baclofen use also increased the frequency of vertigo, dry mouth and sleepiness (Lyon et al. 2011). Nonetheless, the sleepiness result was derived from a study (Lyon et al., 2011) with only 30 participants. Even though RCTs seemed promising, the evidence they present currently cannot be fully relied upon when it comes to treating AUD patients.

The findings of this research are similar to the findings of De Beaurepaire et al. (2019), Garbutt (2018), and Farokhnia et al. (2017), in which results likewise did not point to any benefit of using baclofen to manage AUD. According to De Beaurepaire et al. (2019), while baclofen has had some positive results in some studies, controversies still exit regarding dosing, efficacy and safety concerns. De Beaurepaire et al. (2019) concluded that AUD is ineffective in patients with comorbid conditions, including psychiatric issues, bipolar affective disorder, anxiety, liver disease, epilepsy, respiratory diseases, and Parkinson's Disease. In Garbutt (2018), frequency of alcohol use was measured by the percentage of abstinent days at the end of treatment. Garbutt's research found no difference between the baclofen group and placebo group, indicating no difference between baclofen and standard care in influencing frequency of alcohol use. Finally, in Farokhnia et al. (2017) anxious alcohol-dependent individuals (n = 34) were

randomized to baclofen and placebo groups for a period of 1 year. The outcomes of this study included total amount of alcohol self-administered, alcohol craving, mood and anxiety symptoms, and subjective responses to alcohol intake. According to Farokhnia et al. (2017), self-administered intake was not significantly different in the baclofen group and placebo group. Alcohol craving and anxiety symptoms, however, were better in the baclofen group. Overall, the findings of this study indicate that baclofen might not be effective when it comes to the reduction of withdrawal symptoms. More research regarding management of depression, consumption amount and abstinence days in the treatment of AUD is warranted.

Limitations

Some of the major limitation of the current research included its use of only four studies. The use of only four studies might not give a true reflection of the effectiveness of baclofen on AUD patients, however, RCTs were the only design types included in this systematic review. RCTs are considered to have the most reliable evidence when it comes to evidence-based practice because of the randomization and blinding nature of such studies. Furthermore, all the patients in the four studies were admitted for AUD. Also, the studies were evaluated using a critical appraisal approach, thus increasing the strength of evidence. The differences of the outcomes used in assessing the effectiveness of the reviewed studies served as the main limitation of this research. This highlights the fact that different outcomes are established in alcoholism research and demonstrates the lack of consistency in determining which treatments are most successful.

Recommendations and Implications for Advanced Nursing Practice

This section will provide the recommendations and implications of the findings of this research on nursing practice and education.

Implications for Practice

The outcomes of this research did not point to a significant difference between baclofen and placebo. All of the studies reviewed showed that baclofen was similar to placebo in terms of maintaining continuous abstinence and reducing drinking frequency or amount of drinking. The cross-study analyses of primary studies did not point to any positive implication of baclofen in the treatment and management of AUD. Additionally findings did not support the application of baclofen as a first-line treatment for AUD patients. Though some RCTs have suggested promising outcomes the current evidence regarding use of baclofen as a first-line treatment is still uncertain.

Implications for Research

To better understand the inconsistency of effects shown in this research factors such as dosing schedules, severity of AUD, treatment setting, and status of drinking at the start of the treatment may determine efficiency. One factor that needs special attention in further studies is the titration of dose, to achieve the best therapeutic response. Titration regimes can be beneficial compared to fixed dosing of baclofen in further clinical trials, because of the high individual variation of effective doses (Rolland et al., 2014). Furthermore, to attain the correct implementation of treatment and 'fairness of testing', participants' compliance needs to be monitored to ensure that dosing schedules are strictly followed.

Another issue that needs to be addressed is blinding during treatment, which can increase the level of bias. Even though the four studies included in this review practiced some level of blinding, such as: allocation concealment, blinding of personnel, or blinding of participants, adverse effects can reveal a participant's research treatment assignment. The application of active placebo elements that mimic adverse events of baclofen can prevent an overestimation of effects through response bias, differential attrition, and/or placebo effects (De Beaurepaire et al., 2019). If an inert placebo is applied, testing of blinding integrity by questioning participants about their perceived group allocation can be an easier method that paves the way for retrospective assessment of blinding integrity (Agabio et al., 2018). Therefore, there is a need to further explore the efficacy and safety of baclofen and identify potential moderators and mediators of baclofen's implications on alcohol use.

Recommendations for Education

Compared with placebo, baclofen was noted to make little to no difference to patients who experienced adverse events, dropped out of the treatment, and the time taken for recovery. Also, baclofen made little difference to the number of patients who relapsed as well as the amount of alcohol the consumed after the treatment. Furthermore, the main intervention made little to no difference in the number of days the patients stayed alcohol-free. Also, baclofen might increase the amount of alcohol used, measured by number of drinks per drinking days, which may lead to adverse events such as depression, numbness, somnolence, muscle rigidity. However, there was no significant difference when comparing baclofen and placebo. Greater research is needed in the area of more effective interventions in order to help AUD patients fully recover.

References

Agabio, R., Sinclair, J.M., Addolorato, G., Aubin, H.J., Beraha, E.M., Caputo, F., Chick, J.D., de La Selle, P., Franchitto, N., Garbutt, J.C., & Haber, P.S. (2018). Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. *The Lancet Psychiatry*, *5*(12), 957-960.

American Addiction Centers (AAC). (2019). *Benzodiazepine Addiction: Symptoms and Signs*. Retrieved from https://americanaddictioncenters.org/benzodiazepine/symptoms-and-signs

American Psychiatric Association (2010). *DSM-5: The future of psychiatric diagnosis/Alcohol use disorders*. Washington, DC: American Psychiatric Association.

Beraha, E. M., Salemink, E., Goudriaan, A. E., Bakker, A., de Jong, D., Smits, N., ... & Defourny, H. (2016). Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: a multicentre, randomised, double-blind controlled trial. *European Neuropsychopharmacology*, *26*(12), 1950-1959. https://baclofentreatment.com/wp-content/uploads/2018/01/Beraha-study.pdf

Boels, D., Victorri-Vigneau, C., Grall-Bronnec, M., Touré, A., Garnier, A., Turcant, A., & Le Roux, G. (2017). Baclofen and alcohol-dependent patients: a real risk of severe self-poisoning. *Basic & clinical pharmacology & toxicology*, *121*(4), 353-359.

Brennan, J. L., Leung, J. G., Gagliardi, J. P., Rivelli, S. K., & Muzyk, A. J. (2013). Clinical effectiveness of baclofen for the treatment of alcohol dependence: a review. *Clinical pharmacology: advances and applications*, *5*, 99.

Burns, N., & Grove, S.K. (2010). *Understanding Nursing Research-eBook: Building an Evidence-Based Practice*. Elsevier Health Sciences.

Canadian Agency for Drugs and Technologies in Health. (2014). *Pharmacologic and Non-Pharmacologic Treatments for Alcohol Withdrawal in the Outpatient Setting: A Review of the Clinical Effectiveness, CostEffectiveness, and Guidelines*. Retrieved from https://www.cadth.ca/sites/default/files/pdf/htis/nov-2014/RC0603%20Outpatient%20Alcohol%20Withdrawal%20Treatments%20Final.pdf

Chaignot, C., Zureik, M., Rey, G., Dray-Spira, R., Coste, J., & Weill, A. (2018). Risk of hospitalisation and death related to baclofen for alcohol use disorders: Comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France. *Pharmacoepidemiology and drug safety*, *27*(11), 1239-1248.

Connor, J. P., Haber, P. S., & Hall, W. D. (2016). Alcohol use disorders. *The Lancet*, *387*(10022), 988-998.

Cooney, G., Heydtmann, M., & Smith, I. D. (2019). Baclofen and the Alcohol Withdrawal Syndrome-A Short Review. *Frontiers in psychiatry*, *9*, 773.

De Beaurepaire, R., Sinclair, J., Heydtmann, M., Addolorato, G., Aubin, H.J., Beraha, E.M., Caputo, F., Chick, J.D., de La Selle, P., Franchitto, N., & Garbutt, J.C. (2019). The use of baclofen as a treatment for alcohol use disorder: a clinical practice perspective. *Frontiers in psychiatry*, *9*, 708.

Dixit, D., Endicott, J., Burry, L., Ramos, L., Yeung, S. Y. A., Devabhakthuni, S., ... & Bulloch, M. N. (2016). Management of acute alcohol withdrawal syndrome in

critically ill patients. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *36*(7), 797-822.

Drobes, D.J., Saladin, M.E. and Tiffany, S.T. (2001). Classical conditioning mechanisms in alcohol dependence.

Drummond, D. C. (2001). Theories of drug craving, ancient and modern. *Addiction*, *96*(1), 33-46.

Farokhnia, M., Schwandt, M. L., Lee, M. R., Bollinger, J. W., Farinelli, L. A., Amodio, J. P., ... & Leggio, L. (2017). Biobehavioral effects of baclofen in anxious alcohol-dependent individuals: a randomized, double-blind, placebo-controlled, laboratory study. *Translational psychiatry*, *7*(4), e1108.

Foa, E. B., Yusko, D. A., McLean, C. P., Suvak, M. K., Bux, D. A., Oslin, D., ... & Volpicelli, J. (2013). Concurrent naltrexone and prolonged exposure therapy for patients with comorbid alcohol dependence and PTSD: A randomized clinical trial. *Jama*, *310*(5), 488-495.

Fogarty International Center. (2016). *The National Institute on Alcohol Abuse and Alcoholism (NIAAA): Advancing research on alcohol abuse and dependence*. Retrieved from https://www.fic.nih.gov/News/GlobalHealthMatters/may-june-2016/Pages/niaaa-alcohol-abuse-alcoholism.aspx

Garbutt, J. C. (2018). Use of baclofen for alcohol use disorders in the United States. *Frontiers in psychiatry*, *9*, 448.

Girish, K., Reddy, K.V., Pandit, L.V., Pundarikaksha, H.P., Vijendra, R., Vasundara, K., Manjunatha, R., Nagraj, M., & Shruthi, R. (2016). A randomized, open-label, standard controlled, parallel group study of efficacy and safety of baclofen, and

chlordiazepoxide in uncomplicated alcohol withdrawal syndrome. *Biomedical journal*, *39*(1), 72-80.

Grant, B. F., Chou, S. P., Saha, T. D., Pickering, R. P., Kerridge, B. T., Ruan, W. J., ... & Hasin, D. S. (2017). Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA psychiatry*, *74*(9), 911-923.

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., ... & Hasin, D. S. (2015). Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA psychiatry*, *72*(8), 757-766.

Gulati, P., Chavan, B.S., & Sidana, A. (2019). Comparative efficacy of baclofen and lorazepam in the treatment of alcohol withdrawal syndrome. *Indian journal of psychiatry*, *61*(1), 60.

Hasin, D. S., Kerridge, B. T., Saha, T. D., Huang, B., Pickering, R., Smith, S. M., ... & Grant, B. F. (2016). Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions–III. *American Journal of Psychiatry*, *173*(6), 588-599.

Hauser, P., Fuller, B., Ho, S. B., Thuras, P., Kern, S., & Dieperink, E. (2017). The safety and efficacy of baclofen to reduce alcohol use in veterans with chronic hepatitis C: a randomized controlled trial. *Addiction*, *112*(7), 1173-1183.

Heppe, D.B., Keniston, A., Bendelow, T., McBeth, L., Waring, S., Lyon, J., & Albert, R.K. (2019). Reducing the severity of alcohol withdrawal with oral baclofen: a randomized controlled trial. *Addiction Research & Theory*, *27*(3), 220-225.

Higgins, J. P., Altman, D. G., & Sterne, J. A. (2017). *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration.

Jones, J. D., Comer, S. D., & Kranzler, H. R. (2015). The pharmacogenetics of alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, *39*(3), 391-402.

Leggio, L., Zywiak, W. H., Edwards, S. M., Tidey, J. W., Swift, R. M., & Kenna, G. A. (2015). A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers. *Psychopharmacology*, *232*(1), 233-243. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278944/

Lyon, J.E., Khan, R.A., Gessert, C.E., Larson, P.M., & Renier, C.M. (2011). Treating alcohol withdrawal with oral baclofen: A randomized, double-blind, placebo-controlled trial. *Journal of hospital medicine*, *6*(8), 469-474.

Melnyk, B.M., & Fineout-Overholt, E. eds. (2011). *Evidence-based practice in nursing & healthcare: A guide to best practice*. Lippincott Williams & Wilkins.

Metoyer, P. B. (2014). *Alcohol Use Disorders (AUDs) among university students: A psychometric analysis of craving utilizing the Adolescent-Obsessive Compulsive Drinking Scale (A-OCDS) and proposed DSM-5 AUD criteria*. Retrieved from https://research.libraries.wsu.edu/xmlui/bitstream/handle/2376/5156/Metoyer_wsu_0251E_10561.pdf?sequence=1&isAllowed=y

Minozzi, S., Saulle, R., & Rösner, S. (2018). Baclofen for alcohol use disorder. *Cochrane Database of Systematic Reviews*, (11), 1-70.

Morley, K. C., Baillie, A., Leung, S., Addolorato, G. I. O. V. A. N. N. I., Leggio, L., & Haber, P. S. (2014). Baclofen for the treatment of alcohol dependence and possible role of comorbid anxiety. *Alcohol and alcoholism*, *49*(6), 654-660. https://academic.oup.com/alcalc/article/49/6/654/2888162#54585271

Müller, C. A., Geisel, O., Pelz, P., Higl, V., Krüger, J., Stickel, A., ... & Heinz, A. (2015). High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo-controlled trial. *European neuropsychopharmacology*, *25*(8), 1167-1177. http://baclofentreatment.com/wp-content/uploads/2016/04/BACLADStudy.pdf

Nandrino, J. L., Gandolphe, M. C., Alexandre, C., Kmiecik, E., Yguel, J., & Urso, L. (2014). Cognitive and affective theory of mind abilities in alcohol-dependent patients: the role of autobiographical memory. *Drug and alcohol dependence*, *143*, 65-73.

Oslin, D. W., Leong, S. H., Lynch, K. G., Berrettini, W., O'Brien, C. P., Gordon, A. J., & Rukstalis, M. (2015). Naltrexone vs placebo for the treatment of alcohol dependence: a randomized clinical trial. *JAMA psychiatry*, *72*(5), 430-437.

Perogamvros, L., Pépin, J. L., Thorens, G., Mégevand, P., Claudel, E., Espa, F., ... & Lador, F. (2015). Baclofen-associated onset of central sleep apnea in alcohol use disorder: a case report. *Respiration*, *90*(6), 507-511.

Ponizovsky, A. M., Rosca, P., Aronovich, E., Weizman, A., & Grinshpoon, A. (2015). Baclofen as add-on to standard psychosocial treatment for alcohol dependence: a randomized, double-blind, placebo-controlled trial with 1-year follow-up. *Journal of substance abuse treatment*, *52*, 24-30. http://addictiondomain.com/wp-

content/uploads/2016/12/Baclofen-as-Add-On-to-Standard-Psychosocial-Treatment-for-Alcohol-Dependence-a-Randomized.pdf

Ray, L. A., Bujarski, S., & Roche, D. J. (2016). Subjective response to alcohol as a research domain criterion. *Alcoholism: Clinical and Experimental Research*, *40*(1), 6-17.

Reynaud, M., Aubin, H. J., Trinquet, F., Zakine, B., Dano, C., Dematteis, M., ... & Detilleux, M. (2017). A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients—the ALPADIR study. *Alcohol and Alcoholism*, *52*(4), 439-446.

Rolland, B., Jaillette, E., Carton, L., Bence, C., Deheul, S., Saulnier, F., Bordet, R., & Cottencin, O. (2014). Assessing alcohol versus baclofen withdrawal syndrome in patients treated with baclofen for alcohol use disorder. *Journal of clinical psychopharmacology*, *34*(1), 153-156.

Rolland, B., Jaillette, E., Carton, L., Bence, C., Deheul, S., Saulnier, F., ... & Cottencin, O. (2014). Assessing alcohol versus baclofen withdrawal syndrome in patients treated with baclofen for alcohol use disorder. *Journal of clinical psychopharmacology*, *34*(1), 153-156.

Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 national and state costs of excessive alcohol consumption. *American journal of preventive medicine*, *49*(5), e73-e79.

Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., Jung, J., ... & Hasin, D. S. (2016). Nonmedical prescription opioid use and DSM-5 nonmedical

prescription opioid use disorder in the United States. *The Journal of clinical psychiatry*, *77*(6), 772.

Stewart, L. A., Clarke, M., Rovers, M., Riley, R. D., Simmonds, M., Stewart, G., & Tierney, J. F. (2015). Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *Jama*, *313*(16), 1657-1665.

World Health Organization (WHO). (2018). *Global status report on alcohol and health*. Geneva: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf?ua=1

World Health Organization. Management of Substance Abuse Unit. (2014). *Global status report on alcohol and health, 2014*. World Health Organization.

Yamini, D., Lee, S. H., Avanesyan, A., Walter, M., & Runyon, B. (2014). Utilization of baclofen in maintenance of alcohol abstinence in patients with alcohol dependence and alcoholic hepatitis with or without cirrhosis. *Alcohol and alcoholism*, *49*(4), 453-456.

Appendices

Appendix A – PRISMA Flow Diagram

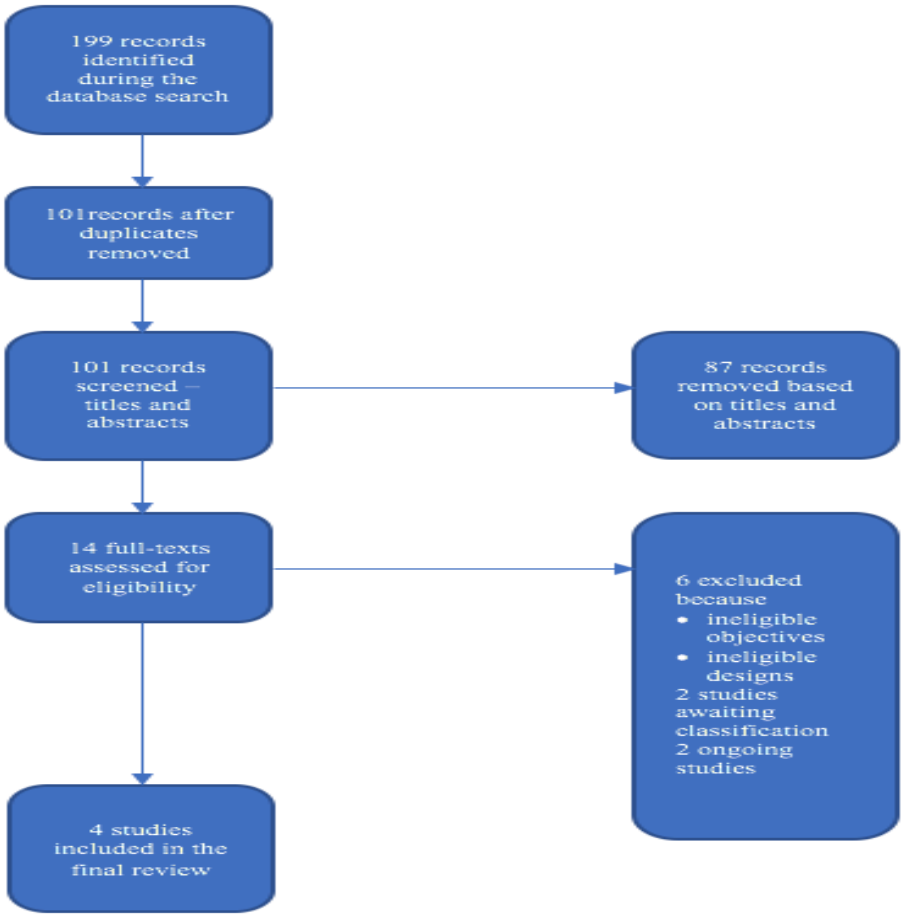

Figure 1: *PRISMA Flow Diagram*

Appendix B

Table B-1

STUDY DESCRIPTION

Heppe, D. B., Keniston, A., Bendelow, T., McBeth, L., Waring, S., Lyon, J., & Albert, R. K. (2019). Reducing the severity of alcohol withdrawal with oral baclofen: a randomized controlled trial. *Addiction Research & Theory*, *27*(3), 220-225.					
AIM/PURPOSE	DESIGN	SITE	SAMPLE	METHODS	PROCEDURES
To determine whether, after 72 hours of admission, fewer patients hospitalized on Internal Medicine services who were at risk for AWS after applying baclofen in their care	A double blind, placebo controlled, randomized trial	Denver Health, a university-affiliated, urban public safety-net hospital	101 medical inpatients who were at risk for developing, or presented with, mild AWS.	Patients were grouped into two groups who received oral medication of either: 1. Baclofen 10 mg, (n=50) or 2. Placebo (n=51) every eight hours for five days or until hospital discharge. All participants also received symptom driven benzodiazepine as directed by SEWS protocol.	Measurements included: - The proportion of patients progressing to moderate or severe AWS - Difference in mean SEWS assessment scores at 24h, 48h, and 72h between groups; peak and cumulative dosage of benzodiazepines over 72h post-enrollment.

Appendix B

Table B-2

STUDY DESCRIPTION

Lyon, J.E., Khan, R.A., Gessert, C.E., Larson, P.M. and Renier, C.M., 2011. Treating alcohol withdrawal with oral baclofen: A randomized, double-blind, placebo-controlled trial. *Journal of hospital medicine*, *6*(8), pp.469-474.					
AIM/PURPOSE	DESIGN	SITE	SAMPLE	METHODS	PROCEDURES
To determine the effect of gamma-Aminobutyric acid (GABA)-B agonist baclofen on the course of acute symptomatic AWS	Prospective, randomized, double-blind placebo-controlled clinical study	Two tertiary-care hospitals in Duluth, Minnesota	31 inpatient adults who were admitted for any reason, including AWS, and judged to be at high risk for AWS	Patients were grouped into two groups who received oral medication of either: 1. Baclofen 10 mg, (n=18) or 2. Placebo (n=13) every eight hours for 72 hours or until hospital discharge. All participants also received symptom driven lorazepam as directed by CIWA-AR protocol.	Measurements included: - AWS severity was assessed using the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-AR) - Lorazepam dose was monitored every eight hours for 72 hours or until hospital discharge

Appendix B

Table B-3

STUDY DESCRIPTION

Girish, K., Reddy, K. V., Pandit, L. V., Pundarikaksha, H. P., Vijendra, R., Vasundara, K., ... & Shruthi, R. (2016). A randomized, open-label, standard controlled, parallel group study of efficacy and safety of baclofen, and chlordiazepoxide in uncomplicated alcohol withdrawal syndrome. *Biomedical journal*, *39*(1), 72-80.					
AIM/PURPOSE	DESIGN	SITE	SAMPLE	METHODS	PROCEDURES
To compare the efficacy and tolerability of baclofen with chlordiazepoxide in uncomplicated AWS.	A randomized, open-label, standard controlled, parallel group study of baclofen, and chlordiazepoxide in AWS	A tertiary-care hospital in India	60 inpatient adults who were admitted for uncomplicated AWS	Patients were grouped into two groups who received oral medication of either: 1. Baclofen 30 mg, (n=30) or 2. Chlordiazepoxide 75 mg (n=30) for 9 days in decremented fixed dosage. Lorazepam was used as a rescue medication.	Measurements included: - The researchers employed the Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale (CIWA-AR) to assess clinical efficacy - Clinical Global Impression scores, symptom-free days, and subject satisfaction scores were used as the secondary efficacy parameters

Appendix B

Table B-4

STUDY DESCRIPTION

Gulati, P., Chavan, B. S., & Sidana, A. (2019). Comparative efficacy of baclofen and lorazepam in the treatment of alcohol withdrawal syndrome. *Indian journal of psychiatry, 61*(1), 60.					
AIM/PURPOSE	DESIGN	SITE	SAMPLE	METHODS	PROCEDURES
To compare the efficacy of baclofen and benzodiazepine (lorazepam) in reducing symptoms of AWS.	A single-center, randomized, open-label study.	An acute care setting in the Department of Psychiatry, GMCH, Chandigarh, in India	66 patients with the diagnosis of alcohol dependence as per ICD-10 criteria were enrolled	Patients were grouped into two groups who received oral medication of either: 1. Baclofen 10 mg, (n=30) 3 times pera or 3. Lorazepam 8-12 mg (n=30). The patients received B1 (100 mg/day through intramuscular route) and psychotherapeutic interventions.	Measurements included: - Reduced severity of alcohol dependence as measured by the Severity of Alcohol Dependence Questionnaire (SAD-Q) - Alcohol withdrawal was measured using the (CIWA-AR).

Appendix C

Table C-1

OUTCOME DATA COLLECTION TABLE

Heppe et al. (2019)				
	All Patients (N =101)	Baclofen (N = 50)	Placebo (N = 51)	*P value*
Progression to moderate or severe AWS within 72 h	n = 29 (29%)	n = 13 (26%)	n = 16 (31%)	0.5507
Highest SEWS score within 72 h,	n = 6 (± 4 SD)	n = 6 (± 4 SD)	n = 6 (± 4 SD)	0.6230
Highest inpatient dosage of benzodiazepines (mg) during the 72h following enrollment	M: 11mg (± 6 SD)	M: 11mg (± 3 SD)	M: 12mg (± 7 SD)	0.1432
Cumulative inpatient dosage of benzodiazepines (mg) over the 72] h following enrollment	M: 76mg (± 58 SD)	M: 66mg (± 51SD)	M: 85mg (± 63 SD)	0.1362

Appendix C

Table C-2

OUTCOME DATA COLLECTION TABLE

Lyon et al. (2011)			
	Baclofen (N = 18)	Placebo (N = 13)	*P value*
Progression to moderate or severe AWS within 72 h	n = 18 (42%)	n = 13 (35%)	0.004
Dosages of lorazepam > 20 mg over 72h following enrollment	n = 1	n = 7	0.004
Dosages of lorazepam >50 mg over the 72h following enrollment	n = 0	n = 4	0.023
Cumulative dosage of lorazepam (mg) over the 72 h following enrollment	0-39mg	1-1035mg	

Appendix C

Table C-3

OUTCOME DATA COLLECTION TABLE

Girish et al. (2016)			
Study Group	**Total CIWA-AR scores DAY 1**	**Total CIWA-AR scores DAY 9**	***p* value**
Baclofen (n=30)	M=23.60 ± 6.483	M=1.133 ± 0.730	$p = 0.475$
Chlordiazepoxide (n=30)	M=23.90 ± 7.038	M=0.133 ± 0.434	

Appendix C

Table C-4

OUTCOME DATA COLLECTION TABLE

Gulati et al. (2019)			
Study Group	**Total CIWA-AR scores DAY 1**	**Total CIWA-AR scores DAY 9**	***p* value**
Baclofen (n=34)	M=15	**M=0	None provided
lorazepam (n=32)	M=40	**M=0	

** Presented Graphically by authors.

Appendix D

CASP Evaluation

Scale	Girish et al. (2016)	Heppe et al. (2019)	Gulati et al. (2019)	Lyon et al. (2011)
Random Sequence	+	+	+	+
Allocation Concealment	+	+	+	+
Blinding of Participants – Objective Outcomes	+	+	+	+
Blinding of Participants – Subjective Outcomes	+	+	+	+
Blinding of Assessors – Objective Outcomes	-	-	+	+
Blinding of Assessors – Subjective Outcomes	+	+	+	+
Incomplete Outcome	+	+	+	+
Selective Reporting	+	+	+	+
Score	7	7	8	8

Appendix E

Cross-Study Analysis

AUTHOR / YEAR	COMPARISONS OR PROTOCOL OF STUDY	Total CIWA scores Day 1	Progression to Moderate or Severe AWS within 72 h Day 3	Total CIWA scores Day 9
Heppe et al. (2019)	Main intervention: baclofen Comparison: *placebo*	N/A	Baclofen *n* = 13 (26%) Placebo *n* = 16 (31%)	N/A
Lyon et al. (2011)	Main intervention: baclofen Comparison: *placebo*	N/A	Progression to moderate or severe AWS within 72 h Baclofen *n* = 18 (42%) Placebo *n* = 13 (35%)	N/A
Girish et al. (2016)	Main intervention: baclofen Comparison: *chlordiazepoxide*	Baclofen *M*=23.60 ± 6.483 Chlordiazepoxide *M*=23.90 ± 7.038	N/A	Total CIWA-AR scores DAY 9 Baclofen *M*=1.133 ± 0.730 Chlordiazepoxide *M*=0.133 ± 0.434
Gulati et al. (2019)	Main intervention: baclofen Comparison: *Lorazepam*	Total CIWA-AR scores DAY 1 Baclofen *M*=15 Chlordiazepoxide *M*=40	N/A	Total CIWA-AR scores DAY 9 Baclofen ****M**=0 Chlordiazepoxide ****M**=0

** Presented Graphically by authors.