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Family Nurse Practitioner Program

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Abstract

Alcohol abuse, complicated by a dependency relationship, is the third leading modifiable cause of death in the United States. In patients with chronic alcohol use disorder who experience a sudden cessation or significant decrease in alcohol consumption, half will experience symptoms of alcohol withdrawal syndrome. Benzodiazepines are the typical first line treatment for alcohol withdrawal. However, benzodiazepines carry with them significant risks and side effects. As a result, ongoing research has taken place to find either an alternative treatment or a method of reducing total benzodiazepine dosage during treatment. Gabapentin is a medication that is primarily used for seizure control and neuralgia, but has also been used in the off-label treatment of alcohol withdrawal syndrome, alone or in addition to benzodiazepines.

The purpose of this project is to perform a literature review of the available research to determine the efficacy of gabapentin in either replacing or augmenting benzodiazepine usage through the alcohol withdrawal period without sacrificing patient outcomes.

Results from available literature since 2012 show evidence in support of gabapentin as an effective treatment, either alone or in conjunction with benzodiazepines, but it is not conclusive. Several studies did show decreased use of benzodiazepines or equal effectiveness when compared head-to-head in some cases. More research is necessary to establish effective dosing of gabapentin as well as if certain populations, such as patients with a reduced creatinine clearance, would still benefit with gabapentin over solitary use of benzodiazepines.

Keywords: gabapentin, benzodiazepines, alcohol withdrawal syndrome

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Background

In 2020, the National Survey on Drug Use and Health found that about half of all Americans above the age of twelve consume alcohol, and 41% of those engage in either heavy or binge drinking (Substance Abuse and Mental Health Services Administration, 2022). In the United States, alcohol use is the third leading cause of death due to modifiable causes (National Institute on Alcohol Abuse and Alcoholism, 2022).

The picture of alcohol abuse is also reflected by habits of drinking that lead to dependence. Native American and White males are most likely to engage in binge or heavy drinking, defined as five, or four if female, or more drinks for more than five days in the past month (Chartier, n.d.; National Institute on Alcohol Abuse and Alcoholism, n.d.a). Despite Native Americans and Whites having higher rates of alcohol use disorder (AUD), Native American, Black, and Hispanic males are most likely to suffer from alcohol-related conditions and dependency (Chartier, n.d.; Delker et al., 2016). Aside from the immediate risks of heavy drinking such as alcohol poisoning or motor vehicles accidents due to driving under the influence, chronic alcohol use is a risk factor for alcoholic hepatitis and cirrhosis, cardiovascular disease, stroke, hypertension, gastrointestinal system and breast cancers, and atrial dysrhythmias (National Institute on Alcohol Abuse and Alcoholism, 2022). Alcoholic hepatitis rates are noted to be higher in men who consume greater than 4.28 standard drinks or women who consume more than 1.43 standard drinks per day for a ten-year period (Heuman, 2019; National Institute on Alcohol Abuse and Alcoholism, n.d.b).

Pathophysiology of Withdrawal

When alcohol is consumed, the gamma-aminobutyric acid (GABA) receptors in the brain become excited, while N-methyl-d-aspartate glutamate (NMDA) receptors are inhibited (Andaluz et al., 2019).

With chronic drinking, the NMDA receptors compensate the inhibition by becoming more tolerant to alcohol (Andaluz et al., 2019). When patients with chronic alcohol abuse suddenly reduce or quit drinking alcohol, half will experience alcohol withdrawal syndrome (AWS), an up-regulation of NMDA receptors due to the lack of inhibition by the alcohol, leading to an excitatory response (Andaluz et al., 2019; Leung et al., 2018). AWS accounts for nearly half of all alcohol-related Emergency Room visits in the United States annually and causes mortality in 3-15% of cases (Morrison et al., 2019; Smith et al., 2022). Severity of AWS is often measured using the Clinical Institute Withdrawal Assessment-Alcohol, revised (CIWA-Ar) scale, a validated assessment tool, (see Tool 1) (Eloma et al., 2018). Table 1 shows the differences in scores, symptoms, and treatments locations for AWS.

Benzodiazepines

Benzodiazepines (BZD) are schedule IV-controlled substances that are widely regarded as standard first-line treatment in AWS patients due to the agonistic effect that BZDs have on GABA receptors causing a decrease in withdrawal symptoms, seizures, and delirium (Drug Enforcement Administration, 2020; Morrison et al., 2019; Wilming et al., 2018). The American Society of Addiction Medicine (ASAM) recommends BZD use in the treatment of AWS in almost all situations (American Society of Addiction Medicine, 2020). BZDs however, carry with them risks of over-sedation, delirium, impaired memory, ataxia, respiratory depression or failure, increased length of hospitalization, increased morbidity, addiction and dependence, over-dosing in patients with hepatic impairment, and increase in post-treatment cravings and relapse (Andaluz et al., 2019; Smith et al., 2022; Stock et al., 2013; Vadiei et al., 2013). Due to these adverse effects of BZD treatment, an alternative treatment or method of decreasing BZD dosage is desirable.

Gabapentin

Gabapentin (GBP) is a medication approved by the Food and Drug Administration for treatment of neuropathic pain and seizure disorders, yet has increasingly been used off-label as a potential

alternative to BZDs, as both a monotherapy and adjunctive therapy with BZDs in treatment of AWS (Drug Enforcement Administration, 2019; Fairbanks et al., 2011; Hammond et al., 2015; Premont, 2022). GBP's exact mechanism of action is unknown, but believed to increase activation of GABA receptors, decrease glutamate availability, and modulate dopamine and norepinephrine levels (Morrison et al., 2019). GBP, in the reviewed studies, is delivered often as a scheduled taper over several days such as in Bates et al. (2020) and Wilming et al. (2018). Unlike BZDs, GBP is better suited than BZDs for use in patients with hepatic dysfunction as it undergoes negligible metabolism by the liver, has only mild cognitive side effects, does not lead to dependence or food-drug interactions with alcohol, and has been shown to decrease alcohol craving and relapse following AWS (Anton et al., 2020; Avitzur, 2004; Morrison et al., 2019; Stock et al., 2013; Vadiei et al., 2013). Care must be taken with GBP when used as an adjunct therapy with BZDs as the two can increase the other's effects, leading to severe or fatal respiratory depression if not monitored (Medscape, 2022a). Since 2016, seven states have added GBP to the controlled substances list as a schedule V drug and another twelve states require reporting of the prescription and refills, although GBP is not a controlled substance on the federal level (Collins, 2021; Premont, 2022). This is due to GBPs effect on the dopaminergic reward system that can cause addiction and the illicit diversion potential amongst chronic pain sufferers who may combine use with illicit opioids to attain a high (Collins, 2021). GBP and BZDs are compared in Table 2.

Methods

Study Purpose and Design

In 2011, a Cochrane review by Amato et al. noted that although some evidence had been found supportive for use of anticonvulsants, such as GBP, the amount and quality of research was insufficient to provide treatment recommendations. Since 2012, only twelve original research studies have been found in the database searches that studied the effectiveness and safety of GBP for AWS. The aim of this literature review is to evaluate the effectiveness and safety of GBP, as compared to BZDs, to treat patients

undergoing AWS. This will be done by comparing CIWA-Ar scores, BZD usage with and without GBP, length of stay, and adverse outcome rates.

To review this topic, a literature review of available original, quantitative studies conducted from 2012 to present was performed. This review was focused on patients in the United States undergoing acute AWS and in which, at least one cohort of the study was treated with GBP and the results were then compared to BZD use.

Search Strategy

Pertinent articles were retrieved by searches of Google Scholar, PubMed, SCOPUS, and San Jose State University OneSearch. Reference lists of included articles were also reviewed to develop additional sources. Search criteria was inspired by Amato et al. (2011), a Cochrane review.

Inclusion and Exclusion Criteria

Search keywords used across the search platforms were “alcohol withdrawal syndrome”, “ethanol withdrawal”, “adult”, “outpatient”, “anticonvulsant”, “gabapentin”, “non-benzodiazepine”, “lorazepam”, “-review”, and “inpatient”. The use of opposing terms of “outpatient” and “inpatient” were not used simultaneously in the same search, but in separate searches in order to find pertinent articles related to varying degrees of alcohol withdrawal symptoms. This was done under a presumption from Hammond et al. (2015) that less severe cases would be more likely to take place as outpatient and could be treated with a GBP monotherapy approach as opposed to the more severe cases taking place inpatient using GBP as an adjuvant therapy to BZD. Articles were included or excluded manually by a single reviewer and were retrieved between February and April of 2022. Exclusion criteria factors included articles prior to 2012, reviews or textbooks, non-English language availability only, or not available as full-text without charge. Additionally, studies that focused on a special population such as geriatric, smokers, drug abuse, or specific treatment of alcohol use disorder as opposed to alcohol withdrawal syndrome were excluded.

Data Extraction and Analysis

These searches generated a total of 1205 articles, which after the application of selection criteria, were decreased to twelve (see Figure 1). Conceptually, these twelve articles were grouped using GBP as a monotherapy or as an adjuvant therapy. The monotherapy articles included Anton et al. (2020), Bates et al. (2020), Leung et al. (2018), and Stock et al. (2013). The adjuvant therapy studies included Andaluz et al. (2019), Fargahi et al. (2021), Levine et al. (2019), Morrison et al. (2019), Nichols et al. (2019), Smith et al. (2022), Vadiei et al. (2019), and Wilming et al. (2018).

In order to address the questions of GBP effectiveness and safety in alcohol withdrawal syndrome patients, articles in each result field were compared and conclusions were drawn based on agreement of results between the articles. In the cases where conflicting articles were present, the outlier article was reviewed further to assess cause of difference (see Table 4). For example, an assessment of alcohol withdrawal symptoms as measured by CIWA-Ar, found that GBP is equally effective to BZDs in the studies of Bates et al. (2020), and Stock et al. (2013). However, Andaluz et al. (2019) found GBP less effective than BZDs. Andaluz et al. notes that the higher CIWA-Ar scores in the GBP group may have been secondary to cohort makeup inequality and subtherapeutic doses of GBP. Due to a greater number of studies with a finding that GBP has similar effectiveness and only one study showing decreased effectiveness, as well as noting that the study by Andaluz et al. had limiting factors that further weakened the findings, the conclusion made is that GBP is equally effective to BZD's when comparing CIWA-Ar scores.

Quality Appraisal

Selected articles were reviewed and applied to a reviewer-adapted matrix provided by the Johns Hopkins Evidence-Based Practice Model for Nursing and Healthcare Professionals Research Evidence Appraisal Tool (JHEBPM), Appendix E. (Johns Hopkins University, 2022a). Study strength was analyzed using JHEBPM Appendix D and F (Johns Hopkins University, 2022b; Johns Hopkins

University, 2022c). The risk of bias in each study was assessed by use of one of two tools provided by the Cochrane review for randomized and non-randomized control trials. The Risk of Bias (RoB2) was used on the studies of Anton et al. (2020) and Stock et al. (2013), as they were both randomized control trials (Sterne et al., 2019). The remaining studies were reviewed by the Risk of Bias in Non-Randomized Studies-of Interventions (ROBINS-I) since the remainder were non-randomized control trials (Sterne et al., 2016).

Measurement

Results were organized to compare primary and secondary outcomes attained in each study. Each outcome result was placed in one of three fields comparing GBP as more, less, or equally effective to BZDs. Primary outcomes analyzed included occurrence of adverse events, BZD use, and effectiveness in controlling withdrawal symptoms. Secondary outcomes included differences in the length of stay in detoxification programs and in the ICU. Limitations were compared between studies and included categories such as subtherapeutic GBP dosage, inequality between treatment groups, control of confounding variables, and retrospective study design.

Three measurement tools assess alcohol withdrawal severity, presence of delirium or oversedation, or to determine dosage of BZDs given. The CIWA-Ar tool scores the severity of alcohol withdrawal and is used to judge effectiveness of GBP versus BZDs as well as use to determine appropriate BZD dosage to those in control or adjuvant groups. CIWA is a validated tool for patients who can communicate, however, is found less reliable in severely delirious or overly sedated patients who are unable to communicate effectively (Eloma et al., 2018). This is notable for intensive care units, where the severity of AWS can often lead to severe confusion and delirium, which impacts effective communication and has been shown to lead to falsely elevated CIWA-Ar scores (Sutton & Jutel, 2016). Effective communication is required for seven of the ten items on the scale; however, CIWA-Ar is used in intensive care units due to a lack of alternative reliable and validated scales (Eloma et al., 2018). This being known, CIWA-Ar is the preferred tool even in ICU in part because no other valid tool exists and the

CIWA-Ar provides safer BZD dosing than fixed dose protocols (Eloma et al., 2018; Sutton and Jutel, 2016). As shown in Tool 1, the CIWA-Ar is a 10-question scale with scores of 0-8, 9-15, 16-20, and >20 indicating minimal, mild, moderate, or severe withdrawal, respectively (Andaluz et al., 2020).

The Richmond Agitation and Sedation Scale (RASS) and Confusion Assessment Method (CAM) tools were used in the outcome measurement of adverse events, by indicating over sedation, agitation, or delirium (see Tool 1, 2, and 3). RASS has been shown to be a reliable, validated, scale for agitation and sedation that is in wide use due to the scale's high interrater reliability, simplicity, and ease of use (Rasheed et al., 2019). RASS is a 10-point scale with scores ranging from -5 to +4, with -5 indicating unresponsiveness, 0 indicating alert and calm, and +4 indicating combative agitation (Rasheed et al., 2019). CAM is a tool used to identify delirium validated for inpatient use with an 88% sensitivity and 100% specificity for delirium (Gusmao-Flores et al., 2012). CAM consists of a four-question screening tool which includes RASS as part of the tool and scores as delirium either present or not present.

Results

Population and Setting

The total number of study participants across all studies numbered 25,024 and were predominantly white males residing in the United States between the ages of 40 and 60 years old. With the exceptions of Anton et al., (2020) and Stock et al., (2013), all studies were performed in inpatient settings.

Study Design, Sample Size and Quality

The articles comparing effectiveness of GBP to BZDs were mostly of retrospective cohort design, although two of the articles were randomized, controlled trials. Across all studies, a total of 25,024 participants were included. Most of these participants, 22,899, were from the single study of Smith et al., (2022). The studies by Andaluz et al., (2019) and Bates et al., (2020) also contained abnormally large sample populations as compared with the remaining studies, 982 and 443 participants each, respectively.

However, the twelve acceptable studies, after criteria exclusions, contained an average sample size of only 87 participants, with a range of 25-129 participants each (see Table 3).

Gabapentin Safety in Withdrawal

The most common reported outcome in the literature was the measurement of adverse event occurrences from the use of GBP. Adverse incomes included such events as rapid response team (RRT) calls, development of delirium tremens, seizures, or transfer to higher level of care. Seven of the twelve studies found no statistically significant difference in occurrence of events between BZD and GBP cohorts (Bates et al., 2020; Leung et al., 2018; Levine et al., 2019; Morrison et al., 2019; Nichols et al., 2019; Vadiei et al., 2013; Wilming et al., 2018). Although not attaining statistical significance of $p < 0.05$, with a p score range of 0.115-0.224, Levine et al. (2019), did note that the additional of GBP as an adjuvant did also reduce episodes of desaturation, Richmond-Agitation Sedation Score (RASS) < -1, and fewer Confusion Assessment Method (CAM) positive days than use of BZD alone.

Gabapentin Effect on Benzodiazepine Use

GBP effectiveness against BZD were measured with two methods across the literature. The first compares the total BZD usage when used alone or with GBP as an adjuvant therapy. The results are varied. When used as an adjuvant, GBP was shown to decrease BZD use by approximately 20-30% in three of the six studies examining this outcome (Levine et al., 2019; Morrison et al., 2019; Wilming et al., 2018). Furthermore, in Fargahi et al. (2021), median BZD use was decreased from 5.5 mg to 0 mg when used with other anticonvulsants as well. Both Andaluz et al. (2019) and Nichols et al. (2019) did not find a difference in amount of BZD used between monotherapy and adjuvant therapy. Although Andaluz et al. found that equivalence was limited in severe AWS, but not in mild to moderate cases. In addition, Andaluz et al. also noted a more rapid decrease in BZD dosing after 35 hours in protocol with the use of a GBP adjuvant. Conversely, only Vadiei et al. (2013) found an increase in BZD dosage with the GBP adjuvant cohort, although they note that this may have been due to other factors such as inadequate dosing of GBP and inequality in severity of AWS between the cohorts.

Gabapentin Effect on AWS Severity

The second metric of effectiveness in AWS is the CIWA-Ar scores. When used as a monotherapy, Stock et al. (2013), in a small, 25 participant study, found that GBP was as effective as a BZD in treatment of mild AWS. Fargahi et al. (2021) and Bates et al. (2020) also used GBP independent of BZD in the cohorts, although they each did add other adjuvant medications such as divalproex, clonidine, valproic acid, and haloperidol. Each study found a decreased CIWA-Ar in the GBP cohort, with Fargahi et al. noting an 89% decrease in CIWA-AR scores and Bates et al. finding a 2.2 point lower maximum peak in CIWA-Ar scores as compared to the BZD cohort. Only Andaluz et al. (2019) noted an increase in CIWA-Ar scores when GBP was used as an adjuvant therapy. Even so, Andaluz et al. notes that the increase may have been related to several factors such as the GBP group tended to be older, have home prescriptions of GBP for non-alcohol reasons, and have selection bias by the providers to have patients with higher initial risk of severe AWS than the control group.

Other Benefits of Gabapentin

Length of stay (LOS), in the context of intensive care (ICU) LOS, treatment protocol LOS, and hospital LOS. Treatment protocol LOS refers to the length of time before the patient no longer met the criteria to be included in the AWS study. Levine et al. (2019) found that using GBP as an adjuvant shortened ICU LOS by 1.3 days. Similarly, Morrison et al. (2019) showed an average decrease of four days in ICU than by using BZDs alone. When using GBP as an adjuvant, treatment protocol LOS and hospital LOS was decreased by as much as one to three days in the studies of Levine et al., Morrison et al., and Smith et al. (2022). In the case of Leung et al. (2018), hospital LOS decreased from 5.07 days to 4.2 days when a GBP taper is used with other, non-BZD medications, although this result is not statistically significant. The studies performed by Bates et al. (2020), Nichols et al. (2019), Vadiei et al. (2013), and Wilming et al. (2018) each showed no appreciable difference in treatment protocol or hospital LOS between GBP as a monotherapy or adjuvant therapy versus BZD.

Other benefits of GBP use in treatment of AWS are the consequences of treatment completion such as likelihood to discharge to home, resumption of alcohol consumption, and readmission rates. Levine et al. (2019) noted that patients in the GBP adjuvant group were more likely to be discharged home as opposed to a rehabilitation center or nursing care facility. Anton et al., (2020) stated that patients taking GBP were more likely to remain abstinent from alcohol, but if they did drink, they were less likely to drink heavily. As with length of stay, these factors do not just affect the patient and their recovery, but also resource utilization and expenses. However, ultimately, Vadiei et al. (2013) states that there are no real differences in readmission rates between cohorts receiving GBP and those who did not (see Table 4)

Limitations of Available Studies.

Limitations were compared between studies and included categories such as subtherapeutic GBP dosage, inequality between treatment groups, control of confounding variables, and retrospective study design (see Table 5).

Discussion

Through review of the literature of the past ten years, a buttressing of prior conclusions is seen without significant additions to knowledge on the subject. It seems that the use of GBP as an adjunctive medication for cases of mild to moderate withdrawal is appropriate and can be beneficial. This is seen across outcomes such as adverse events, decreased BZD use, and decreased CIWA-Ar scores.

In the case of adverse events, the literature points to GBP as positive in avoidance of increasing event rates, particularly when used as an adjuvant to BZD in mild and moderate AWS. Evidence from Stock et al. (2013) leads to the conclusion that GBP has the same effect on CIWA-Ar scores, cravings, and adverse reactions as BZD, but is a very limited study of only 25 patients in mild withdrawal and so the generalizability of the findings is not certain.

What remains questionable is the application of GBP in moderate cases as a monotherapy. The literature in general does not do a good job of delineating efficacy of treatment across the spectrum of

AWS severity. A problem with monotherapy is seen in the study performed by Levine et al. (2019). They note that, out of the 50 patients in their GBP-only cohort, two experienced seizures. Whether this is a significant outcome is unknown due to the study design's lack of sufficient power to analyze such outcomes. The authors of Leung et al. (2018) have concerns that the GBP monotherapy lacks the direct GABA agonism that is provided by BZDs, which can lead to seizures and other potential poor outcomes.

It is also difficult to measure the difference reliably and quantitatively between moderate and severe AWS due to limitations in the CIWA-Ar tool. Confusion and delirium can occur in moderate severity, which can invalidate the CIWA-Ar scores. In practice, this has been associated with falsely high assessment scores and potentially placing a patient as severe when moderate would be a more appropriate designation (Sutton & Jutel, 2016). Due to this uncertainty between the upper scores of moderate and lower scores of severe AWS, it may be more prudent to not use GBP as a monotherapy and be cautious with use of GBP as an adjuvant in moderate cases of AWS as well. Support for this is found in the findings by Andaluz et al. (2019), which show decreasing efficacy and safety in severe AWS.

Other benefits, such as decreased resource utilization as an outpatient, resumption of alcohol use and avoiding readmission are clearly desirable but, in the case of AWS, can be seen as perks of treatment with GBP. True appreciation of those benefits is outside the scope of this project and better suited for a study on GBP of treatment alcohol use disorder or post-AWS care.

Limitations and Gaps

In many of the studies reviewed, control of variables was difficult due to the retrospective nature that limited the researcher's ability to eliminate variances (Andaluz et al., 2019; Bates et al., 2020; Leung et al., 2018; Morrison et al., 2019; Nichols et al., 2019; Vadiei et al., 2013; Wilming et al., 2018). The most likely variable that could alter the results was the inability of researchers to control the dosage of GBP, which were, in many cases, decided by the provider at the time of treatment. As previously mentioned, Vadiei et al. (2013) stated that a prior recommendation for the GBP high-dose taper was to

begin with 1200-2700mg on the first day, yet many studies noted subtherapeutic or nonadherence to a protocol for GBP, sometimes with wide variations in dosing (Andaluz et al., 2019; Bates et al., 2020; Vadiei et al., 2013; Wilming et al., 2018). For example, Wilming et al. (2018) notes GBP doses ranging from 100mg-3600mg per day, with an average of 948mg. Wide ranges, such as those seen with Wilming et al., makes concluding as to whether the drug itself was ineffective or if the dose was insufficient more difficult to discern.

Another limitation involved was the inequality in some of the study cohorts. This was more difficult to control since the decision for assignment to one cohort or the other was decided by the provider (Andaluz et al., 2019; Bates et al., 2020; Leung et al., 2018; Vadiei et al., 2013). For example, Andaluz et al. (2019) notes that their GBP cohort was more likely to include patients who were older, white and who had previous, non-withdrawal related prescriptions of GBP than the control.

Bates et al. (2020) notes that GBP treatment needs to be adjusted for patients with poor renal function, as defined by a glomerular filtration rate less than 60 mL/hr. The difference between the normal renal function and poor renal function protocol on the first day alone is 900mg of GBP. There is also the question stemming from the Andaluz et al. (2019) study that patients who are already on GBP for reasons other than alcohol withdrawal may react differently to the standardized high dose. Both populations face either an actual or a relative subtherapeutic dose of GBP. As stated in the limitations section above, this may affect efficacy of GBP in AWS. Since neither of these populations are particularly rare, research needs to be done to determine whether these lower doses are still therapeutic.

Conclusions and Practice Implications

The current evidence is a developing trend that the use of GBP is a safe treatment for mild and moderate AWS, although whether a monotherapy or adjuvant therapy is generally preferable still requires clarification. AWS may be a dose dependent syndrome, where in mild to moderate cases, GBP monotherapy may be appropriate as noted by Anton et al. (2020), Leung et al. (2018) and Stock et al.

(2013). However, as the cases become moderate to severe, GBP as an adjuvant to BZD may be more appropriate or even contraindicated as Leung et al., Levine et al. (2019), and Vadiei et al. (2013) explained. It is important for further research to examine the limits of effectiveness for GBP therapy both as a monotherapy and as an adjuvant.

To be able to better measure effectiveness or guide treatment in severe cases, a validated tool should be investigated and tested. Sutton & Jutel (2016) note the use of the Minnesota Detoxification scale (MDS), which, at the time, had only been tested at one center involving 36 patients. Having a reliable scale for severe cases would increase the reliability of any study of treatments involving severe AWS.

With the exceptions of Andaluz et al. (2019), Bates et al. (2020), and Smith et al. (2022) the remaining studies were small, with the average population in the monotherapy and GBP adjuvant studies being only 61 and 102 patients, respectively. Questions remain to be answered regarding monotherapy versus adjuvant therapy, dosing, and special populations remain open due to the inability of researchers to manage confounding variables during studies. Once the questions of standardized requirements for treatment have been resolved. Larger studies on the effects of GBP should be performed to determine overall generalizability.

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Appendix A: Tables

Table 1: Alcohol Withdrawal Symptoms and Severity

Withdrawal Severity	**Mild**	**Moderate**	**Severe**
CIWA-Ar score	0 to 8	9 to 15	16 to 67
Symptoms	Hypertension, insomnia, tremors, hyperreflexia, anxiety, headache, palpitations, Gastrointestinal discomfort	Mild symptoms plus hallucinations, withdrawal seizures	Moderate symptoms plus delirium tremens, tachycardia, hyperthermia, agitation, diaphoresis
Time of Appearance from Last Drink	6 to 12 hours	12 to 48 hours	12 to 72 hours
Appropriate Treatment location	Outpatient (only if adequate support, if not, then inpatient care is necessary)	Outpatient or inpatient	Inpatient

(Bayard et al., 2004; Newman et al., 2021)

Table 2: GBP and BZDs compared

Drug	**Gabapentin**	**Benzodiazepines (Lorazepam used as example)**
Food and Drug Administration approved indications	Partial seizures, herpetic neuralgia, restless leg syndrome	Alcohol withdrawal, anxiety, muscle relaxant, panic disorder, seizures, sleep disorders, surgical relaxation and amnesia
Side Effects	Ataxia, dizziness, drowsiness, fatigue, somnolence	Sedation, dizziness, jaundice, fatigue, confusion, vertigo, tremor, respiratory depression, elevated Liver function tests, constipation
Biomechanics	Protein bound, no interaction with CYP450 hepatic enzymes, excreted renally in proportion to creatinine clearance	Protein bound, hepatic glucuronic acid conjugation, excreted as inactive metabolites mostly in urine but also feces
American Society of Addiction Medicine use recommendations	**Monotherapy**-appropriate in mild to moderate uncomplicated cases, or when BZDs contraindicated. **Adjunct therapy**-appropriate in mild and moderate cases Not to be used in severe AWS	Mild, moderate, or severe AWS except when hypersensitive, contraindicated or drug abuse or diversion suspected
BEERs recommendations	Use in low doses in elderly due to ataxia and falls	Avoid use of all BZDs in elderly due to cognitive impairment,

		falls, delirium, fractures and motor vehicle accidents

(American Society of Addiction Medicine, 2020; Hamrick, 2019; Medscape, 2022a; Medscape, 2022b; National Committee for Quality Assurance, 2021; Puckey, 2022)

Table 3: Literature Review Matrix

Author, (Date)	Research Question	Methods	Analysis	Conclusion	Level of Evidence; Risk of Bias
Andaluz et al., (2019)	Do gabapentin augmentation protocols decrease AWS severity and lorazepam dosing as compared to symptom-based lorazepam alone?	Retrospective review of 982 inpatients. CIWA scale used. Gabapentin delivered in fixed doses	-gabapentin decreased CIWA scores -lorazepam doses in mild-mod AWS decreased faster after 35hr in the gabapentin cohort -gabapentin cohort same as lorazepam cohort in mod-severe AWS -Gabapentin and lorazepam cohorts experienced similar lorazepam dosage despite gabapentin experiencing higher CIWA scores	-Gabapentin reduces length of stay in withdrawal in mild to moderate cases of AWS, but not in severe cases.	3B; ROBINS-I low risk
Anton et al., (2020)	Does gabapentin positively affect alcohol withdrawal patients?	Double blind, placebo-controlled randomized control test of 90 outpatients. Used CIWA scale and patient report. Gabapentin delivered in fixed doses	-Compared to placebo, gabapentin significantly decreased heavy drinking	-Gabapentin decreased post treatment heavy drinking and increased abstinence	1A; RoB2 low risk
Bates et al., (2020)	Is gabapentin safe and useful in the treatment of AWS either with use of benzodiazepines or alone?	Retrospective study of 443 inpatients in one of three arms: benzodiazepine only, gabapentin only, or combination therapy. Used CIWA scale. Gabapentin delivered as a tapered dose	-Gabapentin arm had length of stay four hours shorter than the benzodiazepine arm -Gabapentin arm had CIWA scores 2.2 points lower than benzodiazepine arm	Gabapentin is safe and efficacious for inpatient use	3B; ROBINS-I moderate risk
Fargahi et al., (2021)	Does use of antiepileptics, including gabapentin,	Retrospective study of 75 inpatients comparing a benzodiazepine	-Anticonvulsant cohort required a significantly lower benzodiazepine dose than the control.	Anticonvulsants such as divalproex, gabapentin, and valproic acid are safe	3B; ROBINS-I moderate risk

	decrease symptoms and benzodiazepine use in mild-moderate AWS?	control group with an anticonvulsant taper protocol. Intervention breakdown: 77% received gabapentin, 10% received divalproex, and 10% received valproic acid	It also had CIWA scores 89% lower and significantly fewer patients develop delirium than the control. -Black patients experienced 37% shorter length of stay than non-Blacks in the intervention group	and effective in treatment of mild-moderate AWS.	
Leung et al., (2018)	Is a gabapentin taper safe in treatment of alcohol withdrawal?	Retrospective study of 77 inpatients comparing effectiveness of gabapentin taper to benzodiazepines	-Gabapentin group decreased length of stay to 4.2 days compared to benzodiazepines 5.07 days. -No patients in gabapentin group required transfer up to ICU, developed seizures or delirium tremens	Gabapentin is showing encouraging evidence to support safety in treatment of alcohol withdrawal syndrome	3A; ROBINS-I moderate risk
Levine et al., (2019)	How does high dose gabapentin effect benzodiazepine use, alcohol withdrawal symptoms, and hospital length of stay?	Retrospective cohort study of 100 inpatients using a fixed dose gabapentin schedule	-Gabapentin cohort had 20mg decrease in benzodiazepine, lower withdrawal symptoms, a 1.5 day decrease in length of stay, increased likelihood of being discharged home, and no increase in oversedation as compared to benzodiazepines. -Seizures occurred in 2 patients in the gabapentin cohort	Gabapentin is effective in decreasing benzodiazepine dose and hospital length of stay and increases chances of going home. However, the gabapentin cohort did have 2 patients experience seizures which warn against use as a monotherapy.	3A; ROBINS-I low risk
Morrison et al., (2019)	How does the addition of gabapentin to benzodiazepines impact alcohol withdrawal symptoms?	Retrospective chart review of 100 inpatients. Gabapentin delivered as a high dose taper. Includes a pre- and postimplementation group.	-Median benzodiazepine use was decreased by 3mg per day -Length of stay reduced by 2 days post implementation -50% reduction in RRT's -Nearly 50% reduction in CAM-ICU delirium days	Despite decrease in benzodiazepines, analysis suggests it is not solely due to gabapentin. Overall, gabapentin did show improvement in length of stay, severity of symptoms, and transfers to higher levels of care.	3B; ROBINS-I moderate risk

Nichols et al., (2019)	How does the addition of gabapentin to benzodiazepines impact alcohol withdrawal symptoms?	Retrospective cohort study of 83 inpatients at a psychiatric hospital. Gabapentin delivered as fixed dose.	-No significant difference in dose of benzodiazepines was given -Gabapentin group was more prone to have more complicated withdrawals as well as patients receiving scheduled benzodiazepines	No significant differences were found between cohorts. A larger sample size may have found differences though.	3B; ROBINS-I low risk
Smith et al., (2022)	Does the use of benzodiazepine sparing protocols improve mortality, length of stay, ICU admissions, and hospital readmissions?	Retrospective, quality improvement study of 22,899 inpatients in multiple treatment centers. Gabapentin delivered as a taper.	-Post implementation if using order set, mortality increased 1.3%, readmissions decreased 1.9%, ICU length of stay decreased 1.6%. -No changes seen in hospital length of stay. -Post implementation decrease of benzodiazepines	The use of benzodiazepine sparing protocols, including the use of gabapentin, ICU length of stay, benzodiazepine usage, and readmission rates decreased. Mortality increased, but was supposed to be due to differing patient population.	3A; ROBINS-I low risk
Stock et al., (2013)	Does use of gabapentin reduce sedation and alcohol craving in ambulatory withdrawal as compared to chlordiazepoxide?	Double blind, randomized control trial of 25 outpatients undergoing AWS. Used CIWA scale as well as Epworth Sleepiness scale, and Penn Alcohol Craving Scale. Gabapentin delivered as fixed dose.	-In the Gabapentin group, 3 of the 11 patients had to drop out due to worsening symptoms. -Gabapentin group reduced daytime sleepiness -Gabapentin showed a nonsignificant trend in reduction of craving	Gabapentin showed a decrease in daytime sleepiness and reduction of craving; however, the study was unable to maintain adequate size to have good power.	1C; RoB2 low risk
Vadiei et al., (2019)	Can gabapentin decrease benzodiazepine dose during alcohol withdrawal?	Retrospective inpatient study of 129 patients. Doses of gabapentin were decided, free of protocol, by the attending physician.	-Gabapentin group had higher benzodiazepine use, particularly in the first 72hrs -Gabapentin had a higher percentage of severe CIWA scores than the non-gabapentin group -Gabapentin may have been prescribed sub-therapeutically	No difference was found in length of stay, maximum CIWA score in first 48hrs, 30-day readmission rates, or adverse events. Gabapentin group did use more benzodiazepines than the non-gabapentin group, but that could have	3B; ROBINS-I low risk

				been secondary to other factors.	
Wilming et al., (2018)	How does the addition of gabapentin as an adjuvant therapy to benzodiazepine impact benzodiazepine dose and CIWA score?	Retrospective chart review for quality assurance of 55 inpatients	-Gabapentin group decreased benzodiazepine dosage by median of 2.5mg -Gabapentin group had increased length of stay by 0.3 days -Delirium decreased in gabapentin group by 6% -subtherapeutic doses of gabapentin given on average, wide range of doses from 100mg-3600mg	Gabapentin was shown to decrease benzodiazepine use as well as decrease delirium rates. However, there was also a demonstrated increase in length of stay. The doses of gabapentin were not controlled and varied widely.	3C; ROBINS-I moderate risk

Table 4: Research Outcomes Comparison

	GBP improved results	**GBP results similar to BZD**	**GBP worsened results**
As needed BZD dosing	FARGAHI ET AL. (2021) LEVINE ET AL. (2019) MORRISON ET AL. (2019) SMITH ET AL. (2022) WILMING ET AL. (2018)	ANDALUZ ET AL. (2020) NICHOLS ET AL. (2019)	VADIEI ET AL. (2019)
AWS Severity	ANDALUZ ET AL. (2020) FARGAHI ET AL. (2021)	ANTON ET AL. (2020) BATES ET AL. (2020) STOCK ET AL. (2013)	
Hospital/Protocol LOS	LEUNG ET AL. (2018) LEVINE ET AL. (2019) MORRISON ET AL. (2019) SMITH ET AL. (2022)	BATES ET AL. (2020) NICHOLS ET AL. (2019) VADIEI ET AL. (2019) WILMING ET AL. (2018)	
ICU LOS	LEVINE ET AL. (2019) MORRISON ET AL. (2019)		
Heavy Drinking	ANTON ET AL. (2020)		
Abstinence	ANTON ET AL. (2020)		
Gabapentin Safety in AWS	BATES ET AL. (2020)	BATES ET AL. (2020) LEUNG ET AL. (2018) LEVINE ET AL. (2019) MORRISON ET AL. (2019) NICHOLS ET AL. (2019) VADIEI ET AL. (2019) WILMING ET AL. (2018)	
Diurnal Drowsiness	LEVINE ET AL. (2019) STOCK ET AL. (2013)		
Likelihood discharge home	LEVINE ET AL. (2019)		
Readmission rates		SMITH ET AL. (2022) VADIEI ET AL. (2019)	
Alcohol Craving		STOCK ET AL. (2013)	

Table 5: Limitations Comparison

Subtherapeutic GBP Dose/Taper	ANDALUZ ET AL. (2020) BATES ET AL. (2020) VADIEI ET AL. (2019) WILMING ET AL. (2018)
Unequal Cohorts/Groups	ANDALUZ ET AL. (2020) LEUNG ET AL. (2018) LEVINE ET AL. (2019) VADIEI ET AL. (2019) WILMING ET AL. (2018)
Retrospective Study	ANDALUZ ET AL. (2020) BATES ET AL. (2020) LEUNG ET AL. (2018) LEVINE ET AL. (2019) MORRISON ET AL. (2019) NICHOLS ET AL. (2019) SMITH ET AL. (2022) VADIEI ET AL. (2019) WILMING ET AL. (2018)
Poor Control Variables	BATES ET AL. (2020) LEUNG ET AL. (2018) MORRISON ET AL. (2019) SMITH ET AL. (2022)

Appendix B: Tools

Tool 1: Clinical Institute Withdrawal Assessment – Alcohol, revised

Alcohol Withdrawal Assessment Scoring Guidelines (CIWA - Ar)

Nausea/Vomiting - Rate on scale 0 - 7

0 - None
1 - Mild nausea with no vomiting
2
3
4 - Intermittent nausea
5
6
7 - Constant nausea and frequent dry heaves and vomiting

Tremors - have patient extend arms & spread fingers. Rate on scale 0 - 7.
0 - No tremor
1 - Not visible, but can be felt fingertip to fingertip
2
3
4 - Moderate, with patient's arms extended
5
6
7 - severe, even w/ arms not extended

Anxiety - Rate on scale 0 - 7
0 - no anxiety, patient at ease
1 - mildly anxious
2
3
4 - moderately anxious or guarded, so anxiety is inferred
5
6
7 - equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions.

Agitation - Rate on scale 0 - 7
0 - normal activity
1 - somewhat normal activity
2
3
4 - moderately fidgety and restless
5
6
7 - paces back and forth, or constantly thrashes about

Paroxysmal Sweats - Rate on Scale 0 - 7.
0 - no sweats
1- barely perceptible sweating, palms moist
2
3
4 - beads of sweat obvious on forehead
5
6
7 - drenching sweats

Orientation and clouding of sensorium - Ask, "What day is this? Where are you? Who am I?" Rate scale 0 - 4
0 - Oriented
1 – cannot do serial additions or is uncertain about date

2 - disoriented to date by no more than 2 calendar days

3 - disoriented to date by more than 2 calendar days
4 - Disoriented to place and / or person

Tactile disturbances - Ask, "Have you experienced any itching, pins & needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?"
0 - none
1 - very mild itching, pins & needles, burning, or numbness
2 - mild itching, pins & needles, burning, or numbness
3 - moderate itching, pins & needles, burning, or numbness
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Auditory Disturbances - Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?"
0 - not present
1 - Very mild harshness or ability to startle
2 - mild harshness or ability to startle
3 - moderate harshness or ability to startle
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

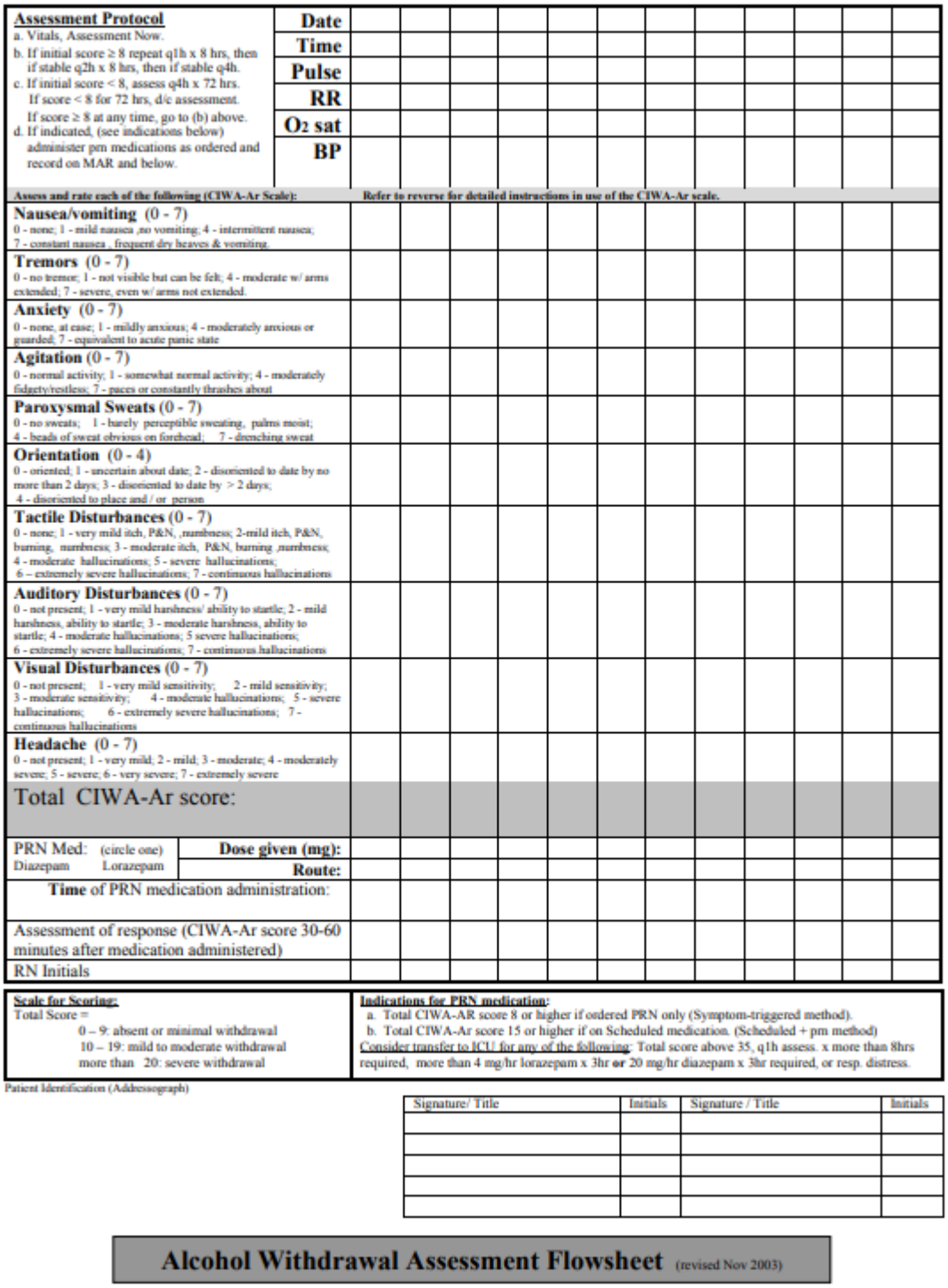
Visual disturbances - Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you or that you know isn't there?"
0 - not present
1 - very mild sensitivity
2 - mild sensitivity
3 - moderate sensitivity
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Headache - Ask, "Does your head feel different than usual? Does it feel like there is a band around your head?" Do not rate dizziness or lightheadedness.

0 - not present
1 - very mild
2 - mild
3 - moderate
4 - moderately severe
5 - severe
6 - very severe
7 - extremely severe

Procedure:

1. Assess and rate each of the 10 criteria of the CIWA scale. Each criterion is rated on a scale from 0 to 7, except for "Orientation and clouding of sensorium" which is rated on scale 0 to 4. Add up the scores for all ten criteria. This is the total CIWA-Ar score for the patient at that time. Prophylactic medication should be started for any patient with a total CIWA-Ar score of 8 or greater (ie. start on withdrawal medication). If started on scheduled medication, additional PRN medication should be given for a total CIWA-Ar score of 15 or greater.
2. Document vitals and CIWA-Ar assessment on the Withdrawal Assessment Sheet. Document administration of PRN medications on the assessment sheet as well.
3. The CIWA-Ar scale is the most sensitive tool for assessment of the patient experiencing alcohol withdrawal. Nursing assessment is vitally important. Early intervention for CIWA-Ar score of 8 or greater provides the best means to prevent the progression of withdrawal.



Assessment Protocol a. Vitals, Assessment Now. b. If initial score ≥ 8 repeat q1h x 8 hrs, then if stable q2h x 8 hrs, then if stable q4h. c. If initial score < 8, assess q4h x 72 hrs. If score < 8 for 72 hrs, d/c assessment. If score ≥ 8 at any time, go to (b) above. d. If indicated, (see indications below) administer prn medications as ordered and record on MAR and below.	**Date**												
	Time												
	Pulse												
	RR												
	O_2 sat												
	BP												
Assess and rate each of the following (CIWA-Ar Scale):	**Refer to reverse for detailed instructions in use of the CIWA-Ar scale.**												
Nausea/vomiting (0 - 7) 0 - none; 1 - mild nausea ,no vomiting; 4 - intermittent nausea; 7 - constant nausea , frequent dry heaves & vomiting.													
Tremors (0 - 7) 0 - no tremor; 1 - not visible but can be felt; 4 - moderate w/ arms extended; 7 - severe, even w/ arms not extended.													
Anxiety (0 - 7) 0 - none, at ease; 1 - mildly anxious; 4 - moderately anxious or guarded; 7 - equivalent to acute panic state													
Agitation (0 - 7) 0 - normal activity; 1 - somewhat normal activity; 4 - moderately fidgety/restless; 7 - paces or constantly thrashes about													
Paroxysmal Sweats (0 - 7) 0 - no sweats; 1 - barely perceptible sweating, palms moist; 4 - beads of sweat obvious on forehead; 7 - drenching sweat													
Orientation (0 - 4) 0 - oriented; 1 - uncertain about date; 2 - disoriented to date by no more than 2 days; 3 - disoriented to date by > 2 days; 4 - disoriented to place and / or person													
Tactile Disturbances (0 - 7) 0 - none; 1 - very mild itch, P&N, ,numbness; 2-mild itch, P&N, burning, numbness; 3 - moderate itch, P&N, burning ,numbness; 4 - moderate hallucinations; 5 - severe hallucinations; 6 – extremely severe hallucinations; 7 - continuous hallucinations													
Auditory Disturbances (0 - 7) 0 - not present; 1 - very mild harshness/ ability to startle; 2 - mild harshness, ability to startle; 3 - moderate harshness, ability to startle; 4 - moderate hallucinations; 5 severe hallucinations; 6 - extremely severe hallucinations; 7 - continuous hallucinations													
Visual Disturbances (0 - 7) 0 - not present; 1 - very mild sensitivity; 2 - mild sensitivity; 3 - moderate sensitivity; 4 - moderate hallucinations; 5 - severe hallucinations; 6 - extremely severe hallucinations; 7 - continuous hallucinations													
Headache (0 - 7) 0 - not present; 1 - very mild; 2 - mild; 3 - moderate; 4 - moderately severe; 5 - severe; 6 - very severe; 7 - extremely severe													
Total CIWA-Ar score:													
PRN Med: (circle one) Diazepam Lorazepam	**Dose given (mg):**												
	Route:												
Time of PRN medication administration:													
Assessment of response (CIWA-Ar score 30-60 minutes after medication administered)													
RN Initials													

Scale for Scoring:
Total Score =
0 – 9: absent or minimal withdrawal
10 – 19: mild to moderate withdrawal
more than 20: severe withdrawal

Indications for PRN medication:
a. Total CIWA-AR score 8 or higher if ordered PRN only (Symptom-triggered method).
b. Total CIWA-Ar score 15 or higher if on Scheduled medication. (Scheduled + pm method)
Consider transfer to ICU for any of the following: Total score above 35, q1h assess. x more than 8hrs required, more than 4 mg/hr lorazepam x 3hr **or** 20 mg/hr diazepam x 3hr required, or resp. distress.

Patient Identification (Addressograph)

Signature/ Title	Initials	Signature / Title	Initials

Alcohol Withdrawal Assessment Flowsheet (revised Nov 2003)

(Keifer Corporation, 2022)

Tool 2- Richmond Agitation and Sedation Score

RASS score

Richmond Agitation & Sedation Scale				CAM-ICU
Score	**Description**			
+4	Combative	Violent, immediate danger to staff		RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive		
+2	Agitated	Frequent non-purposeful movements, fights ventilator		
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous		
0	Alert & calm			
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice	
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)		
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)		RASS < -2 STOP Recheck later
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Touch	
-5	Un-rousable	No response to voice or physical stimulation		

(Nickson, 2015).

Tool 3 – Confusion Assessment Method-ICU-7

The CAM-ICU-7 Delirium Severity Scale

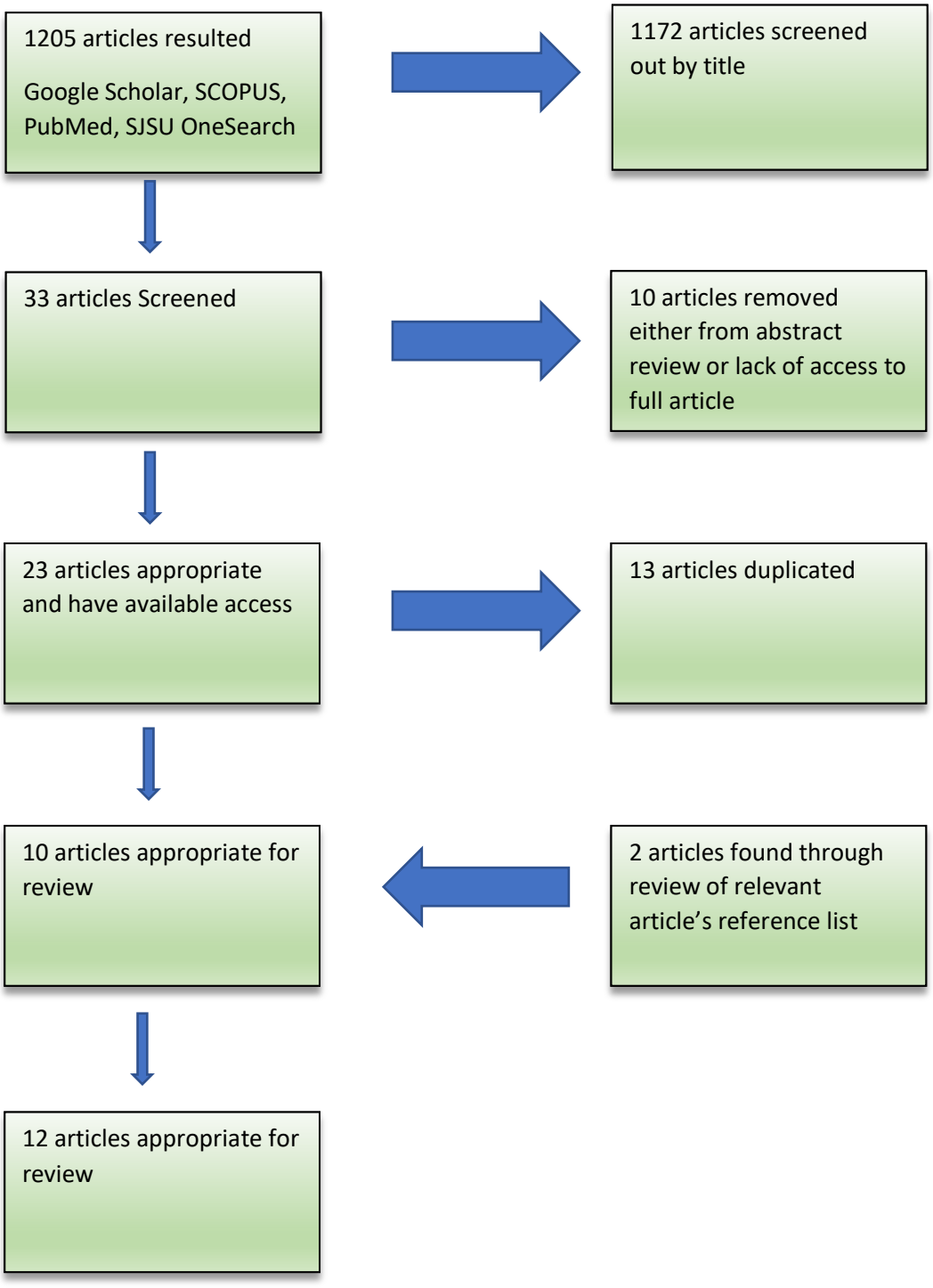
CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; RASS: Richmond Agitation Sedation Scale; SAS: Sedation-Agitation Scale; GCS: Glasgow Coma Scale

(Khan et al., 2017).

Appendix C: Figures

Figure 1: PRISMA Flow Chart



Appendix D: Annotated Bibliography

Andaluz, A., DeMoss, D., Claassen, C., Blair, S., Hsu, J., Bakre, S., Khan, M., Atem, F., & Rush, A. (2019). Fixed-Dose Gabapentin Augmentation in the Treatment of Alcohol Withdrawal Syndrome: A Retrospective, Open-Label Study. The American Journal of Drug and Alcohol Abuse, 46(1), 49-57. https://doi.org/10.1080/00952990.2019.1634085

This is a retrospective study of 982 inpatients receiving gabapentin taper protocol as an adjunctive therapy to benzodiazepines. They result that, although gabapentin does not decrease benzodiazepine usage or CIWA scores, particularly in severe cases of AWS, there exists a dose-dependent shortening of length of stay with mild-moderate cases decreasing CIWA scores faster than the controls. This study is limited by a moderately strong selection bias, favoring more severe cases for the gabapentin arm as well as those patients more likely to already being on gabapentin for non-alcohol related reasons. The authors also note that the gabapentin taper doses may have been subtherapeutic, particularly in those who are not gabapentin naive. Given that the gabapentin arm was more likely to have potentially high scoring patients selected on the outset, yet received a similar dose of benzodiazepines, despite an overly conservative dose of gabapentin, there remains a question as to the efficacy of gabapentin if the cohorts had been more equal and a therapeutic dose of gabapentin would have resulted in a lower dose of benzodiazepines given.

Anton, R.F., Latham, P., Voronin, K., Book, S., Hoffman, M., Prisciandaro, J., & Bristol, E. (2020). Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms. *JAMA Internal Medicine*, 180(5), 728-736. https://doi.org/10.1001/jamainternalmed.2020.0249

This is a study of 90 outpatients, primarily with alcohol use disorder as opposed to alcohol withdrawal syndrome. The article compares the effect of gabapentin versus placebo on abstinence and return to heavy drinking following alcohol cessation. It shows that benefits of gabapentin include increased

abstinence and lower likelihood of returning to binge drinking. As this is an outpatient study, it would be assumed that the patients either experienced no to minimal symptoms of alcohol withdrawal. Because of this, it cannot be concluded that gabapentin would have the same effects on those suffering moderate to severe withdrawal effects. In the purposes of this literature review, the results from this study count as a potential silver-lining of treatment with gabapentin.

Bates, R., Leung, J., Morgan, R., Fischer, K., Philbrick, K., & Kung, S. (2020). Retrospective Analysis of Gabapentin for Alcohol Withdrawal in the Hospital Setting: The Mayo Clinic Experience. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes,* 4(5), 542-549. https://doi.org/10.1016/j.mayocpiqo.2020.06.002

This is a retrospective study of 443 inpatients divided into a gabapentin arm, a benzodiazepine arm, and a combination arm. The results show that gabapentin decreased length of stay and decreased maximum CIWA score without significant differences in adverse reactions, although the authors point out that they did not prepare for statistical analysis of adverse events. The protocol enacted during the study also used other agents to control symptoms such as sodium valproate, clonidine, haloperidol, and thiothixene. These other agents act as a confounding factor since it cannot be confirmed that results are solely from action of gabapentin versus benzodiazepines. From other studies, there is also evidence of a dose-dependent response to gabapentin, with more mild cases responding more than severe cases. However, this study does not differentiate between the levels which may misrepresent gabapentin effectiveness, particularly in severe AWS, in which some studies, like Andaluz et al. (2020), have advocated against the use of gabapentin.

Fargahi, F., Shrestha, R., Rawal, H., Jaar, B., Chilipko, A., Norwood, D., Ji, C., & Yazaji, E. (2021). Impact of Adjuvant Anticonvulsant Medications on Benzodiazepine Use and Delirium in Alcohol Withdrawal Syndrome. (2021). *Primary Care Companion CNS Disorders,* 23(5), 20m02860, https://doi.org/10.4088/PCC.20m02860.

This is a retrospective study of 75 inpatients comparing the effectiveness of anticonvulsants such as divalproex sodium, gabapentin, and valproic acid against benzodiazepines in alcohol withdrawal. The study found that, in mild-moderate AWS, anticonvulsants can significantly decrease CIWA scores, benzodiazepine use, and delirium. There was also a finding that the anticonvulsants led to a 37% decrease in length of stay in Black patients. Most of the patients, 77%, in the intervention cohorts received a gabapentin taper, however, it is unclear if the results came from the gabapentin groups alone or influenced by the other anticonvulsant groups.

Leung, J., Rakocevic, D., Allen, N., Handler, E., Perossa, B., Borreggine, K., Stark, A., Betcher, H., Hosker, D., Minton, B., Braus, B., Dierkhising, R., Philbrick, K. (2018). Use of a Gabapentin Protocol for the Management of Alcohol Withdrawal: A Preliminary Experience Expanding from the Consultation-Liaison Psychiatry Service. *Psychosomatics*, 59(5), 496-505.

This is a study of 77 inpatients undergoing alcohol withdrawal treatment. The study aims to compare the use of a gabapentin taper protocol with a standard benzodiazepine treatment. The results show a decrease in length of stay and no adverse events in the gabapentin cohort. However, the study suffers from multiple limitations which include inconsistent use of psychiatry consults, occasional doses of benzodiazepines prior to start of protocol, and risk of bias. Other adjuvant medications were also used inconsistently which may also skew results.

Levine, A., Carrasquillo, L., Mueller, J., Nounou, M., Naut, E., & Ibrahim, D. (2019). High-Dose Gabapentin for the Treatment of Severe Alcohol Withdrawal Syndrome: A Retrospective Cohort Analysis. *Pharmacotherapy*, 39(9), 881-887.

This is a retrospective cohort study of 100 inpatients comparing the effects that a high dose gabapentin protocol has on benzodiazepine use, severity of symptoms, length of stay and discharge destination. The study found significant positive effects resulting in a decrease of nearly 20mg benzodiazepines, decreasing withdrawal symptoms by day 3, as well as decreasing the length of stay by 1.5 days, and

increasing the chances of the patient being able to go home afterwards. During the study, two patients in the gabapentin cohort did have seizures which warns against the use of gabapentin as a monotherapy in the treatment of alcohol withdrawal syndrome.

Morrison, M., Udeh, E., & Burak, M. (2019). Retrospective Analysis of a Gabapentin High Dose Taper Compared to Lorazepam in Acute Inpatient Alcohol Withdrawal. *The American Journal of Drug and Alcohol Abuse,* 45(4), 385-391. https://doi.org/10.1080/00952990.2019.1602136.

This is a retrospective chart review of 100 inpatients analyzing the difference on benzodiazepine usage and patient outcomes following implementation of a high dose gabapentin taper. Initial findings show dramatic decreases in benzodiazepine doses, length of stay, number of RRT's called, delirium, and transfers to higher levels of care. The statistical analysis does suggest though that the decrease in benzodiazepine dose may have a multivariate root that requires further research. However, gabapentin is described as well tolerated throughout the study. This study is converse to the study performed by Nichols et al., (2019). Further research would be necessary to determine which is more accurate.

Nichols, T., Robert, S., Taber, D., & Cluver, J. (2019). Alcohol Withdrawal-Related Outcomes Associated with Gabapentin use in an Inpatient Psychiatric Facility. *Mental Health Clinician*, 9(1), 1-5. https://doi.org/10.9740/mhc.2019.01.001.

This is a retrospective cohort study of 83 inpatients at a psychiatric hospital to investigate the effect that a gabapentin protocol has on benzodiazepine use and withdrawal severity. The findings of this study failed to reveal any clinically significant effects, finding instead that the gabapentin appeared to have no effect on benzodiazepine use or withdrawal severity. It is noted, however, that the gabapentin group did have higher number of patients with signs of complicated withdrawal and that more patients in that cohort were on scheduled benzodiazepines, although these differences did not reach clinical significance.

Smith, J., Sage, M., Szeto, H., Myers, L., Lu, Y., Martinez, A., Kipnis, P., & Liu, V. (2022). Outcomes After Implementation of a Benzodiazepine-Sparing Alcohol Withdrawal Order Set in an

Integrated Health Care System. *JAMA Network*, 5(2), e220158. https://doi.org/doi:10.1001/jamanetworkopen.2022.0158.

This is a large, multicenter quality improvement study of 22,899 inpatients investigating the effectiveness of benzodiazepine sparing protocols using drugs such as gabapentin low dose taper, gabapentin high dose taper, valproic acid, and clonidine. This study still included benzodiazepines as a central part of treatment but compared whether the protocol had the favorable outcomes of decreased length of stay, decreased readmission, decreased benzodiazepine, and decreased mortality. It found that the protocols did decrease length of stay, benzodiazepine usage, and readmission rates. However, mortality increased, but that was supposed to be due alterations in patient populations. The study notes that aside from the protocol, it also measured interventions not using the protocol, which could confound some of the results due to subtherapeutic dosages of medication.

Stock, C., Carpenter, L., Ying, J., & Greene, T. (2013). Gabapentin Versus Chlordiazepoxide for Outpatient Alcohol Detoxification Treatment. *The Annals of Pharmacotherapy*, 47, 961-969. https://doi.org/10.1345/aph.1R751.

Stock et al., (2013) is a double-blind randomized control trial of 25 outpatients comparing the effects of gabapentin versus chlordiazepoxide. The specific target of the study is to measure daytime sleepiness and alcohol craving; however, it does briefly describe some effects on CIWA scale. The study concludes that gabapentin does decrease daytime sedation and shows a trend in decreasing alcohol craving which is superior to chlordiazepoxide. There is also a one-point difference in CIWA scores in cohorts treated by gabapentin, 7.7, versus chlordiazepoxide, 8.8. But it is unclear whether this is a significant difference. The study also suffers from a small sample size further compounded by patient dropout in the gabapentin cohort, thereby preventing assessment of power.

Vadiei, N., Smith, T., Walton, A., & Kjome, K. (2019). Impact of Gabapentin Adjunct use with Benzodiazepines for the Treatment of Alcohol Withdrawal in a Psychiatric Hospital. *Psychopharmacology Bulletin*, 49(1), 17-27.

This is a retrospective study of 129 inpatients to ascertain the safety and effectiveness of a gabapentin treatment plan as compared to the use of benzodiazepines. The dosing was decided by the physician at the bedside, and at times, was found to be subtherapeutic. Also, the gabapentin group was found to have a bias towards more severe cases of alcohol withdrawal syndrome than the control. The overall findings of this study were that gabapentin had no effect on benzodiazepine dose, length of stay, adverse reactions, or readmission rates when compared to the benzodiazepine group. The limitations of this study are an Achille's heel to its findings and make the findings suspect.

Wilming, C., Alford, M., & Klaus, L. (2018). Gabapentin Use in Acute Alcohol Withdrawal Management. *Federal Practitioner*, 40-45.

This was a retrospective quality assurance study of 55 inpatients to evaluate the impact that gabapentin has on alcohol withdrawal as an adjuvant to benzodiazepines. The study found that addition of gabapentin could lead to decreases in benzodiazepine use as well as delirium. There is also an increase in length of stay in the gabapentin group by 0.3 days. The study notes that the doses of gabapentin were not controlled and varied widely, from anything between 100mg per day all the way to 3600mg of gabapentin per day. This makes it questionable as to the overall results since it cannot be ascertained if the results are due to the presence of gabapentin or due to the dose of gabapentin being given.