University of Nevada, Reno

Gabapentin for Use on Patients with Alcohol Withdrawal Syndrome: An Integrative Review of the Literature

A thesis submitted in partial fulfillment of the
requirements for the degree of
Masters of Science in Nursing

By

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May 2013

University of Nevada, Reno
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THE GRADUATE SCHOOL

We recommend that the thesis

prepared under our supervision by

Heidi Marie Sabol

entitled

Gabapentin for Use on Patients with Alcohol Withdrawal Syndrome: An Integrative Review of the Literature

be accepted in partial fulfillment of the

requirements for the degree of

Masters of Science in Nursing

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May 2013

Abstract

Problem: Up to 2 million Americans suffer from alcohol withdrawal syndrome (AWS) each year. Alcoholism contributes to a significant number of co-morbidities and mortality (Enoch & Goldman, 2002). Some of the most commonly prescribed medications for alcohol withdrawal and dependence have disappointing efficacy and undesirable side effects. The neurotransmitter γ-amino-butyric acid (GABA) disregulation has been the focus of research into the pathophysiology of AWS (Cagetti, Liang, & Spigelman (2003); Olsen, Liang, & Cagetti, 2005). Alcohol increases the effect of GABA. Long term exposure to alcohol causes down-regulation of GABA neuroreceptors (Olsen, Liang, & Cagetti, 2005; Bayard, Mcintyre, Hill & Woodside, 2004). Roberto, et al. (2008) found that gabapentin infused directly into the nucleus of the amygdala reduced ethanol dependence and reversed "behavioral measures of ethanol dependence" in mice. Clemens & Vendruscolo (2008) found the anxiety producing effects of ethanol withdrawal were reversed with application of gabapentin directly to the amygdala of ethanol dependent mice. These studies suggest that more research needs to focus on the role of gabapentin in treating AWS and preventing relapse in alcohol dependent individuals. The purpose of this integrative review was to analyze the peer reviewed body of research on the use of the anticonvulsant gabapentin on patients with AWS.

Methods/procedure/approach: Search terms used were combinations of gabapentin, Alcohol Withdrawal, and Ethanol Withdrawal. Two electronic databases were searched: CINAHL Ebsco Host and PubMed and an ancestry search was performed. Inclusion criteria were English language studies between 2006 and 2012. The search yielded 47

results. Articles were excluded that described treating other substance addictions or for treatment of seizures. The resulting search was narrowed to 13 studies from 4 countries using a total of 319 study participants.

Results/findings/product: Twelve of the 13 studies reviewed revealed gabapentin may be equal to or superior than other treatment regimens currently in use. Gabapentin was shown to be safe, even for patients who drink while taking the medication. Gabapentin was not effective in patients having the most severe or the mildest symptoms.

Conclusion/implications: Additional clinical investigations are indicated to demonstrate whether gabapentin should become more widely used as an adjunct or preferred treatment for alcohol dependence and AWS. The existing body of knowledge is supportive but limited.

Key Words: Alcoholism, Ethanol dependence, Alcohol dependence, Alcohol withdrawal syndrome, Gabapentin, AWS, addictions treatment, addictions pharmacological therapy

Acknowledgement: The Author wishes to thank Sarah Keating, you have encouraged me and changed me so many ways and your courage has inspired me
Also: Bernadette Longo, Stephanie DeBoors, Gary Fisher, Walter Lewis and all the wonderful people who have helped me along the way

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Chapter I – CLINICAL PROBLEM

Introduction

Alcoholism is a major health problem affecting about 15 million Americans (Centers for Disease Control and Prevention, 2010). Alcohol dependence is defined as "a maladaptive pattern of alcohol use leading to clinically significant impairment or distress" (American Psychiatric Association, 2000). Alcohol Withdrawal Syndrome (AWS) is a set of symptoms resulting from sudden discontinued use of alcohol after physical dependence has developed. Up to 2 million Americans suffer from AWS each year. Alcoholism contributes to a significant number of co-morbidities and mortality (Enoch & Goldman, 2002).

There have been advances in the understanding of the neurochemistry and pathophysiology of alcohol dependence and AWS. The brain requires a balance of inhibitory and excitory neurotransmitters to function optimally. Alcohol is thought to suppress the GABAergic, glutamatergic, dopaminergic, serotoninergic and opiatergic systems (Johnson, Swift, Ait-Daoud, DiClemente, Javors, Malcolm, 2004). One of the most important inhibitory neurotransmitters is γ-amino-butyric acid (GABA). Alcohol increases the effect of GABA. Long term exposure causes down-regulation of GABA neuroreceptors (Olsen & Cagetti, 2005; Bayard, Mcintyre, Hill & Woodside, 2004).

Recent studies found that alcohol dependence was closely associated with decreased volume of the amygdala, hippocampus and ventral striatum. The amygdala is associated with the reward and punishment regions of the brain and is involved in

decision making and learning (Wrase, Makris, Braus, Mann, Smolka, Kennedy, 2008). Roberto, Gilpin, O'Dell, Cruz, Morse, Siggins, & Koob (2008) found that gabapentin infused directly into the nucleus of the amygdala reduced ethanol dependence and reversed "behavioral measures of ethanol dependence" in mice. Clemens & Vendruscolo (2008) found the anxiety producing effects of ethanol withdrawal were reversed with application of gabapentin directly to the amygdala in ethanol dependent mice. These studies seem to suggest more research needs to focus on the role of gabapentin in treating AWS and preventing relapse in alcohol dependent individuals.

The onset of symptoms of AWS typically begins within 6 to 72 hours after the last drink and may last up to 7 days. Symptoms include fever, hypertension, anxiety, agitation, tremors, insomnia, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia, auditory, visual and tactile hallucinations, and seizures (Enoch & Goldman, 2002). The severity of symptoms is proportional to the amount of alcohol typically ingested and the length of time of use (Bayard, Mcintyre, Hill, & Woodside, 2004).

The objective of treatment for alcohol dependence and AWS is to reduce the severity of withdrawal symptoms, prevent life threatening complications and prevent relapse (Enoch & Goldman, 2002). Ideal medications for treatment are those that reduce the severity of symptoms, are well tolerated by the patient, and safe for use with patients with decreased liver function. They must also be tolerated well if the patient relapses and ingests alcohol and should not cause additional addiction (Ait-Daoud, Malcolm, & Johnson 2006). The benzodiazepine lorazepam is one of the most commonly used

medications to treat AWS. Lorazepam causes sedation and may cause dependence (Ciraulo, Sands, & Shader, 1998).

Research has focused on GABA disregulation as an important mechanism in the pathophysiology of AWS (Cagetti, Liang, & Spigelman, 2003; Olsen, Liang, & Cagetti , 2005). Anticonvulsive treatment such as carbazipine, valproate, topiramate, and gabapentin has been studied as a result of this revelation. Carbazipine and valproate have hepatotoxicity concerns and topiramate may be sedating (Johnson & Ait-Daoud, 2010). Gabapentin was developed 40 years ago but was not approved in the United States by the Food and Drug Administration (FDA) until 1994 for adjunctive treatment for partial seizures, and later, for post-herpetic neuralgia. Gabapentin was originally designed as a structural analog of GABA which is not metabolized by humans but is renally excreted in an unchanged form, and is not hepatotoxic (McLean, 1994). Gabapentin has been shown by many studies to be effective, yet is well tolerated with a high safety index and can be tapered off to limit dependence. Gabapentin slightly increases risk of suicidal thoughts. Despite these attributes, the off-label use of Gabapentin for AWS remains controversial (Middleton, 2011; Vedula, Bero, Scherer, & Dickersin, 2009).

Statement of the Problem

Some of the most commonly prescribed medications for alcohol withdrawal and dependence are lorazepam, disulfiram, naltrexone, and acamprosate. Lorazepam is primarily used for withdrawal and the others are primarily prescribed for prevention of relapse. They have disappointing efficacy and have undesirable side effects. Furthermore, some are not safe for use by a patient with a high probability of using alcohol while

taking the medication or aren't tolerated well (Ciraulo, Sands & Shader, 1998). There is a need for more effective pharmacological intervention in alcohol withdrawal and dependence. Additionally, the risk of patients relapsing to heavy drinking is greatest during the first few months after abstinence (Anton, et al., 2009). This is a time when the neurotransmission remains disregulated. Some promising research supports the use of the anticonvulsant gabapentin for use with alcohol dependence. Despite this, gabapentin still has not found favor with prescribing physicians.

Purpose of the Integrative Review

A need exists to synthesize the available peer-reviewed research on the use of gabapentin for alcohol dependence and AWS to determine if it is superior to other interventions. The purpose of this integrative review of the literature was to gather data from studies on the use of gabapentin for patients with AWS compared to other pharmacological interventions.

Significance of the Integrative Review

A need exists for more effective pharmacological interventions for alcohol dependence and AWS. This integrative review of the literature assessed the body of knowledge on the use of gabapentin use for AWS. The results will assist health care providers in their understanding of the scientific support of gabapentin for use in the evidence-based treatment of AWS.

Scientific and Theoretical Assumptions

The prior assumptions were that AWS may be treated successfully by pharmacological means. This does not preclude the importance of psychological interventions such as counseling, behavior modification intervention, and group treatment. Rather, it is assumed that pharmacological treatment goes hand-in-hand with psychological interventions such as group therapy and participation in groups like Alcoholics Anonymous. The theoretical assumption for the review was Newman's system's model which views the client as an open system affected by many outside stressors that may cause disequilibrium resulting in disease (Neuman, 1989).

Alcohol dependence was historically seen as psychological or moral failure, but in recent times is understood as a complex disease. The General Systems Theory for the review was utilized as a psychological theory because it views addiction as being influenced by genetic, social and family stressors as well as being affected by disturbance among complex biophysical systems (Himmelsback, 1941).

Question Addressed by the Integrative Review of Literature

The following question was addressed: "To what extent is gabapentin equal to or superior to other medications currently being prescribed as an adjunctive therapy for the treatment of AWS?" Objectives of the integrative review of literature were to synthesize available research on the adjunctive and primary use of gabapentin for use in AWS, and to have this information disseminated to prescribing providers.

Limitations

There were a number of limitations to this integrative review. First, the total number of participants from all of the studies combined remained relatively small. For all

13 identified studies in the literature, there were a total of 319 subjects. Second, the identified studies employed different measuring tools for results and used different dosage regimens of gabapentin for their patients. Third, the studies reviewed were conducted over short time periods without follow-up for delayed effects. Most studies were less than 2 weeks in duration. Despite these limitations, a strength of this integrative review was that almost all of the studies utilized a double-blind, randomized and controlled experimental model.

Conceptual and Operational Definitions

For the basis of this integrative review, the following terms were utilized:

- Alcohol dependence is "a maladaptive pattern of alcohol use leading to clinically significant impairment or distress" (DSM-IV Criteria for Alcohol Dependence).
- Alcohol withdrawal syndrome (AWS) is a set of symptoms resulting from the cessation or reduction in alcohol use that has been "heavy and prolonged" and includes two or more of the following symptoms: sweating, increased pulse rate, increased hand tremor, insomnia, nausea, vomiting, transient visual, tactile or auditory hallucinations, agitation, anxiety and grand mal seizures. To meet the diagnostic criteria, these symptoms must be determined not to be the result of another diagnosis. Furthermore, symptoms may be distressing or cause disruption in social or occupational activities. This set of symptoms results from suddenly discontinuing the use of alcohol after physical dependence has begun (Bayard, Mcintyre, Hill, & Woodside, 2004).

- Heavy drinking is defined as more than 4 drinks per day and more than 14 drinks per week for men. For women, it is more than 3 drinks per day and more than 7 drinks per week (NIAAA, 2012).
- Binge drinking is defined as five or more drinks in a 2 hour period for men and four or more drinks in a 2 hour period for women (NIAAA, 2012).

Theoretical/Conceptual Framework

The theoretical assumption was based on The Neuman System's Model. The underpinnings of this theory are that complex variables underlie diseases and disease processes. The complicated relationships between these many variables contribute to the whole disease process (Neuman, 1989). The model sees health as "optimum system stability" (Neuman, 1989). This lent itself well to the understanding of AWS as a system instability arising from many interconnected factors including the disregulation of the GABA inhibitory neurotransmitter system. This model also provided for the acknowledgement of other complex contributing factors.

Pathophysiology

The cause of AWS is thought to be a disruption in the neurochemical balance of the inhibitory neurotransmitter γ-amino-butyric acid (GABA) and the excitory neurotransmitter glutamate. Alcohol is believed to increase the effects of GABA on the neuroreceptor GABA-alpha (GABA-A). After prolonged exposure to increased levels of GABA, the neuroreceptor GABA-A down-regulates to compensate. This causes both the increased tolerance to alcohol and the symptoms that manifest when alcohol use is decreased or ceased (Bayard, Mcintyre, Hill, & Woodside, 2004).

Chapter II – REVIEW OF LITERATURE

Problem

Half of all Americans report drinking regularly (Centers for Disease Control and Prevention, 2012a). Alcoholism is a major health problem that affects up to 19.3 million Americans (Centers for Disease Control and Prevention, 2010). Eighty-seven percent of those whose drinking may be defined as excessive, do not feel they need treatment. Each year up to 1.5 million Americans seek treatment for alcohol dependence (NSDUH, 2009). It is one of the most common psychiatric disorders affecting as many as 17% of people at some point in their lifetime (SAMHSA, 2012). In the past, alcoholism was seen as a behavioral and moral problem. Recent advances in the understanding of the neurotransmitters and changes in brain function underlying addiction led to better pharmacological interventions.

Demographics. Alcoholism historically affected more men than women. In recent years, the numbers of alcoholics who are female has been rising and is now 14% reporting binge drinking and 3.2% reporting heavy drinking compared to men reporting 17.5% and 5.6% respectively (NSDUH, 2011). Episodes of heavy drinking is highest among the American Indian, Alaskan and Native Hawaiians (24.3%) and lowest among Asians (11.6%) (NSDUH, 2011; Stinson, Yi, Grant, Chou, Dawson, & Pickering, 1998; Kim, Coletti, Williams, & Hepler, 1995). Hispanics tend to consume more alcohol per drinking episode than whites and blacks have the lowest life time prevalence of heavy drinking (Stinson, Grant, & Dufour, 2001; Johnston, O'Malley, & Bachman, 2001). Multiple studies found that heavy drinking was lower among those who regularly attend

church (Kendler & Myers, 2009; Benda, Pope, & Kelleher, 2006). Several other studies documented higher rates of alcohol dependence among those of lower socioeconomic status (NSDUH, 2011; Grant, 1997; Hasin, Stinson, Ogburn, & Grant, 2007; Van Oers, Bongers, Van de Goor, & Garretsen, 1999).

Morbidity and mortality. Alcohol abuse and dependence lead to long term health problems such as cirrhosis, neurological problems, pancreatitis, stroke, coronary artery disease, myocardial infarctions and hypertension. Alcohol abuse is linked to cancer of the mouth, throat, liver colon and breast. Over all age groups, liver cirrhosis is the 12th leading cause of death in the United States (Murphy, Xu, Kochanek, 2012). In addition to disease, alcohol use increases risk of motor vehicle accidents, and injuries such as falls, burns, fire-arm accidents, and drowning. Alcoholism increases psychiatric conditions such as depression, anxiety and suicide (CDC, Alcohol Use and Health, 2012). It is estimated that 80,000 deaths each year are attributable to alcohol making it the 3rd leading cause of lifestyle related death (CDC, Alcohol Related Disease Impact, 2012). In females, alcoholism can lead to miscarriage and fetal alcohol spectrum disorders and is entirely preventable (Centers for Disease Control and Prevention, 2012b).

Effects on the individual, family and society. Besides increased morbidity and mortality, individuals with alcohol abuse and dependence suffer in many other ways. Those who are dependent on alcohol have higher rates of unemployment, hospitalizations, incarcerations, and are less likely to have health insurance (Terza, 2002). Muller (2006) found that 22% to 26% of all hospitalizations are alcohol related. Alcohol consumption has been associated with a 20% increase in divorce rates (Caces, Harford, Williams, & Hanna, 1999) and is linked to incidents of domestic violence and increased

severity of abuse (Testa, Quigley, & Leonard, 2003; Brecklin, 2002). In fact, two thirds of reported domestic violence cases in America involved alcohol (Bureau of Justice Statistics, US Department of Justice, 2006). Alcohol is a contributing factor to child abuse, child neglect and molestation cases (Laslett, Room, Dietze, & Ferris' 2012). Furthermore, it is estimated that 40% of all violent crimes and 40% of motor vehicle accidents involve alcohol (Bureau of Justice Statistics, US Department of Justice, 1998).

The cost to society of alcoholism was estimated to be $ 223 billion per year in a study released by the CDC. This was an estimate of lost productivity, health care expenditures, criminal justice and law enforcement, and motor vehicle accident costs (CDC, Excessive Drinking Costs the US 223 billion, 2011). Hence, the impact of alcohol use and abuse to society is considerable.

Pathophysiology

Alcohol dependence is thought to be the result of a disruption in the neurochemical balance of the inhibitory neurotransmitter γ-amino-butyric acid (GABA) and the excitory neurotransmitter glutamate. Other neurotransmitters affected are opioid, dopamine and serotonin receptors. Alcohol is thought to increase the effects of GABA on the neuroreceptor GABA-alpha (GABA-A). After prolonged exposure to increased levels of GABA, the neuroreceptor GABA-A down regulates to compensate. Alcohol inhibits the production of glutamate causing an up-regulation of N-methyl-D-aspartate (NMDA) receptors. This causes both the increased tolerance to alcohol and the symptoms that manifest when alcohol use is decreased or ceased (Bayard, Mcintyre, Hill, & Woodside, 2004). Frequent episodes of withdrawal can result in irreversible brain damage. Twin

studies as well as adoption studies seem to confirm that genetic risk factors are associated with increased risk of alcohol dependence (Lykoyras, Moussas, & Botsis, 2004; Pasiaux et al, 2001). These genetic studies led to the isolation of genetic subtypes more prone to alcoholism though the exact mechanisms are not yet understood (Wall, 2005). As the Neuman System's Model suggests, health disturbances are a result of complex factors that are inter-related and dependent (Neuman, 1989).

Current Treatment modalities

The gold standard for treating AWS during the initial withdrawal period is the benzodiazepine lorazepam. This medication is intended to prevent or control severe and life-threatening symptoms associated with AWS including seizures. It has been used as an anxiolitic, amnesiac, sedative, and anticonvulsant and is a schedule IV controlled substance. This medication may be titrated to achieve the greatest control in heart rate, blood pressure, agitation and delirium (Miller & Gold, 1998). This medication has several undesirable side effects including sedation, respiratory depression, decreases in motor co-ordination, interactions with alcohol, selling of drugs for street value, and potential for abuse. It must be tapered to prevent additional withdrawal symptoms and is for short term use only. After the initial withdrawal phase, other drugs are added to prevent cravings and relapse.

Three drugs approved for the treatment of alcohol dependence to prevent relapse are disulfiram, naltrexone, and acamprosate. Disulfiram is an aversive medication and has been in use for 4 decades. It works by causing unpleasant side effects if the patient continues to ingest alcohol. Within 10 to 30 minutes of consuming alcohol, the patient experiences chest pain, nausea, vomiting, blurred vision, and headache. Short-term

efficacy is supported in the literature however; disulfiram has been criticized as a treatment because of poor patient compliance rates and is contraindicated in patients with severe renal impairment. In addition, it has no effect on the neurochemical imbalance responsible for AWS (Williams, 2005).

Naltrexone became the second drug approved by the FDA to treat AWS in 1994. The drug works by blocking opioid receptors in the brain, which reinforce the pleasant endorphin mediated effects of alcohol (Leavitt, 2001). A number of studies confirmed the efficacy of naltrexone in reducing relapse to heavy drinking but it is less effective in terms of increasing abstinence. One problem with naltrexone is that it is contraindicated for patients with cross addiction to opioids and in patients with liver dysfunction. Additionally, the effect is slight and leaves healthcare providers looking for a more effective treatment (Garbutt, 2010, Williams, 2005).

Acamprosate has been approved by the FDA for treatment of AWS since 2004. Acamprosate is thought to work by blocking glutaminergicN-methyl-Daspartate receptors and activating 3-aminobutyric acid type A receptors (Williams, 2005). Acamprosate may be used alone or in combination with naltrexone. Acamprosate has been shown to be only modestly effective in increasing the number of days for relapse to heavy drinking and increasing abstinence from drinking but it has a number of undesirable side effects and is contraindicated in patients with cardiovascular disease (Mann, Lehert, & Morgan, 2004, Williams, 2005).

All other medications used for the treatment of alcohol dependence and AWS are not approved by the FDA. Several medications are commonly prescribed off label. Fluoxetine and other selective serotonin reuptake inhibiters (SSRI’s) are recommended

only for patients exhibiting comorbid depressive disorders. Topiramate carries an FDA warning for metabolic acidosis and has adverse side effects such as somnolence, dizziness, ataxia, nausea, and confusion. Nalmefine is available only as an injectable medication and side effects make it undesirable for longer term use.

Table 1

Medications used for treatment of AWS

Drug	FDA Approved	Drug Class	Side Effects	Comments
Lorazepam	No	Benzodiazepine	Sedation, confusion, depression, thoughts of suicide, agitation, hallucinations	Schedule IV controlled substance, may cause cross addiction, may be sold for street value, short term use only
Disulfiram	Yes	Alcohol aversive	Palpitations, nausea, flushing, vomiting, headaches	Poor patient compliance, hepatotoxicity
Naltrexone	Yes	Opiate Antagonist	Nausea, headache anxiety, sedation	Contraindicated in cross addiction to narcotics,
Acamprosate	Yes	Substance abuse treatment agent	Diarrhea, headache, nausea, vomiting, dyspepsia	Avoid using in renally impaired patients
Fluoxetine	No	SSRI	Nausea, headache, sedation, sexual dysfunction	Use only in patients with comorbid depression
Topiramate	No	anticonvulsant	FDA Warning for metabolic acidosis, dizziness, somnolence, ataxia, confusion, nausea	
Nalmefine	No	Opioid antagonist	Nausea, vomiting, tachycardia, dizziness, headache	Only available in injectable form

Table 1

Background of Research

The literature on gabapentin use for alcohol withdrawal syndrome began in 1997 when Watson, Robinson, & Little (1997) found reduced anxiety and seizure activity in ethanol-dependent mice given gabapentin. Bonnet et al. (1999) tried gabapentin use in four patients in conjunction with clomethiazole and found that it reduced the amount of clomethiazole needed. Voris, Smith & Rao, (2003) studied 31 outpatients and 18 inpatients in an open label retrospective study. All patients were given gabapentin and

then given benzodiazepines as needed according to symptoms. They found that for those with mild to moderate symptoms, less benzodiazepine was needed. Those with more severe symptoms did not respond as well to the treatment. Bonnet et al. (2003) studied 61 patients receiving clomethiazole and placebo or clomethiazole and gabapentin. No significant difference was found between the gabapentin group and the placebo group. Since then, only a handful of studies were found on the use of gabapentin in AWS treatment. Of the more current studies conducted to date, the majority support the use of gabapentin in AWS.

Recent animal studies conducted by Roberto et al (2008) and Clemens & Vendruscolo (2008) continue to advance the understanding of the exact mechanisms responsible for alcohol dependence and withdrawal. Specifically, interest has begun to focus on gabapentin's potential to stop or even reverse ethanol effects on the amygdala.

Summary

A need exists for pharmacological therapies that have greater efficacy, high safety indices, fewer side effects, and do not cause cross addiction. Recent advances in the understanding of the neurochemistry contributing to the pathophysiology of alcohol dependence caused many researchers to examine the role of anticonvulsants. Gabapentin has been the subject of several recent studies for its potential as an adjunctive or monotherapy treatment in AWS.

Chapter III - METHODOLOGY

Literature Review Question

The question was "Is gabapentin equal or superior to other medications currently being prescribed as an adjunctive therapy for the treatment of AWS?" The assumption of this integrative review was that available studies would support the use of gabapentin because it is superior to other pharmacological treatment regimens currently used in practice.

Design and Method

This integrative review synthesized data in available studies pertaining to gabapentin for use in treatment of AWS. The synthesis of this knowledge will inform prescribing providers and those conducting future research on the current state of science in this area of study. This review utilized a five stage approach to the integrative review proposed by Whittemore & Knafl (2005). See Table 2 for a summary of the five stage approach.

Table 2
Integrative Review Process

Stage	Application
Problem identification	Pharmacological intervention for AWS in the inpatient or outpatient setting remains ineffective. Current pharmacological interventions have undesirable side effects, are not cross-tolerant with alcohol or have limited efficacy. A need exists for more effective pharmacological intervention.
Literature Search	CINAHL Ebsco Host and PubMed, English language research articles from 2006 to 2012. Ancestry search of available resource lists was also performed.
Data Evaluation	Categories: Gabapentin versus another drug or placebo, gabapentin used in conjunction with another drug, gabapentin safety in presence of alcohol use
Data Analysis	Analysis of quantitative research data of studies using double-blind, randomized placebo controlled measures
Presentation	Quantitative content analysis – table format

The Problem Identified

The current pharmacological interventions most commonly used by prescribing providers for the treatment of alcohol dependence and AWS are inadequate. Many of the medications lack efficacy, are not cross-tolerated with alcohol or have undesirable side effects. A need exists for more efficacious pharmacological treatment options. Recent advances in the understanding of the effects of alcohol on the regulation of GABA neurotransmission suggest that medications that effect GABA regulation may be particularly promising. Studies exist supporting the use of gabapentin for use in AWS; however these studies are relatively few. Variables of interest were gabapentin as compared to other commonly prescribed medications and placebo. Additional variables of interest were the safety of gabapentin in presence of alcohol and the severity of AWS in subjects being studied.

Data Collection / Literature Search

Search terms used were combinations of gabapentin, Alcohol Withdrawal, and Ethanol Withdrawal. Two electronic databases were searched: CINAHL Ebsco Host and PubMed. In addition, an ancestry search was done on the references cited in each relevant research article found. Inclusion criteria were English language studies between 2006 and 2012. The search yielded 47 results. Articles were excluded if they were literature reviews. Additionally, articles that focused on drug withdrawal instead of AWS were excluded. Gabapentin for use in treatment of seizure activity alone was also an exclusionary factor. The resulting search was narrowed to 13 quantitative studies.

Literature Analysis

The available studies compared gabapentin to lorazepam, flumazenil, phenobarbital, Naltrexone and placebo (Anton, Myrick, Wright, Latham, Baros, Waid, & Randall, 2011; Anton Myrick, Baros, Latham, Wright, Stewart, Waid, & Malcolm, 2009; Bonneta, Speckaa, Lewekeb, Nyhuisa & Bangera, 2007; Brower et al, 2008; Chourishi, Raichandani, Chandraker & Chourishi, 2010; Furieri & Nakamura-Palacios, 2007; Malcolm, Myrick, Veatch, Boyle & Randall, 2007; Mariani, Rosenthal, Tross, Singh, & Anand, 2006; Mason, Light, Williams & Drobes, 2009; Myrick, Anton, Voronin, Wang & Henderson, 2007; Myrick et al., 2009; Schacht et al, 2011).

All of the studies found were quantitative. Most were double-blind, randomized, and placebo controlled. All studies were primary source studies. In addition, studies came from a wide variety of sources. Both inpatient and outpatient settings were represented. Participants were volunteers, paid volunteers and convenience sample subjects. The studies were conducted in the United States, Germany, Brazil and India. Both males and females were represented in most studies. The studies examined those with symptoms of AWS from mild to severe. Study participants were from a wide variety of racial and cultural backgrounds.

Categories emerged in the identified studies. Studies were categorized into the following groups: Gabapentin versus another drug or placebo, gabapentin in combination with another drug, and gabapentin in presence of alcohol consumption.

One study reviewed the safety of gabapentin in the presence of alcohol (Bisaga & Evans, 2006), and two studies evaluated gabapentin as monotherapy (Anton, Myrick et al., 2011; Bonnet, Humzavi-Abedi, Specka, Wiltfant & Scherbaum, 2010). The total number of participants for all studies was 319. This literature review synthesizes these data to support the findings from current identified studies in the literature from 2006 to 2012 regarding the efficacy and safety of gabapentin for use in AWS.

Table 3

Papers included in Review

Reference	Country	Sample	Methods	Findings
Anton, R.F., Myrick, H., Baros, A.M., Latham, P.K., Wright, T.M., Stewart, S.H., Waid, R. & Malcolm, R (2009) **	USA	60 alcohol dependent individuals divided into high and low alcohol withdrawal and randomized into 2 study groups	One group with high and low AW was given gabapentin and flumazenil, and one group with high and low AW received placebo in a double-blind, randomized, placebo controlled study. (Level of evidence - III)	The combination of gabapentin with flumazenil was most effective in the high alcohol withdrawal group. In the group with low alcohol withdrawal, gabapentin + flumazenil was less effective than placebo (support – yes)
Anton, R.F., Myrick, H., Wright, T.M., Latham, P.K., Baros, A.M., Waid, L.R., Randall, P.K. (2011).****	USA	150 alcohol dependent individuals randomized into 3 study groups	One group received naltrexone alone, one group received gabapentin plus naltrexone and one group received double placebo in a double-blind placebo controlled randomized trial. (Level of evidence – III)	There was a longer interval to heavy drinking in the gabapentin + naltrexone group, fewer drinking days, fewer drinks per day than the naltrexone alone group. Naltrexone alone and placebo group had similar results. The Naltrexone alone group had poor sleeping. (support – yes)
Bonnet, U., Speckaa, M., Lewekeb, F.M., Nyhuisa, P., Bangera, M. (2007).**	Germany	46 inpatients in 2 psychiatric hospitals randomized into 2 study groups	Half the participants received gabapentin and half received placebo in a double-blind, randomized, placebo controlled trial (Level of evidence – III)	Gabapentin accelerated improvement in mood scores and worked better in individuals with co-morbid depression (support – yes)
Bonnet, U. Hamzavi-Abedi, R., Specka, M., Wiltfant, J., Scherbaum, N. (2010).*****	Germany	37 inpatients with severe AWS randomized into 2 study groups	Groups were divided into "early responder" and "early non-responder" groups and given a high dose or low dose of gabapentin regimen based on response . The study method was not double-blind, not randomized and not placebo controlled. (Level of evidence – IV)	27% of the patients did not respond to treatment, those that did respond deteriorated after a few hours (support – no)
Brower, K.J., Kim, H.M., Strobbe, S., Karam-Hage, M.A., Consens, F., Zucker,	USA	21 outpatients recruited from outpatient	Half of the study participants (n=10) received 1600 mg of Gabapentin and	Gabapentin significantly delayed return to heavy drinking which persisted for 6 weeks after

R.A. (2008).		treatment and by advertisement randomized into 2 study groups	half (n=11) received placebo. The study was randomized and placebo controlled. (Level of evidence – III)	treatment. Both groups reported improvement in sleep. (support – yes)
Chourishi, A, Raichandani, O.P., Chandraker, S., Chourishi, S., (2010) *	India	46 all male in-patients with Mild to Moderate AWS were divided into groups	Half were administered 300mg of gabapentin and half were administered 2 mg of lorazepam over the course of 15 days. Study method was double-blind, randomized and controlled. (Level of evidence – III)	Results were equal however gabapentin was superior in terms of tolerability (support – yes)
Furieri, F.A., Nakamura-Palacios, E.M. (2007)	Brazil	60 male alcohol dependent outpatients consuming 17+ drinks per day divided into 2 groups	Half of the study group received gabapentin and half received placebo in a double-blind, randomized controlled study (Level of evidence - III)	The gabapentin group had a significant reduction in drinks per day, return to heavy drinking, mean heavy drinking days and increase in abstinence days than placebo group (support – yes)

Table 3 Continued

Reference	Country	Sample	Methods	Conclusion
Malcolm, R., Myrick, L.H., Veatch, L.M., Boyle, E., Randall, P.K. (2007).	USA	68 outpatients in treatment for AWS randomized into 4 groups	3 groups received one of 3 dose regimens of gabapentin and one group received lorazepam to compare effect on sleep and depression. The study method was double-blind, randomized and controlled. (Level of evidence III)	Gabapentin was superior to lorazepam in several sleep measures and fewer rebound symptoms were reported. Adverse events were reported in 3 individuals who were all on the lowest dose regimen (2 had seizures and one had syncope). (support – yes)
Mariani, J. J., Rosenthal, R. N., Tross, S., Singh, P., Anand, O. P. (2006).	USA	27 alcohol dependent inpatients with CIWA-Ar >10 – open label	Half the group received gabapentin and half received phenobarbital for 4 days. Those receiving gabapentin could also receive the phenobarbital PRN if needed for symptoms. Study method was open-label, randomized and controlled. (Level of evidence – III)	Gabapentin was equal to Phenobarbital in all measures examined (CIWA-Ar, POMS, Beck Depression inventory, etc) with a higher safety index (support – yes)
Mason, B.J., Light, J.M., Williams, L.D., Drobes, D.J., (2009).	USA	33 alcohol dependent individuals who were paid volunteers randomized into 2 groups	One group received 1200 mg of gabapentin and one group received a placebo; groups were compared for craving for alcohol versus water. Study method was randomized and placebo controlled. (Level of evidence - III)	The gabapentin group had a higher improvement in craving for alcohol versus water and a longer interval to heavy drinking (support – yes)
Myrick, H., Anton, R., Voronin, K., Wang, W., Henderson, S. (2007).	USA	35 non treatment seeking alcohol dependant individuals	The gabapentin group (n=18) was compared to the placebo group (n=17) in terms of tolerability in individuals drinking	There was no difference in effect on drinking or craving. Gabapentin was tolerated well in individuals who continue to consume alcohol. There was no change in mood or sedation.

		randomized into 2 study groups	alcohol in a free-choice lab-bar setting. Study method was randomized and placebo controlled. (Level of evidence – III)	(support – yes)
Myrick, H., Malcolm, R., Randall, P.K., Boyle, E., Anton, R.F., Becker, H.C., Randall, C.L., (2009)	USA	100 treatment seeking outpatients with CIWA-Ar >10 stratified into 2 groups based on number of prior relapses	Half of the study group received 2 dose regimens of gabapentin with and half received lorazepam. Study method was randomized, controlled. (Level of evidence – III)	Gabapentin was superior to lorazepam in terms of abstinence during tapering period. The gabapentin group also reported less craving, anxiety and sedation than the lorazepam group (support – yes)
Schacht, J.P., Randall, P.K., Waid, L.R., Baros, A.M., Latham, P.K., Wright, T.M., Myrick, H., Anton, R.F (2011) ***	USA	60 alcohol dependent individuals who drink a min of 5 drinks per day for 70% of days	The effect of Flumazenil and gabapentin on the improvement in Neurocognitive performance over the course of 15 days. Study method was double-blind, randomized, placebo controlled. (Level of Evidence – III)	Individuals who had higher AW and received a combination of flumazenil and gabapentin had a greater improvement in neurocognitive performance (support – yes)

Note * = double-blind, randomized, controlled
** = double-blind, randomized, placebo controlled
*** = randomized groups between high AW (CIWA >7) and low AW (CIWA <7)
****=randomized placebo controlled
*****= non blind, non randomized, non controlled
(Cochrane Level of evidence from Harris, et al, 2001
Table 3

Three studies compared gabapentin with lorazepam and found gabapentin superior in terms of Clinical Institute Withdrawal Assessment, Alcohol Scale Revised (CIWA-Ar) score, sleep measures, tolerability, side effects, and early return to drinking (Chourishi et al., 2010; Myrick et al., 2009; Malcolm et al., 2007). The CIWA-Ar tool has become the standard tool to assess the severity of AWS (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989; Thase, Fava, DeBattista, Arora, Hughes, 1989; Stuppaeck, Barnas, Falk, 1994).

Chourishi et al., (2010) sought to compare the efficacy and tolerability of lorazepam versus gabapentin in a randomized, double-blind, controlled study of 46 in-patients with mild to moderate AWS for a length of 15 days using the CIWA-Ar Scale. Half of the study participants (n=23) received lorazepam and half (n=23) received gabapentin. The researchers found gabapentin to be equal to lorazepam in terms of

treatment outcome but found that gabapentin was more tolerable in terms of side effects. The most common side effect reported with lorazepam was daytime sleepiness. The study concluded that gabapentin may be superior to lorazepam due to its high safety profile and lack of interaction with alcohol.

Malcolm et al., (2007) sought to compare the effects of gabapentin and lorazepam on sleep patterns in patients being treated for AWS. The study looked at 68 out-patients in a double-blind, randomized, controlled study treated with either gabapentin or lorazepam for 12 days. The study used the Epworth Sleep Scale (Johns, 1991), Beck Depression Scale (Beck, Ward, Mendelson, Mock, Erbaugh, 1961) and CIWA-Ar as measurement tools. The researchers found no significant differences between the gabapentin treated group and the lorazepam treated group in patients who had not had withdrawal symptoms in the past. In patients who had experienced withdrawal symptoms in the past, the results were significant. Patients receiving gabapentin had fewer sleep disturbances and fewer rebound effects than patients receiving lorazepam. There were three adverse events reported in the lowest dose regimen group only (two seizures and one syncopal episode). The study found that early return to drinking was related to persistent insomnia. The researchers concluded that gabapentin may be superior to the standard treatment of lorazepam.

Myrick et al., (2009) compared a high dose regimen and low dose regimen of gabapentin and lorazepam in 100 out-patients with AWS in terms of symptom reduction and alcohol use in a double-blind, randomized clinical trial. Results were measured using the CIWA-Ar scale. CIWA-Ar scores decreased for all groups however the high dose

regimen group saw the greatest improvement in CIWA-Ar score. Additionally, the gabapentin treated groups had less incidence of drinking during the follow up period, less alcohol craving, less anxiety and less sedation than the lorazepam treated group ($p = 0.20$ for 900 mg and $p = 0.30$ for 1200 mg) compared to the lorazepam-treated participants ($p = 0.55$). The researchers concluded that gabapentin may be superior to lorazepam for treatment of AWS symptoms, especially using the higher dose regimen.

Another study compared a combination of gabapentin and flumazenil. Schacht et al, (2011) sought to establish the effect of a combination of gabapentin and flumazenil on neurocognitive performance in patients being treated for AWS. Both medications affect γ-amino-butyric acid (GABA) and glutamate signaling which are related to symptoms associated with AWS. Specifically, they were interested in inhibition response which may be linked to subsequent drinking decisions. The researchers studied 60 patients over 15 days using a neurocognitive performance tool and abstinence as a measure. The researchers found that there was slightly greater neurocognitive performance and response inhibition in patients given the gabapentin and flumazenil combination than those receiving placebo. In addition, they found greater abstinence during the first week of treatment than with the placebo group. The researchers concluded that the combination of gabapentin and flumazenil may improve neurocognitive performance and may improve early abstinence and perhaps later abstinence as well.

Anton, Myrick, Wright, Latham, Baros, Waid, & Randall (2011) studied the effectiveness of gabapentin and naltrexone, naltrexone alone and placebo for preventing relapse. They studied 150 alcohol dependent patients in a randomized controlled study

for 16 weeks. They found that those receiving gabapentin and naltrexone in combination in the first 6 weeks had a longer interval to heavy drinking, fewer heavy drinking days, and fewer drinks per day than the naltrexone alone or placebo alone group. Less sleep quality was associated with more drinking in the Naltrexone alone group. Differences faded in the remaining weeks of the study. The researchers concluded that gabapentin when added to Naltrexone may improve drinking outcomes but the results did not persist over time. The authors point out that it is well established that highest risk of relapse to heavy drinking occurs early on in the treatment. Another significant finding of the researchers was that for participants with a longer history of alcohol dependence, the gabapentin group had better results in preventing early return to heavy drinking.

Three studies compared gabapentin as monotherapy versus placebo (Myrick, et al., 2007; Bonnet, et al., 2007; Brower et al., 2008). They found gabapentin was well tolerated in individuals who continue drinking, may improve mood, especially in those with co-morbid depression, and may be useful for preventing relapse to heavy drinking.

Myrick et al., (2007) sought to evaluate the safety of gabapentin in those who continue to drink. This is an important consideration because those who are alcohol dependent have a high rate of relapse despite taking medications to control their cravings. This infers that medications used for pharmacological treatment for AWS and maintenance of sobriety must be cross-tolerant with alcohol (Bayard, Mcintyre, Hill, & Woodside, 2004). To test the safety of gabapentin, researchers divided 35 non-treatment seeking alcoholic individuals into two groups. One group received gabapentin and one

received placebo in a double-blind study. Both groups were allowed to drink in a controlled lab environment. Gabapentin was found to be well tolerated.

Bisaga & Evans (2006) also evaluated the safety of gabapentin in presence of alcohol in seventeen non-alcoholic volunteers who drink 20 to 60 drinks per week in a double-blind study. Participants were divided into groups receiving either 1000mg of gabapentin, 2000 mg of gabapentin, or placebo. Participants were given four alcoholic beverages followed by a series of tests designed to assess craving for alcohol, cognition, psychomotor function, and physiological responses. Gabapentin decreased balance and affected sedation slightly but had no other apparent subjective or behavioral effects. Gabapentin did not alter the pharmacokinetics of alcohol and did not alter the intoxicating effects of alcohol. This is an optimal outcome because relapse rates among those being treated for alcohol dependence ranges from 20 to 50% according to Moos & Moos, 2006). Due to this, medications used for treatment must be safe if the patient relapses.

Bonnet et al., (2007) studied the effects of gabapentin on mood profile in a randomized, placebo controlled double-blind study of 46 individuals with AWS. Mood profile was significantly improved in the gabapentin group within 48 hours of starting the medication. Results were more marked in a subgroup of the gabapentin group that had co-morbid mild depression. Brower et al., (2008) studied the effects of gabapentin on sleep disturbance versus placebo on 21 alcohol dependent patients in a randomized double-blind controlled study. In this study, researchers found a difference in sleep

improvement between groups and a significant delay of onset to heavy drinking which persisted for 6 weeks.

Mason, Light, Williams, & Drobes (2009) compared gabapentin to placebo in 33 alcohol dependent paid outpatient volunteers randomized into two study groups. The gabapentin group had significant less alcohol craving. Subjects reported improvement in sleep quality and fewer side effects. Researchers concluded that gabapentin may be useful in preventing relapse to heavy drinking and improving sleep quality. Several studies have shown that sleep disturbances are frequently seen in alcohol dependent individuals (Landolt & Gillin, 2001; Roehrs & Roth, 2001; Krystal, Thakur & Roth, 2008; Brower, 2001). Additionally, sleep disturbance worsens as a result of abstinence from alcohol (Brower, (2003; Cohn, Foster, & Peters (2003). Furthermore, sleep disturbance was found to increase the likelihood of relapse in those recovering from AWS (Mason et al., 1999).

Chapter IV RESULTS/CONCLUSIONS

Results

The medication of choice for treating AWS has long been lorazepam, a benzodiazepine. This medication has several undesirable side effects including sedation, respiratory depression, decreases in motor co-ordination, interactions with alcohol, selling of drugs for street value, and potential for abuse. The question to be addressed was: to what extent is gabapentin equal to or superior to other medications currently being prescribed as an adjunctive therapy for the treatment of AWS? The studies presented in this integrative review of the literature show support for the tolerability and efficacy of gabapentin alone or as an adjunctive treatment in AWS. Twelve of the 13 studies reviewed showed support for use of gabapentin in individuals with moderate AWS symptoms. Support is less for individuals with very mild or very severe AWS symptoms. The majority of the studies show that gabapentin has fewer or the same side effects to medications already used. Additionally, studies show that gabapentin has a high safety index.

One study did not show favorable results for gabapentin. In Bonnet, et al (2010), researchers did not use a control group and did not randomize their participants. In addition, this study was not double or single blind. Study participants had severe withdrawal symptoms. Other studies have shown that gabapentin has poor results in patients with severe AWS. The findings from this study may be strongly biased and may have been used on patients least likely to respond to the treatment.

The cost of gabapentin is worthy of note because cost of treatment can effect patient compliance. Gabapentin costs around 29 cents a pill (300mg) compared with lorazepam priced at about 24 cents per pill (2mg). Therefore, the cost is no more burdensome than the cost of medication currently being prescribed. The street value of lorazepam is about $1-4 per pill while gabapentin has no real street value at the present time (California Department of Alcohol and Drug Programs, 2010).

Description of the Integrative Review

This integrative review synthesized the results of 13 different quantitative studies from four countries. The efficacy of gabapentin was compared to several other treatment regimens currently in use using various measuring tools. The total number of participants sampled was 319. Studies reviewed compared the efficacy of gabapentin as a monotherapy or in comparison to other commonly used pharmacological interventions. Almost all the studies used a single or double-blind with placebo, randomized, experimental method.

Summary of Major Findings

Of the studies that evaluated the safety of gabapentin, all confirmed that gabapentin as safe for use even in the presence of alcohol. The studies reviewed found gabapentin to have fewer side effects than other commonly used medications of choice. Studies that used gabapentin as a monotherapy agreed that gabapentin is superior to placebo and equal or superior to other common medications used for AWS. Studies that

used gabapentin in conjunction with other therapies showed greater improvement in drinking outcomes over weeks to months.

One notable finding was that gabapentin may not be useful either in groups with the most severe symptoms or in groups with the least severe symptoms. Bonnet, et al (2010), found that patients with severe symptoms who responded to treatment, later deteriorated.

Most studies reviewed were limited by their small sample size. More studies are warranted but the initial results suggest that more practioners should cautiously add gabapentin to their treatment options when clinically indicated.

Limitations

Studies were limited by their small number of participants. Study size ranged from 17 to 150 subjects. A limitation in synthesizing the data was the lack of homogenous measuring tools used between the studies. Most studies utilized CIWA-Ar scale as a measurement tool but some measured neurocognitive performance scores, profile of mood states (POMS), sleep scales, Beck Depression Inventories, or several other types of measurements. Another limitation is that dosages of gabapentin regimens studied varied widely. A strength of the studies is that all were less than five years old and almost all used single or double-blind, randomized and placebo controlled methodologies.

Chapter V. DISCUSSION

Discussion of Nursing Implications

Advanced practice nurses (APNs) and psychiatric nurses may benefit greatly from this review as they inform their practice and make recommendations for the most evidence based pharmacological treatments to their patients. This review can assist clinical nurses in their education of staff and can improve patient education. APN's can direct the treatment modalities chosen for a client and should lead from the front in areas of emerging research and knowledge.

Recommendations for Future Research

Future research should recruit larger pools of subjects and utilize standard dosing regimens to confirm previous research. Treatment results should be measured with consistent tools so that results between studies are more integrative. Future research should focus on clients with moderate to severe symptoms of AWS but exclude those with mild and very severe symptoms. Studies should include patients who have detoxified and are being treated to prevent relapse.

More is being learned about the neurochemistry involved in alcohol dependence. As Neuman's Systems Modal suggests, AWS is a result of many complex and interrelated neurotransmitters, genetics, and psychosocial factors (Neuman, 1989). Roberto et al. (2008) found that gabapentin infused directly into the nucleus of the amygdala dependence in ethanol responding and reversed "behavioral measures of ethanol dependence" of mice. Clemens & Vendruscolo (2008) found the anxiety

producing effects of ethanol withdrawal were reversed with application of gabapentin directly to the amygdala of ethanol dependent mice. This may lead to changes in the way gabapentin is administered in clinical trials.

Dr. Hugh Myrick, a leading researcher in the use of gabapentin for AWS, (Personal Communication, 2013), stated that gabapentin is the "main medication treatment for outpatient alcohol withdrawal" at the VA mental health services he overseas in Charleston Virginia. He finds it particularly promising when used in combination with naltrexone for prevention of relapse and suggests future studies increase the length of treatment with gabapentin.

Conclusion

More clinical investigations needs to be conducted with due diligence to demonstrate whether gabapentin should become more widely used as an adjunct or preferred treatment for alcohol dependence and AWS. The existing body of knowledge is supportive but limited. Prescribing providers may feel cautiously optimistic about this integrative review of literature's findings to date but additional studies are needed before gabapentin becomes the front-line standard of care.

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