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# **Is gabapentin effective in reducing heavy drinking and alcohol related insomnia in alcohol dependent patients?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “Is gabapentin effective in reducing heavy drinking and alcohol related insomnia in alcohol dependent patients?”

STUDY DESIGN: Review of three English language primary studies, one published in 2008 and two others in 2013.

DATA STUDIES: Three double blind, randomized controlled trials (RCTs) analyzing the effects of gabapentin therapy in attempting to reduce heavy drinking and alcohol related insomnia in alcohol dependent patients were found via PubMed and Cochrane databases.

OUTCOMES MEASURED: The reduction in alcohol consumption and improvement in alcohol related insomnia were measured through the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), Penn Alcohol Craving Scale (PACS), Epworth daytime sleepiness scale, overnight polysomnography (PSG), sleep problem questionnaire, and drinking diaries.

RESULTS: The three double blind RCTs by Brower, Mason, and Stock showed a statistically significant reduction in heavy drinking and alcohol related insomnia at the endpoint of intervention.

CONCLUSION: The RCTs by Brower, Mason, and Stock provided compelling evidence that gabapentin is an effective treatment for heavy drinking in alcohol dependent patients and minimizing alcohol related insomnia.

KEY WORDS: gabapentin and alcohol use

## INTRODUCTION

Alcohol abuse and dependence according to the DSM-V criteria is classified as a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by multiple psychosocial, behavioral, or physiologic features.<sup>1</sup> It's known that alcohol dependency and abuse is commonly associated with psychological issues that has an impact on social well-being and quality of life. Heavy drinking is defined as consuming; 15 or more drinks per week for men and 8 or more for women.<sup>2</sup> There are numerous medical consequences of alcohol abuse that can affect almost every organ system such as trauma/injury, anxiety/depression, hypertension, GI, cardiac, and neurologic symptoms, electrolyte and sleep disturbances, increased liver enzymes, and social or legal problems. There are various treatments for alcohol abuse and dependency but most patients are refractory to them and relapse soon after attempted treatment.<sup>3</sup>

There are an estimated 4-40% of medical and surgical patients that have experienced problems related to alcohol.<sup>4</sup> More than 88,000 deaths/year in the US are directly attributed to alcohol use.<sup>4</sup> Heavy drinking has led to 2.5 million years of potential life lost (YPLL) each year in the US from 2006-2010.<sup>3</sup> It has shortened the lives of those who died by an average of 30 years and is responsible for 1 in 10 deaths among working-age adults 20-64 years old.<sup>3</sup> In the United States alone, the cost of excessive alcohol use reach \$249 billion in 2010.<sup>4</sup> The total amount of total health care loss is \$23.79 billion (11% of the total \$249 billion).<sup>4</sup> From 2006-2014, there was a 47% increase in all alcohol-related emergency department (ED) visits which translated to an average annual increase of 210,000 alcohol-related ED visits.<sup>5</sup> The use of pharmacological treatments can help decrease heavy drinking and provide a better quality of life for those who suffer with alcohol dependency.

Alcohol dependence is a chronic disease that is associated with malnutrition, trauma, and various central nervous system conditions. The pathogenesis of alcohol use and abuse is not known, but genetics, environmental influences, specific personality traits, and cognitive functioning all play a role. It's estimated that genetic factors are responsible for roughly 50% of the vulnerabilities related to alcohol use disorder.<sup>6</sup> There are multiple environmental factors such as intra-familial influences including peer influences, prenatal exposure, and parenting patterns. Phenotypes such as neuroticism, extroversion, and impulsivity are associated with alcohol use as well as cognitive dysfunction.<sup>6</sup> It has also been shown that alcohol abuse is more prevalent in those affected with severe disabilities, other substance use disorders, and various mood disorders.<sup>1</sup> It has been recommended that adults be screened for unhealthy alcohol use.<sup>4</sup>

The treatment for alcohol dependence begins with abstinence. Most are refractory to this type of treatment so further pharmaceutical and supportive therapies are used in attempt to reduce heavy drinking.<sup>4</sup> Pharmaceutical options include opioid antagonists (naltrexone), N-methyl-D-aspartate (NMDA) receptor antagonists (acamprosate), enzyme inhibitors (disulfiram), vitamins (B<sub>1</sub>-thiamine), electrolytes (magnesium), anti-convulsants (gabapentin and topiramate), and supportive therapy (psychotherapy and rehabilitation programs).<sup>7</sup> The method being analyzed in this study is a pharmaceutical approach for those attempting to reduce their heavy drinking and alcohol related insomnia. Gabapentin is mostly used as an anti-convulsant but can also be used as an analgesic and anxiolytic to treat a wide variety of conditions such as fibromyalgia, neuropathic pain, postherpetic neuralgia, hot flashes, restless leg syndrome, seizures, and social anxiety.<sup>8</sup> It is a drug that blocks voltage-dependent calcium channels by binding to its alpha-2-delta subunit.<sup>8</sup> It increases cerebral GABA levels and may modulate the release of glutamate and norepinephrine which may explain its potential to improve sleep, reduce

anxiety, and prevent relapse.<sup>8</sup> The potential efficacy of gabapentin to prevent relapse is particularly notable because it has a low addictive potential, doesn't undergo hepatic metabolism, has few interactions with other medications, is safe when combined with alcohol, and isn't associated with fatal overdoses when taken alone.<sup>8</sup>

## OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is gabapentin effective in reducing heavy drinking and alcohol related insomnia in alcohol dependent patients?”

## METHODS

The articles were searched for and discovered via PubMed and Cochrane Library. They were chosen based on their relevance to the clinical question and if they had patient oriented outcomes (POEMs). The three studies utilized in this review include three double blind RCTs and all contained POEMs. The population consisted of male and female patients that were alcohol dependent and 18 years or older. The intervention used was oral gabapentin versus the control group, a placebo in two trials (Brower<sup>9</sup> & Mason<sup>8</sup>) and chlordiazepoxide in the other (Stock<sup>10</sup>). The outcome measured in all three studies was improvement of heavy drinking and alcohol related insomnia. Key words used to discover the literature included gabapentin and alcohol use. All three articles were published in the English language in peer review journals. Inclusion criteria for this study consisted of alcohol dependent patients who were 18 years or older. Exclusion criteria consisted of individuals under 18 years old, pregnant females, patients who do not suffer from alcohol dependence, and those with an underlying psychiatric illness. Summary of the statistics used include relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), relative risk (RR), Cox Regression, Fisher's Exact Test,

confidence interval (CI), and p-values. This paper evaluates three randomized controlled trials comparing the efficacy of gabapentin in attempt to reduce heavy drinking and alcohol related insomnia in alcohol dependent patients.

**Table 1 – Demographics & Characteristics of Included Studies**

| Study                         | Type             | #Pts | Age            | Inclusion Criteria   | Exclusion Criteria   | W/D | Interventions   |
|-------------------------------|------------------|------|----------------|--|--|-----|---|
| Brower <sup>9</sup><br>(2008) | Double blind RCT | 21   | > 18 years old | - Met DSM-IV criteria for alcohol dependence<br>- Hx of insomnia for >6 months<br>- A desire to abstain from alcohol | - Pregnant or nursing women<br>- < 18 years old<br>- If insomnia is due to a medication<br>- If subject was taking anti-depressant               | 7   | - Regimen of either oral Gabapentin 300 mg or Placebo 300 mg before bed with final target dose of 1500 mg over 6 weeks                              |
| Mason <sup>8</sup><br>(2013)  | Double blind RCT | 150  | > 18 years old | - Met DSM-IV criteria for alcohol dependence<br>- Abstinent from alcohol 3 days prior to randomization               | - CIWA-Ar score > 9.<br>- > 1 month of abstinence<br>- Dependence of another substances<br>- Positive urine drug screen<br>- Psychiatric disease | 65  | - Regimen of oral gabapentin (dosages of 0 [placebo], 900 mg or 1800 mg) over 12 weeks  |
| Stock <sup>10</sup><br>(2013) | Double blind RCT | 26   | > 18 years old | - Met DSM-IV criteria for alcohol withdrawal<br>- Was a military veteran   | - Unstable medical or Axis I psychiatric disease<br>- Co-morbid substance dependence<br>- On medication that affects alcohol dependence          | 9   | - Regimen of oral gabapentin 1200 mg or chlordiazepoxide 100 mg: days 1-3, 900 mg or 75 mg day 4, 600 mg or 50 mg day 5, and 300 mg or 25 mg day 6. |

**OUTCOMES MEASURED**

All outcomes measured in the three trials were based on POEMs that determined the efficacy of gabapentin in the reduction of alcohol consumption and improvement in alcohol related insomnia. Reduction in alcohol consumption was measured by using Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), Penn Alcohol Craving Scale (PACS), Epworth daytime sleepiness scale (ESS), overnight polysomnography, sleep problem questionnaire, and drinking diaries.

## RESULTS

Brower<sup>9</sup> studied 21 patients 18 years or older from outpatient alcohol treatment centers or the surrounding community via advertising. During the screening process, 35 participants were selected but 14 were excluded. This was a double-blinded RCT that consisted of a 1-2 week screening phase followed by a 6 week trial of gabapentin vs. placebo, and a 6 week post trial follow-up visit. Eleven patients were given a placebo and ten were given gabapentin. During the trial, medication was titrated to 5 capsules of either oral gabapentin or placebo 45 minutes prior to bedtime over a 10-day period as tolerated. The active medication, gabapentin, contained 300 mg with a final target dose of 1500 mg prior to bedtime over five days then tapered down over a 4-day period.

The primary drinking outcome variable was survival in days to the first episode of heavy drinking starting at zero days. Drinking outcomes during the first six weeks couldn't be verified for 6 of the 7 non-completers (2 gabapentin subjects) so they were classified as heavy drinkers. Cox Regression and Fisher's exact test were used for baseline variables that correlated with time to heavy drinking (Table 2). Another variable was complete abstinence from alcohol. Three (30%) of the ten gabapentin subjects relapsed to heavy drinking compared to nine (81.8%) of eleven in the placebo group by week six (Fisher's exact test,  $p=0.03$ ). Survival analysis was conducted that showed a significant difference ( $p=0.03$ ) favoring the gabapentin group. Adjusting for relative risk of relapse to heavy drinking, the gabapentin group was much lower (Cox regression,  $RR=0.25$ ,  $p=0.047$ ). Six (60%) of ten subjects in the gabapentin group relapsed to heavy drinking by week 12 versus eleven (100%) of the eleven in the placebo group (Fisher's exact test,  $p=0.04$ ). Survival analysis at 12 weeks again favored the gabapentin group ( $p=0.003$ ).



It showed that bedtime administration of gabapentin had a positive effect and significantly delayed onset of relapse in alcohol dependent patients at both 6 and 12 weeks.

**Table 2 (Brower<sup>9</sup>): Survival to relapse of heavy drinking**

| Patients without relapse to heavy drinking |                    | Relative risk reduction (RRR) | Absolute risk reduction (ARR) | Numbers needed to treat (NNT) |
|--|--------------------|-------------------------------|-------------------------------|-------------------------------|
| Placebo:<br>18%                            | Gabapentin:<br>70% | 2.85                          | 51.8%                         | 1.93                          |

|                  | Cox Regression | P-value | Fisher's exact test |
|------------------|----------------|---------|---------------------|
| Gabapentin group | RR=0.25        | P=0.047 | P=0.03              |

Mason<sup>8</sup> studied 150 patients 18 years or older who were treatment-seeking volunteers with alcohol dependence at The Scripps Research Institute in La Jolla, CA where they provide a broad range of medical services. The study was approved by the Scripps institutional review board (IRB). This was a double blind RCT that had weekly visits through the first 12 weeks as well as at 13 and 24 weeks post treatment. Simple randomization procedures were followed and assigned participants with oral gabapentin, 900 mg or 1800 mg, or a placebo. Subjects were provided weekly medication; each package contained two identical capsules to be taken three times a day. In the active group, the placebo was replaced with an identical 300 mg capsule on the evening of day 1, morning of day 2, afternoon of day 3, and on a similar schedule each day until the assigned fixed dose of 900 mg was achieved on day 4 or 1800 mg on day 6. These participants were maintained on the assigned dose until week 11 and were titrated off in reverse order of initial titration dose. Analysis of mean abstinence duration was based on the rate of

complete abstinence over the 12-week study as well as the rate of no heavy drinking over the 12-week trial.

In Mason's study, 185 subjects were assessed for eligibility but 35 were excluded (19 ineligible and 16 declined to participate). The mean time in study, rate of study completion, and medication compliance didn't differ among treatment groups, nor did the reasons for termination. Upon completion, gabapentin had a significant linear dose effect in increasing the rates of complete abstinence ( $X^2=5.39$ ,  $p=0.02$ ) over the 12-week course of treatment relative to the placebo group. The rate of sustained 12-week abstinence was 4.1% (95% CI, 1.1-13.7%) in the placebo group, 11.1% (95% CI, 5.2-22.2%) in the 900 mg group, and 17.0% (95% CI, 8.9-30.1%) in the 1800 mg group. Gabapentin 1800 mg had the greatest treatment effect with a number needed to treat (NNT) of 8 and an odds ratio (OR)= 4.8 (95% CI, 0.9-35.0), which indicated a large effect size for abstinence. The rate of no heavy drinking was 44.7% (95% CI, 31.4-58.8%) in the 1800 mg group, 29.6% (95% CI, 19.1-42.8%) in the 900 mg group, and 22.5% (95% CI, 13.6-37.2%) in the placebo group. The 1800 mg had a NNT of 5 and OR=2.8 (95% CI, 1.1-7.5), indicating a medium effect size for no heavy drinking. Gabapentin also showed significant linear decreases in the average number of days of heavy drinking per week and number of drinks consumed per week. Drinking outcomes were evaluated for the 65 participants who completed both the 12-week trial and the 24-week follow-up visit. Significant linear dose effects were sustained at week 24 for rate of complete abstinence ( $X^2=4.73$ ,  $p=0.02$ ), number of heavy drinking days per week ( $t=-3.09$ ,  $p=0.002$ ) with an insignificant trend for rate of no heavy drinking ( $X^2=6.43$ ,  $p=0.06$ ). Beneficial effects of gabapentin for treatment of alcohol dependence were found over the 12-week course of treatment on rates of complete abstinence and no heavy drinking, with the greatest effects seen in the 1800 mg group.

**Table 3 (Mason<sup>8</sup>): Rates of no heavy drinking**

|                    | Rate (%) | 95% CI     | CER   | EER   | RBI   | ABI   | NNT |
|--------------------|----------|------------|-------|-------|-------|-------|-----|
| Gabapentin 1800 mg | 44.7%    | 31.4-58.8% | 0.225 | 0.447 | 0.987 | 0.222 | 5   |
| Gabapentin 900 mg  | 29.6%    | 19.1-42.8% | 0.225 | 0.296 | 0.316 | 0.07  | 15  |
| Placebo            | 22.5%    | 13.6-37.2% |       |       |       |       |     |

Stock<sup>10</sup> studied 26 subjects who were veterans, 18 years or older and who met the DSM-IV criteria for alcohol withdrawal. This was a double blind RCT, double-dummy 7-day trial comparing gabapentin to chlordiazepoxide. Gabapentin 300 mg and chlordiazepoxide 25 mg were put into a 7-day medication package and distributed to the subjects. The titration dosing was as followed either gabapentin 1200 mg or chlordiazepoxide 100 mg orally days 1-3, 900 mg or 75 mg day 4, 600 mg or 50 mg day 5, and 300 mg or 25 mg day respectively. Each dose consisted of one active medication capsule and one placebo capsule. Additionally, all subjects received prescriptions for multiple vitamins, folic acid 1 mg, and thiamine 100 mg. Subjects were required to meet every weekday with the clinicians, which included a CIWA-Ar, ESS, PACS, and mental status exam.

Initially, the study had 104 subjects but due to significant changes in the VA's emergency department and mental health department policies, the study was limited to 26 subjects. There were 429 detoxification clinic patients screened but 403 patients were excluded, leaving 26 subjects (25 males and 1 female) who met criteria. Comparisons were made during the early stage (days 1-4) and the late stage (days 5-7), assessing CIWA-Ar, ESS, and PACS. After randomization, 17 subjects were given gabapentin and 9 were given chlordiazepoxide. Baseline ESS scores were well balanced between both groups (6.2 in gabapentin group and 4.7 in chlordiazepoxide). Baseline ESS did not correlate significantly with baseline BAC (Pearson

R=0.30, p=0.14). The adjusted mean ESS did not differ much between groups during the early stage; the ESS was 0.66 higher in the gabapentin group when compared to the chlordiazepoxide group; (95% CI -1.93 to 3.26; p=0.61). During the late stage, the adjusted mean ESS score was lower with gabapentin (mean difference -3.70; 95% CI -7.21 to -0.19; p=0.04). The adjusted mean PACS score didn't differ between groups during the early stage (1.39 lower with gabapentin; 95% CI -6.48 to 3.70; p=0.59). During the late stage, there was a trend toward a lower adjusted mean PACS score in the gabapentin group (mean difference=6.05; 95% CI -12.82 to 0.72; p=0.08). CIWA-Ar scores averaged 7.7 (gabapentin) and 8.8 (chlordiazepoxide) at baseline (range 0-20) and were well balanced between the groups (p=0.64). Both groups showed reduction during the 7-day trial, with gradual reduction in withdrawal symptoms severity. Mixed-model analysis showed no significant difference in adjusted follow-up mean scores between the groups in the early or late stage.

**Table 4 (Stock<sup>10</sup>): Results for Early and Late Stage Treatment**

|         | Early stages (Days 1-4): |                  |                     | Late stage (Days 5-7) |                  |                     |
|---------|--------------------------|------------------|---------------------|-----------------------|------------------|---------------------|
|         | Gabapentin               | Chlordiazepoxide | (95% CI)<br>p-value | Gabapentin            | Chlordiazepoxide | (95% CI)<br>p-value |
| ESS     | 5.97                     | 5.31             | 0.61                | 2.65                  | 6.35             | 0.04                |
| PACS    | 15.66                    | 17.05            | 0.59                | 10.74                 | 16.78            | 0.08                |
| CIWA-Ar | 5.86                     | 6.64             | 0.60                | 4.33                  | 3.29             | 0.62                |

**DISCUSSION**

Brower's study showed that bedtime administration of gabapentin significantly delayed the onset of relapse in alcohol dependent patients selected for clinical insomnia at 6 and 12 weeks.<sup>9</sup> Complete abstinence from drinking wasn't associated with those taking gabapentin but

the proportion of subjects that relapsed to heavy drinking was smaller in the gabapentin group at the end of treatment. However, caution needs to be exercised, as this was a pilot study with a small sample size. Two major limitations were a lack of funds that hindered recruitment for a larger sample size and the study didn't consist of subjects who didn't suffer from insomnia. The high attrition rate (7 of 21 subjects at 6 weeks) was another limitation that could have been due to payments for which \$150 of the total reimbursement (\$325) could be obtained by week 3 of the study.<sup>9</sup>

Mason's study demonstrated beneficial effects of gabapentin for the treatment of alcohol dependence over the 12 week course of treatment on the rates of complete abstinence and no heavy drinking.<sup>8</sup> The best results were found in those subjects who were given the maximum amount of gabapentin (1800 mg). It had a favorable safety profile, and there were no unexpected or serious drug related adverse events or differences in study discontinuation rates owing to adverse events.<sup>8</sup> This study showed that the subjects symptoms of sleep disturbance and related daytime dysfunction significantly improved with gabapentin relative to the placebo. Gabapentin effectively treated alcohol dependence and relapse associated symptoms involving craving, mood, and sleep.<sup>8</sup> It has been used by physicians for other indications resulting in familiarity with its pharmacology, pharmacokinetics, and adverse effects which has allowed gabapentin to be used more readily for alcohol dependence.<sup>8</sup>

Stock's study showed that subjects who received a fixed dose tapering regimen of gabapentin to treat alcohol withdrawal experienced significantly reduced daytime sleepiness but an insignificant trend toward reduction in alcohol craving by the end of their treatment period compared to those who took chlordiazepoxide.<sup>10</sup> Dropout rates were similar for both groups. This trial demonstrated that gabapentin is a better alternative for benzodiazepines due to

speculation that it may dampen kindling (neural sensitization leading to progressive worsening of subsequent withdrawal episodes), is safer, less likely to interact with or increase sedation if alcohol is consumed, and may be as effective as benzodiazepines in treating alcohol withdrawal.<sup>10</sup> One of the major limitations was the sample size, however, after reassignment of the study outcome measures and statistical analysis plan, the size was sufficient to determine treatment effect of ESS and PACS scores.<sup>10</sup> Although there was a trend toward treatment effect on the PACS score, the difference seen in this small sample size didn't reach significance.<sup>10</sup> It supports gabapentin as a tolerable medication that is less sedating, leads to less cravings in outpatients treated for alcohol withdrawal but due to the small sample size, there isn't enough information to generalize these results.<sup>10</sup>

## CONCLUSION

Based on the three RCTs reviewed, there is convincing data supporting the benefits and efficacy of using gabapentin to reduce heavy drinking and alcohol related insomnia in alcohol dependent patients. Studies showed that most patients would abstain from heavy drinking during the clinical trial as well as up to one month after completion of the trial. However, further studies should include those who don't suffer from insomnia and assess for discontinuation syndromes. Testing gabapentin alone and in combination with cognitive-behavioral therapy for insomnia will also be important, given the early success of the latter in treating alcohol-dependent subjects. Larger studies with a more diverse population of patients with alcohol dependence were suggested to extend and replicate the findings. If these factors were taken into account then one could more assuredly say that gabapentin is effective in reducing or eliminating heavy drinking and alcohol related insomnia in alcohol dependent patients

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