Self-Reported Sleep, Sleepiness, and Repeated Alcohol Withdrawals: A Randomized, Double Blind, Controlled Comparison of Lorazepam vs Gabapentin

Robert Malcolm, M.D.; L. Hugh Myrick, M.D.; Lynn M. Veatch, Ph.D.; Elizabeth Boyle, M.S.W.; Patrick K. Randall, Ph.D.

Study Objectives: Insomnia is a central symptom of alcohol withdrawal and increases relapse potential. The primary objective of this study was to compare the efficacy of gabapentin to lorazepam in alleviating sleep disturbances and daytime sleepiness during an episode of alcohol withdrawal. The secondary objective of this study was to determine if drug treatment efficacy differed by the patient history of previous treatments for alcohol withdrawal.

Methods: Outpatients in treatment for alcohol withdrawal received a 4-day fixed-dose taper of gabapentin or lorazepam in a double-blind, randomized, controlled trial with an 8-day follow-up. Daily across a 5 day outpatient treatment and Days 7 and 12 post-treatment, patients self-reported daytime sleepiness using the Epworth Sleepiness Scale. Self-reports of depression (Beck Depression Inventory) were completed at Days 1, 5, 7 and 12. Staff assessed daily alcohol withdrawal using the Clinical Institute Withdrawal Assessment for Alcohol. From these instruments, self-reported sleep and sleepiness were extracted and assessed in the context of limited (0-1) or multiple (2 or more) previously treated alcohol withdrawal episodes.

Results: Patients with limited previous withdrawals reported similar treatment effects on self-reports of sleep and sleepiness for gabapentin and lorazepam. In contrast, patients with multiple previous alcohol withdrawals receiving gabapentin reported reduced sleep disturbances and sleepiness in comparison to those receiving lorazepam.

Conclusions: During treatment for alcohol withdrawal, gabapentin as compared to standard therapy with lorazepam, was superior on multiple sleep measures, in patients who had previous withdrawals. Lorazepam subjects experienced rebound symptoms. Early drinking was related to persisting insomnia with both drugs.

Keywords: Alcohol withdrawal, sleep, insomnia, benzodiazepine, lorazepam, gabapentin, sensitization, randomized clinical trial, detoxification, anticonvulsant


Insomnia is a central symptom of alcohol withdrawal; it is one of 8 core criteria in the DSM-IV diagnosis of alcohol withdrawal. Historically, clinicians have observed that the inability to sleep during alcohol withdrawal often is a harbinger of delirium tremens and, conversely, a good night’s sleep early in the course of alcohol withdrawal often precedes an amelioration of withdrawal symptoms.

The restorative forces of sleep extend into the post-withdrawal time frame as well. Brower and colleagues found a highly significant sleep difference among alcoholics who were followed up 5 months after initial detoxification and treatment. They found that while 30% of individuals with no complaints of insomnia during treatment for alcohol withdrawal later relapsed to alcohol use, 60% of individuals with insomnia during treatment for alcohol withdrawal later relapsed. Alcohol dependence is associated with other syndromes that are also likely to disrupt sleep, such as anxiety, depression, sleep disordered breathing, and increased frequency of periodic leg movements. Furthermore, many alcoholics with documented periods of abstinence continue to show fragmented sleep, reduced delta sleep, and difficulty falling asleep.

As relapses to drinking are recurring events in alcoholism, so too are repeated withdrawals. The severity of a current alcohol withdrawal episode in any given patient depends on a number of factors. Four very significant factors include: the presence of comorbid medical disorders, the quantity of alcohol consumed prior to cessation, the duration of that episode of drinking, and the number of previous withdrawal events over the lifetime of the patient. This last factor, the number of previous withdrawal episodes, is the focus of this study. That is, what are the effects of past single vs multiple withdrawals on current sleep and sleepiness in the present withdrawal treated by lorazepam and gabapentin?

Ballenger and Post examined the clinical presentation of several hundred patients who had repeated episodes of treated alcohol withdrawal syndrome. They found that repeated episodes of alcohol withdrawal syndrome were likely to worsen with each successive episode, and they postulated that this might be an “in vivo” model of neuronal sensitization, or kindling, as pro-

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Address correspondence to: Robert Malcolm, MD, Professor of Psychiatry, Pediatrics and Family Medicine, 67 President St., P.O. Box 250861, Charleston, SC 29425, Tel: (843)792-5214; Fax: (843)792-7353; E-Mail: malcolmr@musc.edu
posed by Goddard and colleagues. Subsequently, several animal studies have found an intensification of some withdrawal symptoms in animals that have gone through prior repeated withdrawals. Over a dozen studies have found that alcoholic patients who have undergone multiple withdrawals are likely to have more severe withdrawal symptoms than patients having their first or second alcohol withdrawal. These symptoms include craving for alcohol, heavy drinking after treatment, cognitive impairment, and seizures. These symptoms are less responsive to benzodiazepine treatment than those in patients without multiple withdrawal episodes, even when years of drinking and quantities of drinking are equated. To the best of our knowledge, studies of subjective complaints of sleep disturbance during an episode of treated alcohol withdrawal have not been examined in the context of a limited number (0-1) of previous withdrawals vs history of multiple withdrawal episodes (2 or more).

In a previous study evaluating the anticonvulsant carbamazepine vs lorazepam to treat alcohol withdrawal, we found that the carbamazepine treated group had improved sleep, and this finding persisted into the post-treatment period. Individuals taking lorazepam had improved sleep during treatment as measured by a self-report scale, but rebound insomnia occurred immediately after treatment, and sleep remained poor in the immediate post-detoxification period. We did not assess improvement in sleep by carbamazepine or lorazepam in the context of multiple previous withdrawals. Carbamazepine has compared well to some benzodiazepines for the treatment of alcohol withdrawal in a few small double-blind, placebo-controlled trials. Carbamazepine is not ideal for treatment of alcohol withdrawal; it is limited by multiple interactions with other medications and infrequent but toxic effects related to low serum sodium, bone marrow dyscrasias, and hepatotoxicity.

In our most recent experimental clinical work comparing anticonvulsants to benzodiazepines, (unpublished observations) we chose gabapentin because of its favorable side effect profile, lack of interactions with other medications, lack of hepatic metabolism, and a favorable report of sleep improvement in alcoholics. Using an animal model, we have shown that gabapentin is effective in reducing sensitization after multiple alcohol withdrawals. We hypothesized that gabapentin would have superior effects to lorazepam in reducing self-reported measure of sleep difficulties during alcohol withdrawal in the group who had undergone multiple previous treated (sensitized) withdrawals in the past. Excessive daytime sleepiness, to the best of our knowledge, has not been extensively evaluated in a large sample of patients during alcohol withdrawal. Accordingly, we measured daytime sleepiness using the Epworth Sleepiness Scale. We did not formulate any prediction regarding daytime sleepiness, since both gabapentin and lorazepam can produce sedation. We also evaluated the probability of a return to drinking behavior and its relationship to insomnia during and following treatment.

METHODS

Subjects

Subjects were treatment-seeking patients, 21-70 years old, of both sexes and multiple ethnic groups, who met DSM-IV criteria for alcohol dependence and for current alcohol withdrawal syndrome (AWS). All patients were recruited through referrals from university clinics, emergency departments, community advertise-
ments, and word-of-mouth. All subjects had to demonstrate cognitive capacity to give informed consent, and subjects with breath alcohol levels (BAL) above 80 mg/dL were re-consented on their second day of treatment. All informed consent procedures were approved by the Medical University of South Carolina (MUSC) Institutional Review Board (IRB). Subjects had to have a Mini Mental State Exam score of 26 (30 maximum) or higher and have the clinically judged capacity to give study consent. Subjects had to be judged medically stable and not likely to require hospitalization for medical complications within 10 days of entry into the study. Subjects had to have a score of 10 or higher (indicating moderate or greater withdrawal) on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar). Subjects were required to have a negative urine drug screens for benzodiazepines, other sedative-hypnotics, opiates, and amphetamine. Subjects were excluded from the study if they had a history of taking medications known to ameliorate or intensify the AWS. These included, but were not limited to, tricyclic antidepressants, anticonvulsants, antipsychotics, alpha-adrenergic agonists, beta-blockers, calcium channel antagonists, calcium agonists, SSRIs, SNRIs, and buspirone. Patients were allowed to use nicotine and caffeine. Subjects were excluded with a diagnosis of any other substance-dependence syndrome other than alcohol dependence, with the exception of cannabis, and cocaine. Subjects were excluded if they had a history of idiopathic epilepsy, schizophrenia, bipolar disorder, or dementia. Subjects with liver function tests 4 times higher than the upper range of normal were excluded from the study per IRB request. Subjects with a history of hepatic encephalopathy, jaundice, ascites, insulin-dependent diabetes mellitus, or renal insufficiency were also excluded.

PROCEDURES

Initial eligibility screening was generally performed by phone, with participants providing an estimated amount of daily alcohol use and, whenever possible, the number of previous medicated withdrawals along with brief medical screening history. Subjects were questioned regarding medications which might confound or complicate alcohol withdrawal treatment. Subjects’ initial appointments for baseline measures and in-person screening were generally scheduled between 9 a.m. and noon. This was to promote standardization of baseline data collection, first dose of study medication, and decreased variability of measuring medication effects, diurnal sleep and wake patterns. For similar reasons, subjects were generally started on Mondays, Tuesdays, or Wednesdays for initial baseline assessment.

Based on our previous open-label pilot work, subjects were randomized to receive 1 of 3 doses of gabapentin or lorazepam. Medications prepared for the project were identical capsules prepared and distributed by the Alcohol Research Center Shared Scientific Core pharmacists under supervision by the University Research Pharmacy Office. A medications compliance log was maintained with subjects’ return of medication blister-packs and receipt of new medications. Medications used in the study were identical capsules, containing gabapentin 400 mg, gabapentin 300 mg, gabapentin 200 mg, and lorazepam 2 mg. On the first day of alcohol withdrawal treatment, the high-dose gabapentin group received 400 mg three times a day for 3 days and 400 mg twice daily for 1 day. The mid-range gabapentin dose was 300 mg 3 times a day for 3 days and 300 mg twice daily.
for the last day. The 200 mg dosing group was dosed identically. Lorazepam 2 mg was administered 3 times a day for the first 3 days of the study and 2 mg twice daily on the last day of treatment. Subjects were randomized using a stratified, permuted block method. Stratification was based on previous alcohol treatment history (0-1 or >1 past treated alcohol withdrawals) and sex (male or female). In the present study, because of the relatively small number of subjects in each treatment arm that had undergone 2 or more withdrawals, we elected to aggregate all subjects in the gabapentin arms into one group and then compare that group to the group receiving lorazepam treatment. No placebo dosing arm was used, due to the potential serious consequences of untreated alcohol withdrawal and to the availability of effective comparison treatments. Day 5 was the first follow-up day without medication, Day 7 was the second follow-up day without medication, and Day 12 was the third follow-up day without medications.

**Study Measures**

**Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)**

This is a clinician-rated checklist. It is a multidimensional instrument assessing nausea and vomiting, tremor, sweating, tactile and visual disturbances, auditory disturbances, orientation, senso-rium, anxiety, headache, and insomnia. Items 1-10 are included in the overall assessment for total score. Item 11 (insomnia) is, by convention, not included in the overall score and was scored and analyzed separately for the present study. Table 1 depicts Item 11 of the CIWA-Ar. Response 0 is “able to sleep uninterrupted.” Response 1 is “complains of difficulty falling asleep.” Response 4 is “awake one-half of time.” Response 7 is “awake throughout the night.” High scores indicate poor sleep. In the present study, all investigators, co-investigators, project coordinators, and research assistants were trained with mock subjects and clinical patients in withdrawal assessment prior to starting the study and periodically retrained to achieve high congruence in scoring of this instrument. For the majority of subjects seen in this study, one individual (the project coordinator, EB) scored the CIWA-Ar. This was rated in all subjects on a daily basis for each visit and generally between the times of 9 a.m. and noon. The CIWA-Ar Item 11 was our outcome variable in also examining the probability of drinking the next day.

**Beck Depression Inventory (BDI)**

This is a 21-item self-rating questionnaire evaluating multiple dimensions of mood and depression. Item 16, which was the item analyzed separately for this study, asks “which of these statements best describes the way you have been feeling during the past few days?” Responses in order include “I can sleep as well as usual,” “I don’t sleep as well as I used to,” “I wake up 1-2 hours earlier than usual and find it hard to get back to sleep,” and “I wake up several hours earlier than I used to and can’t get back to sleep.” A high score indicates poor sleep. A previous study using this instrument and single item analysis of Item 16 reported that a 1 point change in this item represented a 25% clinical improvement. The BDI was administered at baseline, Day 5 (one day after the end of medication treatment), and for both follow-up visits on Days 7 and 12. The scale was modified to tell subjects that for Days 5, 7, and 12 to use the interval of the previous time since the last administration of the scale as their evaluation interval.

**Epworth Sleepiness Scale**

This is a subject self-rating scale that uses 8 items on which an individual might have the propensity to fall asleep during the daytime. Each item is rated as to the probability of falling asleep on a scale of 0 to 3. The Epworth scale was administered each morning and subjects were asked to rate their degree of sleepiness for the previous 24 hours. The Epworth scale has been studied in a variety of disorders leading to excessive daytime sleepiness and used as a measure of medication effects.

**Number of Previous Withdrawals**

As with our previous study, we used a semi-structured standard interview to question subjects about the number of previous withdrawal episodes they had been treated for in the past. We used a modified version of the Cognitive Lifetime Drinking History. Both inpatient and outpatient treated withdrawal episodes were counted. Subjects were asked about a list of commonly used medications (benzodiazepines, barbiturates, etc.), using both generic and trade names. Patients who were treated with vitamins, supportive care, and no specific medication to ameliorate withdrawal symptoms were not counted as having a treated withdrawal.

**Other Procedures**

All subjects were given a breath alcohol test at the start of each daily visit to obtain a breath alcohol level (BAL). The time since last drink was also recorded. Additional measures made at appropriate intervals were Timeline Followback of Drinking Behaviors, electrocardiographic examination, and appropriate physical and laboratory assessments. These and other assessments are reported in our treatment outcome paper. (unpublished observations of L.H. Myrick)

In summary, subjective reports of sleep were studied in the context of drug treatment, current withdrawal severity, and depressive symptoms. Daytime sleepiness was assessed by self-report using the Epworth Sleepiness Scale. Secondary analysis further evaluated the impact of previous treatments for alcohol withdrawal on these measures.

**Statistical Analyses**

Subjects were randomized using a stratified permuted block method in which individuals with particular characteristics were assigned to medication groups with constraint that the assignment was balanced within successive blocks of subjects. We used a relatively small block size of \(q=4\) in order to promote a

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**Table 1**—Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)

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<th>Insomnia Item 11</th>
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<td>Able to sleep uninterrupted</td>
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<td>Awake one-half of time</td>
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<td>Awake throughout the night</td>
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high degree of balance. Stratifications were based on the intersection of previous alcohol treatment history (0-1 or more than 1 past treated withdrawals) and sex (male or female). Therefore this method balanced treatment assignment in each of the combinations formed by crossing these 2 stratification variables.

All sleep-related dependent variables (CIWA-Ar-11, Beck-16, and Epworth) were analyzed as a mixed model (SAS Proc Mixed) with an unstructured variance/covariance matrix. Preliminary model estimates on the primary CIWA-Ar scores revealed that in addition to the reduction in variance as scores declined across time, simple covariance structures (heterogeneous compound symmetry, heterogeneous autoregressive, etc.) fit less well by likelihood ratio criteria than did the unstructured matrix. The same was true for most of the secondary variables in the main study, so all dependent variables were analyzed with the unstructured matrix. The same was true for most of the secondary variables in the main study, so all dependent variables were analyzed with the unstructured matrix. Further, dependent variables across the treatment and follow-up periods were conditioned on the baseline measurement for each and on the drinks per day variable derived from the immediate pre-detoxification period (14 days). These adjustments were particularly important in analyses distinguishing between different previous alcohol withdrawal histories, as these covariates often differ between the groups and may otherwise obscure or confound the interpretation of treatment results.

The basic design utilized a two way factorial, drug treatment (gabapentin vs lorazepam), and the within subject variable time for each dependent measure. Separate analyses were completed for the 2 study phases (treatment and follow-up) with additional analysis considering differences by day completed to further delineate results when justified by significant interactions.

A secondary analysis was completed to address the history of previous alcohol treatment. This design utilized a three way factorial (previous alcohol withdrawal history (0-1 vs >1), drug treatment (gabapentin vs lorazepam), and the within subject variable time which differed for different dependent measures. A variety of simple effects (e.g., drug by time within previous alcohol treatment levels) were used to further delineate results when justified by significant or near significant interactions.

The relationship between insomnia and next-day drinking was analyzed using a multilevel logistic regression. Scores on the CIWA-Ar-11 variable were used as predictors for dichotomized drinking (drinking vs not drinking) on the subsequent day. A random regression model was employed in which slopes are permitted to vary between individual subjects and hypotheses tested regarding the population of slopes in the two groups.

RESULTS

The sample consisted of 449 patients screened by phone for the study, 281 patients screened in person for the study, and 101 subjects signing informed consent at baseline and receiving at least one dose of study medication. Figure 1 is a flowchart of subject disposition. Seventy-five subjects received 4 days of medicated treatment, and 68 subjects completed follow-ups at Days 5, 7, and 12. The sample consisted of 25% females, 15% African Americans, 3% Native Americans, and 1% Hispanic Americans. The number of prior medicated withdrawals of the patients ranged from 0 to 5. The subject population had a mean age of 41 years, a mean educational level of 13.4 years, and a mean income of $2,023/month. The mean duration of alcohol use was 15 years. Sixty-five percent of patients reported 0-1 medication-treated alcohol withdrawals, and 35% reported 2 or more withdrawals from alcohol that were treated with medication. Age, sex, number of years drinking, number of standard drinks in the 14 days prior to study entry, income, educational level, and number of previously treated withdrawals did not differ statistically between medication treatment groups. There were no differences in medication compliance among the groups.
Adverse Events

The study was initially designed to compare 3 doses of gabapentin (totaling 600 mg, 900 mg, and 1200 mg/day) to three 2 mg doses of lorazepam. Eleven individuals were randomized to the low-dose gabapentin group (200 mg three times daily); 3 of them experienced significant adverse events (2 with seizure-like activity during treatment, 1 with a syncopal episode requiring emergency room assessment), indicating that this dose was ineffective. At the request of the Data Safety Monitoring Board, this dose was discontinued and no further recruitment of subjects was made for this dose. The eleven subjects in this group completed the study and their data was included in the gabapentin dataset. No serious adverse events were experienced by patients randomized to high-dose or mid-range gabapentin or 2 mg lorazepam doses. There were no differences in self-reported side effects between participants treated with gabapentin vs lorazepam (p = .74). Throughout the trial there was a trend for gabapentin subjects to report more “high” (intoxication)(p = .17). The gabapentin subjects had a trend of more pruritus (p = .17). One gabapentin participant was withdrawn due to rash and urticaria (treated with diphenhydramine, followed by a complete recovery. No patients experienced delirium tremens in either the gabapentin or lorazepam group. There was a trend for lorazepam participants to report more sedation (p = .12).

Clinical Institute Withdrawal Assessment for Alcohol-Revised Sleep Assessments

Self-reports of insomnia, as assessed from Item 11 of the CIWA-AR, were differentially affected by drug administration, both during treatment and follow-up. Patients receiving 600 mg, 900 mg and 1200 mg gabapentin did not differ and are combined in the analysis. Depicted in Figure 2A are the trajectories prior to initiation of drug treatment, during treatment and through the follow-up period. Across the days of treatment, a drug by treatment day effect was found (F_{1,62} = 2.77, p = .049). Post hoc analysis of this interaction indicated that on the first day of treatment, self-reports of insomnia were significantly lower in patients receiving lorazepam in comparison to gabapentin (F_{1,62} = 7.48, p = .008). In contrast, in the follow-up period, subjects previously taking lorazepam experienced increased insomnia, while gabapentin subjects continued to report a reduction in insomnia. These impressions were supported by statistical analysis indicating both a drug by follow-up day effect (F_{1,52} = 4.82, p = .032), as well as a significant difference on the 1st follow-up day in self-reports of insomnia with subjects previously receiving lorazepam reporting higher levels of insomnia in comparison to prior gabapentin treatment (F_{1,59} = 4.07, p = .048).

Analysis also identified a main effect of prior treatment history of withdrawal on this measure of insomnia, both during treatment (F_{1,60} = 6.08, p = .016) as well as into the follow-up period (F_{1,57} = 4.41, p = .04). Depicted in Figure 2 are trajectories of the CIWA-AR Item 11 insomnia rating for patients with a history of limited (0-1) (Figure 2B) and multiple (>1) (Figure 2C) previous treatments for alcohol withdrawal. In patients with a limited treatment history, there was a trend for lorazepam treatment to reduce self-reports of insomnia during treatment (F_{1,60} = 3.45, p = .068). In the follow-up period, prior lorazepam treatment initially resulted in increased insomnia (F_{1,52} = 7.55, p = .008), while insomnia levels reported by subjects previously receiving gabapentin remained stable. A similar, but more pronounced effect was seen among patients with a history of multiple previous alcohol treatments. During treatment, lorazepam significantly reduced self-reports of insomnia on the first day of treatment (F_{1,60} = 3.68, p = .013). At the final follow-up day, insomnia reported by subjects previously receiving lorazepam treatment were significantly higher than all other subject groups (F_{3,60} = 2.89, p = .043).

Beck Depression Inventory Sleep Assessments

Overall, lorazepam and gabapentin were equally efficacious in reducing this measure of sleep difficulty during treatment, evidenced as a nonsignificant drug effect during treatment (p>.14). However, during the follow-up period, significant differences
were noted by prior drug treatment across the period ($F_{1,59} = 5.02$, $p = .029$). While discontinuation of gabapentin treatment did not alter this measure, patients previously treated with lorazepam reported increased sleep difficulty, an effect which did dissipate by the end of the study (data not shown). Further analysis indicated that prior treatment history interacted with drug treatment, both during treatment and follow-up ($F_{1,57} = 9.49$, $p = .003$) and ($F_{1,57} = 5.28$, $p = .025$), respectively. Depicted in Figure 3 are the scores on the sleep-related item of the Beck Depression Inventory for subjects with limited (Figure 3A) and multiple (Figure 3B) previous treatments for alcohol withdrawal. During treatment, while there were no significant differences among patients with a limited treatment history ($p>.65$), a highly significant drug main effect was noted among patients with a history of multiple prior treatments ($F_{1,57} = 18.15$, $p = .0001$); subjects receiving lorazepam reported significantly higher levels of sleep disturbance during treatment and follow-up than those receiving gabapentin ($F_{1,57} = 6.98$, $p = .011$).

**Epworth Sleepiness Scale**

Reports of daytime sleepiness, assessed using the Epworth Sleepiness Scale, during treatment and follow-up for patients treated with lorazepam or gabapentin are depicted in Figure 4. An overall main effect of drug on sleepiness during treatment was noted in the analysis ($F_{1,65} = 4.42$, $p = .0394$) with patients receiving lorazepam reporting significantly more sleepiness than those receiving gabapentin. Post hoc analysis by treatment day indicated the effect to be most pronounced on day 3 of withdrawal ($F_{1,65} = 5.54$, $p = .022$). Additional analysis indicated that prior treatment history had no impact on this effect ($p>.78$). No significant differences were noted during the follow-up period.

**Relationship of Insomnia to Next-Day Drinking**

The probability of drinking as a function of Item 11 from the CIWA-Ar (reflecting sleep difficulty on the preceding night) for subjects receiving gabapentin or lorazepam treatment is depicted in Figure 5. In this figure, the best fitting linear functions of log(likelihood) = f(CIWA-Ar-11) have been converted to probabilities for presentation purposes. For both drug treatment groups, increasing difficulty with sleep on any night increased the likelihood of drinking on the subsequent day. For examples, 70% of subjects rating a 7 on CIWA-Ar Item 11 (“Awake throughout the night”) drank the next day. The slope of the log-likelihood function for the steeper gabapentin function was $B=.27$, SE=.09, $t(215)=3.1$, $p = .002$. The lorazepam slope was shallower, but not significantly different ($t(215)=-1.28$, $p = .21$) from the gabapentin slope. A random slopes model was fit, though we were unable to detect significant individual differences in the slope of the prediction ($x^2(60) =53.8$, $p>.5$). Intercepts (probability of sleep with theoretical scores of zero on CIWA-Ar-11) did differ between the drug groups ($t(60)=2.079$, $p = .037$). In the absence of insomnia (i.e. CIWA Item 11 score of 0), subjects treated with lorazepam had a higher probability of drinking the next day.
DISCUSSION

Outpatients being treated for mild to moderate alcohol withdrawal received a fixed-dose taper for 4 days of gabapentin or lorazepam in a double-blind, randomized, controlled trial. Sleep and daytime sleepiness were assessed using subjective rating instruments, and additional analyses evaluated the impact of limited (0-1) or multiple (2 or more) previously treated alcohol withdrawal episodes. Overall, patients receiving lorazepam reported less insomnia and more sleepiness early in treatment than patients receiving gabapentin. However, upon completion of treatment and discontinuation of drug administration, patients previously treated with lorazepam reported increased insomnia and daytime sleepiness, while patients previously treated with gabapentin continued to report improvements in these self-reported measures of sleep.

By examining the sample based on the number of previous treated alcohol withdrawals, we saw some interesting differences emerge between lorazepam and gabapentin ratings of insomnia and sleepiness. For the group that had gone through minimal withdrawals (0-1), lorazepam was better in quickly improving sleep. However, rebound insomnia was seen when lorazepam was stopped (Figure 2B). In the multiple previous withdrawal group, sleep improved only briefly with lorazepam, while insomnia worsened, even during treatment (Figure 2C). Sleep deteriorated further in the post-treatment week. The gabapentin group showed slowly improving sleep over the treatment week, and this improvement was sustained in the post-treatment period. The BDI sleep score provided further evidence of differences between lorazepam and gabapentin in the multiple previously treated withdrawal groups at Day 5, Day 7, and Day 12 (Figure 3B). Gabapentin was superior to lorazepam in reducing insomnia as assessed by the BDI, an effect sustained throughout the post-treatment week. Epworth scores indicated less daytime sleepiness in the gabapentin group than the lorazepam group (Figure 4).

Several studies have found that alcoholic patients who have undergone multiple withdrawals are likely to have more severe withdrawal symptoms than those undergoing a first or second episode of withdrawal. These symptoms include seizures, craving for alcohol, heavy drinking after treatment, and cognitive impairment; the symptoms are less responsive to benzodiazepine treatment than similar symptoms in patients having their first or second alcohol withdrawal, even when years of drinking and quantities of drinking are controlled.19 The present study suggests that, among alcoholics with a history of multiple withdrawals, lorazepam is less effective than gabapentin in reducing insomnia.

The strong relationship between sleep disruption and drinking on the following day was independent of days into treatment and monitored sleep difficulty. In this case, the only time at which gabapentin-treated subjects were more likely to drink than lorazepam subjects occurred during the first 2 days of treatment, during which the gabapentin-treated subjects were most likely to report sleep disruption. A rebound in drinking (and other symptoms) occurred when subjects were taken off lorazepam, at which time they showed more severe sleep disruption than the gabapentin-treated individuals. While these data cannot establish a causative link between insomnia and drinking, these results are supportive of other studies that suggest sleep disruption is a determinant of early relapse.

The mechanisms of action of gabapentin and lorazepam are dissimilar. As a benzodiazepine, lorazepam’s effects are due to actions in the inhibitory GABA system where benzodiazepines act as agonists, allosterically binding to the benzodiazepine recognition site on the GABA<sub>A</sub> receptor.24 In contrast to the identified mechanisms of action for lorazepam, many biological mechanisms for gabapentin’s actions have been proposed, but thus far the only specific receptor binding is at the alpha(2)delta subunit of voltage-gated calcium channels.25 The effect of this subunit on sleep is unknown, however, studies in rat have identified high levels of this subunit in brain areas involved in sleep and arousal homeostasis.26 Clinically, in adults with localized epilepsy, 300 and 600 mg of gabapentin increased slow wave sleep, and 600 mg slightly decreased REM sleep.27 In nonalcoholics, single-dose gabapentin improved several sleep outcome measures previously disrupted by a loading of alcohol.28 Gabapentin reduced Stage 1 sleep, reduced the number of awakenings, and increased slow wave sleep. A 600 mg dose of gabapentin slightly reduced REM sleep. In an open-label trial of gabapentin and trazodone in abstinent alcoholics with persistent insomnia, gabapentin was the superior agent in improving sleep as measured by the Sleep Problems Questionnaire.21

Why should gabapentin exert superior effects in the multiple withdrawal group? The neural processes regulating sleep are composed of an integrated network of cortical and subcortical structures utilizing a number of neurotransmitters and neurohormones. Acetylcholine, amines and orexin are the prominent wake-promoting neurotransmitters while the interaction of GABAergic, cholinergic and amnergic neurotransmission controls NREM and REM sleep. It is this balanced interplay among these various brain sites and neurotransmitter systems which is disrupted during alcohol withdrawal and further exacerbated with repeated withdrawal. In preclinical models, repeated exposure to alcohol with abrupt cessation leads to an imbalance of excitatory and inhibitory amino acid neurotransmitters.10,19 Indeed, GABA<sub>A</sub> functions are reduced during withdrawal, and glutamatergic functions are increased, with extracellular glutamate increasing with each cycle of ethanol withdrawal.19 It is perhaps this imbalance of the ratio of reduced inhibitory neurotransmitter in relation to in-
creased excitatory neurotransmitter that gives the picture of poor sleep at night and lack of sleepiness in the daytime for the multiple previous detoxification group. Since there is no placebo control group, it is difficult to tell whether gabapentin is superior specifically, or simply that lorazepam is a less adequate treatment.

There are several limitations to the present study. While less than 25% of the initially screened subjects enrolled in the study, the dropout rate between initial screening and subject enrollment is in the normal range, comparable to other alcohol withdrawal studies. Objective electrophysiologic measures of sleep (PSG) and daytime sleepiness (MSLT) would have been preferable, but certainly would be a daunting task in outpatients in a sample size this large. Numerous factors which could have been more rigorously examined for their influence on sleep were not studied here. There are some limitations to the use of the Epworth Sleepiness Scale. First, this scale is novel for this situation, and it has not been validated for alcohol withdrawal. Secondly, this scale is not typically used to measure “next day” sleepiness. Finally, this scale includes a hazardous situation (Item #8) that subjects were asked to imagine rather than report the actual situation since driving was discouraged. We did not examine the relationship of sleep to caffeine intake, or routine sleep hygiene measures. We did not use a multidimensional standardized rating scale of sleep disturbance. Subjective history of alcohol withdrawal may be inaccurate. Despite these limitations, our findings across instruments are generally consistent and are supported by findings from other studies with patients and preclinical models.

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