INTRODUCTION

Patients in early alcohol recovery have high rates of sleep disturbances. The rates of insomnia in this population could be as high as 36–72% (Foster et al., 1998; Brower et al., 2001). During early recovery, alcoholic patients have increased sleep onset latency (SL) and a decreased total sleep time (TST) (Drummond et al., 1998). Sleep efficiency and the percent of slow-wave sleep are also reduced in early recovery. Sleep problems may continue for many months following alcohol withdrawal. Subjective sleep measures did not show improvement over 12 weeks in one longitudinal study (Cohn et al., 2003).

On subjective reports, increased SL and poor sleep quality have been associated with an increased risk of relapse even after accounting for the severity of drinking and other Axis I diagnoses (Foster et al., 1998). An increased SL and a decreased TST on polysomnograms are also associated with relapse (Drummond et al., 1998). A decreased REM latency and increased REM density are also found to be associated with early relapse (Gillin et al., 1994). Although there is evidence to suggest that alcohol is associated with a worsening of sleep-disordered breathing and periodic limb movements (PLMS), most research has concentrated on insomnia occurring in the context of alcohol dependence (Brower, 2001). In this systematic review, we limit ourselves to the treatment of insomnia in patients with alcohol dependence.

It follows intuitively that treating sleep problems adequately in this patient population may lead to a reduction in relapse. The treatment of insomnia in alcoholic patients has been poorly studied. In addition, treating sleep problems in alcoholics in recovery is complicated by the fact that some of the most commonly used medications to treat insomnia are thought to have a high abuse potential and clinicians are rightfully wary of using them in this patient population. A survey found that a majority of clinicians did not offer these patients any medication (Friedmann et al., 2003). Although a previous paper has examined this topic, a systematic review of all pharmacological agents has not been performed (Arndt et al., 2007). In order to synthesize the available literature and to provide clinicians with the best current evidence on treating insomnia in alcoholic patients, we conducted a systematic review of the pharmacological treatment of sleep problems in alcohol recovery.

METHODS

We attempted to identify all studies of pharmacological agents used to treat sleep problems in patients with alcoholism. In accordance with the Quorum statement, we performed a search of all common databases including PubMed, EMBASE, Psych Info and Medline. The search terms used were alcohol, insomnia/sleep and treatment/management individually and in combination. There were no year/language restrictions. We also manually searched through all recent addiction psychiatry/medicine and sleep journals and also all relevant references which were identified from other studies which met inclusion criteria.

The inclusion criteria were all studies of patients with a diagnosis of alcohol dependence which included objective or subjective measures of sleep. Even studies which did not provide relapse data were included. We included all open-label and placebo-controlled trials. Case reports and case series were excluded.

The search was performed in August 2009 and initially revealed 1239 abstracts. After a review of the titles and abstracts, 19 abstracts met inclusion criteria. One additional study was identified by our manual search of references. Most of the initial abstracts were excluded as they either did not have any information regarding sleep or the primary diagnosis was not alcohol dependence. The flow of the initial search and the results are shown in Fig. 1.

TREATMENT

Pharmacological Treatment of Insomnia in Alcohol Recovery: A Systematic Review

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RESULTS

Trazodone

Trazodone is a sedating antidepressant which acts predominantly on the serotonergic system. It is one of the most commonly prescribed sleep aids in patients with alcohol dependence (Friedmann et al., 2003). It is not habit forming and has no abuse potential which might explain why it is frequently prescribed in patients with alcohol addiction. Our search revealed two studies of trazodone used to treat sleep problems following cessation of alcohol use.

A small, placebo-controlled trial of 16 patients following detoxification and a 2-week washout period revealed an improvement in some polysomnographic (PSG) sleep measures (Le Bon et al., 2003). Trazodone was started at 50 mg and gradually increased to a dose of 200 mg. In cases where this was not tolerated, a dose of 150 mg was used. A polysomnogram was performed on Days 1, 2 (prior to receiving trazodone), Day 3 (first dose of trazodone, 50 mg) and on Day 28. No drinking measures were used in this study.

Wake-time after sleep onset (WASO) was improved on Days 3 and 28. Sleep efficiency was improved on Day 3, but on Day 28 the difference between the trazodone group and the placebo group was not significant. The total non-rapid eye movements sleep percentage was also improved on Day 3 but not on Day 28. Clinical global impression (CGI), a clinician rating of the severity of the patient’s illness and Hamilton Depression Rating Scale (HAM-D) scores were significantly improved in the trazodone group (Guy, 1976).

A large, NIAAA-supported, placebo-controlled trial conducted over a period of 24 weeks in 173 patients right after detoxification revealed that trazodone significantly improved sleep. Patients were prescribed trazodone in the range of 50–150 mg (average of 100 mg) for 12 weeks and following this the trazodone was discontinued (Friedmann et al., 2008).

Trazodone improved sleep as measured by the Pittsburgh Sleep Quality Index (PSQI) at 1 month (Cohen’s d: 0.5) and at 3 months (Cohen’s d: 0.93). Following discontinuation, sleep measures reverted to placebo level.

Abstinence rates were no different between the trazodone and the placebo groups, both being low at 9.1 vs. 14.1%, respectively. However, only 25.3% of patients in this trial reported having received formal alcohol treatment following detoxification. The number of drinks/drinking day were no different between the trazodone and placebo groups at 1 and 3 months. However, after trazodone was discontinued at 3 months, the trazodone groups had a greater increase in the number of drinks per drinking day. In other analyses, the trazodone group also showed a smaller increase in the number of days abstinent.

Gabapentin

Gabapentin is a sedating anticonvulsant medication which is a γ-aminobutyric acid analog. It has been used to treat pain, and there is also evidence that it might treat alcohol withdrawal (Mariani et al., 2006). Gabapentin has also been investigated for potential use as sleep aid in patients following alcohol cessation. Our search revealed one open-label trial and four randomized control trials of gabapentin as a sleep aid for patients following cessation of alcohol use.

An open-label trial compared gabapentin (888 ± 418 mg; range 300–1800 mg) against trazodone (105 ± 57 mg; range 50–300 mg) in 55 patients over 4–6 weeks. Five patients dropped out due to daytime drowsiness. Both groups reported improvement in sleep as measured by the Sleep Problems Questionnaire (SPQ) (Jenkins et al., 1988). However, the gabapentin group reported more improvement in SPQ scores as compared with the trazodone group. No relapse measures were used. Also, patients of the trazodone group were more likely to report daytime tiredness (Karam-Hage and Brower, 2003).

A double-blind trial comparing gabapentin against lorazepam for the treatment of alcohol withdrawal over a 4-day period provided data on daytime sleepiness (Myrick et al., 2009). A total of 100 individuals were randomized to receive gabapentin (900 mg tapering to 600 mg or 1200 mg tapering to 800 mg) or lorazepam (6 mg tapering to 4 mg). The patients were followed for a total of 12 days. Gabapentin was administered in three divided doses through the day, as was the lorazepam.

The daytime sleepiness as measured by the Epworth scores was lower in the high-dose gabapentin group when compared with the lorazepam group. Although the follow-up period was short, the authors did comment on the probability of patients returning to heavy drinking. Patients of the gabapentin group were more likely to drink on the first day of medication. Although the probability of relapse was low on the following days, it increased slowly over the
post-treatment period. On lorazepam patients were absten
ton the first medication day, they showed an increased prob-
ability of drinking thereafter, showing peaks at Day 2 and on
Day 6.

A randomized, double-blind trial compared gabapentin
(1200 mg), valproate (1500 mg) and placebo for the acute

treatment of alcohol withdrawal over 5 days and for 4 weeks
later (Trevisan et al., 2008). A total of 57 patients were ran-
domized to gabapentin, valproate or placebo in addition to
benzodiazepines in the first 5 days of detoxification.

Following this initial phase, the gabapentin, valproate and
placebo were continued for 4 weeks. However, gabapentin
was administered in three divided doses over the day rather
than as a single dose at night.

There were no differences in sleep as measured by the
PSQI between the three groups. Also, the three groups did
not differ based on the number of drinking days, heavy
drinking days or the number of drinks. Abstinence rates were
not different among the three groups.

Another randomized, placebo-controlled trial of 21 patients
compared gabapentin (1500 mg) with placebo over 6 weeks.
Patients with insomnia which persisted after a week of absti-

ence, in the absence of withdrawal symptoms, received a
single-blind placebo run in for a week. During this period, the
subjects were instructed to maintain their usual sleep schedule
and at the end of the week an initial PSG was performed.

Subsequently, they were randomized to either gabapentin or
placebo for 6 weeks. Following this, they were tapered off the
medication over 4 days. A follow-up visit was scheduled at
12 weeks (6 weeks following the discontinuation of the medi-
cation) (Brower et al., 2008).

SPQ scores were available for 14 out of 21 patients at
6 weeks and for 11 out of 21 patients at 12 weeks. Although
there was a significant improvement in SPQ scores over the
6 weeks for the entire group, there were no significant differ-
ences between the gabapentin and the placebo groups at
either 6 or 12 weeks. PSG was performed at the end of the
placebo run-in period and after 3 weeks. No significant
change over time was observed on the PSG. On the SPQ
scores, there was a non-significant trend for patients on gaba-
pentin to do worse between 6 and 12 weeks when compared
with the placebo group. This was because sleep in gabapen-
tin group worsened once it was discontinued, while SPQ
scores in the placebo group continued to improve. On the
PSG measures, there was a trend for patients on gabapentin
to have worse SL. Another interesting finding was that
patients with a higher change in SPQ scores were less likely
to relapse.

Drinking outcomes were limited by lack of data in 6 out
of 21 patients. There were no differences in relapse rates
between the two groups. The relative risk of relapse to heavy
drinking was lower in the gabapentin group.

Another randomized control trial of 60 patients who had
their last drink no more than 72 h prior to randomization
compared a combination of intravenous flumazenil adminis-
tered as 2 mg boluses for two consecutive days and gabapen-
tin (1200 mg) administered nightly for 39 days against
placebo (Anton et al., 2009). These patients were instructed
not to drink on the night prior to the administration of fluma-
zenil. They were assessed on Weeks 2 and 6 following ran-
domization. Sleep was assessed using the Insomnia Severity
Index (ISI) and the Epworth Sleepiness Scale (ESS).

The patients in this trial were divided into those with high
alcohol withdrawal and low alcohol withdrawal according to
their Clinical Institute Alcohol Withdrawal (CIWA) scores at
baseline (Foy et al., 1988). Those with CIWA scores >7
were considered high withdrawal and 16 out of 60 qualified.

There appeared to be an interaction between the alcohol
withdrawal severity and medication group. Those with low
alcohol withdrawal had better sleep if on active medication
and those with high alcohol withdrawal appeared to do better
if on placebo.

The effect on drinking measures was the opposite with the
high alcohol withdrawal group having more days of absti-

ence and longer time to first heavy drinking if on the active
medication. This was also true for complete abstinence.

Zopiclone

Zopiclone is a non-benzodiazepine benzodiazepine receptor
agonist that is currently unavailable in the USA. An enantio-

mer of zopiclone; eszopiclone is available in the USA and is
FDA approved for the treatment of insomnia. Although it is
commonly prescribed for the treatment of insomnia in the
general population, there is some concern that this medi-
cation may have abuse potential (Hajak et al., 2003). This
is likely to be a reason these medications are less commonly
prescribed in the addiction populations. Our search revealed
a single, double-blind trial comparing zopiclone with
lorzmetazepam.

Fifty-four patients were entered in the study of which
52 patients were analyzed. The patients were tapered off
alcohol and then underwent a 2-day placebo run in period
following which they were randomized to receive the active
medication. Twenty-seven patients received 7.5 mg of zopi-
clone at night, while 25 patients received 1 mg lormetazepam
(dose equivalent of 6.5 mg of diazepam) (Ansoms et al.,

Sleep was measured using the Spiegel Sleep Questionnaire
and mood and behavior at awakening was measured using a
visual analog scale. All the sleep measures showed a trend
improvement over the 5-day treatment period. The time to fall
asleep was the only measure which improved sig-

ificantly in the lormetazepam group. The zopiclone group
showed significant improvements in daytime mood and be-

havior and were reporting more attentiveness and being more
alert. No measures of alcohol relapse were included.

Topiramate

Topiramate is a sedating anti-seizure (or anticonvulsant)
medication that is thought to help reduce relapse to alcohol.
A single, large, multicenter trial of 371 alcoholic subjects
was performed over 14 weeks. Patients in this trial were ran-
domized to topiramate (50–300 mg) or placebo, and absti-

nence was required during the study period. Sleep was
measured using the Medical Outcomes Study Sleep Scale.
Topiramate use was associated with a reduction in sleep dis-
turbance. Topiramate was also associated with a significant
reduction in obsessional thoughts and compulsions about
using alcohol and with a reduction in the percentage of
heavy drinking days (Johnson et al., 2008).
Carbamazepine

Carbamazepine is an anticonvulsant which is thought to treat acute alcohol withdrawal (Malcolm et al., 2002). Two studies have measured the impact of carbamazepine on sleep in patients with alcohol dependence.

A randomized control trial compared carbamazepine against lorazepam in 136 individuals with alcohol dependence over the course of 5 days. Patients received tapering schedules of carbamazepine and lorazepam over the period of the trial. Sleep was measured using a visual analog scale. Sleep measures, adjusted for time since last drink, revealed no differences on Days 1 and 5, but the carbamazepine group was significantly better on Days 7 and 12 when compared with lorazepam. No relapse measures were included (Malcolm et al., 2002).

Another randomized, double-blind, placebo-controlled trial of carbamazepine in patients with alcohol dependence over 7 days revealed that subjective measures of sleep were significantly better in the carbamazepine group. No relapse measures were used in this trial either (Bjorkqvist et al., 1976).

Acamprosate

Acamprosate is a medication which is thought to be a functional glutamate antagonist. It is thought to help reduce drinking-related parameters in a certain proportion of alcohol-dependent patients (Boothby and Doering, 2005). Acamprosate is thought to have no effects on the sleep of subjects not dependent on alcohol. A single, double-blind, placebo-controlled trial of 24 male alcoholics compared the impact of acamprosate on PSG sleep measures against placebo (Stanet et al., 2006).

The patients with alcohol dependence were chosen such that they had low CIWA scores (<8) and did not require benzodiazepines to treat alcohol withdrawal. They were prescribed acamprosate (666 mg t.i.d.) for 8 days prior to alcohol discontinuation and for 15 days following this. Polysomnograms were performed on Day 2 and Day 15 following commencement of acamprosate or placebo.

Acamprosate improved WASO and Stage 3 of sleep and also increased the REM latency but did not impact SL or TST. No relapse measures were used in this trial.

Quetiapine

Quetiapine is an atypical antipsychotic, which is sedating. It is occasionally used off label to treat sleep problems. Although it was initially considered to have low abuse potential, this has recently been questioned (Sansone and Sansone, 2010). Our search revealed a single, open-label trial of quetiapine used to treat psychiatric symptoms and alcohol consumption and cravings.

In this open-label trial, 28 patients with alcohol dependence along with other major Axis I diagnoses received flexible doses of quetiapine (300–800 mg/day) for 16 weeks following 5–10-day detoxification (Martinotti et al., 2008). Sleep measures were obtained from the HAM-D insomnia items. There was a significant reduction in the HAM-D insomnia middle (r = 0.99; P = 0.0002) and insomnia late items (r = 0.98; P = 0.001).

The authors unfortunately do not comment on the changes in the sleep items at further follow-up visits. Although there is a significant reduction in the gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine transaminase (ALT) and mean corpuscular volume (MCV) over the study period, there was a 25% drop-out rate, while 32% of patients relapsed to heavy drinking.

Magnesium

An open-label trial of 11 patients evaluated subjective changes in sleep using the PSQI and also changes in sleep measures on polysomnogram following a 4-week trial of magnesium (10 mmol in the a.m. and 20 mmol in the p.m.) (Hornyak et al., 2004).

Patients were detoxified from alcohol and were prescribed magnesium 1 week following detoxification. They received magnesium for 4 weeks, and polysomnograms were performed 2 weeks following detoxification and again at 4 weeks. Subjective changes in sleep were measured using the PSQI (Buysse et al., 1989).

PSQI scores improved significantly over the course of treatment. On PSG measures, only the SL improved significantly over the course of the trial. The authors further divided the groups into those whose PLMS improved (7 out of 11) and those whose PLMS worsened (4 out of 11). On subgroup analyses, the TST of patients with a decrease in PLMS was significantly improved with treatment.

The authors also compared changes in the GGT, CDT, AST and ALT over the course of treatment. The group with a reduction in PLMS also demonstrated a significant reduction in CDT and GGT values over the course of treatment.

Benzodiazepines

Benzodiazepines are extensively used for the treatment of acute alcohol withdrawal. There is a concern about continuing to prescribe these agents after acute detoxification due to the cross tolerance and also concerns about cross addiction and the possibility of precipitating a relapse. Medications such as triazolam and temazepam are some of the commonly used benzodiazepines for the treatment of insomnia.

An open-label trial assessed the use of triazolam (0.5–1 mg) in 23 patients with alcohol dependence over 28 days. Sleep was measured using a sleep diary. Only 12 out of 23 patients completed the trial and were included in the analyses. Over the duration of the trial, there was a significant improvement in self-reported depth of sleep and duration of sleep. There was also a significant reduction in the number of awakenings. Of the initial 23 patients, 4 relapsed to alcohol use (Fabre et al., 1977).

Diazepam was compared with tetrabamate in an open-label trial of 23 patients with alcohol dependence. Patients received 25 mg/day of diazepam for 3 days, 15 mg/day for 3 days and remained on 6 mg/day till PSG. Tetrabamate was similarly dosed at 2700, 1800 and 900 mg/day. Polysomnography was carried out between 15.5 ± 2.7 days for the diazepam group and between 15.1 ± 2.2 days for the tetrabamate group. The TST and N2 sleep was significantly increased in the diazepam group. N3 sleep was significantly increased in the tetrabamate group.
<table>
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<tr>
<th>Authors</th>
<th>Drug (dosage)</th>
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<th>Duration of trial</th>
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<td>Sleep diaries</td>
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<td>PSG</td>
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<td>PSG and PSQI</td>
<td>Reduced sleep latency on PSG and improved sleep quality on PSQI. Variable changes in PLMS. Both groups improved but gabapentin group improved more significantly. Trazodone group had more day time sedation.</td>
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<td>Gabapentin (888 ± 418 mg) vs. Trazodone (105 ± 57 mg)</td>
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<td>4–6 weeks</td>
<td>4 or more weeks</td>
<td>Sleep Problems Questionnaire</td>
<td>Sleep Problems Questionnaire</td>
<td>Middle and late insomnia was significantly reduced at 2 weeks, no other sleep data presented.</td>
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<td>Martinotti et al. 2008</td>
<td>Quetiapine (300–800 mg)</td>
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<td>Myrick et al. 2009</td>
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<td>Zopiclone (7.5 mg) vs. Lormetazepam (1 mg)</td>
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<td>Speigel Sleep Questionnaire</td>
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<td>Le Bon et al. 2003</td>
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<td>PSG</td>
<td>PSG</td>
<td>Sleep efficiency was increased, reduced awakenings, improved non-REM sleep time and WASO.</td>
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<td>Friedman et al. 2008</td>
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<td>PSQI</td>
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</tr>
<tr>
<td>Myrick et al. 2007</td>
<td>Gabapentin (1200 mg)</td>
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<td>Actively drinking</td>
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<td>ESS</td>
<td>No difference between the two groups on ESS at Day 6.</td>
</tr>
<tr>
<td>Anton et al. 2009</td>
<td>Gabapentin(1200 mg) + flumazenil (2 mg incremental boluses on Days 1 and 2)</td>
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<td>39 days</td>
<td>0 days</td>
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<td>ESS, PSQI and ISI</td>
<td>Low alcohol withdrawal (AW) group (CIWA &lt; 7) had better sleep on active drug and high AW did better on placebo. Active medication group had low ESS scores.</td>
</tr>
</tbody>
</table>
Insomnia is very common in alcohol recovery and is a robust predictor of relapse. Insomnia also has a significant impact on quality of life and mood and could have a detrimental effect on the patient’s physical health. The literature regarding the treatment of insomnia in patients with alcohol dependence is sparse and limited by various factors (Brower, 2003).

Insomnia is defined as ‘a complaint of difficulty initiating sleep, difficulty maintaining sleep or waking up too early or sleep that is poorly restorative in nature’ and is poorly correlated to PSG findings (ICSD, 2005). Questionnaires used to measure insomnia are varied and not all of them are standardized. The studies in our systematic review used different measures of insomnia, making comparisons difficult. In addition, the studies have had varying patient populations, in different types of alcoholism treatment and in various stages of recovery. The course of sleep problems in early recovery is poorly understood and comparing studies recruiting patients who are in different stages of recovery is difficult. The studies have not uniformly measured alcohol relapse, with some studies not including any measures to identify alcohol relapse. This is a very important aspect of any study of pharmacological agents in patients with alcohol dependence and its absence seriously limits the utility of a study.

Trazodone is an agent that is most commonly used to treat sleep problems in this patient population (Friedmann et al., 2003). In a double-blind study, it did result in an improvement on the CGI. However, among sleep measures, only the WASO was improved at 28 days when compared with placebo. Another large study of trazodone showed a significant improvement in PSQI scores at 3 months and deterioration to placebo level after discontinuation. However, this study did raise some concerns regarding the potential of trazodone to decrease the number of days abstinent. This has been called into question in a retrospective analysis in a different population (Kolla et al., 2011).

Gabapentin has the advantage of being exclusively renally cleared. This could be an advantage in patients with alcohol-induced liver damage. The studies with gabapentin in this patient population have had contrasting results. An open-label trial found that gabapentin and trazodone improved sleep when compared with placebo on subjective measures. However, two well-conducted randomized control trials did not find any difference between gabapentin and placebo on PSG and subjective measures, with one study finding a non-significant trend of worsening of sleep on gabapentin. Some studies have found that gabapentin could enhance abstinence from alcohol but these have not included sleep measures (Furieri and Nakamura-Palacios, 2007).
property of gabapentin could be an effect common to other antiepileptic drugs. However, there are also concerns about the possible abuse potential of gabapentin which could limit its use in this patient population (Markowitz et al., 1997).

Non-benzodiazepine and benzodiazepine receptor agonists are among the most commonly prescribed agents for insomnia in the general population. However, there are concerns that these drugs could be abused (Hajak et al., 2003). Our search identified a single study of zopiclone used to treat insomnia in alcoholics. This study was of short duration and did not include any relapse measures. Further systematic research into the use of these agents is required before we can conclude whether they are efficacious or harmful in this patient population.

Open-label trials showed some promise for both magnesium and bright light. Their use in this group of patients should be investigated further given their low side-effect profile and abuse potential. Acamprosate, which is used to enhance sobriety in alcoholics also influences their sleep and has been shown to improve WASO and Stage 3 sleep in a placebo-controlled trial. A large, double-blind study of topiramate indicated improvements in sleep and in relapse measures, but the data regarding sleep were minimal.

CONCLUSIONS

The research into treating insomnia in alcoholics is limited. Insomnia in this patient population is an important target symptom which lends itself to both easy measurement and potential treatment. Given its association with relapse further systematic research in this area is required. Trazodone and gabapentin have been studied more frequently when compared with other agents, but the evidence to support their use is still equivocal with studies resulting in conflicting findings. Nonetheless, at this point in time, these agents have the most evidence to support their use in this population.

REFERENCES


