

Trazodone for Sleep Disturbance After Alcohol Detoxification: A Double-Blind, Placebo-Controlled Trial

Peter D. Friedmann, Jennifer S. Rose, Robert Swift, Robert L. Stout, Richard P. Millman, and Michael D. Stein

Background: Trazodone is a commonly prescribed off-label for sleep disturbance in alcohol-dependent patients, but its safety and efficacy for this indication is unknown.

Methods: We conducted a randomized, double-blind, placebo-control trial of low-dose trazodone (50 to 150 mg at bedtime) for 12 weeks among 173 alcohol detoxification patients who reported current sleep disturbance on a validated measure of sleep quality or during prior periods of abstinence. Primary outcomes were the proportion of days abstinent and drinks per drinking day over 6-months; sleep quality was also assessed.

Results: Urn randomization balanced baseline features among the 88 subjects who received trazodone and 85 who received placebo. The trazodone group experienced less improvement in the proportion of days abstinent during administration of study medication (mean change between baseline and 3 months: -0.12 ; 95% CI: -0.15 to -0.09), and an increase in the number of drinks per drinking day on cessation of the study medication (mean change between baseline and 6 months, 4.6; 95% CI: 2.1 to 7.1). Trazodone was associated with improved sleep quality during its administration (mean change on the Pittsburgh Sleep Quality Index between baseline and 3 months: -3.02 ; 95% CI: -3.38 to -2.67), but after it was stopped sleep quality equalized with placebo.

Conclusions: Trazodone, despite a short-term benefit on sleep quality, might impede improvements in alcohol consumption in the postdetoxification period and lead to increased drinking when stopped. Until further studies have established benefits and safety, routine initiation of trazodone for sleep disturbance cannot be recommended with confidence during the period after detoxification from alcoholism.

Key Words: Alcohol-Related Disorders, Sleep Disturbance, Insomnia, Trazodone.

ALCOHOLISM HAS IMPORTANT public health impact (O'Connor and Schottenfeld, 1998), and sleep disturbance is common among alcohol-dependent persons (Stein and Friedmann, 2006). Their rate of sleep problems is highest (36% to 72%) during periods of abstinence (Brower, 2003). Sleep disturbance after alcohol detoxification might contribute to relapse through abnormalities in sleep architecture (i.e. effects on rapid eye movement or slow-wave sleep) or in a general way such as through prolonged sleep latency, fatigue, depression, or anxiety (Brower, 2003; Stein and Friedmann, 2006). Ingestion of alcohol quickly corrects many of these sleep disturbances (Wagman and Allen, 1975). In this

manner, sleep problems during periods of abstinence contribute to the conditioned response to resume drinking in alcohol-dependent persons (Drummond et al., 1998; Vitiello, 1997).

Pharmacological management of sleep disturbance during early remission from alcohol dependence has been proposed to reduce relapse to alcohol (Brower, 2003). Off-label trazodone is among the most frequently prescribed agents for insomnia, even though the evidence supporting this indication is limited (Mendelson, 2005; Walsh and Schweitzer, 1999). It is the sleep agent most commonly prescribed by experts in addiction medicine for alcohol-dependent patients with sleep problems (Friedmann et al., 2003). Trazodone is commonly prescribed for alcohol-dependent patients with sleep problems because it is considered to be less habit-forming than benzodiazepine receptor agonists commonly prescribed for insomnia (Longo and Johnson, 2000). In the general population, trazodone decreases sleep latency (Ware and Pittard, 1990; Yamadera et al., 1999), improves sleep efficiency (Haffmans and Vos, 1999; Parrino et al., 1994), increases restorative slow-wave sleep (Ware and Pittard, 1990), and exerts anxiolytic effects (Liebowitz and El-Mallakh, 1989). Trazodone is well tolerated (Feighner and Boyer, 1988), appears safe in combination with alcohol (except, perhaps, in massive overdose; Goering et al., 2000), has low abuse potential

From the Program to Integrate Psychosocial and Health Services, Research Service, Providence Veterans Affairs Medical Center (PDF, RS), Providence, Rhode Island; Department of Medicine, Warren Alpert Medical School of Brown University and Rhode Island Hospital (PDF, JSR, RPM, MDS), Providence, Rhode Island; and Decision Sciences Institute, Pacific Institute for Research and Evaluation (RLS), Providence, Rhode Island.

Received for publication November 21, 2007; accepted May 7, 2008.

Reprint requests: Peter D. Friedmann, MD, MPH, Program to Integrate Psychosocial and Health Services, Research Service, Providence Veterans Affairs Medical Center, 830 Chalkstone Avenue, Providence, RI; Fax: (401) 457-3311; E-mail: pfriedmann@lifespan.org

Copyright © 2008 by the Research Society on Alcoholism.

DOI: 10.1111/j.1530-0277.2008.00742.x

(Rush et al., 1999), and induces sleep at bedtime dosing (Fabre, 1990).

Empirical evidence of trazodone's safety and effectiveness as a soporific agent in alcohol-dependent patients is limited. One small placebo-controlled trial suggested that trazodone improved sleep efficiency after alcohol detoxification (Le Bon et al., 2003). To examine whether trazodone improves drinking outcomes and sleep quality among sleep-disturbed, alcohol-dependent patients after detoxification, we performed a randomized, double-blind, placebo-controlled trial of short-term, low-dose trazodone (50 to 150 mg) at bedtime.

METHODS

Setting

The Institutional Review Boards of the Miriam Hospital and the Providence VA Medical Center, and the Clinical Trials Board of SSTAR of Rhode Island approved the Soporific Intervention to Enhance Sleep and Treatment of Alcoholism study. Recruitment occurred at a short-term inpatient detoxification program for indigent persons. The standard 3- to 5-day protocol provides chlordiazepoxide on days 1 to 3 as needed. After detoxification, patients are referred to residential or outpatient treatment; sleep management is not a typical feature of the treatment plan.

Participants

Research staff screened alcohol-dependent patients. Inclusion criteria were: alcohol as the principal substance, DSM-IV criteria for current alcohol dependence, sleep disturbance during previous periods of abstinence or a global score of 5 or greater on the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), age between 18 and 65 years, adequate contraception if female, and ability to understand instructions. Exclusion criteria were: DSM-IV criteria for current dependence on drugs other than nicotine, or Axis I disorder (subjects with "substance-induced mood disorder," or dysthymia were not excluded; First et al., 1995); current suicidality (Miller et al., 1986); psychotropic, antidepressant, anxiolytic, or antidipsogenic (naltrexone, disulfiram, and acamprosate) medication; proerectile, herbal, or sleep medication; pregnancy/lactation, ischemic heart disease, cardiac arrhythmias, priapism, or hypotension; history of obstructive sleep apnea, emphysema, or poorly controlled diabetes mellitus with nocturia 2 or more times per night; life expectancy 6 months or less; inability to identify at least 1 contact person; or no address provided for the period after discharge.

Study Allocation

Eligible subjects completed informed consent and a baseline interview. Urn randomization software allocated subjects to bedtime trazodone or identical placebo while ensuring balance by gender, depressive symptoms (19 or below vs. 20 or above on the Beck Depression Inventory-II; Beck et al., 1996), and homelessness in the previous 30 days (yes/no; Stout et al., 1994). All subjects received a sleep hygiene pamphlet (American Sleep Disorders Association, 1997). Study medication was dispensed as scored 50-mg tablets with a cap that recorded the date and time of each opening (MEMS; Apres, Union City, CA). Subjects were instructed to begin with 1 tablet 1 hour before bedtime, and titrate dosage until they reached a balance between sleep response and morning lethargy, or up to 3 tablets maximum. Study medication ceased after 12 weeks.

Participants received \$20, \$30, \$40, and \$50 for 4 respective interviews (weeks 0, 4, 12, 24), and \$5 for each daily sleep log returned weekly during the first 4 weeks (Monk et al., 1994). In addition to the outcomes described below, interviews assessed depressive

symptoms (Beck et al., 1996), and treatment services received (McLellan et al., 1992). Checklists completed at the assessments and by telephone 2-weeks after trazodone initiation monitored medical conditions, medications, and side effects.

Outcomes

Alcohol consumption was assessed with a well-established calendar method (Sobell and Sobell, 1992). During the baseline interview, subjects recalled the number of standard drinks taken on each of 90 days prior to entry into the detoxification program. Each follow-up interview assessed alcohol consumption since the previous interview. From the calendar, primary outcomes were the proportion reporting complete abstinence by the end of the study (6-month follow-up), the proportion of days abstinent (the number of nondrinking days reported during the period divided by the total number of days for which data were available), the number of drinks per drinking day (the total number of drinks reported during the period divided by the number of days on which alcohol consumption was reported), and the proportion of heavy drinking days (the number of days participants reported drinking at least 4 (women) or 5 (men) drinks during the period divided by the total number of days for which data were available). For the measure of complete abstinence, those who did not complete all follow-ups were assumed to have resumed drinking, and were therefore coded as not having achieved complete abstinence by the end of the study. Serum gamma-glutamyltransferase (GGT) was tested at each assessment point.

Global sleep quality during the past month was measured using the PSQI (Buysse et al., 1989; Carpenter and Andrykowski, 1998). *Health Status* was assessed with the 12-item Medical Outcomes Study Short Form-12 (Ware et al., 1995).

Statistical Methods

We examined potential covariates by testing interactions of study condition by time by whether participants believed they were receiving active medication, baseline commitment to abstinence, and days of psychosocial treatment (inpatient treatment, medication, Alcoholics Anonymous, relapse prevention meetings, and/or individual or group discussion) in the first month. Logistic regression was used to test for treatment differences in the proportion who achieved complete abstinence by the end of the study, controlling for the proportion of days abstinent at baseline. Mixed linear regression analyses with full information maximum likelihood (FIML) estimation compared the other drinking outcome trajectories by treatment condition across baseline, 1-, 3-, and 6-month intervals. Each model assessed linear and quadratic change over time, treatment differences at baseline, and treatment by linear and quadratic time interactions. FIML allows available data from all participants to contribute to the estimation of intercepts and slopes. An alternative procedure, multiple imputation, replaced missing values in a total of 20 data sets based on gender, age, race, treatment group, homelessness, depressive symptoms, as well as baseline and available follow-up values for the primary and secondary outcomes; results (not shown) approximated those from the FIML estimation (Schafer, 1997).

To characterize the magnitude of change over time, mean difference scores were calculated by subtracting the mean estimated change from baseline to each follow-up for the treatment group from the mean estimated change from baseline to follow-up for the placebo group. Predicted values from the mixed linear regression analyses generated these difference scores. We used a standard method to obtain Cohen's *d* treatment effect size by dividing the mean difference scores by the placebo group baseline standard deviation (SD; Cohen, 1988). Cohen's *d* values of 0.20, 0.50, and 0.80 represent small, moderate, and large effect sizes, respectively.

We calculated statistical power for a repeated measures regression model with 2 groups and attrition over time using the RMASS2

statistical power analysis program (Hedeker and Barlas, 1999). With a sample size of 173, we have power of 0.80 to detect a moderate effect size of 0.45.

RESULTS

From June 2002 to January 2006, 2437 alcohol-dependent patients were screened (Fig. 1) Among the 1922 ineligible individuals, 5.6% denied sleep problems, 45% were drug dependent, and 28% received psychotropic medication. Research assistants were unable to approach 206 individuals and

135 refused. One duplicate placebo subject was deleted post-randomization. The trazodone ($N = 88$) and placebo groups ($N = 85$) did not differ at baseline on any measured characteristic (Table 1). Subjects were primarily male and Caucasian. Mean age was 41 years. Most (73%) reported 12 or more years of education and one-third was unemployed. Participants were heavy drinkers, having been abstinent only 21% of the 90 days prior to the baseline assessment, and consuming an average of 22 drinks per drinking day during that period.

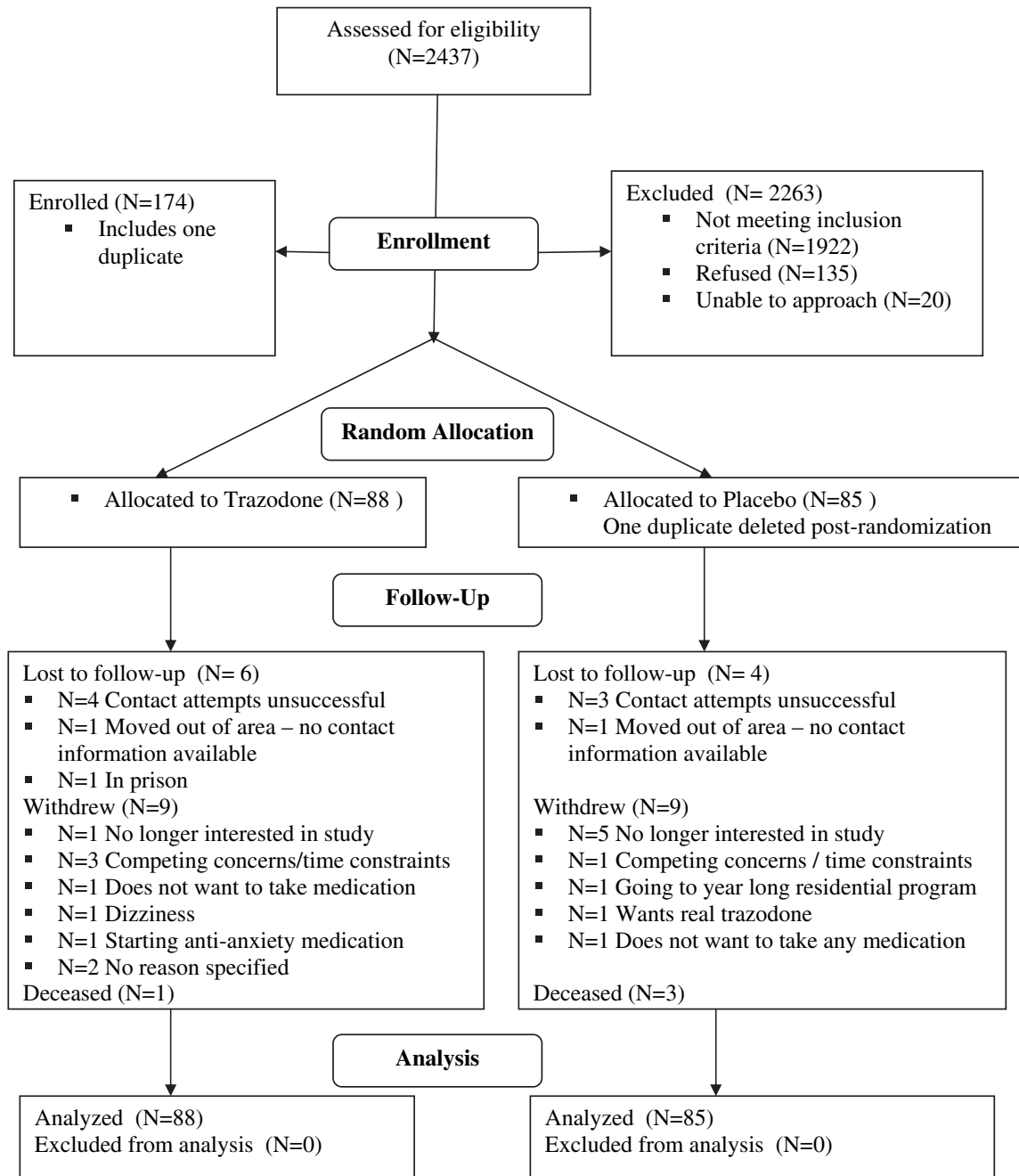


Fig. 1. CONSORT flowchart.

Table 1. Participant Characteristics at Enrollment

	Trazodone, <i>N</i> = 88	Placebo, <i>N</i> = 85	<i>p</i> -value
Age	41 (6.8)	41 (7.7)	0.80
% Female	9.8	7.5	0.36
% Caucasian	87.1	85.2	0.73
% 12+ years of school	75.6	72.6	0.63
% Unemployed	35.8	33.0	0.25
% Homeless	20.2	21.4	0.62
% Depressed	31.2	28.9	0.73
Past 3-month drinking			
Mean proportion of days abstinent	0.23 (0.29)	0.18 (0.24)	0.22
Mean drinks per drinking day	22.2 (13.8)	21.5 (11.4)	0.70
Mean proportion of heavy drinking days	71.6	78.5	0.10
% Using other medication	94.3	94.1	0.97
Serum gamma glutamyltransferase	116.9 (170.9)	144.3 (162.0)	0.35
Sleep quality	12.2 (3.6)	11.6 (3.3)	0.28
SF-12 Mental Health Composite Score	33.8 (13.0)	35.1 (11.0)	0.54
SF-12 Physical Health Composite Score	46.4 (8.1)	45.3 (8.4)	0.42

Values in parentheses represent SDs.

Of the 32 participants (18.5%) lost to follow-up, 20 (11.6%) were lost after the baseline, 9 (5.2%) after the 1-month and 3 (1.7%) after the 3-month assessment. Attrition rates did not differ by treatment group at any point. Participants who were lost to follow-up also did not differ from retained subjects on age, race, gender, education level, employment status, homelessness, depressive symptoms, or baseline measures of proportion of days abstinent, number of drinks per drinking day, sleep quality, and health status. However, participants lost to follow-up who had completed the 4-week sleep log reported taking the study medication on 62.8% (*N* = 14) of days compared with 85.5% (*N* = 106) of days for retained participants (*p* = 0.002). Participants lost to follow-up who completed a 2-week telephone check-in (*N* = 20) did not differ on the number of reported side effects, nor were they more or less likely to believe they were taking trazodone compared with retained participants.

The study conditions did not differ in their rated baseline commitment to abstinence (Hall et al., 1990) (mean ± SD: 5.54 ± 1.23 and 5.58 ± 0.92 for the trazodone and placebo groups, respectively), nor did they differ in self-reported use of other medications (either prescribed or over the counter) for help with sleep, anxiety, emotional problems, alcohol detoxification, drinking prevention, drug use stabilization, and/or to block the effects of other drugs either at baseline or follow-up. At the 1-month follow-up (McLellan et al., 1992), 72.7% reported having received informal intervention (attending at least 1 Alcoholics Anonymous meeting), 25.3% reported formal treatment, and 2% reported no intervention at all after leaving the detoxification program. Compared with the placebo group, the trazodone group tended to be more likely to attend Alcoholics Anonymous [odds ratio (OR): 1.91; 95% CI: 0.91 to 4.03; *p* = 0.09], but the 2 groups did not differ in the mean number of days of psychosocial intervention at the 1-month follow up (5.55 ± 6.23 and 5.55 ± 4.35 for the trazodone and placebo groups, respectively). No significant moderator effect over time was

detected for any of these covariates; hence, they were excluded from the mixed linear regression models for drinking and secondary outcome variables.

Drinking Outcomes

Mixed linear regression results indicated a linear increase in the proportion of days abstinent over time and a quadratic effect (Table 2), which indicates a leveling off in the rate of change over time. A linear decrease in the number of drinks per drinking days and the proportion of heavy drinking days also leveled off over time.

The trazodone group showed a smaller increase in the proportion of days abstinent at all time points relative to the placebo group (Fig. 2A); effect sizes for the estimated mean difference between groups in the change in the proportion of days abstinent were moderate from baseline to 1-month (Cohen's *d*: -0.22), 3-month (Cohen's *d*: -0.50), and 6-month (Cohen's *d*: -0.51) follow-up assessments. No clinically significant differences between the treatment groups were detected in the number of drinks per drinking day from baseline to the 1- and 3-month assessments. However, by the 6-month assessment, the trazodone group had a greater increase relative to the placebo group in the number of drinks per drinking day (Cohen's *d*: 0.41), such that the estimated number of drinks per drinking day exceeded that of the placebo group (Fig. 2B). Finally, compared with placebo, the trazodone group showed a smaller decrease in the proportion of heavy drinking days through the 3-month follow-up (Cohen's *d*: -0.53), followed by a smaller increase from 3 to 6 months (Fig. 2C).

After controlling for the proportion of days abstinent at baseline, logistic regression analyses indicated no differences in the probability of complete abstinence by study condition: only 9.1% of the trazodone group and 14.1% of the placebo group achieved complete abstinence at the 6-month follow-up (adjusted OR: 0.60; 95% CI: 0.23 to 1.56; *p* = 0.30).

Table 2. Mixed Linear Regression Results for Drinking Outcomes and Secondary Outcomes of Sleep Quality and Quality of Life

Predictor variables	Unstandardized parameter estimate (95% CI)					
	Drinking outcomes		Secondary outcomes			
	Proportion of days abstinent	Mean drinks per drinking day	Proportion of heavy drinking days	Sleep quality	SF-12 Mental Health Composite	SF-12 Physical Health Composite
Linear slope	0.28** (0.22, 0.35)	-5.18* (-8.33, -2.02)	-0.27** (-0.36, -0.21)	-3.43 (-4.18, -2.68)	7.39** (4.93, 9.84)	0.01 (-1.50, 1.52)
Quadratic slope	-0.04** (-0.05, -0.03)	0.79* (0.28, 1.30)	0.04** (0.03, 0.05)	0.47** (0.35, 0.59)	-0.97** (-1.36, -0.59)	-0.01 (-0.25, 0.23)
Baseline intervention difference	-0.03 (-0.12, 0.05)	-0.32 (-3.85, 3.20)	0.06 (-0.03, 0.14)	-0.12 (-1.15, 0.91)	-0.06 (-3.53, 3.42)	-1.10 (-3.24, 1.04)
Intervention difference in linear slope	0.06 (-0.03, 0.15)	0.68 (-3.84, 5.20)	-0.07 (-0.17, 0.02)	1.94** (0.87, 3.01)	-1.16 (-4.65, 2.32)	0.81 (-1.34, 2.96)
Intervention difference in quadratic slope	-0.01 (-0.02, 0.01)	-0.24 (-0.98, 0.49)	0.01 (-0.01, 0.02)	-0.31** (-0.48, -0.14)	0.29 (-0.26, 0.84)	-0.10 (-0.44, 0.24)

Mixed linear model including linear and quadratic change in the outcomes over time (measured at baseline 1-, 3-, and 6-month intervals), intervention difference at baseline, and interaction by linear and quadratic time interactions.

* $p < 0.01$; ** $p < 0.001$.

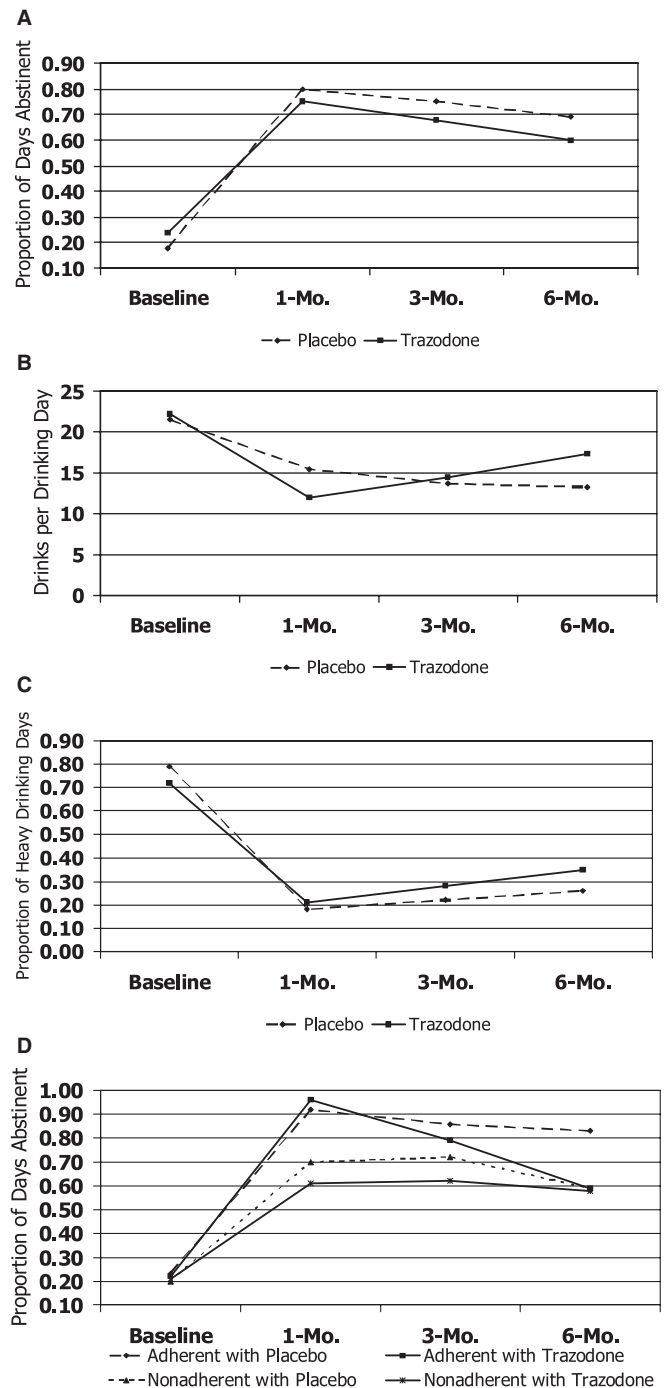


Fig. 2. (A) Trajectory of abstinence days. (B) Trajectory of drinks per drinking days. (C) Trajectory of heavy drinking days. (D) Trajectory of abstinence days by treatment adherence.

Biological Verification of Drinking

Serum GGT drawn at baseline ($N = 133$), 1 month ($N = 99$), 3 months ($N = 86$), and 6 months ($N = 95$) verified self-reports of abstinence. Participants reporting abstinence over the prior 2 weeks had a 32% decrease in GGT level from baseline, compared with a 2% decrease in GGT those who reported drinking. Participants reporting

abstinence in the prior 2 weeks had a mean GGT of 56.0 ± 71.0 compared with 129.0 ± 171.6 for those reporting any drinking ($p = 0.07$).

Secondary Outcomes

Sleep quality did not differ by treatment group at baseline, but linear and quadratic treatment effects emerged (Table 2). Sleep quality improved more for the trazodone group than the placebo group at the 1- and 3-month follow-ups, with a moderate effect size from baseline to the 1-month assessment (Cohen's d : -0.50) and a large effect from baseline to the 3-month follow-up (Cohen's d : -0.93). However, sleep quality degraded for the trazodone group between the 3- and 6-month assessments (Fig. 2D); such that sleep quality was equal for both groups at the 6-month assessment. Trazodone similarly improved mental health status modestly from baseline through 3 months (Cohen's d : -0.18), then leveled off. Physical health status did not improve over time or by treatment.

Adherence and Side Effects

Reported adherence with the medication was high during the first month (Table 3). MEMS data correlated with self-

report ($\rho = 0.34$, $p = 0.003$; $N = 76$) but suggested lower adherence. Either way adherence did not differ between groups. Participants in both groups reported taking an average of 2 pills per day over the first 4 weeks. In a mixed linear regression model, the number of pills per day increased similarly in both groups (unstandardized $\beta = 0.01$; 95% CI: -0.01 to 0.03 ; $p = 0.27$). The trazodone group tended to report more dry mouth, but other side effects were not reported more often than in the placebo group (Table 3). The 2 groups did not differ in the number of reported side effects, although those in the treatment group more often believed they were probably or definitely taking trazodone.

Participants who reported less than full adherence with study medication in the first month had had fewer days abstinent at baseline than those who reported 100% adherence (unstandardized $\beta = -0.12$; 95% CI: -0.22 to -0.02 ; $p = 0.02$) Mixed linear regression analyses examined interactions between self-reported adherence and treatment condition on the trajectories of the outcome variables. Significant interactions emerged for proportion of days abstinent (unstandardized $\beta = 0.03$; 95% CI: 0.01 to 0.04 ; $p = 0.001$; $N = 120$) and sleep quality (unstandardized $\beta = -0.20$; 95% CI: -0.39 to -0.02 ; $p = 0.029$; $N = 120$). Fully adherent subjects in both groups and partially adherent trazodone subjects experienced the greatest increases in the proportion

Table 3. Comparison of Study Medication Adherence and Side Effects by Study Condition

	Trazodone	Placebo	<i>p</i> -value
% Days took medication			
By self-report (N^a)	82.4 (63)	83.3 (57)	0.87
From MEMSCAP data (N)	43.4 (51)	37.7 (46)	0.38
Mean \pm SD number of pills per day (M^a)	1.98 ± 0.7 (63)	1.98 ± 0.6 (57)	0.97
Side effects reported, % (N^b)	3.06 ± 3.3 (64)	3.67 ± 3.5 (64)	0.27
Dry mouth	37.5 (24)	23.9 (16)	0.13
Morning drowsiness	31.3 (20)	48.5 (32)	0.05
Weight gain	23.8 (15)	28.4 (19)	0.69
Increased thirst	23.8 (15)	31.3 (21)	0.43
Daytime tiredness	21.9 (14)	36.9 (24)	0.08
Nervousness	18.8 (12)	19.4 (13)	1.0
Decreased interest in sex	14.8 (9)	10.6 (7)	0.60
Headache	14.1 (9)	23.9 (16)	0.19
Fast heartbeat	12.5 (8)	9.0 (6)	0.58
Muscle aches	12.5 (8)	14.9 (10)	0.80
Decreased appetite	11.1 (7)	10.5 (7)	1.0
Diarrhea	10.9 (7)	7.5 (5)	0.35
Dizzy on standing	9.4 (6)	6.0 (4)	0.52
Runny nose	7.8 (5)	22.7 (15)	0.03
Confusion	7.8 (5)	7.5 (5)	1.0
Difficulty concentrating	6.3 (4)	14.9 (10)	0.16
Uncontrolled hand movements	6.3 (4)	9.0 (6)	0.74
Rash	6.3 (4)	3.0 (2)	0.33
Decreased urine flow	6.3 (4)	3.0 (2)	0.43
Painful/prolonged erections	5.8 (3)	0.0 (0)	0.24
Nausea/vomiting	4.7 (3)	9.0 (6)	0.49
Breathing trouble	4.7 (3)	1.5 (1)	0.36
Blurred vision	3.2 (2)	10.5 (7)	0.17
Constipation	3.1 (2)	9.0 (6)	0.27
Swelling of hands/feet	1.6 (1)	6.0 (4)	0.37
Mean \pm SD number of side effects reported ($M^{b,c}$)	3.06 ± 3.3 (64)	3.67 ± 3.5 (64)	0.27
% Believed they were taking trazodone (N^b)	79.0 (49)	48.5 (32)	0.0003

^aFrom daily sleep log data over the first 4 weeks (total $N = 121$).

^bFrom 2-week follow-up data (total $N = 128$).

^cLog-transformed variable.

of days abstinent during the first 3 months, which declined in the 3- to 6-month interval (Fig. 2C). Among subjects who were partially adherent with placebo, abstinence days reached a plateau after the first month. Trazodone subjects and fully adherent placebo subjects experienced the greatest improvements in sleep quality during the first 3 months, which dissipated in the 3- to 6-month interval. In the partially adherent placebo group, sleep quality did not improve further after 1 month.

DISCUSSION

In this randomized trial of sleep-disturbed, alcohol-dependent patients, compared with placebo controls, the trazodone group experienced less improvement in abstinence days and an increase in the number of drinks per drinking day with cessation of the study medication. Trazodone was associated with improved sleep quality during its administration, but after it was stopped sleep quality equalized with placebo.

Few studies have evaluated trazodone as a sleep aid among newly detoxified alcohol-dependent patients. Le Bon et al. (2003) performed a double-blind, placebo-controlled clinical trial among 18 insomniac, alcohol-dependent patients who returned after a 2-week washout period after alcohol detoxification. Over 4 weeks of follow-up, polysomnographic studies revealed that trazodone reduced awakenings and enhanced sleep maintenance. Trazodone also produced subjective improvements on the Clinical Global Impression Scale. These improvements in sleep maintenance and global impression are consistent with the observation in the present study that trazodone increased subjective sleep quality.

Although the scope of this study limited the ability to perform polysomnography on all participants, the trade-off was the ability to examine trazodone's effects on alcohol-related outcomes. Despite short-term effects on sleep quality, this study dampens enthusiasm for the widespread practice of prescribing trazodone for sleep-disturbance after alcohol detoxification. We cannot discern the reason for the decrement in abstinence days in the trazodone group, but preclinical research has suggested that trazodone's metabolite *m*-chlorophenylpiperazine exerts ethanol-like effects and induces alcohol craving in recently detoxified alcoholics (Krystal et al., 1994). Similarly obscure is the reason for the exacerbation of drinking severity upon stoppage of trazodone but not placebo. One prior study suggested that trazodone can alleviate symptoms of alcohol withdrawal (Roccatagliata et al., 1980). Although causal direction is uncertain, one can speculate that postacute alcohol withdrawal symptoms including sleep disturbance, reemerged with cessation of trazodone and triggered alcohol consumption. Concern about the cessation of trazodone leading to more drinking is salient because research and clinical experience suggest that medication adherence is problematic in alcohol-dependent populations (Swift, 1999). Rebound effects on sleep disturbance, anxiety, and depressive symptoms with abrupt cessation of trazodone, and whether a slow taper might prevent them, merit further study.

The study's strengths include a randomization procedure that balanced possible baseline confounders; a double-blind, placebo-controlled design, a reasonable rate of follow-up in a socially disconnected sample; and sophisticated analyses that examined several methods for handling missing data. The study's major weaknesses are its relatively small sample size, single site, and heavy drinking population; its findings generalize best to alcohol-dependent populations requiring inpatient detoxification. In addition, little is known about the types or intensity of subsequent alcohol treatment, although days of treatment appear balanced between study conditions.

Other limitations are typical for studies of alcohol-dependent populations. Alcohol consumption outcomes derive from self-report, which provide useful estimates but might reflect underreporting (Del Boca and Noll, 2000; Sobell and Sobell, 1990); that said, GGT generally confirmed reported alcohol use. Participants' self-reports may overstate the severity of sleep problems (Currie et al., 2004), although a recent report suggests that subjective sleep measures predict recurrent drinking better than does polysomnography in this population (Conroy et al., 2006). Standardized research assessments and procedures partly mitigate measurement bias (Del Boca and Noll, 2000; Sobell and Sobell, 1990). Many subjects guessed their study allocation, but uncertainty about the accuracy of their guesses during the course of the study should limit the effect of expectation bias on their reports. Study attrition could have introduced follow-up bias, but follow-up rates did not differ by baseline characteristics and were typical for similar studies (Hansten et al., 2000). Adherence with study medication was fair; thus, the results likely reflect real-world effect rather than efficacy among alcohol-dependent populations. The extensive exclusions for medical and psychiatric comorbidities and other drug dependence further suggest that these findings generalize best to "pure" alcohol-dependent patients who are increasingly rare in medical and addiction treatment settings.

It remains possible that the combination of trazodone with antidipsogenic medications (such as naltrexone or acamprostate) or psychosocial interventions (such as relapse prevention) might improve outcomes compared with a similarly treatment-receiving placebo group; future research should examine this possibility. Nonetheless, based on current findings, we conclude that trazodone, despite a short-term effect on sleep quality, cannot be recommended with confidence for the management of sleep disturbance during the period after detoxification from alcohol dependence. Although this study is not definitive, its findings increase the probability that trazodone use or cessation might impede improvements in alcohol consumption during the early postdetoxification period. This finding contradicts clinical "common sense" that has assumed that as insomnia might be related to relapse, hypnotic treatment would decrease recurrent drinking. However, it is consistent with the traditional recommendation that alcohol-dependent patients should avoid all sedative-hypnotic medications during recovery, because of their potential to trigger relapse. In this regard, some treatment centers and

recovery groups have been known to prohibit even over-the-counter remedies such as diphenhydramine. That said, very little clinical information exists on the use of any hypnotic agent or its cessation in the alcohol-dependent population (Brower, 2003). Until further studies have established benefits and safety, the pharmacological treatment of sleep disturbance should be initiated with caution among patients in early recovery from alcohol dependence.

ACKNOWLEDGMENTS

The National Institute on Alcohol Abuse and Alcoholism (R01AA13243) supported this study (ClinicalTrials.gov Identifier, NCT00027053). Dr. Friedmann directs the Program to Integrate Psychosocial and Health Services in Chronic Disease and Disability, a Targeted Research Enhancement Program (TRP 04-179) supported by the Department of Veterans Affairs Health Services Research & Development Service, at the Providence Veterans Affairs Medical Center (Rhode Island). The authors thank the patients and staff of SSTAR of Rhode Island, G. Linda Bigden, Anthony Charuvastra, Jumi Hayaki, Debra Herman, Susan Ramsey, Kristina Richards, M. Andrea Monckeberg, and Hossein Zia. The views expressed in this article are the authors' and not necessarily those of the National Institute on Alcohol Abuse and Alcoholism or Department of Veterans Affairs.

REFERENCES

- American Sleep Disorders Association (1997) Sleep Hygiene. Behaviors that Help Promote Sound Sleep. American Sleep Disorders Association, Rochester, MN.
- Beck AT, Steer RA, Brown GK (1996) Manual for Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX.
- Brower KJ (2003) Insomnia, alcoholism and relapse. *Sleep Med Rev* 7:523–539.
- Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 28:193–213.
- Carpenter JS, Andrykowski MA (1998) Psychometric evaluation of the Pittsburgh sleep quality index. *J Psychosom Res* 45:5–13.
- Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd edn. Erlbaum, Hillsdale, NJ.
- Conroy DA, Todd AJ, Brower KJ, Strobbe S, Consens F, Hoffmann R, Armitage R (2006) Perception of sleep in recovering alcohol-dependent patients with insomnia: relationship with future drinking. *Alcohol Clin Exp Res* 30:1992–1999.
- Currie SR, Malhotra S, Clark S (2004) Agreement among subjective, objective, and collateral measures of insomnia in postwithdrawal recovering alcoholics. *Behav Sleep Med* 2:148–161.
- Del Boca FK, Noll JA (2000) Truth or consequences: the validity of self-report data in health services research on addictions. *Addiction* 95(Suppl. 3):S347–S360.
- Drummond S, Gillin JC, Smith TL, DeModena A (1998) The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcohol Clin Exp Res* 22:1796–1802.
- Fabre LF (1990) Trazodone dosing regimen: experience with single daily administration. *J Clin Psychiatry* 51:23–26.
- Feighner JP, Boyer WF (1988) Overview of USA controlled trials of trazodone in clinical depression. *Psychopharmacology* 95:S50–S53.
- First M, Spitzer R, Williams J, Gibbons M (1995) *Structured Clinical Interview for DSM-IV – Patient Version*. NY State Psychiatric Institute, New York.
- Friedmann PD, Herman DS, Freedman S, Lemon SC, Ramsey S, Stein MD (2003) Treatment of sleep disturbance in alcohol recovery: a national survey of addiction medicine physicians. *J Addict Dis* 22:91–103.
- Goeringer KE, Raymon L, Logan BK (2000) Postmortem forensic toxicology of trazodone. *J Forensic Sci* 45:850–856.
- Haffmans PM, Vos MS (1999) The effects of trazodone on sleep disturbances induced by brofaromine. *Eur Psychiatry* 14:167–171.
- Hall SM, Havassy BE, Wasserman DA (1990) Commitment to abstinence and acute stress in relapse to alcohol, opiates, and nicotine. *J Consult Clin Psychol* 58:175–181.
- Hansten ML, Downey L, Rosengren DB, Donovan DM (2000) Relationship between follow-up rates and treatment outcomes in substance abuse research: more is better but when is “enough” enough? *Addiction* 95:1403–1416.
- Hedeker D, Barlas S (1999). *RMASS2: Repeated Measures with Attrition: Sample Sizes for 2 Groups* [Computer software]. University of Illinois at Chicago, Division of Epidemiology & Biostatistics, Chicago, IL.
- Krystal JH, Webb E, Cooney N, Kranzler HR, Charney DS (1994) Specificity of ethanollike effects elicited by serotonergic and noradrenergic mechanisms. *Arch Gen Psychiatry* 51:898–911.
- Le Bon O, Murphy JR, Staner L, Hoffmann G, Kormoss N, Kentos M, Dupont P, Lion K, Pelc I, Verbank P (2003) Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 23:377–383.
- Liebowitz NR, El-Mallakh RS (1989) Trazodone for the treatment of anxiety symptoms in substance abusers. *J Clin Psychopharmacol* 9:449–451.
- Longo LP, Johnson B (2000) Treatment of insomnia in substance abusing patients. *Psychiatr Ann* 28:154–159.
- McLellan AT, Alterman AI, Cacciola J, Metzger D, O'Brien CP (1992) A new measure of substance abuse treatment. Initial studies of the Treatment Services Review. *J Nerv Ment Dis* 180:101–110.
- Mendelson WB (2005) A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry* 66:469–476.
- Miller I, Bishop S, Norman W, Dow M (1986) The modified scale for suicidal ideation: reliability and validity. *J Consult Clin Psychol* 54:724–725.
- Monk TH, Reynolds CF, Kupfer DJ, Buysse DJ, Coble PA, Hayes AJ, MacHen MA, Perie SR, Ritenour AM (1994) *The Pittsburgh Sleep Diary*. *J Sleep Res* 3:111–120.
- O'Connor PG, Schottenfeld RS (1998) Patients with alcohol problems. *N Engl J Med* 338:592–602.
- Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, Terzano MG (1994) Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. *Psychopharmacology (Berl)* 116:389–395.
- Roccatagliata G, Albano C, Maffini M, Farelli S (1980) Alcohol withdrawal syndrome: treatment with trazodone. *Int Pharmacopsychiatry* 15:105–110.
- Rush CR, Baker RW, Wright K (1999) Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacology (Berl)* 144:220–233.
- Schafer JL (1997) *Analysis of Incomplete Multivariate Data*. Chapman & Hall, Boca Raton, FL.
- Sobell LC, Sobell MB (1990) Self-report issues in alcohol abuse: state of the art and future directions. *Behav Assess* 12:77–90.
- Sobell LC, Sobell MB (1992) Timeline followback: a technique for assessing self-reported alcohol consumption, in *Measuring Alcohol Consumption: Psychological and Biological Methods* (Litten RZ, Allen J eds), pp 41–72. Humana Press, New Jersey.
- Stein MD, Friedmann PD (2006) Disturbed sleep and its relationship to alcohol use. *Subst Abuse* 26:1–13.
- Stout RL, Wirtz PW, Carbonari JP, Del Boca FK (1994) Ensuring balanced distribution of prognostic factors in treatment outcome research. *J Stud Alcohol Suppl* 12:70–75.
- Swift RM (1999) Medications and alcohol craving. *Alcohol Res Health* 23:207–213.

- Vitiello MV (1997) Sleep, alcohol and alcohol abuse. *Addict Biol* 2:151–158.
- Wagman A, Allen RP (1975) Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. *Adv Exp Med Biol* 59:453–466.
- Walsh JK, Schweitzer PK (1999) Ten-year trends in the pharmacological treatment of insomnia. *Sleep* 22:371–375.
- Ware JE, Kosinski M, Keller SD (1995). *How to Score the SF-12 Physical & Mental Health Summary Scales*, 2nd edn. The Health Institute, New England Medical Center, Boston, MA.
- Ware JC, Pittard JT (1990) Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. *J Clin Psychiatry* 51(Suppl.):18–22.
- Yamadera H, Suzuki H, Nakamura S, Endo S (1999) Effects of trazodone on polysomnography, blood concentration and core body temperature in healthy volunteers. *Psychiatry Clin Neurosci* 53:189–191.