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TRAZODONE FOR SLEEP DISTURBANCE DURING METHADONE MAINTENANCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract

BACKGROUND—To test whether trazodone, one of the most commonly prescribed medications for treatment of insomnia, improves subjective and/or objective sleep among methadone-maintained persons with sleep complaints, we performed a randomized, double-blind, placebo-controlled trial with six month follow-up.

METHODS—From eight methadone maintenance programs in the northeastern United States, we recruited 137 persons receiving methadone for at least one month who reported a Pittsburgh Sleep Quality Index (PSQI) score of six or higher. Two-night home polysomnography (PSG) was completed at baseline and one month later, with morning surveys and urine drug toxicologies. Interviews assessed sleep over the past 30 days at baseline and 1-, 3-, and 6- month follow-ups.

RESULTS—Participants averaged 38 years of age, were 47% male, and had a mean PSQI total score of 12.9 ($\pm$ 3.1). At baseline, intervention groups did not significantly differ on 10 PSG-derived objective sleep measures and 11 self-reported measures. Over 88% (n = 121) of participants completed the PSG at 1-month. Without adjusting p-values for multiple comparisons, only 1 of 21 sleep measure comparisons was statistically significant ($p < .05$). The effect of trazodone on mean PSQI scores during the six-month follow-up was not statistically significant ($p = .10$). Trazodone neither significantly increased nor decreased illicit drug use relative to placebo.

CONCLUSIONS—Trazodone did not improve subjective or objective sleep in methadone-maintained persons with sleep disturbance. Other pharmacologic and non-pharmacologic treatments should be investigated for this population with high rates of insomnia.

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Keywords

Trazodone; Methadone; Opiate dependence; Sleep

1.0 INTRODUCTION

More than three quarters of persons receiving methadone maintenance therapy (MMT), an effective treatment for opioid dependence, report sleep complaints (Oyefeso et al., 1997; Peles et al., 2006; Stein et al., 2004). Neither duration nor dose of methadone treatment is associated with subjective sleep disturbance, but severity of sleep symptoms in methadone-maintained persons has been associated with comorbid psychiatric disorders, chronic pain, and other drug use (Peles et al., 2006; Stein et al., 2004). Subjective sleep complaints in this population have been corroborated by polysomnographic studies by our group and others (Sharkey et al., 2009; Wang and Teichtahl, 2007), demonstrating sleep abnormalities such as decreased REM and decreased slow wave sleep. Methadone patients also have high rates of sleep disordered breathing, both central sleep apnea and obstructive sleep apnea, although neither accounts for complaints of disturbed sleep (Sharkey et al., 2010; Teichtahl et al., 2001; Wang et al., 2005).

There are several postulated mechanisms to explain insomnia among methadone patients. Opioids decrease acetylcholine release in some brain regions, such as the pontine reticular formation, decreasing REM sleep (Lydic and Baghdoyan, 2005). Acute opioid administration suppresses inhibitory GABAergic transmission in the dorsal raphe nucleus, promoting wakefulness (Watson et al., 2007). A third potential pathway to sleep disruption in MMT patients is opioid-induced reduction of the nucleoside adenosine in the basal forebrain (Nelson et al., 2009). The possibility that lower levels of adenosine – a neurochemical modulator of the homeostatic drive for sleep – may be responsible for sleep disturbances in MMT patients is further supported by the observation that MMT patients fail to show typical recovery responses after a sleep-deprivation challenge (Trksak et al., 2010).

Methadone patients with sleep disturbance obtain, on average, less than 6 hours of sleep (Sharkey et al., 2010). These short sleep durations represent sleep restriction that could manifest in daytime impairment (Balkin et al., 2008), lower methadone treatment adherence, and increased relapse risk through behavioral and physiologic mechanisms. Poor sleep efficiency has been associated with daytime symptoms such as cognitive difficulties and risk of injury and motor vehicle accidents (National Sleep Foundation, 2009; Solowij et al., 2002). More than half of MMT patients report use of both illicit drugs and approved medications to help with sleep (Burke et al., 2008; Peles et al., 2006). Yet those who report using illicit drugs also report more sleep-related problems and greater functional impairment (Burke et al., 2008).

Trazodone, a triazolopyridine derivative, chemically and pharmacologically distinct from other antidepressants, is the second most commonly prescribed medication for treatment of insomnia in the United States (Mendelson et al., 2004). Due to its sedating qualities, it has been prescribed off-label for insomnia at sub-therapeutic antidepressant doses of 100mg or less (Walsh and Schweitzer, 1999). Small open label trials have reported that trazodone affects objective measures of sleep, reducing REM sleep and increasing slow wave sleep (SWS) (Montgomery et al., 1983). Improved sleep latency, sleep efficiency, and sleep duration have been demonstrated in depressed patients with insomnia (Saletu-Zyhlarz et al., 2002) and in antidepressant-induced insomnia (Nierenberg et al., 1994).

Trazodone is often prescribed to persons with drug and/or alcohol problems (Friedmann et al., 2003). Trazodone is popular among substance abuse treatment providers because it is non-addictive, available as a generic agent, has no restrictions on prescription duration, and is not associated with abuse liability, high overdose risk, or life-threatening withdrawal syndromes (Crome and Ali, 1986; de Jonghe and Swinkels, 1992).

Two placebo-controlled studies of trazodone for alcohol dependent persons—another substance use disorder associated with sleep problems—have been promising in terms of sleep outcomes (Friedmann et al., 2008; Le Bon et al., 2003). These trials enrolled sleep-disturbed alcohol-dependent patients following detoxification. In a small study in which sleep was measured with polysomnography, trazodone reduced awakenings and enhanced sleep maintenance (Le Bon et al., 2003). However, in a larger trial, trazodone was associated with improved subjective sleep quality (Pittsburgh Sleep Quality Index) over three months, but produced an increase in the number of drinks per drinking days and a lowering of abstinence after its cessation (Friedmann et al., 2008). Trazodone has never been tested in opioid dependent persons.

In the current randomized, double-blind, placebo-controlled clinical trial, we tested whether trazodone improves subjective judgment of sleep (in particular, total sleep time (TST) and global sleep quality), and/or objective sleep (in particular, TST and sleep efficiency) measures among methadone-maintained persons with sleep complaints.

2.0 METHODS

2.1 Participants

Participants were recruited from eight methadone maintenance treatment (MMT) clinics in the Providence, Rhode Island metropolitan area using posted flyers (“Having trouble sleeping?”). Interested MMT patients were screened by study staff at their respective clinics during dosing hours. The study was approved by the Institutional Review Board of Butler Hospital.

Eligibility criteria included a Pittsburgh Sleep Quality Index (PSQI) score of six or higher (Buysse et al., 1989), indicating clinically significant insomnia, the ability to speak, read, and understand English and plans to continue MMT for at least 6 months. Exclusion criteria included: symptoms suggestive of schizophrenia, psychotic disorder, or gross cognitive dysfunction; current use (last 30 days) of trazodone or psychotropic medications; inability or refusal to terminate the use of proerectile agents; pregnancy, lactation, or inability or refusal to use birth control throughout the study period for female participants; and unstable housing such as a shelter or halfway house.

Between January 2006 and November 2009, 442 individuals completed the study eligibility screen. The most common reasons for ineligibility (n=235) included: unstable housing (n=96); current use of contraindicated medication (n=50), plans to leave MMT in less than 6 months (n=47); symptoms suggestive of schizophrenia, psychotic disorder, or gross cognitive dysfunction (n=43); and PSQI score lower than 6 (n=40). Seventy eligible individuals refused study participation. The remaining 137 individuals consented to enroll in the study (Figure 1).

2.2 Study Schedule

Participants agreed to four assessments over 6 months (baseline, 1-, 3-, and 6-months) performed at their methadone clinic. Two-night home sleep studies were performed starting the day of the baseline assessment and the 1-month assessment, with a brief questionnaire performed in the morning following each sleep study night (see Kurth, et al., 2009 for

details). At each assessment, participants were asked to complete daily sleep diaries beginning the week prior to the sleep studies. Participants were reimbursed for all assessments and each completed home sleep study night. After the baseline assessment, participants were randomized to one of the two study groups. Research staff was blinded to treatment condition.

2.3 Treatment

Participants were randomized to trazodone 50mg or placebo using computer generated random numbers without stratification by background characteristics. The blind was maintained by a staff member not otherwise associated with the current project who had no contact with participants. Study medication was provided in identical capsule form, and ninety capsules were provided to participants the morning after the second night of the baseline polysomnography. Research staff instructed participants to take 1–3 capsules as needed at bedtime, so that participants could self-titrate to an effective dose ranging from 50–150mg. After the 1-month follow up assessment, participants were given an additional 180 pills with the same instructions. Adherence to the medication protocol was monitored through pill counts at follow up visits, self report in participant sleep diaries, and on the questionnaire following home sleep studies.

We did not provide any behavioral therapy to address sleep problems. All participants were given a sleep hygiene brochure (American Academy of Sleep Medicine, 1997) once at the completion of the baseline interview.

2.4 Polysomnography

Participants were scheduled for two consecutive nights of baseline unattended polysomnography, and two consecutive nights at the 1-month follow up. PSG recordings were made using portable recorders (Compumedics, Charlotte, NC, USA). Not all participants were able to complete two sleep study nights; when two nights were completed, we used data from the longer PSG night (Kurth et al., 2009). Researchers set up the study in the participant's home before his or her usual bedtime on the evening of PSG. Before set-up, participants performed a breathalyzer (BAL) and provided a urine sample for toxicological analysis (6-Panel KO Autosplit Drug Test Cup; Drug Detection Devices, Ltd., Alpharetta, GA). Research assistants were instructed not to continue if a participant exhibited symptoms of intoxication; no participant had BAL > .02 or behavior suggesting acute intoxication on the PSG night.

Objective sleep was measured using standard PSG techniques as previously described (Kurth et al., 2009; Sharkey et al., 2010; Sharkey et al., 2009) including electroencephalography, electrooculography, and electromyography. Respiration was monitored with nasal/oral airflow, nasal pressure transducers, pulse oximetry, and intercostal and abdominal respiration belts. EKG was monitored with electrodes on the chest. Researchers started the recordings and viewed signals for good quality before leaving participants' homes; they returned the following morning to collect equipment and administer the morning questionnaire, on which participants reported bedtime, wake up time, an estimate of TST, and number of awakenings, sleep quality, and use of study medication.

PSG was scored in 30-second epochs according to Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968) by a trained scorer who maintained > 90% concordance with a second trained scorer. The following measures were derived: *Sleep period time*, defined as the interval between the first and last epoch scored as sleep; *Minutes of total sleep time* (TST); *Sleep efficiency*, calculated by dividing TST by sleep period time $\times 100$; *Apnea/*

Hypopnea index (number of apneas and hypopneas per hour of sleep); and *Arousal index* (number of electroencephalographic arousals per hour of sleep).

2.5 Measures

Questionnaires included demographics, measures of drug and alcohol use and dependence, addiction severity, psychological symptoms, medical conditions, and medications. The baseline interview included a checklist of symptoms of potential medication side effects to be compared to an identical list completed at follow-ups.

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to assess sleep quality over the past 30 days at the 1-, 3- and 6-month follow-ups. Participants completed a self-report daily morning sleep diary during the week preceding PSG in which they recorded bedtime, time to fall asleep, number of awakenings, time awake during the night, wake up time, and a subjective measure of “feeling rested.” *Diary time in bed* was calculated as the duration between bedtime and wake up time. *Diary total sleep time (TST)* was calculated by subtracting sleep latency and time awake during the night from *Diary time in bed*. *Diary sleep efficiency* was calculated by dividing *Diary TST* by *Diary time in bed* $\times 100$. Each sleep measure was averaged over the reported days. Most participants had 7 days of complete diary data; the average number of completed diary days was 6.2 (± 1.2 days). We included participants with 3–7 diary days because sleep diary analyses in other populations indicate that reliable sleep estimates can be obtained with ≥ 3 days of data (Thomas and Burr, 2009).

2.6 Analytical Methods

T-tests and chi-square tests are used to compare intervention groups with respect to demographic characteristics, baseline patterns of substance use, objective and subjective measures of sleep quality, adherence to study prescribed medications, and loss to follow-up. In this intent-to-treat analysis, change in sleep quality between baseline and 1-month was assessed by calculating change (gain) scores (month 1 minus the baseline estimate) for each evaluated sleep parameter. We report mean change in sleep parameters for each intervention group and the t-test for differences in mean change.

Our study was sufficiently powered ($\beta = .83$) to detect moderate effect sizes for our primary outcome comparison, as defined by Cohen (1988). To provide a sense of the substantive magnitude of intervention group differences we report Cohen’s standardized effect size, d , for all sleep indices. We used ordinary least squares (OLS) regression to estimate the effects of intervention on change in sleep quality parameters adjusting for years of age, gender (1 if male), and race (1 if Caucasian).

In ancillary analyses, we used the *ice* and *mim* programs (Royston, 2007) in Stata to generate and analyze 10 imputed data sets to determine if our results were sensitive to subject attrition. These analyses were limited to the primary subjective outcomes of PSQI global scores, and total sleep time and sleep efficiency as assessed by polysomnography. Additionally, we replicated the primary outcomes analysis but limited the analysis sample to participants who reported taking their prescribed study medication (either trazodone or placebo) on the night of their 1-month polysomnography. Additionally, we used mixed linear and logistic regression models to analyze the PSQI data that were collected at all follow-up assessments.

3.0 RESULTS

3.1 Baseline Participant Characteristics and Follow-Up

Participants averaged 38.2 (± 8.6) years of age, 64 (46.7%) were male, 117 (85.5%) were non-Hispanic Caucasian (Table 1). The mean PSQI total score was 12.9 (± 3.06), 14.1% had apnea index scores ≥ 5 , and 27.4% had been enrolled in MMT < 90 days. Mean methadone dose at baseline was 100.3 (± 52.6) mg. More than 90% reported cigarette use; on average, participants reported smoking 14.4 (± 8.5) cigarettes per day. In the 30 days prior to baseline, 22.6%, 32.1%, 25.5%, 23.4%, and 32.9% reported using any alcohol, opioids, sedatives, cocaine, or cannabis, respectively. Intervention groups did not differ significantly ($p > .05$) on any of the baseline characteristics described in Table 1 or in attrition at month 1 ($\chi^2 = 1.20$, $p = .27$).

Over 88% ($n = 121$) of participants completed the PSG at 1-month. Between group differences in use of prescribed study medications ($\chi^2 = 0.60$, $p = .44$) at 1-month were not significant. Ninety-three participants (79.5%) reported they had used the prescribed study medication on the night of the 1-month PSG.

3.2 Baseline Subjective and Objective Sleep Measures

In Table 2 we compare intervention groups on 10 objective sleep measures derived from PSG and 11 self-reported measures assessed as part of the baseline interview, morning surveys, and sleep diaries prior to receiving study medication. Most between group differences were small and did not approach statistically significant levels. Compared to those randomized to trazodone, placebo group participants reported significantly higher mean sleep quality ratings on the morning survey ($t = 2.11$, $p = .04$) and restfulness ratings on the sleep logs ($t = 1.96$, $p = .05$) at baseline.

3.3 Changes in Objective and Subjective Sleep Measures: Baseline to One-Month

Table 3 gives baseline means, follow-up means, and change in mean objective and subjective sleep parameters by intervention group. For example, between baseline and 1-month, mean PSQI scores decreased 2.9 and 3.9 points among those randomized to placebo and trazodone, respectively; the difference in mean change was not significant ($p = .145$). As a measure of substantive effect size independent of the scale on which parameters were measured we also calculated Cohen's standardized effect, d . Without adjusting p -values for multiple comparisons, only 1 of 23 comparisons reported in Table 3 was statistically significant at the .05 level. As reported on the morning survey, subjective total sleep time increased by about 45.5 minutes among those receiving trazodone compared to 9.8 minutes in the placebo group ($t = -1.99$, $p = .05$); the standardized effect size was .373.

As an auxiliary analysis we used OLS regression to estimate the effect of trazodone on change in sleep parameters, adjusted for years of age, gender (1 if male), and race (1 if Caucasian). The adjusted effect of trazodone on change in total sleep time, as reported on the morning survey, was not significant ($b = 0.48$, $t = -1.49$, $p = .14$). P -values for all other between group comparisons reported in Table 3 exceeded .10 and the substantive magnitude of trazodone effects, as indicated by Cohen's d , were generally small to very small. Adjusting for age, gender, and race, the trazodone effects were otherwise consistent with the results reported in Table 3.

Analysis of toxicology data indicated that intervention groups did not differ significantly with respect to use of opioids ($\chi^2 = 0.86$, $p = .35$), cocaine ($\chi^2 = 0.8$, $p = .35$), cannabinoids ($\chi^2 = 0.74$, $p = .39$), or benzodiazepines ($\chi^2 = 0.75$, $p = .39$) on the morning immediately following either the baseline or the 1-month PSG night. Additionally, no significant

differences were found with respect to self-reported caffeine ($\chi^2 = 0.01$, $p = .92$) or cigarette use ($\chi^2 = 1.28$, $p = .26$) in the 4 hours prior to the PSG. We also found no significant between group differences with respect to change in daily frequency of alcohol use ($t_{132} = -0.51$, $p = .61$), opioids ($t_{132} = 0.16$, $p = .87$), cocaine ($t_{132} = -1.06$, $p = .29$), benzodiazepine ($t_{132} = -1.17$, $p = .24$), or cannabis use ($t_{132} = 1.21$, $p = .23$) between baseline and 1-month.

While most sleep outcomes were assessed only at 1-month, PSQI scores were available at 3- and 6-month assessments. To further evaluate trazodone effects, we used a mixed effects linear regression model that included baseline PSQI score, age, gender, ethnicity, and the linear effect of time as covariates. The coefficient giving the effect of trazodone on mean PSQI scores during follow-up was not statistically significant ($b = -.82$, $z = -1.63$, $p = .102$). We also dichotomized PSQI total scores at the suggested threshold with scores of 6 or higher screening positive for sleep disorder; using mixed-effects logistic regression with the covariates described above the intervention arms did not differ significantly with respect to the likelihood of having sub-threshold PSQI scores at follow-up ($OR = 2.10$, $z = 1.64$, $p = .101$).

To assess sensitivity to attrition we used multiple imputation (10 imputed data sets) to generate and analyze primary outcomes of PSQI global scores, and total sleep time and sleep efficiency as assessed by PSG. Results were consistent with those presented here.

3.4 Changes in Objective and Subjective Sleep Measures Among Persons Reporting Medication Adherence

We replicated the analysis reported in Table 3, but restricted the sample to the 47 placebo and 46 trazodone participants who reported taking the prescribed study medications on the night during which the PSG and morning surveys were completed at 1-month follow-up. Results based on polysomnography were generally consistent with those reported in Table 3. Some differences on subjective sleep quality measures require mention, however. Between group differences in the reduction in global PSQI scores were substantively larger ($d = -.39$) and marginally significant ($t_{91} = -1.87$, $p = .07$); mean reductions were 3.0 and 4.5 among those randomized to placebo and trazodone, respectively. On the morning survey, trazodone recipients reported an average reduction of .89 awakenings per night compared with a reduction of .46 among placebo recipients ($t_{91} = -1.90$, $p = .06$); the corresponding standardized effect was .401. Those randomized to trazodone also reported significantly improved ($t_{91} = -2.37$, $p = .02$) restfulness ratings on the morning survey ($d = .50$). Directionally consistent but somewhat weaker trends were observed on the sleep logs. The average number of awakenings decreased 1.23 times per night for the trazodone group compared with .72 times per night for the placebo group ($t_{51} = -1.42$, $p = .16$); the average restfulness rating increased .43 units among those randomized to trazodone but decreased .10 units among placebo recipients ($t_{51} = 1.86$, $p = .069$). The standardized effects were $-.409$ and $.533$ for number of awakenings and restfulness ratings, respectively.

3.5 Side Effects by Intervention Condition

In Table 4 we report the number and percentage of participants who reported an increase in frequency of 16 physical symptoms between baseline and 1- and 3-month assessments. Between baseline and 1-month, participants randomized to trazodone were significantly more likely to report increased thirst or dry mouth ($p = .001$) and decreased appetite ($p = .04$). Significant ($p = .02$) differences with respect to increased thirst or dry mouth only persisted to the 3-month follow-up.

4.0 DISCUSSION

In the first randomized, placebo-controlled trial testing a sleep medication for opioid dependent persons, a population with extraordinarily high rates of sleep problems, we found that trazodone did not improve subjective or objective sleep in methadone-maintained persons with sleep disturbance. There are several possible explanations for this negative finding.

First, although trazodone is among the most commonly prescribed medication for insomnia, there is little empirical support for its clinical efficacy. Even in the general population, where it is widely used, there are few randomized clinical trials examining trazodone's effects. In the only placebo-controlled trial of trazodone for primary insomnia, 306 persons were treated with 50mg per night for 2 weeks (Walsh et al., 1998). Trazodone demonstrated statistically significant improvement in sleep duration and sleep quality during week 1, but not week 2, and objective measures of sleep were not collected. Most other studies of trazodone have examined the effects in depressed populations, enrolled small numbers of patients, were not placebo-controlled, did not exceed 6 weeks in duration, and did not show consistent objective efficacy (Mendelson, 2005).

It is possible that trazodone had no significant effect on past-month subjective sleep (PSQI scores) among methadone patients because overall medication adherence was low. We do not have a daily measure of or biological confirmation of medication adherence, but because participants reported significant difficulty with insomnia, we expected the level of adherence to their sleeping medication to be high. When we performed a sub-analysis of the 93 persons (68%) who reported medication use (average dose=92.6mg) on the night of the follow-up PSG, those randomized to trazodone reported fewer awakenings and significantly improved restfulness ratings on the morning survey ($d = .42$ and $d = .50$ respectively). These findings suggest trazodone, when used, may have modest effects on subjective sleep (although the statistical significance is limited by multiple comparisons). These subjective improvements were not corroborated by PSG improvements. Our findings might have been more robust if a higher dose of trazodone was used and/or if our sample size was larger. One dose-finding study suggests that 100 mg is more effective than 50 mg among depressed patients with sleep disturbance (Mashiko et al., 1999). But higher doses are associated with more frequent side effects, including drowsiness and impaired next-day function that lead to discontinuation (Ather et al., 1985).

The third explanation for our negative findings may be that trazodone does not specifically target any of the postulated mechanisms of sleep disturbance in opioid dependent persons. Indeed, the mechanism of action of trazodone's sedating effects is not known.

Finally, methadone-maintained persons have many ongoing risks for the chronic insomnia they experience. Methadone-maintained individuals have high rates of depressive symptoms and chronic pain that may interfere with sleep. Nine in ten participants smoked cigarettes, most used caffeine, and a minority used other illicit drugs (e.g., cocaine) that interfere with sleep. Ongoing use of illicit drugs that affect sleep reflects the real-world experience of persons in methadone maintenance treatment, and suggests the difficulty of demonstrating an efficacious treatment for insomnia.

Importantly, neither urine toxicological data from the 1-month PSG night (reflecting drug use over the past several days) nor self-reports during the first month of treatment suggest that trazodone is systematically increasing or decreasing illicit drug use relative to placebo in this population.

This study's strengths include a randomized, double-blind, placebo-controlled design, an excellent rate of follow-up that did not differ between groups in a vulnerable population, and the inclusion of both subjective and objective sleep measures. We have previously published a comparison of different approaches to assessing sleep disturbance in this population (Sharkey et al., 2011). In addition, our study was sufficiently powered to detect moderate effect sizes; however, the magnitude of between group differences we observed was generally small. The study is limited by participants' self-reports that may overstate the severity of sleep problems, and our lack of measures regarding the effects of sleep disturbance on daytime function.

Despite the absence of supporting data and its off-label use for the treatment of insomnia, trazodone remains popular for persons with drug and alcohol disorders because of its lack of restriction on prescription duration and its perceived absence of risk. Our data demonstrate that trazodone is well-tolerated in this population and appears safe in combination with methadone. Besides dry mouth, other side effects were not reported more often in the trazodone group than in the placebo group. We did not perform electrocardiograms, but torsades de pointes, characterized by prolongation of the QTc has been observed in rare patients receiving trazodone (Mazur et al., 1995), although the majority of studies have found that trazodone did not have a significant or lasting effect on QT interval (Mendelson, 2005). Torsades has also been reported in persons receiving methadone (Demarie et al., 2011; George et al., 2008), suggesting future studies that include high doses of trazodone should perform electrocardiograms.

Sleep restriction reduces physical and emotional well-being (Haack and Mullington, 2005). Sleep disruption lowers pain thresholds (Baghdoyan, 2006; Roehrs et al., 2006) and intensifies pain, a chronic problem for many methadone patients (Rosenblum et al., 2003). We speculate that shortened sleep and daytime sleepiness might impair engagement with treatment leading to continued drug use or relapse. The symptoms and consequences of insomnia in MMT patients merit efficacious treatment.

Trazodone, as a stand-alone pharmacotherapy, is not that treatment, based on this first study of an intervention for methadone patients with sleep disturbance. Other pharmacologic and non-pharmacologic treatments should be investigated for this population. Attention to common co-morbid conditions that may contribute to sleep disturbance in methadone patients, such as mental health disorders, chronic pain, and ongoing substance use, should be emphasized. Combined medication and behavioral therapy protocol have been efficacious in other populations (Morin et al., 2009) and warrant testing here. If the current widespread use of trazodone continues without these considerations, providers should expect high failure rates.

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Figure 1.
Enrollment

Table 1

Background Characteristics by Intervention Group (n = 137).

	Mean (SD)			t (p =)
	Total (n = 137)	Placebo (n = 68)	Trazodone (n = 69)	
Years Age	38.2 (8.6)	38.5 (8.7)	38.0 (8.8)	0.34 (.76)
PSQI Total Score	12.9 (3.1)	12.8 (3.0)	13.1 (3.1)	-0.60 (.55)
Cigarettes / Day	14.4 (8.5)	14.7 (8.57)	14.1 (8.4)	0.38 (.71)
Methadone Dose (mg)	100.3 (52.6)	98.1 (54.2)	102.4 (51.4)	-0.46 (.65)
	n (%)			χ^2 (p =)
Gender (Male)	64 (46.7%)	29 (42.7%)	35 (50.7%)	0.34 (.90)
Ethnicity				
Caucasian	117 (85.4%)	61 (89.7%)	56 (81.2%)	3.86 (.15)
African-American	10 (7.3%)	2 (2.9%)	8 (11.6%)	
Hispanic	10 (7.3%)	5 (7.4%)	5 (7.3%)	
Employed Part or Full-Time	46 (33.6%)	22 (32.4%)	24 (34.8%)	0.09 (.76)
New to MMT (< 90 days)	37 (27.4%)	18 (27.3%)	19 (27.5%)	0.00 (.97)
Current Rx Sleep Meds (Yes)	6 (4.4%)	3 (4.4%)	3 (4.4%)	0.00 (.99)
Recent Alcohol Use (Yes)	31 (22.6%)	16 (23.5%)	15 (21.8%)	0.06 (.80)
Recent Heroin Use (Yes)	28 (20.4%)	15 (22.1%)	13 (18.8%)	0.22 (.64)
Recent Other Opiate Use (Yes)	20 (14.6%)	10 (14.7%)	10 (14.6%)	0.00 (.97)
Recent Sedative Use (Yes)	35 (25.6%)	17 (25.0%)	18 (26.1%)	0.02 (.88)
Recent Cocaine Use (Yes)	32 (23.4%)	18 (26.5%)	14 (20.3%)	0.73 (.39)
Recent Cannabis Use (Yes)	45 (32.9%)	23 (33.8%)	22 (31.9%)	0.06 (.81)
Study Med MO1 PSG (Yes)	93 (79.5%)	47 (82.5%)	46 (76.7%)	0.60 (.44)
Completed Baseline PSG (Yes)	131 (95.5%)	63 (92.7%)	68 (98.6%)	2.85 (.09)
Completed MO 1 PSG (Yes)	121 (88.3%)	58 (85.35)	63 (91.4%)	1.20 (.27)

Table 2

Subjective and Objective Indicators of Baseline Sleep by Intervention Group

	Mean (SD)			t (p =)
	Total (n = 137)	Placebo (n = 68)	Trazodone (n = 69)	
Global PSQI Score	12.9 (3.0)	12.8 (3.0)	13.1 (3.1)	-0.60 (.55)
PSG Parameters	(n = 131)	(n = 63)	(n = 68)	
Sleep Period Time	428 (127)	420 (139)	435 (116)	-0.66 (.51)
Total Sleep Time	341 (125)	325 (137)	355 (113)	-1.34 (.18)
Sleep Efficiency	83.0 (11.6)	82.6 (11.6)	83.2 (11.7)	-0.30 (.76)
% Stage 1 Sleep	2.6 (3.0)	2.9 (3.9)	2.4 (1.6)	1.05 (.30)
% Stage 2 Sleep	66.5 (11.7)	66.2 (12.0)	66.8 (11.5)	-0.26 (.80)
% Slow Wave	13.0 (9.1)	13.9 (9.9)	12.3 (8.3)	1.00 (.32)
% REM	17.8 (8.9)	17.0 (9.3)	18.6 (8.6)	-1.02 (.31)
% Time Awake	17.1 (11.6)	17.4 (11.6)	16.8 (11.7)	0.30 (.76)
Arousal Index	9.4 (9.4)	9.1 (10.5)	9.6 (8.4)	-0.27 (.79)
Apnea Index	2.7 (8.8)	3.4 (11.0)	2.0 (6.2)	0.85 (.40)
Morning Survey	(n = 131)	(n = 63)	(n = 68)	
Min. Sleep Period Time ^a	450 (125)	453 (88)	447 (153)	0.26 (.79)
Min. Total Sleep time	317 (104)	332 (101)	304 (106)	1.53 (.13)
Sleep Efficiency ^a	71.7 (18.8)	73.2 (18.1)	70.2 (19.5)	0.90 (.37)
Times Awakened	3.2 (1.0)	3.1 (0.9)	3.3 (1.0)	-0.64 (.52)
Sleep Rating	3.2 (0.7)	3.4 (0.8)	3.1 (0.7)	2.11 (.04)
Sleep Diary Parameters^b	(n = 90)	(n = 49)	(n = 41)	
Avg. Sleep Period Time	461 (103)	461 (90)	461 (117)	0.01 (.99)
Avg. Total Sleep Time	334 (129)	329 (124)	339 (136)	-0.36 (.72)
Avg. Sleep Onset Latency	47.3 (39.5)	49.7 (44.2)	44.5 (33.4)	0.63 (.53)
Avg. Sleep Efficiency	71.1 (22.7)	70.4 (22.3)	71.8 (22.3)	-0.28 (.78)
Avg. # Awakenings	2.8 (1.1)	2.8 (1.0)	2.8 (1.3)	-0.07 (.94)
Avg. Restfulness Rating	2.6 (0.9)	2.7 (0.7)	2.4 (1.0)	1.96 (.05)

^a Data on bed time and arise time were missing for 1 subject. Comparisons are based on 63 controls and 67 persons randomized to trazodone.

^b Comparisons are based on 90 subjects who provided a minimum of 3 nights of valid sleep log data during the week prior to baseline.

Table 3
Mean and Change in Mean Objective and Subjective Sleep Parameters, Baseline to Follow-UP, by Intervention Group.

	PLACEBO (n = 67)			TRAZODONE (n = 67)			p = ^a	d ^b
	Baseline	Posttest	Change	Baseline	Posttest	Change		
Global PSQI Score								
Baseline to 1 Month	12.8	9.8	-2.9	13.0	9.1	-3.9	.15	.25
Baseline to 3 Months ^c	12.8	9.2	-3.6	13.1	8.1	-5.0	.07	.32
Baseline to 6 Months ^d	12.6	9.2	-3.5	12.9	8.4	-4.5	.16	.26
PSG Parameters								
	(n = 56)			(n = 63)				
Sleep Period Time (Minutes)	434.0	400.4	-33.6	441.6	414.1	-27.5	.80	.05
Total Sleep Time (Minutes)	337.6	344.1	6.6	360.1	355.9	-4.2	.62	.09
Sleep Efficiency (%)	82.7	85.3	2.6	83.4	85.8	2.32	.90	.02
Stage 1 Sleep (%)	2.3	2.5	0.2	2.4	2.4	0.0	.67	.08
Stage 2 Sleeps (%)	66.7	63.3	-3.4	66.9	63.3	-3.7	.90	.02
Slow Wave Sleep (%)	13.6	14.5	0.9	12.2	14.5	2.3	.46	.14
REM Sleep (%)	17.4	17.9	0.5	18.5	19.9	1.4	.66	.08
Time Awake (%)	17.3	14.7	-2.6	16.6	14.2	-2.3	.90	.02
Arousal Index	9.8	9.5	-0.3	9.5	8.8	-0.7	.26	.21
Apnea Index	3.7	2.0	-1.8	2.2	2.8	0.6	.77	.05
Morning Survey								
	(n = 55)			(n = 60)				
Min. Sleep Period Time ^{aa}	454.9	443.2	-11.7	436.6	449.1	12.5	.23	.23
Min. Total Sleep time	339.6	349.4	9.82	310.0	356.7	45.5	.05	.37
Sleep Efficiency ^a	74.9	79.7	4.8	71.9	80.1	8.2	.33	.19
Times Awakened	3.1	2.6	-0.5	3.3	2.6	-0.7	.32	.19
Sleep Rating	3.4	3.2	-0.2	3.1	3.2	0.1	.12	.29
Sleep Diary								
	(n = 41)			(n = 35)				
Avg. Total Sleep Time	330.6	389.4	58.8	336.2	406.1	69.9	.67	.10
Avg. Sleep Onset Latency	50.4	38.5	-11.9	44.6	36.6	8.0	.69	.10
Avg. Sleep Efficiency	69.2	81.6	12.4	71.3	84.5	13.3	.87	.04

	PLACEBO (n = 67)			TRAZODONE (n = 67)			p = <i>a</i>	<i>d^b</i>
	Baseline	Posttest	Change	Baseline	Posttest	Change		
Avg. # Awakenings	1.2	0.7	-0.6	1.1	0.5	-0.6	.23	.28
Avg. Restfulness Rating	2.7	2.8	0.1	2.4	2.7	0.3	.46	.17

^aProbability of t-statistic testing the equality of mean change scores.

^bCohen's (1988) standardized difference in mean change scores.

^cSixty-two placebo and 63 trazodone participants were observed at 3-months.

^dSixty-one placebo and 62 trazodone participants were observed at 6-month.

Increases in Physical Symptom Severity by Treatment Assignment.

Subjects rated the frequency with which they experienced each symptom on a 4-point scale with 0 = "none of the time", 1 = "some of the time", 2 = "most of the time", and 3 = "all of the time." Subjects were coded as having increased symptom severity if the score at follow-up was higher than at baseline.