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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 6-month follow-up.

Methods: From eight methadone maintenance programs in the northeastern United States, we recruited 137 persons receiving methadone for at least 1 month who reported a Pittsburgh Sleep Quality Index (PSQI) score of six or higher. Two-night home polysomnography (PSG) was completed at baseline and 1 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 (±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 6-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.

1. 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

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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 h 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 subtherapeutic antidepressant doses of 100 mg 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. 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 (Fig. 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 50 mg 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 to 150 mg. 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