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Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: A randomized clinical trial

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ABSTRACT

Mental health is an important medical issue in perinatal care, and there is increasing evidence that insomnia during pregnancy is associated with postpartum depression (PPD). Therefore, the present study evaluated the effect of insomnia treatment during the third trimester of pregnancy on PPD symptoms. Fifty-four pregnant women with insomnia were randomly assigned to trazodone, diphenhydramine, or placebo treatment. Sleep quality was measured by actigraphy at baseline, and after 2 and 6 weeks of treatment. In addition, depression was assessed 2 and 6 weeks after delivery. Trazodone and diphenhydramine improved sleep profile compared to placebo after 6 weeks of treatment. Further, depressive symptoms were reduced 2 and 6 weeks after delivery in trazodone and diphenhydramine groups compared to placebo. No differences in depressive symptoms were observed between the trazodone and diphenhydramine groups. These findings indicate that insomnia treatment with trazodone or diphenhydramine during the third trimester of pregnancy may prevent PPD.

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1. Introduction

Perinatal mental health is an important issue for the well-being of a mother and her newborn. Postpartum depression (PPD) is a common major medical condition associated with childbearing that affects 10–15% of women (Gavin et al., 2005; Meltzer-Brody, 2011). PPD is defined by depressive symptoms that include tearfulness, despondency, sleep disturbance, emotional lability, feelings of guilt, changes in appetite, suicidal ideation, memory loss, fatigue, difficulty concentrating, and irritability (Robertson et al., 2004; Ross et al., 2005). PPD has been increasingly observed during the first year after delivery, and has negative effects on an infant's well-being and development that may lead to cognitive, behavioral, and emotional problems in childhood and adolescence (O'hara and Swain, 1996).

There are multiple risk factors for the development of PPD that include antenatal depression, lack of social support, child-care stress, adolescent pregnancy, poor relationship satisfaction, difficult infant temperament, history of mood disorders, low self-esteem, and drug abuse (Grace et al., 2003; Bernard-Bonnin, 2004; Studd and Panay, 2004). Furthermore, several studies have demonstrated that sleep disruption is a significant risk factor for postpartum mood disturbance (Dorheim et al., 2009; Goyal et al., 2009; Bei et al., 2010; Marques et al., 2011). The physiological, hormonal, and metabolic changes that occur during pregnancy often disrupt the mother's sleep–wake cycle (Sharma and Franco, 2004; Lee, 2006; Okun et al., 2009a, 2009b). More specifically, pregnancy is associated with nightly awakenings and reduced sleep efficiency. Further, loss of the sedative effects of endogenous progesterone may lead to postpartum insomnia (Okun et al., 2009a, 2011), and prior work suggests that sleep disruption during and after pregnancy may contribute to the development of postpartum mood disorders (Ross et al., 2005; Dorheim et al., 2009; Bei et al., 2010; Okun et al., 2011).

There are number of important factors regarding the treatment of depression during pregnancy which can influence the severity and persistence of depressive symptoms. For instance, treatment of depression with typical antidepressant medication during pregnancy and the postpartum period may have detrimental effects on prenatal and childhood development (Pearlstein, 2008). However, several studies have demonstrated that treatment of depression with trazodone – a 5-HT_{2A} receptor antagonist – during pregnancy does not increase the risk of birth defects, and results in limited drug exposure to the infant through breast feeding (Verbeeck et al., 1986; Einarson et al., 2003; Einarson

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and Einarson, 2005). In addition, trazodone is preferred over other antidepressant medications for treatment of patients with simultaneous insomnia and depression (Roth et al., 2011). A single dose of trazodone before bedtime is an effective regimen which not only improves sleep efficacy, but also shortens sleep onset latency (Mashiko et al., 1999). On the other hand, diphenhydramine is a traditional H1 histamine receptor antagonist with sedative properties that can be safely used during pregnancy to improve sleep quality and quantity (Unno et al., 2012).

Given that prior work has demonstrated a relationship between insomnia during pregnancy and PPD (Bei, et al., 2010; Marques, et al., 2011), we designed a randomized clinical trial to evaluate the effects of insomnia treatment during the third trimester of pregnancy on the development of PPD. Pregnant women with insomnia were randomly assigned to one of three treatment groups (trazadone, diphenhydramine, or placebo) and were followed until 6 weeks after delivery to determine whether insomnia treatment decreases the symptoms of PPD.

2. Materials and methods

2.1. Subjects

All procedures were approved by the institutional ethics committee of Kermanshah University of Medical Sciences (KUMS). This randomized placebo-controlled clinical trial was conducted from October 2008 to April 2012 at KUMS. Sixty-seven pregnant Persian women (gestational ages from 26 to 30 weeks) seeking treatment for sleep disturbance at the psychiatric outpatient clinic at KUMS were recruited to participate in this study. All participants provided written informed consent in compliance with the KUMS ethics board. Volunteers underwent a routine physical examination and ultrasonographic assessment, and those with gestational diabetes mellitus, hypertension, preeclampsia, or a history of chronic somatic disease, fetal disorder, or drug abuse were excluded from the study. Further, volunteers with a history of sleep or mood disorders prior to their pregnancy as well as any previous antidepressant use were excluded from participation. Participants underwent a structured psychiatric interview using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and completed the global sleep assessment questionnaire (GSAQ) to screen for subjective sleep problems (Roth et al., 2002). The psychiatric interview was performed to exclude volunteers with any other psychiatric disorder such as baseline depression, as well as to confirm the diagnosis of insomnia for which participants were originally referred for treatment. Six volunteers did not meet our inclusion criteria and were excluded from further participation. The 61 remaining subjects were in good physical health and were randomly assigned to one of three treatment groups. Participants either received a single dose of trazodone (50 mg/day), diphenhydramine (25 mg/day), or placebo. Medications were self-administered 1 h before bedtime. Participants were blind to their treatment type throughout the study.

2.2. Sleep monitoring and psychiatric assessment

Wrist actigraphy (*Ambulatory Monitoring, Inc. USA*) was used to monitor total sleep time and sleep efficiency objectively. The actigraph is a portable device (similar to a wrist watch) that records patient movement to assess sleep parameters such as total sleep time, sleep onset latency, number and duration of awakenings, and sleep efficiency (i.e. the ratio of total sleep time to the amount of time spent in bed) (Tahmasian et al., 2010; Khazaie et al., 2010; Khazaie et al., 2011; Sadeh, 2011; Tahmasian et al., 2013). Participants wore the actigraph for three consecutive days (72 h) during three different assessment periods (pre-treatment baseline, and after 2 and 6 weeks of treatment). In addition, psychiatric interviews were completed 2 and 6 weeks after delivery to evaluate the effect of insomnia treatment on the symptoms of PPD. DSM-IV-TR criteria and the Edinburgh postnatal depression scale (EPDS) were used to assess symptoms of depression during the psychiatric interviews (Cox et al., 1987). The EPDS is a self-rating questionnaire of depressive symptoms during the postnatal period. The questionnaire consists of 10 short statements. Participants marked one of four possible answers that best described their mood during the prior week. Montazeri and colleagues have previously demonstrated that the Persian version of the EPDS is a reliable and valid questionnaire for puerperal depression with test reliability 0.77 at time 1 and 0.86 at time 2 and test–retest reliability 0.80 (Montazeri et al., 2007). The EPDS is not a diagnostic tool for depression. Therefore, the DSM-IV-TR was used to determine whether participants met diagnostic criteria for depression. All clinical evaluations were completed by a psychiatrist who was blind to the study design and participants' treatment group assignment. Routine obstetric care was provided by the patient's gynecologic clinic at KUMS during the study.

2.3. Statistical analysis

Statistical analyses were performed using SPSS (version 16.0) with a significance threshold of $p < 0.05$. Repeated Measures Analysis of variance (ANOVA) was used to assess differences between the trazadone, diphenhydramine, and placebo groups in total sleep duration and sleep efficacy at three separate treatment times (i.e. baseline, and after 2 and 6 weeks of treatment). ANOVA was also used to assess differences postnatal depression symptoms for the three treatment groups (trazadone, diphendydramine, and placebo), 2 and 6 weeks after delivery. Tukey tests were used for post-hoc comparisons of significant effects identified by ANOVA.

3. Results

Sixty-one volunteers met criteria for participation in this study. However, six of these participants (two trazodone, two diphenhydramine, and two placebo group subjects) could not be reached for follow-up in subsequent components of the study and were excluded from all data analyses. In addition, one participant in the control group was diagnosed with postpartum psychosis during the psychiatric assessment completed 2 weeks after delivery. She was admitted to the hospital where antipsychotic drugs were administered and her participation in the study was discontinued. Thus, a total of 54 participants completed the study and were included in all data analyses (Fig. 1, Flow diagram). Participants were matched by age and randomly assigned to either Trazodone ($n=18$, age 26.6 ± 5.6), Diphenhydramine ($n=19$, age 27 ± 4.9), or Placebo ($n=17$, age 25.5 ± 4.4) treatment groups. The details of demographic characteristics of study participants were similar for all treatment groups (Table 1).

3.1. Sleep state

Sleep monitoring based on objective actigraphic assessment at baseline, and 2 and 6 weeks after the start of treatment are shown in Fig. 2. Repeated Measures ANOVA of sleep duration revealed significant main effects for treatment group ($F[2, 51]=45.26$; $p < 0.0001$) and treatment time ($F[1, 51]= 1078.00$; $p < 0.0001$), as well as a treatment group × time interaction ($F[2, 51]=54.09$; $p < 0.0001$). Similar results were observed for sleep efficacy, demonstrating significant main effects for treatment group ($F[2, 51]=46.99$; $p < 0.0001$) and treatment time ($F[1, 51]= 1973.00$; $p < 0.0001$), and a treatment group × time interaction ($F[2, 51]= 80.36$; $p < 0.0001$). At baseline, both total sleep duration and sleep efficacy were similar for all groups ($F[2, 51] < 1.00$). After 2 weeks of treatment, there were still no significant differences between treatment groups on sleep duration ($F[2, 51]=0.95$; $p=0.392$) and sleep efficacy ($F[2, 51]=2.42$; $p=0.099$). However, after 6 weeks of treatment, differences in sleep duration ($F[2, 51]=45.14$; $p=0.0001$) and sleep efficacy ($F[2, 51]=263.46$; $p=0.0001$) were observed. Post-hoc Tukey tests revealed significantly longer sleep durations in the trazodone ($p < 0.0001$) and diphenhydramine ($p < 0.0001$) groups than the placebo group. No differences in sleep duration were observed between trazodone and diphenhydramine treatment groups ($p=0.601$). Furthermore, post-hoc Tukey tests revealed that sleep was more efficient in the trazodone (86.3%; $p < 0.0001$) and diphenhydramine (86.6%; $p < 0.0001$) groups than the placebo group (66.7%) after 6 weeks of treatment. No differences in sleep efficacy were observed between trazodone and diphenhydramine treatment groups ($p=0.966$).

3.2. Postnatal depressive state

Two weeks after delivery, there were significant differences in EPDS scores between treatment groups ($F[2, 51]=3.53$; $p < 0.037$; Table 2). Post-hoc Tukey tests revealed significantly lower EPDS scores in the trazodone ($p=0.033$) and diphenhydramine

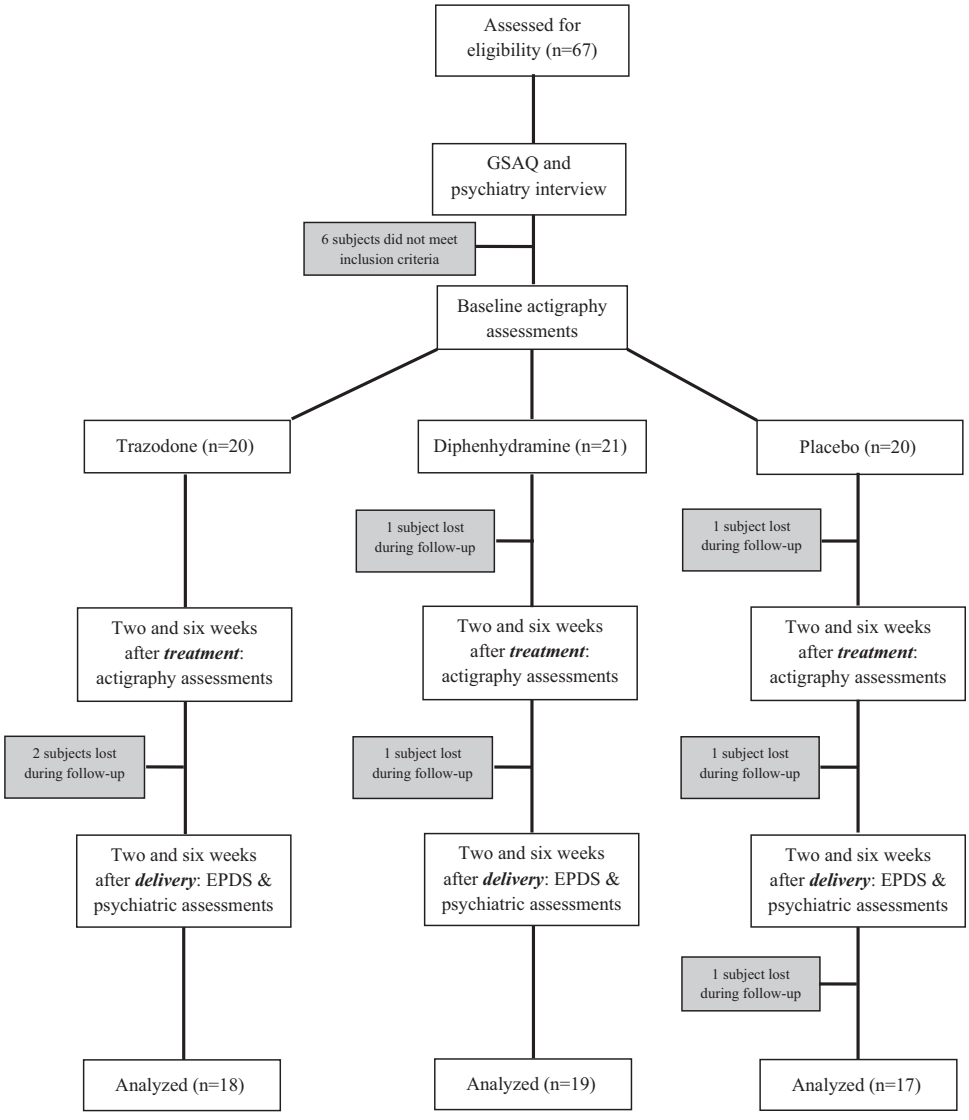

Fig. 1. Study design, screening, enrollment, and follow-up of the participants.

Table 1
Demographic characteristics of the three treatment groups.

	Trazodone ($n=18$)	Diphenhydramine ($n=19$)	Placebo ($n=17$)	p-Value
Age (year)	26.6 ± 5.6	27 ± 4.9	25.5 ± 4.4	0.677
Parity (N)	1.1 ± 0.9	1.1 ± 0.8	1 ± 0.8	0.944
Gestational age at the beginning of the study (week)	28.2 ± 2.8	27.7 ± 2.3	28.1 ± 2.8	0.877
Gestational age at delivery (week)	38.1 ± 0.8	38 ± 0.8	38.5 ± 1.1	0.217

($p=0.047$) groups than in the placebo group. No differences in EPDS scores were observed between trazodone and diphenhydramine treatment groups ($p=0.989$). Similar effects were observed 6 weeks after delivery ($F[2, 51]=11.35$; $p=0.0001$). Post-hoc Tukey tests revealed significantly lower EPDS scores in the trazodone ($p=0.0001$) and diphenhydramine ($p=0.001$) groups than the placebo group. No differences in EPDS scores were observed between trazodone and diphenhydramine treatment groups ($p=0.941$) 6 weeks after delivery.

3.3. Side effects

Day time sleepiness was the most frequent side-effect reported by participants in both trazodone and diphenhydramine groups. However, none of the participants discontinued their treatment or terminated their participation in the study. No neonatal abnormalities were observed during this study. Mean apgar scores at 1 and 5 min were similar for all groups ($p > 0.05$; data not shown), and neonatal intensive care was not required for any of the infants.

4. Discussion

The present study investigated the effect of insomnia treatment during the third trimester of pregnancy on the subsequent development of PPD symptoms. Trazodone (an antidepressant medication with sedative effects) and diphenhydramine (a first generation antihistamine with sedative properties) were compared to placebo

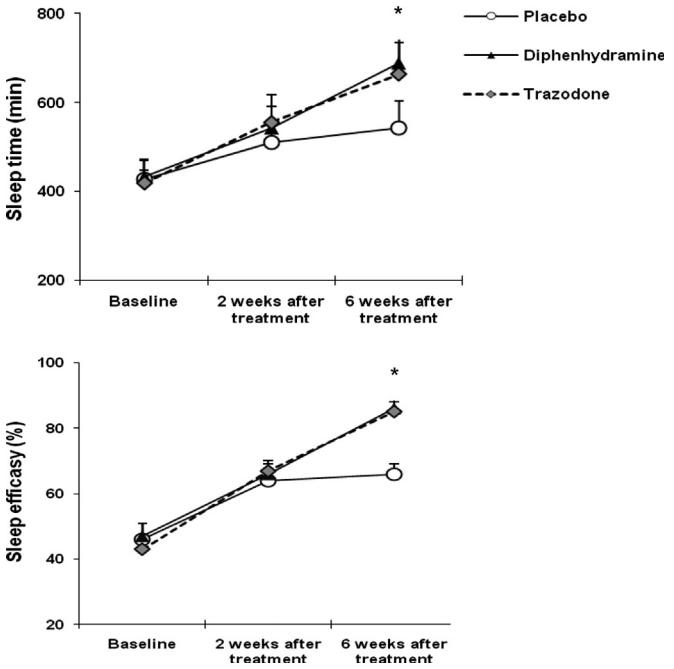

Fig. 2. Total sleep time and sleep efficacy. Sleep time and efficacy were similar for trazadone, diphenhydramine, and placebo treatment groups at baseline and after two weeks of treatment. However, greater sleep time and efficacy were observed in the trazadone and diphendydramine groups compared to the placebo group after six weeks of treatment. * Indicates significant difference ($p < 0.05$).

Table 2
EPDS scores 2 and 6 weeks after delivery.

	Trazodone ($n=18$)	Diphenhydramine ($n=19$)	Placebo ($n=17$)	p-Value
2 Weeks after delivery	6.5 ± 5.2	6.8 ± 5.5	11.7 ± 7.8	0.037*
6 Weeks after delivery	5.1 ± 1.8	5.3 ± 2	7.9 ± 1.7	< 0.0001*

* Indicates significant difference ($p < 0.05$).

to determine whether these interventions reduce postpartum depression symptoms. The primary findings of this randomized clinical trial are as follows: (i) sleep efficacy and total sleep time were improved by trazodone and diphenhydramine treatment compared to placebo. (ii) trazadone and diphenhydramine treatment during the third trimester of pregnancy reduced the PPD symptoms of patients (assessed 2 and 6 weeks after delivery). (iii) Sleep quality and depressive symptoms did not differ between trazodone and diphenhydramine groups.

PPD is a severe psychiatric disorder that often affects women's health after delivery and can interfere with the mother's relationship with her child. Therefore, new mothers should be regularly evaluated for PPD symptoms and provided appropriate psychiatric treatment when necessary. However, factors that influence the development of PPD may be encountered well before the birth of a child. Specifically, pregnancy is associated with hormonal and psychosocial changes that alter sleep patterns, especially during the third trimester (Sharma and Franco, 2004; Lee, 2006; Okun, et al., 2009b). Reductions in total sleep duration and sleep efficiency are often experienced during the third trimester of pregnancy and the subsequent postpartum period. Sleep disruption during the third trimester of pregnancy may play an important role in the development of PPD (Wilkie and Shapiro, 1992). For example, related work in nulliparous women has demonstrated that subjective sleep disturbance, especially delayed sleep onset, is associated with depressive symptoms during the third trimester and postpartum period (Goyal et al., 2009). Similarly, women with PPD report poorer subjective sleep quality than non-depressed women 2 months after delivery even though objective sleep differences, measured by actigraphy, were not observed (Dorheim et al., 2009). However, the sleep disruption associated with PPD does not appear to be solely subjective given that other research using actigraphy to objectively monitor sleep quality has observed that women with PPD have longer sleep onset latencies, greater number of awakenings during sleep, and poorer sleep efficacy than women without depression (Posmontier, 2008). Despite the growing body of literature on sleep and mood disorders associated with pregnancy, relatively little prior work has investigated the effect of insomnia treatment during pregnancy on the development of PPD. The findings from the present study suggest that insomnia treatment during the third trimester improves sleep quality, which may in turn reduce the symptoms of PPD.

Our findings are consistent with recent work that indicates there is a strong relationship between sleep disruption and mood disturbance. For example, the severity of mood disturbance is associated with the amount of sleep impairment, and the treatment of sleep disturbance improves mood (Lunsford-Avery et al., 2012). Further, antidepressant medications improve sleep quality and are frequently prescribed to manage sleep disruption. In addition, antidepressant medications may have a protective effect against sleep deprivation-induced anxiety (Kumar and Garg, 2009). Trazodone as an antidepressant medication is widely prescribed for the treatment of insomnia. Trazodone's action as a 5-HT_{2A} receptor antagonist mediates its therapeutic benefit for anxiety and depression. Trazodone's inhibitory effect on serotonin reuptake and 5-HT_{2C} receptor binding are relatively weak and appears to have a relatively minor contribution to its general treatment effect. However, trazadone is also a 5-HT_{1A} partial agonist which likely contributes to its antidepressant and anxiolytic effects. Trazadone's antagonistic action on 5-HT2 receptors improves not only sleep continuity, but also promotes slow wave sleep (Marek et al., 1992; Raffa et al., 1992; Odagaki et al., 2005). Further, in contrast to other antidepressant medications, trazodone does not suppress REM sleep (Kumar and Garg, 2009). Diphenhydramine also has sedative effects and is widely used as a nonprescription sleep aid to treat insomnia. Diphenhydramine is a first generation H1 histamine receptor antagonist that's anticholinergic actions are mediated by muscarinic receptor binding. High concentrations of drugs like diphenhydramine can also have heterogeneous receptor actions, such as the inhibition of dopamine, norepinephrine, or serotonin transporter systems (Gilboa et al., 2009; Unno et al., 2012).

Previous studies have demonstrated that the use of trazodone and similar types of antidepressants during pregnancy is safe and does not increase the risk of major birth malformations above the baseline rate of 1–3% found in the general population (Mashiko et al., 1999; Roth et al., 2011). Further, diphenhydramine and other antihistamines can be used safely during pregnancy. Prior research indicates that the consumption of antihistamines during pregnancy does not increase the risk of birth defects (Gilboa et al., 2009). There were no abortions, major birth malformations, or still births in the present study.

To our knowledge, the present study is the first randomized clinical trial to assess the effect of trazodone and diphenhydramine treatment of sleep disturbance in pregnant women, and evaluate the efficacy of these interventions on the subsequent development of PPD symptoms. Our findings demonstrate that trazodone and diphenhydramine treatment are well tolerated, improve sleep quality during pregnancy, and prevent the development of PPD symptoms. These

findings suggest that the sleep quantity and quality of pregnant women should be regularly evaluated and appropriately treated when necessary to moderate the development of PPD symptoms. Limitations of the present study include (i) a relatively small sample size that is inadequate to detect a clear clinical difference in the treatments evaluated; (ii) additional follow up (i.e. beyond the 6 week evaluation) was not completed in this study, but is recommended for future research given that symptoms of depression may develop over the first 12 weeks of the post-partum period; (iii) three nights of actigraphy monitoring may be insufficient to adequately assess sleep/wake patterns; and (iv) drug serum levels were not measured, and should be considered in the design of future research on this topic, though, we prescribed low-dose medications in this study. In summary, we suggest that the treatment of sleep disturbance with trazodone or diphenhydramine during the third trimester of pregnancy may prevent the development of PPD symptoms. However, future clinical trials with a larger sample size are needed to confirm these findings.

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