Send Orders for Reprints to reprints@benthamscience.ae

Current Psychiatry Reviews, 2015, *11*, 63-83

Treatment of Insomnia, Insomnia Symptoms, and Obstructive Sleep Apnea During and After Menopause: Therapeutic Approaches

Joshua Z. Tal[1,2], Sooyeon A. Suh[1,3], Claire L. Dowdle[1,4] and Sara Nowakowski[1,5,*]

[1]Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Stanford, CA 94305, USA; [2]Palo Alto University, Palo Alto, CA 94304, USA; [3]Sungshin Women's University, Department of Psychology, Seoul, Republic of Korea; [4]PGSP -Stanford Psy. D. Consortium, Palo Alto, CA 94304, USA; [5]University of Texas Medical Branch, Department of Obstetrics and Gynecology, Galveston, TX 77555, USA

Abstract: Understanding sleep complaints among menopausal women is an emerging area of clinical and research interest. Several recent reviews have focused on mechanisms of menopausal insomnia and symptoms. In this review, we present a discussion on the most relevant and recent publications on the treatment of sleep disorders for menopausal women, with a focus on menopause-related insomnia, insomnia symptoms, and obstructive sleep apnea. We discuss both nonpharmacological and pharmacological treatments, including cognitive-behavioral therapy for insomnia (CBT-I), complementary and alternative medicine, hormone replacement therapy, sedative hypnotics, antidepressants, and continuous positive airway pressure. In addition, we briefly discuss methods and considerations of assessment of sleep disorders in menopausal women.

Keywords: Complementary and alternative medicine, insomnia, insomnia symptoms, menopause, obstructive sleep apnea, pharmacology, sleep disorders.

INTRODUCTION

Menopause, defined as the cessation of menstruation for at least one year, is due to the degeneration of ovaries and follicles, in addition to fluctuating ovarian hormone levels. Decreased ovarian function precedes menopause in the climacteric or peri-menopausal period. Menstrual cycle changes and vasomotor symptoms decline at a gradual rate, long before menses cease. Psychological and physiological issues often accompany menopause-related vasomotor changes in the form of hot flashes, bleeding irregularities, sexual dysfunction, mood changes, cognitive declines and/or sleep disturbance [1, 2].

As the 470 million postmenopausal women worldwide increases by 1.5 million women annually, and are expected to reach a total of 1.2 billion by 2030, approximately 50 - 85% of these women will experience menopause-related vasomotor symptoms [1, 3, 4]. There is a wide variability in the duration of menopause-related symptoms, with many women reporting symptoms decreasing within one year of menopause, while other women complain of persistent vasomotor symptoms for up to, or more than thirty years [5]. Complaints of sleep disturbance, usually in the form of intermittent awakenings, are one of the frequently reported behavioral symptoms of menopause. Studies utilizing diagnostic tools of wrist actigraphy and the Insomnia Severity Index (ISI) have justified insomnia as a prevalent concern in this population [6-10]. Clinical diagnoses of moderate to severe insomnia have been demonstrated in 9.5 - 33% of peri- or postmenopausal women [6, 7]. Large population-based studies confirm these findings, demonstrating 28 - 64% of peri- or postmenopausal women report insomnia symptoms [8, 9].

Beyond its prevalence, sleep disturbance in menopausal women is also associated with negative consequences in numerous domains. Bolge *et al.*'s [10] survey of 141 postmenopausal women with sleep disturbance and 1305 premenopausal women without insomnia, depicted that sleep disturbance was significantly correlated with occupational impairment and increased visits to the emergency room. Other associations with menopause-related sleep difficulties include mood disturbance, hot flashes, hypertension, use of anti-hypertensive medication, melatonin acrophase offset, and lower global functioning [2].

Objective sleep research utilizing polysomnography (PSG) has documented decreased sleep efficiency, with increased sleep onset latency and increased wakefulness after sleep onset in postmenopausal women compared to premenopausal women [11, 12]. There are many possible factors that can contribute to this phenomenon, including the co-occurrence of hot flashes and mood symptomology [13]. In addition, sleep disruption in menopause may be exacerbated or caused by primary sleep disorders such as obstructive sleep apnea (OSA) [14]. OSA is defined by an apnea hypopnea index of 5, indicating at least 5 complete or

*Address correspondence to this author at the University of Texas Medical Branch, Department of Obstetrics and Gynecology, 301 University Boulevard, Galveston, TX 77555-0587, USA; Tel: (409) 772-3996; Fax: (409) 747-5129; E-mail: sanowako@utmb.edu

1875-6441/15 $58.00+.00

partial obstructions of the airway per hour, usually resulting in an awakening [15]. Signs and symptoms of OSA include loud snoring, daytime sleepiness, shortness or gasping for breath, witnessed apnea episodes, dry mouth and morning headaches.

Although the exact mechanism is not clear, studies have demonstrated an increased risk for OSA after the menopausal transition. One large population-based study of 589 women in the Wisconsin Sleep Cohort Study demonstrated 3.5 times risk of OSA in post-menopausal compared to pre-menopausal women, when controlling for age, body composition and lifestyle as confounding variables [16]. One hospital-based study [17] found that although pre- and postmenopausal women present with similar signs and symptoms when referred to sleep studies, the prevalence of sleep-disordered breathing tended to be higher (86.2% versus 79.4%, respectively) and more severe (68.1% versus 35.8%, respectively) in postmenopausal versus premenopausal women. It has been proposed that decreases in levels of progesterone, a respiratory stimulant, are implicated to increase the risk for sleep disordered breathing (SBD) [18].

Sleep disturbances during menopause are additionally implicated in the high prevalence of clinical depression and depressed mood during and after the menopause transition [19, 20]. The relationship between sleep and depression can be described as bidirectional: sleep disturbance can be both a consequence of clinical depression as well as an instigator of depressed mood. Previous studies have demonstrated that sleep disturbance mediates the expression of depressed mood in peri- and postmenopausal women [19-21]. It has also been suggested that depression provides an additive effect on sleep disturbance in this population [22]. Clark and colleagues, however, found no relationship between sleep disturbance and depressed mood in peri- and postmenopausal women [23]. Regardless of mechanism, depressed mood is implicated in the treatment of menopause related insomnia and sleep disturbance. In terms of treatment, there are no specific studies examining treatment of comorbid insomnia and depression in peri- or postmenopausal women. There are several studies, however, that examine treatment for sleep disturbance and comorbid conditions, including depression, and found that treatments for sleep disturbance enhanced treatment of depression or alleviated depressed symptoms altogether [24-26].

METHODS

This review summarizes current findings on the assessment and treatment of menopause-related sleep disorders. This review was completed through a systematic review of the literature regarding the treatment of insomnia and obstructive sleep apnea in peri- and post-menopausal women. The databases searched included PsycINFO, PsycNET, MEDLINE, and PubMed. Keywords used in the search included "menopause," "insomnia," "sleep disorder," "pharmacology" and "alternative medicine." A thorough and systematic examination of the literature was completed for each subsection of the paper. Studies included in the following review are summarized in Tables **2**-**4**, according to the sleep issue it examines.

DIAGNOSTIC CONSIDERATIONS

Discussions of the diagnostic complexities of insomnia are quite common. Sleep can be disturbed for a variety of reasons. It can be affected by comorbidities. In addition, sleep disturbance can cause and/or exacerbate comorbidities. The duration of sleep disturbance can be variable, from days to lifelong. All these variables pose a challenge to defining insomnia as a distinct disorder. In the case of hot flashes and insomnia symptoms coinciding with menopause, the understanding of insomnia may be formidable. According to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [27] if a patient concurrently meets criteria for Primary Insomnia (such as 1 month of sleep disturbance and clinically significant distress or impairment), and experiences hot flashes, the diagnosis for primary insomnia may be ruled out, as these symptoms would be deemed due to a general medical condition. If the insomnia began prior to the hot flashes, or potentially precipitated or exacerbated the vasomotor symptoms, however, a diagnosis of Sleep Disorder Due to a General Medical Condition, Insomnia Type, may not adequately capture the important features and resulting treatment considerations.

The recent revision of the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [28] attempts to encompass the bidirectional nature of insomnia and increased the minimum duration of symptoms from one to three months. The DSM-5 combines both primary and secondary insomnia into Insomnia Disorder, with specifications for comorbidities. The DSM-5's nullification of causality in the diagnosis expresses the complex diagnostic nature of insomnia, where true causality cannot always be established. The DSM-5's classification of Insomnia Disorder suggests that regardless of cause, the patient's insomnia need to be a focus of treatment to improve the patient's condition, other comorbidities, and quality of life.

Although treatment considerations should minimize consideration of causality in the treatment of insomnia, qualitative distinctions are still important considerations. Severe, chronic insomnia and mild, transient insomnia have different implications for treatment. For the purposes of this treatment review, we will investigate studies inculcating individuals with full diagnostic criteria for insomnia, denoted by the term *insomnia* [29]. Due to the paucity of studies utilizing the diagnostic criteria of the DSM-5's Insomnia Disorder, *insomnia* will refer to the qualitative aspects of the diagnosis of insomnia in accordance with the DSM-IV, such as the duration and impact requirements. We will additionally review studies attempting to treat individuals with symptoms of sleep disturbance, without fulfilling the complete criteria, which will be termed *insomnia symptoms* [29].

ASSESSMENT AND INTERVENTION

Subjective Assessments: Conducting a Clinical Interview

The essential diagnostic tool for insomnia is a clinical interview. Information collected during the clinical interview should provide sufficient information about the nature and impact of the insomnia symptoms, the developmental course,

and specific features to assist the clinician in arriving at a diagnosis and formulating treatment recommendations. Inquiry about comorbid medical and psychiatric conditions, social history, and other menopausal complaints (hot flashes, night sweats, incontinence, diminished libido, vaginal dryness, fatigue, depressed mood) can also be informative [15, 30].

Administering other self-report questionnaires, such as the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index, or the Epworth Sleepiness Scale [31] may also help determine severity of symptoms and level of sleepiness that may be associated with other sleep disorders, such as OSA. The ISI is a particularly robust diagnostic tool, as it is validated to encompass the diagnostic criteria of the DSM-IV [32] (See Table **1** for a list of the self-report measures utilized for menopause-related sleep issues).

Objective Assessments: Polysomnography and Wrist Actigraphy

PSG and wrist actigraphy provide two objective measures of sleep quality. PSG utilizes night electroencephalography (EEG), electromyography and electrooculography to detect brain wave, movement and eye rhythm changes to demonstrate sleep cycles. The American Academy of Sleep Medicine (AASM) recommends PSG as the ideal diagnostic tool for sleep breathing disturbances, periodic limb movements and overall sleep disturbance [33]. Alternatively, wrist actigraphy utilizes a portable watch device to detect movement for multiple nights at a time. Wrist actigraphy has been validated as an accurate diagnostic tool for insomnia [34] and periodic limb movements [35]. Although not used for the diagnosis of insomnia, PSG is used to rule out other sleep-related disorders, such as OSA and periodic limb movements, to therefore confirm a primary diagnosis of insomnia [33, 35].

INSOMNIA

Non-pharmacological Treatments

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Hormonal fluctuation and vasomotor symptoms such as night sweats may be the initial cause of insomnia symptoms, but physiological arousals, behavioral conditioning, and misguided coping attempts appear to prolong insomnia [36], as described by Spielman and Glovinsky's three factor model of insomnia [37]. Spielman [37] posits that chronic insomnia can develop when poor sleep is induced by physical factors (i.e., hot flashes) or other disposing factors, is precipitated by life stressors, and is perpetuated by maladaptive coping strategies. According to this model, postmenopausal women's distress about poor sleep can lead to dysfunctional efforts to induce sleep and can cause conditioned arousal, whereby the bed becomes a cue for arousal rather than sleep. These behavioral factors can maintain the sleep problem even after the causative effects of vasomotor symptoms have been eliminated [36]. CBT-I teaches skills to undermine the cognitive and behavioral factors that maintain insomnia, regardless of the cause.

CBT-I is a brief and effective non-pharmacological intervention for insomnia. CBTI is a structured, skill-focused psychotherapy that consists of cognitive therapy (challenging irrational/distorted beliefs about sleep); behavioral techniques (sleep restriction, stimulus control therapy, relaxation techniques) and sleep education about sleep hygiene. The techniques of cognitive behavioral therapy have been applied to menopausal symptoms (e.g., hot flashes, depression), thus providing the opportunity to create a multicomponent behavioral intervention targeting multiple menopausal symptoms. A description of each CBTI component and some ways they could be potentially tailored to menopausal women is outlined below.

Sleep Restriction

Sleep restriction involves limiting the amount of time spent in bed to the amount of actual total sleep time, which is typically derived from 1 to 2 weeks of sleep diary data. It is usually indicated in patients whose sleep efficiency (total sleep time/time in bed × 100) is less than 85%. Sleep restriction systematically reduces time in bed to a degree that is less than the patient is accustomed to, thus utilizing the homeostatic drive of sleep to increase sleep consolidation. The patient's sleep efficiency is carefully monitored in subsequent follow-up sessions and modified throughout treatment based on sleep diary information and patient report.

Stimulus Control

The main objective of stimulus control is to have the patient limit the amount of time spent awake in bed and re-associate the bed and bedroom with sleep to regulate sleep-wake schedules. The guidelines that are discussed with the patient include the following: 1) only going to bed when sleepy; 2) using the bed and bedroom only for sleep and sexual activity; 3) leaving the bed and bedroom if unable to fall asleep for longer than 15 to 20 minutes, and return only when sleepy; and 4) keeping a fixed wake time in the morning every day.

Cognitive Therapy

Cognitive therapy is designed to challenge maladaptive beliefs and attitudes that serve to maintain insomnia (e.g., "If I don't get my 8 hours sleep, I'm useless."). Worrying, faulty attributions, or unrealistic expectations of sleep may lead to increased emotional arousal, and thus lead to additional sleep disturbance, reinforcing the beliefs, and causing a vicious cycle. Challenging dysfunctional thoughts associated with sleep is believed to decrease the anxiety and arousal associated with insomnia. The first step is to increase the patient's aware of his/her dysfunctional thoughts of sleep, which is usually done through self-monitoring or questionnaires. Once sleep cognitions are identified, the next task is to help the patient challenge dysfunctional thoughts through guided discovery and collaborative empiricism. Instead of regarding cognitions as an absolute truth, the patient is encouraged to view his/her thoughts as one of the many possible interpretations (e.g., "I don't even know whether I'll get good sleep tonight."). The final step is to replace dysfunctional cognitions with more adaptive, realistic, and alternative interpretations based on past

Table 1. Self-report measures.

Self-Report Measure	Insomnia or Symptoms	Focus of Attention	Number of Questions	Type of Questions	Cutoff Scores	
Insomnia Severity Index (ISI)	Insomnia, validated with the DSM-IV	Nature, severity and impact of insomnia.	7	5-point Likert scale 0 = "No problem" - 4 = "Very severe problem"	0-7 = No insomnia 8-14 = Subthreshold insomnia 15-21 = Moderate insomnia 22-28 = Severe insomnia	
Pittsburgh Sleep Quality Index (PSQI)	Insomnia symptoms.	Nature and severity of sleep quality disturbances.	19	Open ended questions and various 4-point Likert scales.	0-5 = Good sleep quality >5 = Poor sleep quality	
Epworth Sleepiness Scale (ESS)		Insomnia and sleep-disordered breathing symptoms.	Daytime sleepiness as a result of sleep disturbance.	8	4-point Likert Scale 0 = "No chance of dozing" - 4 = "High chance of dozing"	0-9 = Normal sleepiness 10-15 = Clinical levels of fatigue 16-24 = Severe clinical levels of fatigue
Sleep and/or Hot Flash Diary		Insomnia and/or hot flash symptoms	Nature and quality of sleep quality disturbance.	At least 4, depending on author's purpose and specificity of inquiry.	Mostly open ended question, asking questions about incidence times and numbers, sleep and wake times, hours of sleep, number of occurrences of activities and/or beverages during the day, severity ratings, etc.	No official score method, but depending on purposes, total sleep time, wake after sleep onset, average bedtime, average number of hot flashes, average severity rating, fatigue levels, etc.
Menopause Rating Scale (MRS)		Insomnia symptoms	Quality of menopause related symptoms	11, 1 for sleep.	5-point Likert scale 0 = "None" - 4 = "Very severe"	Continuous with higher scores indicating higher severity. Three subscales and total score: Psychological symptoms (depressed, irritable, anxious, exhausted), Somato-vegetative symptoms (sweating/flush, cardiac sleeping disorders, joint and muscle), and Urogenital symptoms (Sexual problems, urinary complaints, vaginal dryness)
Women's Health Questionnaire (WHQ)		Insomnia symptoms	Quality of health related symptoms prevalent in middle aged women	36, 3 for sleep.	4-point Likert scale 0 = "No, no at all - 4 = "Yes, definitely"	Continuous with higher scores indicating higher severity. 11 subscales: Depressed mood, somatic symptoms, anxiety/fears, vasomotor symptoms, sleep problems, sexual behavior, menstrual symptoms, memory/concentration, attractiveness.

evidence (e.g., " Although it is difficult to function the next day after a poor night's sleep, I have historically been able to get most important tasks of the day done".

In addition, menopausal women experiencing hot flashes may also have maladaptive thoughts related to hot flashes (e.g., "If I had a hot flash and someone noticed, it would be

Table 2. Insomnia treatment studies.

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Afonso *et al.* (2012)	Yoga	Postmenopausal women	Randomized; Tx1 = Yoga (n=15) Tx2 = Passive Stretching (n=14) Tx3 = Wait list control (n=15)	2 sessions a week for 16 weeks.	0%	No	ISI	Both yoga and passive stretching significantly decreased insomnia scores compared to the control.
Oliveira *et al.* (2011)	Therapeutic Massage	Postmenopausal women	Pilot; Tx = Therapeutic massage (n=7)	2 sessions a week for 8 weeks	0%	1 year	Sleep diary and PSG	Post treatment: Sleep Diary showed increased sleep latency and subjective sleep quality. PSG showed increased REM latency and increased stage 3 sleep. 1 year follow-up: 2 subjectively improved since post-treatment, 3 maintained sleep improvements, 2 relapsed.
Kung *et al.* (2011)	Auricular acupuncture	Postmenopausal women	Tx = Auricular acupuncture (n=45)	Nightly for 4 weeks	0%	No	PSQI	Increases in total sleep duration and sleep efficiency, and decreases in sleep latency.
Antonijevic *et al.* (2000)	Estrogen replacement therapy	Postmenopausal women	Within subject; Tx = Estrogen patch (n=11)	Two patches per week, two weeks	0%	No	PSG	Increases in total minutes of REM sleep.
Schiff *et al.* (1972)	Estrogen replacement therapy	Postmenopausal women	Randomized, double blind; Tx1 = Oral estrogen (n=9) Tx2 = Placebo control (n=7)	One month	0%	No	PSG	Increases in REM sleep and decreases in sleep latency.
Bliwase (1992)	Estrogen replacement therapy	Elderly women	Subjective separation into "good sleepers" (n=22) and "poor sleepers" (n=16)	No treatment	N/A	No	PSG	Using estrogen did not differentiate good from poor sleepers.
Pickett *et al.* (1989)	Progesterone and estrogen replacement therapy	Postmenopausal women	Tx = Combined oral estrogen and progesterone	7 days	0%	No	PSG	No differences before and after administration of hormones.
Purdie *et al.* (1995)	Progesterone and estrogen replacement therapy	Postmenopausal women	Randomized; Tx1 = Combined oral estrogen and progesterone (n-16) Tx2 = Placebo control (n=14)	12 weeks	0%	No	PSG	No significant differences between groups.
Montplaisir *et al.* (2001)	Estrogen compared with combined estrogen and progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estrogen (n=11) Tx2 = Combined oral estrogen and progesterone (n=10)	6 months	0%	No	PSG	Combination estrogen and progesterone increased sleep efficiency by 8%, while estrogen alone showed no effects on sleep efficiency.

Table 2. contd….

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Saletu *et al.* (2001)	Progesterone and estrogen replacement therapy	Postmenopausal women diagnosed with insomnia	Within subject; Tx1 = Placebo control Tx2 = Combined oral estrogen and progesterone (n=55)	4 months	0%	No	PSG and subjective report	Combination estrogen and progesterone depicted moderate, yet non-significant improvements in wake-time after sleep onset, sleep initiation and sleep maintenance sampled by PSG, while subjective improvements of wakefulness and efficiency were reported.
Soares *et al.* (2006)	Eszopiclone (Lunesta)	Peri- or early postmenopausal women diagnosed with insomnia related to the menopausal transition	Randomized; Tx1 = Eszopiclone 3mg (n=201) Tx2 = Placebo (n=209)	4 weeks	12.4%	No	ISI	58% of those treated with eszopiclone displayed a reduction of ISI score to "non significant clinical insomnia", versus 35% of the placebo group.
Joffe *et al.* (2006)	Eszopiclone (Lunesta)	Peri- and postmenopausal women	Randomized, crossover; Tx1 = Eszopiclone 3mg (n=30) Tx2 = Placebo (n=29)	11 weeks	22%	No	ISI and sleep diaries	Compared with placebo, eszopiclone reduced the ISI score by 8.7 ± 1.4 more points on eszopiclone than on placebo, without a significant time-by-treatment interaction. The sleep diary revealed significant sleep latency reductions without significant time-by-treatment interactions, but sleep efficiency, wake-time after sleep onset and total sleep time did display significant time-by-treatment interactions.
Dorsey *et al.* (2004)	Zolpidem (Ambien)	Peri- and postmenopausal women diagnosed with insomnia related to the menopausal transition	Randomized; Tx1 = Zolpidem 10mg (n=68) Tx2 = Placebo (n=73)	4 weeks	11%	No	Subjective sleep reports	Zolpidem group reported significantly increased total sleep time, decreased wake time after sleep onset, and decreased number of awakenings compared to those in the placebo group.
Ensrud *et al.* (2012)	Escitalopram (Lexapro)	Peri- and postmenopausal women with hot flashes	Randomized; Tx1 = Escitalopram 10-20mg (n=104) Tx2 = Placebo (n=101)	8 weeks	5%	No	ISI and PSQI	Escitalopram was more effective than placebo in decreasing ISI scores (41% decrease vs. 21% decrease) and PSQI scores (32% decrease vs. 17% decrease) relative to baseline scores.

awful and humiliating."). By applying cognitive therapy techniques to menopause related cognitions, women can be taught to apply these skills to unhelpful thoughts about hot flashes. Women who cope with hot flashes by using disclosure to others or self-talk (e.g., "Letting the flash pass without being hooked by the feelings") report less distress about hot flashes.

Relaxation Training

Relaxation techniques can be effective in reducing physiological hyperarousal related to sleep disturbance. Relaxation provides a method for decreasing arousal prior to initiating sleep. Common relaxation techniques include progressive muscle relaxation, which involves alternately tensing and relaxing different muscle groups in the body; deep breathing techniques, which involve diaphragmatic breathing; body scanning, which involves focusing on a body-part sequence that covers the whole body; and autogenic training, which involves visualizing a peaceful scene and repeating autogenic phrases to deepen the relaxation response.

Sleep Hygiene

Although there is insufficient evidence for sleep hygiene to be an option for single therapy, it is usually provided in conjunction with other treatment modalities. Sleep hygiene

Table 3. Insomnia symptom treatment studies.

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Keefer & Blanchard (2005)	Group CBT for Climactic Symptoms	Peri- and postmenopausal women experiencing vasomotor symptoms	Tx1 = Group CBT-C (n=11) Tx2 = Waitlist Control/Delayed CBT-C (n=8)	8 weeks	0%	No	Daily vasomotor symptom diary	Compared with the waitlist control group, the CBT-C group displayed significantly less total vasomotor symptoms, although the effect was moderate.
Green *et al.* (2013)	Group CBT	Peri- and postmenopausal women experiencing vasomotor symptoms	Pilot; Tx = CBT (n=8)	10 weeks	0%	No	Hot flash diary Interference Scale and PSQI	The group CBT treatment significantly reduced hot flashes, depressed mood and anxiety, but results were not significant for sleep disturbance.
Mann *et al.* (2012)	Group CBT	Women experiencing menopausal symptoms after breast cancer treatment	Randomized; Tx1 = CBT (n=47) Tx2 = Usual care (n=49)	6 weeks	17%	2 week and 20 week	Women's Health Questionnaire	Compared to the control group, the CBT group demonstrated significant reductions up in sleep disturbance and depressed mood at 20 week follow-up, but not in hot flashes.
Carmody *et al.* (2011)	Mindfulness-Based Stress Reduction	Late perimenopausal and early postmenopausal women experiencing vasomotor symptoms	Randomized; Tx1 = MBSR (n=57) Tx2 = Wait list control (n=53)	8 weeks	9.3%	1, 12, 16, 20 week follow ups.	Daily hot flash diary	In the MBSR group, there was a significant reduction in the degree of bother of the hot flashes at 9 weeks (14.7% vs. 6.7%) and at 20 weeks (21.6% vs. 10.5%), compared with the control group. Although there was a significant difference between MBSR and control in perceived sleep quality, the within subject differences were not significant.
Borud *et al.* (2009)	Acupuncture	Postmenopausal women experiencing vasomotor symptoms	Randomized; Tx1 = Acupuncture (n=134) Tx2 = Wait list control (n=133)	12 weeks	7%	No	Daily hot flash diary	In the acupuncture group, there was a significant, albeit mild, reduction in the frequency of hot flashes per 24 hours, compared with the control group (5.8 vs. 3.7). In addition, there was a significant increase in hours of sleep in the acupuncture group, compared to the control group (0.42 hours vs. 0.14 hours).
Hacul *et al.* (2011)	Isovlavones (soy)	Postmenopausal women with sleep disturbance	Randomized; Tx1 = Oral isoflavones (80mg; n=19) Tx2 = Oral placebo (n=19)	16 weeks	2%	No	PSG	Relative to the placebo control group, the isoflavones group demonstrated significant improvements in sleep efficiency (from 77.9% to 83.9% vs. 77.6% to 81.2%), decreases in the intensity and number of hot flashes, and decreases the frequency of subjective insomnia (89.5% to 36.9% vs. 94.7% to 63.2%)
Cohen *et al.* (2013)	Omega-3 Supplements	Peri- and postmenopausal women with vasomotor symptoms	Randomized; Tx1 = Oral omega-3 (n=177) Tx2 = Oral placebo (n=178)	12 weeks	2%	No	ISI and PSQI	No significant differences between the omega-3 group in vasomotor or sleep variables, relative to control.

Table 3. contd….

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Rotem & Kaplan (2007)	Black cohosh	Peri- and postmenopausal women with vasomotor symptoms	Randomized; Tx1 = Oral black cohosh preparation (n=25) Tx2 = Oral placebo (n=25)	12 weeks	30%	No	Subjective sleep quality rating	Relative to the placebo control group, the black cohosh group demonstrated significant increases sleep quality scores (70% increase vs. 21% increase), decreases in hot flash mean scores (73% decrease vs. 38% decrease) and decreases in night sweats mean scores (69% decrease vs. 29% decrease)
Vermes, Banhidy & Acs (2005)	Black cohosh	Peri- and postmenopausal women	Tx1 = Oral black cohosh preparation (n=2016)	12 weeks	0%	No	Kupperman Menopausal Index	Black cohosh led to significant decreases in the insomnia item scores.
Hachul *et al.* (2008)	Estrogen compared with combined estrogen and progesterone compared with progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estrogen for 12 weeks, followed by estrogen and progesterone for 12 weeks (n=14) Tx2 = Oral placebo for 12 weeks, followed by progesterone for 12 weeks (n=19)	24 weeks	0%	No	PSG	Objective sleep factors (efficiencies, latencies) were not significantly improved, but the combination of estrogen and progesterone to be more effective than estrogen alone in decreasing the prevalence of PLM (8.1% vs. 2.1%), hot flashes (14.2% vs. 0%) and bruxism (11.1% vs. 0%). However, hormone therapy decreased the prevalence of arousal in both groups
Kalleinen *et al.* (2008)	Estrogen and progesterone therapy	Pre- and postmenopausal women	Randomized; Premenopausal Tx1 = Oral cyclic estrogen and progesterone (n=9) Tx2 = Oral placebo (n=8) Postmenopausal Tx1 = Oral continuous estrogen and progesterone (n=9) Tx2 = Oral placebo (n=9)	6 months	11%	No	PSG	Sleep quality measure were not significantly benefited from estrogen and progesterone therapy in neither premenopausal nor postmenopausal women, compared to placebo.
Schussler *et al.* (2008)	Progesterone Replacement Therapy	Postmenopausal women who did not report poor sleep as motivation for the study	Randomized, crossover; Tx1 = Oral progesterone for 3 weeks followed by 2 week washout followed by placebo for 3 weeks (n=5) Tx2 = Oral placebo for 3 weeks followed by 2 week washout followed by progesterone for 3 weeks (n=5)	8 weeks	0%	No	PSG	Progesterone alone depicted significant reductions in time spent awake and a significant increase in REM sleep in the first third of the night, compared to placebo effects.

Table 3. contd….

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Heinrich & Wolf (2005)	Estrogen compared with combined estrogen and progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estradiol (n=12) Tx2 = Oral estradiol and progesterone (n=10) Tx3 = Oral placebo (n=13)	24 weeks	31% (prior to analysis)	No	Subjective sleep report (in a depression questionnaire)	There were no significant differences on sleep quality between the three groups.
Tranah *et al.* (2010)	Present hormone therapy users compared with past hormone therapy users compared with no hormone therapy users	Postmenopausal women	Naturalistic; Tx1 = Present hormone therapy users (n=424) Tx2 = Past hormone therapy users (n=1,289) Tx3 = No hormone therapy users (n=1,410)	4 consecutive 24 hour periods	N/A	No	Actigraphy	Postmenopausal women currently using HT, compared to past HT users and those who have never used HT, had improved sleep quality for two of five actigraphy measures: shorter wake after sleep onset (WASO) and fewer long-wake (5 minutes or longer) episodes. Sleep efficiency (SE), sleep latency, and nap-time did not differ between the three groups
Gambacciani *et al.* (2011)	Estrogen and progesterone replacement therapy	Postmenopausal women	Randomized; Tx1 = Oral estradiol and drosperinone (n=35) Tx2 = Oral calcium (n=35)	12 weeks	26%	3 months	Women's Health Questionnaire	At 12 weeks, the estradiol and drosperinone group experienced significant improvements in sleep problems, vasomotor and somatic symptoms, compared to those in the control group.
Soares *et al.* (2006)	Escitalopram (Lexapro) compared with estrogen and progesterone replacement therapy	Peri- and postmenopausal women with depressive disorders and menopause related symptoms	Randomized; Tx1 = Oral escitalopram (10-20mg; n=20) Tx2 = Oral ethinyl estradiol and norethindrone acetate (n=20)	8 weeks	10%	No	PSQI	Both treatment groups experienced significant increases in sleep variables, however there was no significant differences between the two treatments.
Joffe *et al.* (2007)	Duloxetine	Postmenopausal women with Major Depressive Disoder	Pilot; Tx1 = Oral duloxetine (60-120mg; n=20)	8 weeks	25%	No	PSQI	Duloxetine led to significant increases in sleep measures.
Stearns *et al.* (2003)	Paroxetine (Brisdelle)	Postmenopausal women	Randomized; Tx1 = Oral placebo (n=56) Tx2 = Oral paroxetine (12.5mg; n=51) Tx3 = Oral paroxetine (25mg; n=58)	6 weeks	15.8%	No	Daily hot flash diary.	Both high and low dose paroxetine significantly decreased hot flash frequency and severity relative to placebo. Low dose displayed highest tolerability and compliance ratings.

Table 3. contd….

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Stearns *et al.* (2007)	Paroxetine (Brisdelle)	Postmenopausal women, with 80% cancer survivors	Randomized crossover; Tx1 = Oral paroxetine (10mg) followed by placebo (n=37) Tx2 = Oral placebo followed by paroxetine (10mg; n=39) Tx3 = Oral paroxetine (20mg) followed by placebo (n=38) Tx4 = Oral placebo followed by paroxetine (20mg; n=37)	9 weeks	29%	No	Daily hot flash diary and Medical Outcomes Study Sleep Problems Index	Both high and low dose paroxetine significantly decreased hot flash frequency and severity relative to placebo. Low dose displayed highest tolerability and compliance ratings. Low dose was the only treatment that significantly reduced sleep symptoms relative to placebo.
Pansini *et al.* (1994)	Trazadone	Postmenopausal women	Pilot; Tx1=Oral trazadone (75mg; n=25)	3 months	0%	No	Kupperman Menopausal Index	Trazadone led to significant decreases in insomnia, anxiety and irritability scores. The intensity of hot flushes appeared reduced, but was not statistically significant.
Dobkin *et al.* (2009)	Ramelteon (Rozeram)	Peri- and postmenopausal women with sleep latency insomnia	Open label pilot; Tx1 = Ramelteon 8mg (n=20)	6 weeks	30%	No	Sleep diary	Ramelteon was effective in improving subjective reports of sleep latency, total sleep time, and sleep quality.
Dolev (2011)	Mirtazapine followed by prolonged-release melatonin add-on	Perimenopausal women with insomnia symptoms without depression	Case studies: Tx1=Oral Mirtazapine (15mg) followed by PRN oral prolonged release melatonin (2 mg; n=11)	3 months	0%	No	PSQI	The mirtazapine/ melatonin combination led to significant decreases in global insomnia scores, as well as sleep latency time.

consists of recommending a variety of behaviors and tending to environmental factors (e.g., light, bedroom temperature) that are conducive to sleep and may decrease discomfort related to nocturnal hot flashes. Examples of sleep hygiene instructions include wearing lighter pajamas to bed and keeping a second pair near the bed, using lighter bedding and layering, keeping the ambient room temperature cool, keeping a fan nearby and a cool beverage near the bed, limiting caffeine products throughout the day, avoiding alcohol and smoking, and obtaining exercise away from bedtime (> 4 hours).

CBT-I has been shown to be more efficacious than zopiclone for short- and long-term management of adult insomnia [38]. CBT-I has also been shown to be efficacious for the treatment of insomnia [39] in randomized trials comparing CBT-I to sedative hypnotics in older adults [40]. Furthermore, CBT-I is virtually side effect free, while sedative hypnotics may be accompanied by cognitive or gastrointestinal side effects [38, 39]. CBT-I may be beneficial for insomnia in menopausal women; however, to date, no randomized clinical trials have been conducted to examine efficacy of CBT-I in menopausal women or special treatment considerations in this population.

Complementary and Alternative Medicine

Yoga

Recent attention has been given to the efficacy of yoga-based protocols on reducing menopause-related vasomotor symptoms [41, 42]. There are, however, few studies focusing on the benefits of yoga on menopause-related insomnia. One randomized clinical trial with 44 postmenopausal women by Afonso *et al*. [41] demonstrated that both a standardized yoga intervention and a passive stretching active control intervention significantly reduced incidences of insomnia as assessed by the ISI. Yoga additionally decreased anxiety, depression, vasomotor symptoms and menopause-related quality of life scores. Furthermore, when compared against the wait-list control group, yoga significantly decreased

Table 4. Sleep disordered breathing treatment studies.

Study Author	Treatment Assessed	Population	Group Design and Initial Sample Size	Treatment Length	Attrition Rates	Follow up	Outcome Measure	Results
Guilleminault *et al.* (2002)	Cognitive behavioral therapy for insomnia (CBT:I) and respiratory treatments (CPAP or turbinactomy)	Postmenopausal women with chronic insomnia. Half had Upper Airway Resistance Syndrome	Randomized; Tx1 = UARS group with respiratory treatment (n=15 CPAP; n=15 turbinactomy) Tx2 = UARS group with CBT:I treatment (n=32) Tx3 = Normal breathers with immediate CBT:I (n=34) Tx4 = Normal breathers with delayed CBT:I (n=34)	6 months between baseline and post treatment assessments. CBT:I was 6 sessions over 8 weeks.	2%	No	Subjective sleep quality Visual Analog Scales, 7 days of actigraphy, PSG, and sleep logs.	Respiratory treatments in patients with UARS, significantly decreased complaints of daytime fatigue, compared to the other groups. Regardless of the presence of UARS, CBT:I decreased sleep latency, compared to respiratory treatments and control.
Pickett *et al.* (1989)	Estrogen and progesterone replacement therapy	Women with complete overihysterecto my	Tx1 = 7 days of oral placebo followed by 7 days of oral estrogen and progesterone (n=9)	14 days	0%	No	PSG	Estrogen and progesterone led to significant decreases in the average number of sleep disordered events (apnea-hypopnea index).
Saaresranta *et al.* (2006)	Estrogen replacement therapy (oral, gel, and/or patch)	Postmenopausal women with hysterectomy	Non-randomized; Tx1 = No estrogen (n=11) Tx2 = Previous estrogen use (n=22) Tx3 = Present short term estrogen use (n=11) Tx4 = Continuous estrogen use (n=22)	5 years	3%	No	PSG	Long term estrogen use predicts higher mean overnight arterial oxyhemoglobin saturation levels and lower numbers of sleep disordered events (apnea-hypopnea index).
Polo-Kantola *et al.* (2003)	Estrogen replacement therapy	Postmenopausal women with hysterectomy	Randomized, crossover; Tx1 = Transdermal estrogen for 3 months followed by 1 month washout followed by placebo for 3 months (n=30) Tx2 = Transdermal placebo for 3 months followed by 1 month washout followed by estrogen for 3 months (n=32)	7 months		No	PSG through static charge sensitive bed	Marginal, but non-significant improvements in sleep disordered symptoms after treatment with estrogen.

insomnia symptomology, vasomotor symptoms and menopause-related quality of life scores. Yoga appears to be a promising treatment option for the alleviation of menopause-related insomnia; however, larger randomized trials with objective insomnia and sleep measurements, such as actigraphy and PSG, are needed to confirm its therapeutic benefits.

Therapeutic Massage

In addition to yoga, the effectiveness therapeutic massage (TM) has been investigated in attenuating symptoms of menopause-related insomnia. TM is the manipulation of deeper layers of muscle and connective tissue using various techniques, to enhance function and aid in the healing process, decrease muscle reflex activity, inhibit motor-neuron excitability, and promote relaxation and well being. In a recent pilot study evaluating the effectiveness of TM on seven postmenopausal women with insomnia (difficulty falling asleep or insomnia symptoms at least three times a week), Oliveira and colleagues [43] found that the administration of sixteen, bi-weekly, hour-long TM sessions was correlated with a decrease in the severity of subjective insomnia and anxiety-depressive symptoms, as measured with sleep diaries, the Beck Depression Inventory (BDI), and the State Trait Anxiety Inventory (STAI). Further, they found a decrease in REM latency and increased percent time spent in deeper stage 3 sleep, as measured by PSG before and after TM. Upon one-year follow-up, two participants reported insomnia relapse, two reported better sleep than before treatment, and three reported no problems with sleep. Although this finding is potentially promising, larger studies of randomized, placebo-controlled design are needed to draw more definite conclusions about the clinical significance of TM for menopausal insomnia.

Auricular Acupressure

An additional alternative medicinal treatment for alleviating insomnia is auricular acupressure (AA). AA is

based on an ancient Chinese technique that utilizes pressure on discrete pressure points in the ear to stimulate bodily function [44]. In a study of 45 Taiwanese women with postmenopausal insomnia who received a four-week course of daily AA therapy using five bilateral magnetized pellets, Kung *et al*. [44] found significant increases in subjective sleep quality based on the PSQI.. The authors conclude that AA intervention may contribute to the improvement of postmenopausal insomnia by increasing parasympathetic cardiac activity while decreasing sympathetic cardiac activity. The lack of randomly assigned control group, however, was a major limitation of this study.

Exercise

Llanas *et al*. [45]'s reported on two case studies used PSG to assess a physiotherapeutic treatment on postmenopausal related insomnia. The exercise treatment was composed of active stretching, passive stretching, active strengthening, and massage therapy. The treatment occurred for two ninety-minute sessions, twice a week for six months. The authors posit that exercise and fitness would exert positive effects on menopausal insomnia. They found that one patient experienced a significant increase in REM sleep and in total sleep efficiency, while the other patient experienced a reduction in sleep latency and an increase in slow wave sleep.

Pharmacological Treatments

Hormone Replacement Therapy

Vasomotor symptoms begin when the menstrual cycle ceases, as a result of reduced estrogen and progesterone levels. This hormonal reduction is associated with the onset of menopausal symptoms, such as hot flashes, irritability, depressed mood, fatigue, and insomnia. Physiologically, hot flashes occur when lowered estrogen levels cause peripheral and central temperature increases. Primary pharmacological treatments for menopause-related vasomotor symptoms including insomnia revolve around replacing the diminished levels of estrogen and/or progesterone levels. The added estrogen contributes to sleep through metabolizing norepinephrine, serotonin and acetylcholine, which consequently increases REM cycles [46]. Antonijevic, *et al*. [47] confirmed mild REM sleep increases with PSG in 11 postmenopausal women administered with estrogen. Progesterone stimulates benzodiazepine receptors, causing the release of gamma-aminobutyric acid (GABA), a sedating neurotransmitter that can potentially facilitate sleep [46]. Taken together, the menopause facilitated fluctuations and ultimate decline in estrogen and progesterone can impact sleep.

There is a paucity of studies exploring the direct effects of hormone replacement therapy (HRT) on sleep; however, some studies provide evidence of characteristic sleep reduction variables. Randomized controlled trials that have explored the effects of estrogen and progesterone on sleep efficiency have resulted in mixed results. Some studies found significant subjective sleep disturbance alleviation using estrogen replacement therapies [48, 49] while others found polysomnographic evidence of slightly increased REM sleep and shorter sleep latencies compared to placebo [50, 51]. These studies are limited by their small sample sizes. Other studies, however, found no significant sleep differences between estrogen administered and non-estrogen administered patients through analysis of multiple PSG recording nights [52, 53].

Progesterone/estrogen combination studies have demonstrated small subjective sleep quality improvements, with one study [54] utilizing PSG recordings and a placebo control group finding no significant sleep quality differences. Montplaiser *et al*. [55] compared an estrogen only group to an estrogen and micronized progesterone group utilizing PSG. They found the combination group significantly reduced participant's sleep efficiency by 8%, with the estrogen-only group showing no effects [55]. Saletu *et al*.'s [56] randomized, placebo and estrogen/progesterone treatment study on 55 postmenopausal women diagnosed with insomnia displayed moderate, yet non-significant improvements in wakefulness after sleep onset when measured with PSG post-treatment. Although there were no objective improvements, there were significant improvements regarding subjective ratings of sleep quality and wakefulness.

HRT's inconclusive treatment properties were further complicated by the Women's Health Initiative's (WHI) revelation, which indicated a 29% increased risk of heart disease and 26% increased risk of breast cancer [57]. Although there is no significant risk of death from HRT, these statistics are undoubtedly concerning. As a result, the WHI recommended a maximum of 5 years of HRT at low doses. One large sample survey (n=1876) [58] of women seeking alternatives to HRT reported other side effects, including breast tenderness, abnormal bleeding and increased body weight. The risks and side effects of HRT have caused much concern among patients experiencing vasomotor symptoms, and therefore many peri- and postmenopausal women are seeking alternatives to HRT [46].

Sedative Hypnotics

Benzodiazepine and Non-benzodiazepine Hypnotics

A short-acting non-benzodiazepine hypnotic may be warranted for short-term use for acute, initial insomnia. Tolerance, withdrawal, dependence, and exacerbation of depression may occur when hypnotics are used longer than 2 weeks, and the discontinuation of treatment may elicit rebound insomnia [59]. Furthermore, somnambulism and complex sleep behaviors have emerged in the literature as a notable, but rare, side effect of sedative hypnotics [60-63]. The side effects of zolpidem, a popular non-benzodiazepine hypnotic, have been noted by the United States Food and Drug Administration, and in 2013, they released a public drug safety warning about the next day impairments [64]. They recommend reducing the doses of zolpidem to the lowest effective dose possible, 5mg, especially in women [64]. It is important to note that many of the studies evaluating zolpidem use prior recommended doses, and may not be reflective of its current efficacy and side effect profile in women. Although the long-term effects of hypnotics are unknown, increased mortality has been linked with hypnotic use [65, 66]. Zaleplon (Sonata) and zolpidem (Ambien) are more effective in treating problems with initiating sleep, but

less effective with problems maintaining sleep. Soares *et al*. [67] enrolled 410 peri- or early postmenopausal women with insomnia (aged 40-60 years) in a double-blind, placebo-controlled study and found eszopiclone (Lunesta 3 mg) significantly decreased ISI scores, in addition to improved mood, quality of life, and menopause-related symptoms.

In a recent randomized, placebo-controlled crossover trial by Joffe and colleagues [68]; sleep, mood, hot flashes, and quality of life were examined in 59 peri- and postmenopausal women, ages 40-65, with sleep onset and/or sleep maintenance insomnia, with co-occurring hot flashes, and depressive and/or anxiety symptoms. The authors found that eszopiclone reduced insomnia severity and improved all sleep parameters, depressive and anxiety symptoms, quality of life, and nighttime hot flashes compared to placebo. A limitation of this study was the relative homogenous sample of women, which was mostly comprised of Caucasian, postmenopausal, non-obese women whom reported few hot flashes at baseline. Additionally, women treated with hormonal therapy or antidepressants were not excluded from the study. Finally, outcomes were not measured beyond the 11-week trial and it was thus difficult to conclude if the improvements in insomnia and other vasomotor symptoms remained over time. These newer generation non-benzodiazepines have less tolerance, withdrawal, and dependence liability than traditional benzodiazepines, thereby reducing abuse potential. However, they still have habit-forming properties, and long-term use remains undesirable [69].

Zolpidem indicated favorable improvements on subjective sleep quality in a four-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group, outpatient study [70] on 141 peri- and postmenopausal women complaining of sleep maintenance difficulty in addition to nocturnal hot flashes, hot flashes or night sweats. Dorsey and colleagues [70] found that those in the zolpidem group reported significantly increased total sleep time, decreased wake time after sleep onset, and decreased number of awakenings throughout the duration of the study compared to those in the placebo group. Those in the zolpidem group did not report a significant improvement in quality of life or ability to function, and also experienced significantly more incidences of dizziness (8.8%), backache (7.4%), and irritability (4.4%). Despite the side effects of zolpidem and the observed placebo effect, the authors conclude that zolpidem was a generally safe and effective treatment for menopause-related insomnia, as measured by self-report in this cohort of peri- and postmenopausal women.

Ramelteon

Several other psychopharmacological approaches have emerged in the field of insomnia treatment. In a six-week, prospective, open-label trial of ramelteon (8 mg), a selective melatonin receptor agonist, Dobkin and colleagues [71] observed significant improvements in latency to sleep onset, total sleep time and sleep efficiency from sleep diary data in 20 healthy peri- and postmenopausal American women with insomnia. Using self-report measures, they also found improvements in sleep quality, sleep impairment, daytime functioning, quality of life and mood. There was a non-significant effect of ramelteon on wake after sleep onset (WASO), which is the primary complaint in menopausal women experiencing hot flashes. The investigators observed no tolerance or rebound over the course of the trial and only 40% of women reported side effects, most of which were mild. However, because this was an uncontrolled, non-randomized pilot study, in which 6 out of 20 participants dropped out, no objective sleep data was collected and the results are thus inconclusive.

Integrated Cognitive Behavioral Therapy for Insomnia (CBT-I) and Brief Sedative Hypnotic Use

Morin *et al*. [72] investigated a novel 2 stage protocol utilizing brief sedative hypnotic use and CBT-I. In a prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia (mean insomnia duration of 16.4 ($\pm$13.6) years) patients treated with combined therapy initially, followed by CBT-I alone obtained the best long-term outcomes. This was evidenced by higher remission rates (68%) at the six-month follow-up compared with patients who continued to take zolpidem (42%) during extended therapy. During the initial six-week treatment phase, the investigators found the main effect of CBT-I was on improving sleep latency, wakefulness after sleep onset, and sleep efficiency. Nevertheless, during the 6-month extended therapy phase and six-month follow-up period, combined therapy produced a higher remission rate compared with CBT-I alone (56% vs 43%). The authors conclude that during acute therapy, the addition of hypnotic medication to CBT-I produced added benefits, which are optimized by discontinuing medication during maintenance CBT-I in long-term treatment. Although this study did not examine the treatment of insomnia specifically in menopausal women, 60.6% of participants were female, and mean age (SD) for participants was 50 (10.1) years. An additional strength of this study was the use of both subjective and objective measures of sleep (daily sleep diaries and seven nights of PSG). The homogeneous sample limits the generalizability of these findings, since all patients were Caucasian, employed (73.3%), and predominantly married or in a common-law relationship (68.1%).

Antidepressants

Selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs and SNRIs) have proven to be efficacious in mitigating menopause-related depression [73]. Other randomized, controlled trials have demonstrated modest capabilities of various antidepressants in reducing hot flashes [74]. There are limited studies on the direct effects of antidepressants on insomnia. Ensrud *et al*. [75] recently investigated escitalopram (Lexapro)'s effects on insomnia in a randomized, controlled clinical trial of 205 peri- and postmenopausal women with hot flashes and without major depression. At week eight, escitalopram was more effective than placebo in decreasing ISI scores (41% decrease vs. 21% decrease) and PSQI scores (32% decrease vs. 17% decrease) relative to baseline scores. There was no significant difference in the presence of newly emergent adverse events between groups. The results of this study are limited by its short duration, and thus more research is needed to justify the use of antidepressants for insomnia treatment.

INSOMNIA SYMPTOMS

Non-pharmacological Treatments

Cognitive Behavioral Therapy

Many therapies have been investigated for their abilities to reduce night sweats, which would aid in decreasing sleep awakenings, and thus indirectly target insomnia symptoms. Cognitive behavioral therapy may have an additive effect for post-menopausal insomnia symptoms by providing education and teaching skills to cope with climacteric symptoms associated with menopausal symptoms. CBT for the treatment of climatic symptoms (CBT-C) may include (1) psychoeducation, which involves shared discussion around symptoms and experiences of menopause; (2) cognitive strategies that assist women in identifying and re-evaluating negative and/or catastrophic thoughts about themselves, the menopausal transition, their hot flashes and other menopausal symptoms; (3) behavioral strategies which involves increasing women's participation in health related activities such as relaxation (e.g., paced respiration), regular exercise, and eliminating behaviors that might exacerbate hot flashes (e.g., rushing, smoking, alcohol intake, caffeine intake, and spicy food intake); and (4) monitoring hot flashes and night sweats daily [76]. A group format CBT-C (for hot flashes, insomnia symptoms, and depression) has been applied peri- and postmenopausal women with promising results. Green *et al*. recently applied CBT-C to an 8 person pilot trial and found significant reductions in frequency and interference of hot flashes, depression, anxiety and quality of life [77]. Sleep disruption as assessed by the PSQI was reduced post-treatment, but the decreased scores were not significant [77]. Mann *et al*. tested the efficacy of a group CBT-C format on 96 women displaying menopausal symptoms after breast cancer treatment [78]. Compared to the control group, the CBT group demonstrated significant reductions in insomnia symptoms and depressed mood as assessed by a self-report measure at 20 weeks follow-up [78]. There were no significant reductions in hot flashes both post-treatment and at 20 weeks follow-up [78]. Results from this study are limited in application to peri- and postmenopausal women, as menopausal status was never confirmed in the study participants. In general, more research is needed on the effects of CBT-C on menopause related insomnia symptoms.

Mindfulness-based Stress Reduction

Mindfulness-based stress reduction (MBSR) has been explored in its capacity to reduce vasomotor symptoms, in addition to subjective insomnia symptoms, with moderate success. In a randomized trial of 110 peri- and post-menopausal women (47 to 69 years old) experiencing an average of 5 or more moderate to severe hot flashes and/or night sweats per day in the past week, Carmody and colleagues [79] found that women receiving MBSR, compared to those in the wait-list control group experienced clinically significant improvements in the degree of bother from hot flashes and night sweats in the previous 24 hours. Furthermore, the MBSR group also experienced improvements in subjective sleep quality, menopause-related quality of life, anxiety, and perceived stress. Improvements were maintained at 3 months post treatment without any "booster" intervention. Major limitations of this study include the lack of an active control group, a homogenous sample of mostly Caucasian and educated women, and that only 63% of women provided 80% or more of bothersome ratings in their hot flash diaries.

Complementary and Alternative Medicine

Acupuncture

Researchers have investigated acupuncture as a potential treatment for decreasing vasomotor and sleep problems [80]. In a multicenter, randomized, controlled trial of 267 post-menopausal Norwegian women, Borud *et al*. [80] found that 10 sessions of individualized acupuncture treatment paired with advice on self-care significantly decreased hot flash frequency and intensity compared to the control group. Furthermore, acupuncture improved sleep and somatic symptom dimensions of the Women's Health Questionnaire. Nevertheless, the external validity of this study is questionable, as more than 60% of the participants had previously used acupuncture and were thus self-selecting. Furthermore, due to the nature of acupuncture treatment, double-blind, sham-controlled studies are difficult to design and implement. This study suggests, however, that acupuncture and self-care can relieve hot flash intensity and frequency as well as increase health-related quality of life, including sleep measures, in postmenopausal women.

Isoflavens (Soy)

Hachul *et al*. [81] in a randomized controlled trial of 37 postmenopausal Brazilian women (age 50 to 65) found that 80 mg of soy-derived isoflavones taken daily for 4 months significantly improved sleep efficiency, as measured by baseline and post-treatment PSG (from 77.9% to 83.9% in isoflavone group versus 77.6% to 81.2% in placebo group), decreased the intensity and number of hot flashes, and decreased the frequency of subjective insomnia symptoms (89.5% to 36.9% in isoflavone group; 94.7% to 63.2% in placebo group). Measuring objective sleep efficiency with PSG is a strength of the study, but the small sample size (n=37) is a limitation.

In a recent randomized, controlled study of 634 Italian women with typical menopausal symptoms and mild psychoaffective/insomnia symptoms not requiring psychopharmacological therapy, Agosta *et al*. [82] found that a 12-week treatment of a soy isoflavones mixture (n=300) was effective in improving hot flushing, nocturnal sweating with awakenings, palpitations and vaginal dryness. Additionally, the group receiving magnolia bark extract, a natural anxiolytic, in addition to the soy treatment (n=334), showed improvement on psycho-affective symptoms associated with menopause, including anxiety, irritability and insomnia symptoms. Rates of adverse events were minimal and similar between both groups.

Omega-3 Supplements

Beyond soy, omega-3 supplements have gained popularity for treatment of a variety of issues, including hot flashes [83]. The pharmacodynamics are not completely understood, with research implicating the serotonin and dopamine systems in its pathways [84]. Nevertheless, due to its widespread accessibility, peri- and postmenopausal

women use these supplements to reduce their hot flashes [83]. After mixed efficacy results from small-scale pilot studies, Cohen *et al*. [84] set out to examine the efficacy of omega-3 supplements for hot flashes and insomnia symptoms within a structured, large-scale (n=355), multi-site, randomized control trial. Upon examination of the results, the investigators found no significant differences between the omega-3 supplement group and the control group on hot flashes per day, bother of hot flashes, ISI scores and PSQI scores [84]. This study is limited by its breadth, as it attempted to analyze the efficacies of exercise, yoga and omega-3 within the same groups [84].

Black Cohosh (Cimicifuga Racemosa, syn.: Actaea Racemosa)

Black cohosh has become a popular herbal alternative to HRT for alleviating vasomotor symptoms, especially in European and Asian countries [85, 86]. The exact pharmacodynamic properties of black cohosh have not been established, with some studies suggesting a selective estrogen effect [87], and others describing a serotonergic and dopaminergic receptor blocking effect [88]. Many studies have demonstrated significant hot flash reductions in self-report measures [88, 89], with few directly investigating sleep symptoms. In one recent randomized clinical evaluation of a black cohosh and ginseng based supplement, Rotem *et al*. [90] substantiated considerable decreases on a sleep intensity question relative to a placebo group (70% decrease vs. 21% decrease) after 12 weeks of treatment. Additionally, this black cohosh mixture was more effective than placebo in decreasing hot flash mean scores (73% decrease vs. 38% decrease) and night sweats mean scores (69% decrease vs. 29% decrease) relative to baseline scores. Although these significant results denote efficacy of black cohosh, the final results are questionable due to high drop out rates from both placebo and treatment groups, small group sizes, and non-significant differences before week 12 measurements.

A Hungarian study [91] on 2016 women presenting vasomotor complaints and who had rejected HRT or for whom HRT was contraindicated, demonstrated modest, but significant reductions on a insomnia symptom question (2.17 points) using Ramifemin, a popular black cohosh mixture. This study was limited by its lack of placebo group, its homogenous response rate and the questionable validity of its self-report menopause measure [91]. As both studies illustrate, the methodological concerns with black cohosh mixture prevent us from recommending this supplement for reducing menopause-related insomnia symptoms.

Pharmacological Treatments

Hormone Replacement Therapy (HRT)

The efficacy of HRT for sleep and mood disturbances remains unclear, with some studies finding no benefit and others yielding positive results. Exogenous estrogen reportedly decreases sleep latency and awakenings after sleep onset, while increasing total sleep time, presumably due to decreases in hot flashes [92]. The marked subjective improvement in sleep with HRT [92], however, is contrasted with a lack of consistent sleep improvement when assessed with PSG [93]. Estrogen is the drug of choice when treating hot flashes, but its efficacy in treating insomnia symptoms is unclear. In a thorough review of the literature, Parry *et al*. [94] noted that compared to placebo, treatment with estrogen reduces frequency and duration of night-time wakefulness, increases amount of REM sleep, decreases hot flash frequency and improves mood. Treatment with conjugated estrogen appears to reduce sleep latency, increase REM minutes and percent, improve vasomotor symptoms and objective/subjective sleep efficiency and sleep quality. Similarly, transdermal estradiol is also associated with increased sleep quality, reduced sleep latency and number of awakenings, and improvement in somatic, mood and vasomotor symptoms.

Additionally, Hachul *et al*. [95] examined the effects of estrogen and progesterone on sleep in 33 postmenopausal women, finding the combination of estrogen and progesterone to be more effective than estrogen alone in decreasing the prevalence of periodic limb movements (PLM; 8.1% vs. 2.1%), hot flashes (14.2% vs. 0%) and bruxism (11.1% vs. 0%). Nevertheless, the authors found both estrogen and estrogen/progesterone to be effective in decreasing arousals and sleep fragmentation [95].

Recent work by Kalleinen and colleagues [96] on 17 premenopausal (aged 45-51 years) and 18 postmenopausal (aged 58-70 years) women who slept in a laboratory for two nights before and after 6 months of estrogen-progestin treatment (EPT) disputes this trend. Compared to placebo, premenopausal women receiving EPT had more awakenings from stage 1 sleep, and postmenopausal women with EPT had a greater total number of awakenings and decreased slow wave activity than the corresponding placebo group. While the limited findings were mostly unfavorable to EPT, one cannot conclude that EPT deteriorates sleep more than placebo. Although this study showed that neither middle-aged cycling premenopausal women nor older postmenopausal women benefit from estrogen-progestin treatment in terms of their sleep quality, treatment with progesterone alone has shown significant reductions in time spent intermittently awake [97]. Further a significant increase in REM sleep in the first third of the night in postmenopausal women was seen with progesterone treatment [97].

Furthermore, in a study [98] examining the effects of estradiol or estradiol/progesterone treatment on sleep quality, mood, depressive and menopausal symptoms in older healthy women who have undergone hysterectomies, Heinrich and Wolf also reported no significant effects. This placebo-controlled double-blind study examined the effects of estradiol (2 mg), estradiol plus progesterone (100 mg) or placebo at baseline, at 4 weeks and 24 weeks, using three questionnaires. The results indicated no effect on mood, well-being, menopausal symptoms, sleep quality and depressive symptoms.

In a multi-site, population based study of 3,123 postmenopausal community-dwelling aged women, Tranah and colleagues [99] found that postmenopausal women currently using HRT, compared to past HRT users and those who have never used HRT, had improved sleep quality for two of five actigraphy measures: shorter wake after sleep onset (WASO) and fewer long-wake (5 minutes or longer)

episodes, both of which are related to sleep fragmentation. Sleep efficiency, sleep latency, and nap-time did not differ between the three groups. One limitation of this study was that actigraphy was only measured for 4 days. Additional limitations included several significant demographic differences between the groups with current HRT users slightly younger and more likely to be married, never HRT users more likely to have a higher BMI and more medical conditions, and past HRT users more likely to score higher on an anxiety scale.

In a prospective, randomized controlled trial of low-dose HRT on qualify of life, metabolic parameters, and blood pressure in 70 healthy, post-menopausal Caucasian women, Gambacciani and colleagues [100] found that participants who took beta-estradiol (1 mg/day; E2) plus drospirenone (2 mg/day; DRSP) for 6 to 12 weeks, compared to those in the control group, experienced significant improvements in sleep problems, vasomotor and somatic symptoms, anxiety/ fears, depressed mood, and sexual behavior as measured by the Women's Health Questionnaire. Three months after treatment, the researchers also found that E2+DRSP treatment significantly decreased waist circumference, blood insulin values, and systolic blood pressure. This study was limited by the small, homogeneous sample, lack of a placebo control, high drop-out rate in the control versus treatment group during the 3-month follow-up phase (42.8% vs 8.6%), and failure to control for behavioral modifications (e.g. in diet or exercise) that may have confounded findings.

Antidepressants

Using antidepressants to treat sleep disruption in the absence of depression is not recommended [101]. Their mechanisms for treating insomnia include blocking wake-promoting neurotransmitters (acetylcholine, histamine, norepinephrine, serotonin, and dopamine) for sleep enhancement. Among them, the main sedating effects are caused by the anticholinergic and antihistamine effects [102]. Some antidepressants and mood stabilizers (e.g., venlafaxine, gabapentin) may ameliorate mood and vasomotor symptoms but may aggravate insomnia symptoms. Escitalopram (an SSRI) was more effective than estrogen and progesterone therapy in improving depressive symptoms in peri- and postmenopausal women, while having a positive impact on other menopause-related symptoms [103]. Although serotonin was shown to be ineffective in treating vasomotor symptoms [104], SSRIs like duloxetine appear to significantly improve menopausal sleep, mood, vasomotor, and physical symptoms [105]. In a double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy in the treatment of vasomotor symptoms in menopause, Archer *et al*. [106] found that hot flash severity and nighttime awakenings were significantly reduced at weeks 4 and 12 in postmenopausal women (n= 458) experiencing 50 or more moderate to severe hot flushes per week. All three groups showed a reduction in hot flashes from baseline to week 12, with the group receiving 100 mg/d achieving 65.4% reduction, the group receiving 150 mg/d achieving a 66.6% reduction, while the placebo group had a 50.8% reduction. This study reported a higher number of adverse events in the active groups in week one only. Their findings provide evidence of an effective non-hormonal treatment for menopausal hot flashes associated with nocturnal sleep fragmentation.

Recently, an SSRI named paroxetine (trade name Brisdelle) received approval by the United States Food and Drug Administration (FDA) to treat moderate to severe menopause related hot flashes [107]. Paroxetine CR is the first non-hormonal treatment for hot flashes approved by the FDA. The FDA based its decision on two randomized control trials. The studies [108] randomized 165 postmenopausal women to one of three groups: placebo, 12.5mg/d or 25.0/ mg/d. The study was conducted in 17 sites across the United States, including urban, suburban and rural clinics. At the end of 6 weeks, paroxetine CR significantly reduced frequency and severity of hot flashes by around 20% more than placebo. Although insomnia symptoms were not directly measured, 14.3% of study participants taking paroxetine reported insomnia symptoms as an adverse side effect to the treatment. The second study [109] entered 151 postmenopausal women into a randomized crossover control design, utilizing both 10mg and 20mg doses of paroxetine CR. More than 80% of the patient population was breast cancer survivors, while the first study contained only 7.3%. Similar to the first study, both doses of paroxetine significantly decreased hot flash frequency and severity, up to 30% more than placebo after 9 weeks of treatment. The authors in both studies conclude that the low dose paroxetine is recommended for clinical use due to higher levels of tolerability and compliance. This study was limited by its high drop out rate (29%). In terms of insomnia symptoms, the low dose paroxetine was the only group to display significant sleep improvements relative to the placebo group. The complete effects of paroxetine remain to be examined utilizing more objective sleep measures.

Other antidepressents beyond SSRIs have been examined for their insomnia symptom relief. The FDA recently approved doxepin, a tricyclic antidepressant with antihistamine effects, for the treatment of primary and comorbid chronic insomnia, [110]. In the high dose range, doxepine has anti-histamine, anticholinergic, anti-serotonergic and anti-adrenergic effects, but in hypnotic doses (<10 mg), it has a relatively pure anti-histamine effect. Doxepin has been shown to have both sleep initiation and maintenance improvements in the nights following use in several randomized control trials in both middle and older aged adults, as assessed by PSG [111-115]. As of yet, doxepin has not been tested in menopausal related insomnia symptoms.

Other sedating antidepressents have been evaluated in connection to menopause related insomnia symptoms, such as trazodone and mirtazapine, but they are not FDA approved for the treatment of insomnia without comorbid depression [110]. Trazadone was the most widely used medication for insomnia until 2002, but despite its popular use, there are limited studies focused on efficacy and safety of insomnia without depression [116-118]. In terms of menopausal related insomnia symptoms without depression, there are a few studies examining its efficacy [119] Pansini *et al*. [119] showed significantly reduced subjective insomnia symptoms in postmenopausal women, as assessed by the Kupperman Menopausal Index. The study is limited by uncontrolled sample of 25 women; many had comorbid

depression and anxiety, and it is unclear if the remission in affective symptoms mediated the decrease in insomnia symptoms. At the present state of the research, trazadone is not recommended for treatment of menopausal related insomnia symptoms without depression.

Mirtazapine, similarly sedating antidepressant, has shown some mild evidence to treat menopause related depression that is unresponsive to HRT [120]. Dolev [121] exhibited significant sleep improvements in 11 case studies of perimenopausal women taking mirtazapine in combination with prolonged release melatonin. Although this is not evidence for its efficacy, it does show that there may be developments in the treatment of menopause related insomnia symptoms using antidepressents. Of note, 63% of the women experienced significant weight gain as a side effect to treatment, most of which reduced following the treatment. Despite their sedating effects, use of antidepressents are generally not advised for routine use in menopause-related insomnia symptoms without depression, as the sedating effects tend to be short live and side effects are common.

SLEEP APNEA AND SLEEP-DISORDERED BREATHING

Non-pharmacological Treatments

Continuous Positive Airway Pressure

Exploring treatment options for menopause-related SDB is an important endeavor, as postmenopausal women are almost 3 times more likely to display OSA and other SDB abnormalities [122]. Various treatment modalities are used to alleviate snoring, OSA, and SDB. Much like insomnia, rigorous evaluation and a detailed history are important aspects of diagnosing sleep-related breathing disorders. A full overnight PSG with EEG, EOG, EMG, a temperature regulated thermistor, a pressure regulated thermocouple, and respiratory effort belts are the standard for diagnosing OSA, although 4 channel monitoring devices can diagnose patients, especially those with a high pre-test probability for OSA.

Continuous positive airway pressure (CPAP) and auto-CPAP have been shown to be efficacious, and are the treatment of choice for OSA [123]. Problems arise with CPAP treatment for menopause-related SDB, as many people find the equipment cumbersome, and compliance reports indicate only 40 - 50% of patients prescribed CPAP are adherent [124, 125]. The effectiveness of CPAP requires that patients use their device on a regular nightly basis. To further complicate CPAP use in postmenopausal women, the few gender studies conducted on CPAP compliance indicate that women tend to be less compliant with CPAP [126, 127], with increased age being an additional factor implicated with non-compliance [126]. McArdle *et al.*'s [128] longitudinal on 1211 patients prescribed with CPAP found that patients who refused CPAP were more likely to be female and referred by a specialist, two factors that would apply to postmenopausal women seeking sleep apnea treatment. Although many factors weigh against postmenopausal CPAP, women diagnosed with OSA with an AHI over 5 should be advised to adhere to use CPAP using psychoeducation and support tools, as CPAP is non-invasive and efficacious.

When comparing CPAP against CBT-I for comorbid insomnia and SDB, one study found a differential effect of each treatment in postmenopausal women. For postmenopausal patients with both chronic insomnia and upper airway resistant syndrome (UARS), a milder SDB issue, the study demonstrated that CBT-I the optimal treatment for reducing sleep latency, while SDB treatment (nasal CPAP or radiofrequency/turbinactomy) is the optimal treatment for relieving daytime fatigue was [129]. Both types of treatment should be taken into consideration for a patient presenting with comorbid insomnia and SDB.

Pharmacological Treatments

Hormone Replacement Therapy

Based on assertions that higher premenopausal estrogen and progesterone levels might account for the lower incidence of breathing-related sleep disorders in premenopausal women relative to postmenopausal women, a number of studies have tested whether administration of estrogen and progesterone might decrease SDB in menopausal women, with inconsistent results. Pickett *et al.* [53] found the combination of estrogen and progestin significantly decreased the number and duration of apnea/hypopneas in a randomized PSG based study. Similarly, Saaresranta *et al.* [130] observed that estrogen use and an especially high serum estradiol concentration predicted higher mean overnight arterial oxyhemoglobin saturation, which suggests estrogen therapy may have favorable respiratory effects. CPAP therapy, however, was found to be more successful than estrogen therapy in reducing episodes of apneas and hypopneas. Other studies show no significant improvements in the number of apneas in post-menopausal women with sleep apnea when treated with estrogen and/or medroxyprogesterone [131]. In a 2003 study using PSG, Polo-Kantola and colleagues [132] found that estrogen replacement therapy only had a minor effect on sleep apnea and no effect on partial airway obstruction in 62 post-menopausal women. Further, research on pharmacological suppression of estrogen and progesterone in healthy young women have demonstrated that although participants subjectively noticed some increased snoring, there was no increase in PSG measured arousals or sleep fragmentation to suggest that lack of hormones leads to SDB [133]. Thus, while hormonal changes that occur during the menopausal transition may increase risk of apnea, sleep quality appear to be only slightly improved by exogenous administration of hormone therapy.

CONCLUSION

In the peri- and postmenopausal population, insomnia, hot flashes, and depression are closely interrelated and should be taken into account when considering treatment options. Insomnia and insomnia symptoms relating to hot flashes should be inquired about in gynecological primary care settings with menopausal women. If insomnia is present, menopausal patients should be referred to a board certified sleep physician, sleep center, or behavioral sleep

medicine specialist. Cognitive-behavioral therapy for insomnia alone or with pharmacological interventions appears to be a promising treatment for menopausal insomnia; however, the efficacy remains unknown until randomized clinical trials are conducted.

Complementary and alternative treatments such as yoga, TM and exercise may be helpful as a complement to other treatments for insomnia, but as of yet have not proved their efficacy as stand-alone treatments. If pharmacological interventions are warranted for insomnia treatment, HRT may be effective for some women, particularly those with vasomotor symptoms. A short-acting nonbenzodiazepine hypnotic, like zolpidem and zaleplon, may be used in the short term (less than two weeks) for acute insomnia, but not recommended for long-term use. Antidepressants such as SSRIs, appear to be effective in treating insomnia in menopausal women, presumably by relieving underlying depression. Secondary insomnia symptoms should be treated within the framework of other symptoms. MBSR presents as an effective non-pharmacological treatment for insomnia symptoms, in addition to cognitive behavioral therapy for climacteric symptoms. More research is needed to determine if they can be prescribed as standalone treatments. Soy and black cohosh remain questionable standalone treatments for insomnia symptoms due to methodological concerns. HRT should be considered carefully for treatment of insomnia symptoms with vasomotor symptoms. When considering treatment with HRT, menopausal women should discuss the benefits and risks with their physicians. Estrogen and progestins should be used at the lowest doses for the shortest duration needed to achieve treatment goals. Paroxetine is the only antidepressant that is FDA approved for hot flash treatment and may be efficacious. It is important to remember that insomnia and SDB, the two most common sleep disorders, are best managed by providers with sleep medicine expertise. If patients report symptoms consistent with SDB, OSA, RLS, PLMS, or other sleep disorders, a referral to a sleep specialist is recommended. If both SDB and insomnia are contemporaneously diagnosed, CPAP is considered the standard of treatment recommended treatment in menopausal women and should be attempted first before trying alternatives.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] World Health Organization: Research on the menopause in the 1990s. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1996; 866: 1-107.

[2] Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: A comprehensive review. Health Qual Life Outcomes 2005; 3(1): 47.

[3] Avis NE, Crawford SL, McKinlay SM. Psychosocial, behavioral, and health factors related to menopause symptomatology. Womens Health 1997; 3(2): 103-20.

[4] Mohyi D, Tabassi K, Simon J. Differential diagnosis of hot flashes. Maturitas 1997; 27(3): 203-14.

[5] Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am J Obstet Gynecol 2007; 196(2): 97-106.

[6] Ensrud KE, Stone KL, Blackwell TL, Sawaya GF, Tagliaferri M, Diem SJ, *et al*. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. Menopause 2009; 16(2): 286-92.

[7] Arakane M, Castillo C, Rosero MF, Peñafiel R, Pérez-López FR, Chedraui P. Factors relating to insomnia during the menopausal transition as evaluated by the Insomnia Severity Index. Maturitas [Internet]. 2011 [cited 2012 Aug 30]; Available from: http://www.sciencedirect.com/science/article/pii/S0378512211000594

[8] Ohayon MM. Severe hot flashes are associated with chronic insomnia. Arch Intern Med 2006; 166(12): 1262-8.

[9] Polo-Kantola P, Saaresranta T, Polo O. Aetiology and treatment of sleep disturbances during perimenopause and postmenopause. CNS Drugs 2001; 15(6): 445-521.

[10] Bolge SC, Balkrishnan R, Kannan H, Seal B, Drake CL. Burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings among women with menopausal symptoms. Menopause. 2010; 17(1): 80-6.

[11] Hachul de Campos H, Brandao LC, D'Almeida V, *et al*. Sleep disturbances, oxidative stress and cardiovascular risk parameters in postmenopausal women complaining of insomnia. Climacteric 2006; 9(4): 312-9.

[12] Shaver JL, Giblin E, Paulsen V. Sleep quality subtypes in midlife women. Sleep 1991; 14(1): 18-23.

[13] Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. Semin Reprod Med 2010; 28(5): 404-21.

[14] Benetó A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. Sleep Med Rev 2009; 13(4): 287-93.

[15] Summers MO, Crisostomo MI, Stepanski EJ. Recent developments in the classification, evaluation, and treatment of insomnia. Chest 2006; 130(1): 276-86.

[16] Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003; 167(9): 1181-5.

[17] Anttalainen U, Saaresranta T, Aittokallio J, *et al*. Impact of menopause on the manifestation and severity of sleep-disordered breathing. Acta Obstet Gynecol Scand 2006; 85(11): 1381-8.

[18] Andersen ML, Bittencourt LRA, Antunes IB, Tufik S. Effects of progesterone on sleep: a possible pharmacological treatment for sleep-breathing disorders? Curr Med Chem 2006; 13(29): 3575-82.

[19] Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. Climacteric 2001; 4: 243-249

[20] Brown JP, Gallicchio L, Flaws JA, Tracy JK. Relations among menopausal symptoms, sleep disturbance and depressive symptoms in midlife. Maturitas 2009; 62(2): 184-9.

[21] Baker A, Simpson S, Dawson D: Sleep disruption and mood changes associated with menopause. J Psychosom Res 1997; 43(4): 359-69.

[22] Joffe H, Soares CN, Thurston RC, White DP, Cohen LS, Hall JE. Depression is associated with worse objectively and subjectively measured sleep, but not more frequent awakenings, in women with vasomotor symptoms. Menopause 2009; 16(4): 671-679.

[23] Clark AJ, Flowers J, Boots L, Shettar S. Sleep disturbance in mid-life women. J Adv Nurs 1995; 22(3): 562-8.

[24] Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep 2008; 31(4): 489-495.

[25] Taylor DJ, Lichstein KL, Weinstock J, Sanford S, Temple JR. A pilot study of cognitive-behavioral therapy of insomnia in people with mild depression. Behav Ther 2007; 38(1): 49-57.

[26] Dolan DC, Taylor DJ, Bramoweth AD, Rosenthal LD. Cognitive-behavioral therapy of insomnia: a clinical case series study of patients with co-morbid disorders and using hypnotic medications. Behav Res Ther 2010; 48(4): 321-27.

[27] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000.

[28] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington, Va.: American Psychiatric Association; 2013.
[29] Morin CM, Bélanger L, LeBlanc M, *et al*. The natural history of insomnia: A population-based 3-year longitudinal study. Arch Intern Med 2009; 169(5): 447-53.
[30] Alexander JL, Neylan T, Kotz K, Dennerstein L, Richardson G, Rosenbaum R. Assessment and treatment for insomnia and fatigue in the symptomatic menopausal woman with psychiatric comorbidity. Exp Rev Neurother 2007; 7(11 Suppl): S139-55.
[31] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14(6): 540-5.
[32] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001; 2(4): 297-307.
[33] American Academy of Sleep Medicine. The international classification of sleep disorders. 3rd ed. Darien Ill: American Academy of Sleep Medicine; 2014.
[34] Lichstein KL, Stone KC, Donaldson J, Nau SD, Soeffing JP, Murray D, *et al*. Actigraphy validation with insomnia. Sleep 2006; 29(2): 232-9.
[35] Gschliesser V, Frauscher B, Brandauer E, Kohnen R, Ulmer H, Poewe W, *et al*. PLM detection by actigraphy compared to polysomnography: A validation and comparison of two actigraphs. Sleep Med 2009; 10(3): 306-11.
[36] Krystal AD, Edinger J, Wohlgemuth W, Marsh GR. Sleep in peri-menopausal and post-menopausal women. Sleep Med Rev 1998; 2(4): 243-53.
[37] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987; 10(4): 541-53.
[38] Sivertsen B, Omvik S, Pallesen S, *et al*. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. JAMA 2006; 295(24): 2851-8.
[39] Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia. JAMA 2001; 285(14): 1856-64.
[40] Sivertsen B, Omvik S, Pallesen S, Bjorvatn B, Havik OE, Kvale G, *et al*. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults. JAMA 2006; 295(24): 2851-8.
[41] Afonso RF, Hachul H, Kozasa EH, de Souza Oliveira D, Goto V, Rodrigues D, *et al*. Yoga decreases insomnia in postmenopausal women: a randomized clinical trial. Menopause 2012; 19(2): 186-93.
[42] Cohen BE, Kanaya AM, Macer JL, Shen H, Chang AA, Grady D. Feasibility and acceptability of restorative yoga for treatment of hot flushes: A pilot trial. Maturitas 2007; 56(2): 198-204.
[43] Oliveira D, Hachul H, Tufik S, Bittencourt L. Effect of massage in postmenopausal women with insomnia: a pilot study. Clinics (Sao Paulo) 2011; 66(2): 343-6.
[44] Kung YY, Yang CC, Chiu JH, Kuo TB. The relationship of subjective sleep quality and cardiac autonomic nervous system in postmenopausal women with insomnia under auricular acupressure. Menopause 2011; 18(6): 638-45.
[45] Llanas AC, Hachul H, Bittencourt LR, Tufik S. Physical therapy reduces insomnia symptoms in postmenopausal women. Maturitas 2008; 61(3): 281-4.
[46] Eichling PS, Sahni J. Menopause related sleep disorders. J Clin Sleep Med 2005; 1(3): 291-300.
[47] Antonijevic IA, Stalla GK, Steiger A. Modulation of the sleep electroencephalogram by estrogen replacement in postmenopausal women. Am J Obstet Gynecol 2000; 182(2): 277-82.
[48] Blum M, Zacharovitch D, Pery J, Gilerowitch M. Estrogen replacement therapy (ERT) by a special regimen in the years following menopause. Clin Exp Obstet Gynecol 1989; 16(1): 9-11.
[49] Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Insomnia in Japanese peri- and postmenopausal women. Climacteric 2010; 13(5): 479-86.
[50] Schiff I, Regestein Q, Tulchinsky D, Ryan KJ. Effects of estrogens on sleep and psychological state of hypogonadal women. JAMA 1979; 242(22): 2405-7.
[51] Scharf MB, McDannold MD, Stover R, Zaretsky N, Berkowitz DV. Effects of estrogen replacement therapy on rates of cyclic alternating patterns and hot-flush events during sleep in postmenopausal women: a pilot study. Clin Ther 1997; 19(2): 304-11.
[52] Bliwise NG. Factors related to sleep quality in healthy elderly women. Psychol Aging 1992; 7(1): 83-8.
[53] Pickett CK, Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Moore LG. Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. J Appl Physiol 1989; 66(4): 1656-61.
[54] Purdie DW, Empson JA, Crichton C, Macdonald L. Hormone replacement therapy, sleep quality and psychological wellbeing. Br J Obstet Gynaecol 1995; 102(9): 735-9.
[55] Montplaisir J, Lorrain J, Denesle R, Petit D. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause 2001; 8(1): 10-6.
[56] Saletu B, Anderer P, Gruber G, Mandl M, Gruber D, Metka M, *et al*. Insomnia related to postmenopausal syndrome: Sleep laboratory studies on differences between patients and normal controls, and influence of an estrogen-progestogen combination with dienogest versus. Drugs Today 2001; 37: 39-62.
[57] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3): 321-33.
[58] Vermes G, Bánhidy F, Ács N. The effects of Remifemin® on subjective symptoms of menopause. Adv Ther 2005; 22(2): 148-54.
[59] Voshaar RCO, van Balkom AJLM, Zitman FG. Zolpidem is not superior to temazepam with respect to rebound insomnia: a controlled study. Eur Neuropsychopharmacol 2004; 14(4): 301-6.
[60] Sharma A, Dewan VK. A case report of zolpidem-induced somnambulism. Prim Care Companion J Clin Psychiatry 2005; 7(2): 74.
[61] Yang W, Dollear M, Muthukrishnan SR. One rare side effect of zolpidem—sleepwalking: a case report. Arch Phys Med Rehabil 2005; 86(6): 1265-6.
[62] Dolder CR, Nelson MH. Hypnosedative-Induced Complex Behaviours. CNS Drugs 2008; 22(12): 1021-36.
[63] Hwang T-J, Ni H-C, Chen H-C, Lin Y-T, Liao S-C. Risk predictors for hypnosedative-related complex sleep behaviors: a retrospective, cross-sectional pilot study. J Clin Psychiatr 2010; 71(10): 1331-5.
[64] Center for Drug Evaluation and Research. FDA drug safety communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist) [Internet]. 2013 [cited 2014 Jun 26]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm
[65] Kripke DF, Klauber MR, Wingard DL, Fell RL, Assmus JD, Garfinkel L. Mortality hazard associated with prescription hypnotics. Biol Psychiatr 1998; 43(9): 687-93.
[66] Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012; 2(1): e000850.
[67] Soares CN, Joffe H, Rubens R, Caron J, Roth T, Cohen L. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. Obstet Gynecol 2006; 108(6): 1402-10.
[68] Joffe H, Petrillo L, Viguera A, *et al*. Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial. Am J Obstet Gynecol 2010; 202(2): 171 e1-171 e11.
[69] Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. Addiction 2003; 98(10): 1371-8.
[70] Dorsey CM, Lee KA, Scharf MB. Effect of zolpidem on sleep in women with perimenopausal and postmenopausal insomnia: a 4-week, randomized, multicenter, double-blind, placebo-controlled study. Clin Ther 2004; 26(10): 1578-86.
[71] Dobkin RD, Menza M, Bienfait KL, Allen LA, Marin H, Gara MA. Ramelteon for the treatment of insomnia in menopausal women. Menopause Int 2009; 15(1): 13-8.
[72] Morin CM, Vallieres A, Guay B, *et al*. Cognitive behavioral therapy, singly and combined with medication, for persistent

insomnia: a randomized controlled trial. JAMA 2009; 301(19): 2005-15.

[73] Zanardi R, Rossini D, Magri L, Malaguti A, Colombo C, Smeraldi E. Response to SSRIs and role of the hormonal therapy in post-menopausal depression. Eur Neuropsychopharmacol 2007; 17(6): 400-5.

[74] Loprinzi CL, Sloan J, Stearns V, Slack R, Iyengar M, Diekmann B, *et al*. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol 2009; 27(17): 2831-7.

[75] Ensrud KE, Joffe H, Guthrie KA, Larson JC, Reed SD, Newton KM, *et al*. Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial. Menopause 2012; 19(8): 848-55.

[76] Keefer L, Blanchard EB. A behavioral group treatment program for menopausal hot flashes: results of a pilot study. Appl Psychophysiol Biofeedback 2005; 30(1): 21-30.

[77] Green SM, Haber E, McCabe RE, Soares CN. Cognitive-behavioral group treatment for menopausal symptoms: a pilot study. Arch Womens Ment Health 2013; 16(4): 325-32.

[78] Mann E, Smith MJ, Hellier J, Balabanovic JA, Hamed H, Grunfeld EA, *et al*. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): A randomised controlled trial. Lancet Oncol 2012; 13(3): 309-18.

[79] Carmody JF, Crawford S, Salmoirago-Blotcher E, Leung K, Churchill L, Olendzki N. Mindfulness training for coping with hot flashes: results of a randomized trial. Menopause 2011; 18(6): 611-20.

[80] Borud EK, Alraek T, White A, *et al*. The Acupuncture on Hot Flushes Among Menopausal Women (ACUFLASH) study, a randomized controlled trial. Menopause 2009; 16(3): 484-93.

[81] Hachul H, Brandao LC, D'Almeida V, Bittencourt LRA, Baracat EC, Tufik S. Isoflavones decrease insomnia in postmenopause. Menopause 2011; 18(2): 178-184.

[82] Agosta C, Atlante M, Benvenuti C. Randomized controlled study on clinical efficacy of isoflavones plus Lactobacillus sporogenes, associated or not with a natural anxiolytic agent in menopause. Minerva Ginecol 2011; 63(1): 11-7.

[83] Lucas M, Asselin G, Merette C, Poulin MJ, Dodin S. Effects of ethyl- eicosapentaenoic acid omega-3 fatty acid supplementation on hot flashes and quality of life among middle-aged women: a double-blind, placebo- controlled, randomized clinical trial. Menopause 2009;16: 357-366.

[84] Cohen LS, Joffe H, Guthrie KA, Ensrud KE, Freeman M, Carpenter JS, Learman LA, Newton KM, Reed SD, Manson, JE, Sternfeld B, Caan B, Freeman EW, LaCroiz AZ, Tinker LF, LaForce CB, Larson JC, Anderson GL. Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial. Menopause 2013; 21(4): 1-8.

[85] Palacio C, Masri G, Mooradian AD. Black cohosh for the management of menopausal symptoms : a systematic review of clinical trials. Drugs Aging 2009; 26(1): 23-36.

[86] Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeyneloglu HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. Adv Ther 2007; 24(2): 448-61.

[87] Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas 2003; 44: S67-S77.

[88] Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. *In vitro* effects of the Cimicifuga racemosa extract BNO 1055. Maturitas 2003; 44: S31-S38.

[89] Vermes G, Bánhidy F, Ács N. The effects of Remifemin® on subjective symptoms of menopause. Adv Ther 2005; 22(2): 148-54.

[90] Rotem C, Kaplan B. Phyto-Female Complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study. Gynecol Endocrinol 2007; 23(2): 117-22.

[91] Alder E. The Blatt-Kupperman menopausal index: a critique. Maturitas 1998; 29(1): 19-24.

[92] Sarti CD, Chiantera A, Graziottin A, *et al*. Hormone therapy and sleep quality in women around menopause. Menopause 2005; 12(5): 545-51.

[93] Polo-Kantola P, Erkkola R, Irjala K, Helenius H, Pullinen S, Polo O. Climacteric symptoms and sleep quality. Obstet Gynecol 1999; 94(2): 219-24.

[94] Parry BL, Martinez LF, Maurer EL, Lopez AM, Sorenson DL, Meliska CJ. Sleep, rhythms and women's mood. Part II: Menopause. Sleep Med Rev 2006; 10(3): 197-208.

[95] Hachul H, Bittencourt LR, Andersen ML, Haidar MA, Baracat EC, Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. Int J Gynecol Obstet 2008; 103(3), 207-12.

[96] Kalleinen N, Polo O, Himanen SL, Joutsen A, Polo-Kantola P. The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women. Climacteric 2008; 11(3): 233-43.

[97] Schussler P, Kluge M, Yassouridis A, *et al*. Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. Psychoneuroendocrinology 2008; 33(8): 1124-31.

[98] Heinrich AB, Wolf OT. Investigating the effects of estradiol or estradiol/progesterone treatment on mood, depressive symptoms, menopausal symptoms and subjective sleep quality in older healthy hysterectomized women: a questionnaire study. Neuro-psychobiology 2005; 52: 17-23.

[99] Tranah GJ, Parimi N, Blackwell T, *et al*. Postmenopausal hormones and sleep quality in the elderly: a population based study. BMC Womens Health 2010; 10: 15.

[100] Gambacciani M, Rosano G, Cappagli B, Pepe A, Vitale C, Genazzani AR. Clinical and metabolic effects of drospirenone-estradiol in menopausal women: a prospective study. Climacteric 2011; 14(1): 18-24.

[101] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; 4(5): 487- 504.

[102] Kryger M, Roth T, Dement WC. Principles and Practice of Sleep Medicine, 5th ed, 2011; Philadelphia: Elsevier.

[103] Soares CN, Arsenio H, Joffe H, *et al*. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. Menopause 2006; 13(5): 780-6.

[104] Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 2007; 109(4): 823-30.

[105] Joffe H, Soares CN, Petrillo LF, *et al*. Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. J Clin Psychiatry 2007; 68(6): 943-50.

[106] Archer DF, Seidman, L, Constantine GD, Pickar JH, Oliver, S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. Am J Obstet and Gynecol 2009; 200(2): 172.e1-10.

[107] Fischer A. FDA approves the first non-hormonal treatment for hot flashes associated with menopause [press release].Silver Spring: U.S. Food and Drug Administration; 2013.

[108] Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: A randomized controlled trial. JAMA 2003; 289(21): 2827-34.

[109] Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C, *et al*. Paroxetine is an effective treatment for hot flashes: Results from a prospective randomized clinical trial. J Clin Oncol 2005; 23(28): 6919-30.

[110] Food and Drug Administration. (2010, March 17). *Doxepin: FDA approved labeling text NDA 22036*. Retrieved July 11, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022036lbl.pdf

[111] Hajak G, Rodenbeck A, Voderholzer U, Riemann D, Cohrs S, Hohagen F, *et al*. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatr 2001; 62(6), 453-463.

[112] Krystal A D, Durrence H H, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep 2010; 33(11), 1553-61.

[113] Krystal A D, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, Roth T. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep 2011; 34(10): 1433-42.

[114] Roth T, Rogowski R, Hull S, Schwartz H, Koshorek G, Corser B, *et al*. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep 2007; 30(11): 1555-61.

[115] Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, *et al*. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatr 2008; 69(10): 1557-64.

[116] Walsh JK. Drugs used to treat insomnia in 2002: Regluatory-based rather than evidence-based medicine. Sleep 2004; 27(8): 1441-2.

[117] Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor, and polysomnographic effects of trazodone in primary insomniacs. J Sleep Res 2011; 20: 552-8.

[118] Walsh J, Erman M, Erwin C, *et al*. Subjective hypnotic efficacy of trazadone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol 1998; 13, 191-8.

[119] Pansini F, Albertazzi P, Bonaccorsi G, Zanotti L, Porto S, Dossi L, *et al*. Trazodone: a non-hormonal alternative for neurovegetative climacteric symptoms. Clin Exp Obstetr Gynecol 1994; 22(4), 341-344.

[120] Joffe, H., Groninger, H., Soares, C., Nonacs, R., & Cohen, L. S. An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. J Women Health Gender-Based Med 2001; 10(10), 999-1004.

[121] Dolev, Z. Case series of perimenopausal women with insomnia treated with mirtazapine followed by prolonged-release melatonin add-on and monotherapy. Arch Women Mental Health 2011; 14(3): 269-73.

[122] Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest 2001; 120(1): 151-5.

[123] To KW, Chan WC, Choo KL, Lam WK, Wong KK, Hui DS. A randomized cross-over study of auto-continuous positive airway pressure versus fixed-continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology 2008; 13(1): 79-86.

[124] Weaver TE, Reishtein J, Sawyer amy m. Adherence to CPAP treatment and functional status in adult obstructive sleep apnea. In: Pack AI, editor. Sleep apnea : pathogenesis, diagnosis, and treatment. 2nd ed. London; New York: Informa Healthcare; 2011.

[125] Lamberg L. Menopause not always to blame for sleep problems in midlife women. JAMA 2007; 297(17): 1865-6.

[126] Pelletier-Fleury N, Rakotonanahary D, Fleury B. The age and other factors in the evaluation of compliance with nasal continuous positive airway pressure for obstructive sleep apnea syndrome. A Cox's proportional hazard analysis. Sleep Med 2001; 2(3): 225-32.

[127] Lewis KE, Seale L, Bartle IE, Watkins AJ, Ebden P. Early predictors of CPAP use for the treatment of obstructive sleep apnea. Sleep 2004; 27(1): 134-8.

[128] McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term Use of CPAP Therapy for Sleep Apnea/Hypopnea Syndrome. Am J Respir Crit Care Med 1999; 159(4): 1108-14.

[129] Guilleminault C, Palombini L, Poyares D, Chowdhuri S. Chronic insomnia, premenopausal women and sleep disordered breathing: part 2. Comparison of nondrug treatment trials in normal breathing and UARS post menopausal women complaining of chronic insomnia. J Psychosom Res 2002; 53(1): 617-23.

[130] Saaresranta T, Polo-Kantola P, Virtanen I, Vahlberg T, Irjala K, Polo O. Menopausal estrogen therapy predicts better nocturnal oxyhemoglobin saturation. Maturitas 2006; 55(3): 255-63.

[131] Hensley MJ, Saunders NA, Strohl KP. Medroxyprogesterone treatment of obstructive sleep apnea. Sleep 1980; 3(3-4): 441-6.

[132] Polo-Kantola P, Rauhala E, Helenius H, Erkkola R, Irjala K, Polo O. Breathing during sleep in menopause: A randomized controlled, crossover trial with estrogen therapy. Obstet Gynecol 2003; 102(1), 68-75.

[133] D'Ambrosio C, Stachenfeld NS, Pisani M, Mohsenin V. Sleep, breathing, and menopause: the effect of fluctuating estrogen and progesterone on sleep and breathing in women. Gend Med 2005; 2(4): 238-45.

Received: September 12, 2013 Revised: August 01, 2014 Accepted: September 27, 2014