Review Article

Menopause and Sleep Disorders

Vishal R. Tandon, Sudhaa Sharma[1], Annil Mahajan[1], Akhil Mahajan[2], Apurva Tandon[3]

Departments of Pharmacology and Therapeutics, [1]Obst and Gyane and [2]Internal Medicine, Government Medical College, Jammu, Jammu and Kashmir, India, [3]Acharya Shri Chander College of Medical Sciences & Hospital Sidhra Jammu, Jammu and Kashmir, India

Submitted: 19-Jan-2022
Revised: 02-Feb-2022
Accepted: 02-Feb-2022
Published: 02-May-2022

Abstract

Women are likely to suffer from sleep disorders more in comparison to men during menopause and with advancing age. The incidence of sleep disorders ranges from 16% to 47% at peri-menopause and 35%–60% at postmenopause. Insomnia with or without associated anxiety or low lying depression and Mood disorder is most common associated manifestations. Sleep disorders and insomnia largely remain a clinical diagnosis based on the subjective complaints of patients. Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic or acute insomnia. Treatment of associated anxiety, depression, or psychosis is most important. Tricyclic antidepressant, Selective Serotonin Reuptake Inhibitors (SSRI), Melatonin, Duloxetine, Fluoxetine, Imipramine, Nortriptyline or Amitriptyline and other drugs such as Eszopiclone, Escitalopram, Gabapentin, Quiteiapine, Citalopram, Mirtazapine followed by long-acting Melatonin and Ramelteon, also are very useful for the management of various sleep disorders. Hormone replacement therapy presently lacks concrete evidence to be used in menopausal women for sleep disorder. Sleep hygiene practices, self-hypnosis, meditation, and exercise play a very important role.

Keywords: *Anxiety obstructive sleep apnea, insomnia, menopause, mood disorders, sleep disorders*

Introduction

With the changes in the biological life cycles and the extreme hormonal change and with advancing age, women are at an increased risk for sleep disturbances such as insomnia, poor sleep quality, and sleep deprivation, as well as sleep disorders such as OSA, restless legs syndrome (RLS), depression, and various mood and anxiety-related disorders.[1] There is emerging evidence that menopause-associated hormone loss contributes to this elevated risk of sleep disorders, but age is also an important factor.[2] The current review will discuss various aspects of menopause and sleep disorder in light of available scientific evidence.

Epidemiology

The incidence increases from 16%–42% to 39%–47% at peri-menopause and 35%–60% at postmenopause. Difficulty in sleeping has been reported in 38% of the elderly women's and age-adjusted rates have been reported highest in the late perimenopausal (45.4%) and surgically postmenopausal (47.6%) women.[3] Studies have reported that 33%–51% of women show a dramatic increase in sleep disturbance in the mid-life years, a time when they enter menopause, i.e., during transition from peri-menopause to menopause.[4]

The menopausal transition is associated with rise in insomnia-related symptoms, particularly difficulty in staying asleep, which has a negative impact on the quality of life. Vasomotor symptoms (VMS) are a key component of sleep disruption during the said transition.[5] Further, studies have shown a high association between fibromyalgia and early, late perimenopause and surgical menopause to be one of the another factors for high incidence of sleep disorder occur during transition of menopause.[6]

Access this article online

Quick Response Code:

Website: www.jmidlifehealth.org

DOI: 10.4103/jmh.jmh_18_22

Address for correspondence: Dr. Vishal R. Tandon, Department of Pharmacology, Government Medical College, Jammu, Jammu and Kashmir, India.
E-mail: dr_vishaltandon@yahoo.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Tandon VR, Sharma S, Mahajan A, Mahajan A, Tandon A. Menopause and sleep disorders. J Mid-life Health 2022;13:26-33.

Associated Co-Morbidity and Risk Factors

The most commonly encountered co-morbid disease with sleep disorders in menopausal women includes restless leg syndrome, periodic leg movement syndrome, depression, and anxiety. Epidemiological studies state that women experience sleep-related difficulties and depressive symptoms around times usually when there is alteration in the levels of sex hormones such as at the time of puberty and menopause.[7] Further, the sleep disorders during menopause can be an independent risk associated with arterial stiffness in menopause and can result into higher incidence of cardiovascular-related morbidity and mortality.[8]

Obstructive sleep apnea (OSA) is another very common comorbid condition associated with sleep disorder. It is a chronic adult disorder which is characterized by episodes of recurrent upper-airway obstruction, accompanied by frequent reopening of the airway during sleep.

OSA is associated with oxidative stress, intermittent hypoxia, sympathetic overactivity, thus leading to high cardiovascular mortality and morbidity. It is more common in males than females, and this is attributed to the differences in anatomy and functional respiratory components. However, women take over men after menopause as far incidence of OSA is concerned.[9] OSA has also enhanced the risk of systemic arterial hypertension and arrhythmias, especially atrial fibrillation. Further, one of the studies has suggested the association of sleep disturbance among postmenopausal women and increase incident cardiovascular disease and type 2 diabetes.[10] Similarly, another study conducted by Im *et al*.[11] supported significant associations of type 2 diabetes mellitus with sleep-related manifestations among midlife women.

Further, in postmenopausal women, high BMI and abdominal obesity are sources of sleep disturbances, decreasing deep sleep, and sleep efficiency while increasing the risk of OSA.[12]

It is also well known that the prevalence of sleep-disordered breathing (SDB) among postmenopausal women is increased in patients with obesity or metabolic comorbidities. Metabolic comorbidities thus contribute to SDB regardless of the degree of obesity.[13] Further, conditions such as gastro-esophageal reflux disease, diabetic neuropathy, vitamin D deficiency, and related muscle cramps also have been found associated with sleep disorder among postmenopausal women. Many drugs such as beta-blockers, bronchodilators, corticosteroids, diuretics, stimulating antidepressants, central nervous system stimulants also are known to affect the sleep quality adversely.

Gender Difference for Sleep Disorders

Women usually have a better quality of sleep as compared to men, which is evident by longer sleep times, shorter sleep-onset latency, and higher sleep efficiency. Despite all this, women generally tend to have more sleep-related complaints than men. The amount of slow-wave sleep slowly declines with age both in men as well as women.

Normal physiologic periods, which are associated with alteration in hormone levels such as puberty, menstruation, pregnancy, and menopause, all are associated with alterations in the sleep patterns. Studies of insomnia support a female preponderance, with increased divergence of prevalence among men and women in the elderly age group. RLS also has a slight female predominance, while rapid eye movement sleep behavior disorder and Kleine–Levin syndrome are more frequently seen in men.[14]

There are many ways in which women experience sleep differently from men. The new research is unraveling the novel aspects of sleep pathology in women and the significance of sex hormones in determining the sleep regulation as well as arousals and possibly the etiology of sleep-related disorders.

Moreover, studies indicate that during the periods of hormonal alterations, women get predisposed to various sleep-related disturbances like decline in sleep quality and sleep deprivation, as well as other sleep disorders such as OSA, RLS, and insomnia.[1]

Women are more likely than men to complain of insomnia, headache, irritability, and fatigue than the typical symptoms of loud snoring and breathing cessation during sleep.

Premenopause versus Postmenopause and Sleep Disorder

Compared with pre/perimenopausal women, postmenopausal women were more often reported to have difficulty in the onset of sleep and possible sleep-onset insomnia disorder. Postmenopausal women were also more likely to screen positive for OSA in comparison to premenopausal women. The two groups did not vary on sleep dissatisfaction, daytime somnolence, sleep-maintenance insomnia disorder, and rest less leg syndrome.[15]

In another study, total sleep time in pre- and postmenopausal women was similar but shorter than in young women. Sleep efficiency followed the same pattern, being 93.4% in young women, 84.3% in premenopausal and 80.2% in postmenopausal. Pre- and

postmenopausal women had decreased slow-wave sleep (duration or activity) and increased wake time after sleep onset (duration or frequency). Insomnia complaints were more frequent after the menopause. Sleepiness and mood scores were almost comparable in all age groups. Reaction speeds declined with increasing age. After the menopause, better cognitive performance was associated with more rapid eye movement sleep.

Objective sleep measures varied to a significant extent among the young and postmenopausal women. These variations might be more because of the physiological process of aging than the rapid changes throughout the menopause since similar sleep patterns were already present in the premenopausal women. The complaints regarding increase in the duration of sleep after menopause were not associated with disturbances in the objective sleep quality, mood, or cognitive performance.[16]

Pathogenesis

Circadian rhythm is an internal biological clock which initiates commencement and monitoring of various physiological processes. This circadian pacemaker is located in the suprachiasmatic nucleus present in the hypothalamus. The circadian clock undergoes many changes throughout the life, at both physiological and molecular levels. The existence of sex differences does exist, and so the consequences of sleep disturbances associated with menopause are a good example. Endogenous secretion of melatonin decreases with increase in age and varies with gender, and in menopausal women, it is associated with a significant reduction in the melatonin levels, thus affecting the sleep patterns.[17]

The level of melatonin decrease (especially at nighttime) with age, more so during the peri- menopausal period. Postmenopausal women usually have increased sleep latency time as well as more awakenings during the middle of the night and in the early morning. Although these sleep-related complaints in menopause may be multifactorial (such as poor sleep hygiene, depression, primary sleep disorders, SDB, fibromyalgia), decreased melatonin secretion and the disturbance in the circadian oscillator system are also of substantial relevance, both with regard to the sleep-disturbing symptoms and to the direct impairment of sleep regulation. These sleep disorders have been treated by hormonal supplementation with melatonin along with improvement in sleep hygiene and the support of this hypothesis is that melatonin is an important determinant of sleep in advancing age and in menopause which ultimately decides the quality and quantity of sleep.[18] Thus, the endogenous secretion of melatonin decreases with aging across among women, menopause is associated with a significant reduction in melatonin levels.[19,20]

Reproductive hormones have an overall protective effect on sleep apnea in women of premenopausal age group. Progesterone stimulates the benzodiazepine receptors, gamma-aminobutyric acid receptors and thus induces sleep and works as anxiolytic. Premenstrual falls in progesterone levels are associated with sleep disturbance. Similar has been postulated to be responsible for increased incidence of sleep disorder during peri-menopasual and postmenopausal period.

Similarly, estrogen is involved in norepinephrine, serotonin, and acetylcholine metabolism. It increases the rapid eye moment (REM) sleep, total sleep time and decrease sleep latency, and spontaneous arousals. It is also known to have a thermoregulatory effect at night and indirectly improves sleep. Further, by regulating 5HT, it may also exert antidepressant effect and indirectly also contribute in improving sleep quality.

Spectrum of Clinical Presentation

Sleep disorders in the menopause are common. Although these disorders may be directly because of the menopause and/or due to the associated VMS, the etiology being multifactorial, which includes wide array of associated conditions. They may simply emerge as a part of the physiological process of aging and not being particularly related to decrease in estrogen levels or, alternatively, because of other conditions such as breathing or limb movement syndromes, depression, anxiety, co-morbid medical diseases, medication, pain and/or psychosocial factors. The wide spectrum of sleep disorders encountered in menopausal women include insomnia, nocturnal breathing disturbances, and the associated sleep disorders that accompany the restless leg syndrome, periodic leg movement syndrome, depression, and anxiety.[21]

Chronic insomnia (difficulty in sleep for >3 weeks) is usually common among postmenopausal women and is often associated with anxiety, depression or pscychosis, or mood disorders. If not treated adequately along with treatment of associated problem at least for 3 to 6 months may be very commonly associated with withdrawal or rebound insomnia. Incidence of short-term insomnia (difficulty in sleep for 3–21 days) is more common overall, but higher incidence during transition period of menopause is observed. It may require treatment for more than 3 weeks in majority of the cases.

Transient insomnia (difficulty in sleep for 1–3 days) can be encountered with equal propensity in younger age

women, peri-menopause or menopause. May require treatment for few days or may not require treatment at all.[22]

Insomnia is very common among the postmenopausal women age group and further increases the risk of depression in this already-vulnerable population.[23]

The relatively less common sleep disorders during peri-menopausal or menopausal women's include, Bruxism: Involuntarily grinding or clenching of the teeth while sleeping; Hypopnea syndrome: Abnormally shallow breathing or slow respiratory rate while sleeping; Narcolepsy excessive daytime sleepiness; Cataplexy a sudden weakness in the motor muscles that can result in collapse to the floor; Night terror/sleep terror disorder: abrupt awakening from sleep with terror*;* Parasomnias: disruptive sleep-related events involving inappropriate actions during sleep stages - sleep walking; Periodic limb movement disorder*:* Sudden involuntary movement of arms and/or legs during sleep, for example kicking the legs. Also known as nocturnal myoclonus; Rapid eye movement behavior disorder*:* Acting out violent or dramatic dreams while in REM sleep; RLS An irresistible urge to move legs; *Sleep paralysis*: is characterized by temporary paralysis of the body shortly before or after sleep. Sleep paralysis may be accompanied by visual, auditory or tactile hallucinations; Sleepwalking\ or somnambulism; Nocturia: A frequent urge to the bathroom to urinate at night for quite a couple of times. It differs from enuresis, or bed-wetting, in which the person is not aroused and still sleeping, but the bladder nevertheless empties and Somniphobia*:* a state of extreme anxiety and fear for even the thought of going to sleep.

Screening and Investigations

Since sleep disorders in postmenopausal women cannot be attributed to hormone changes only, as there are other disorders which can cause sleep problems in these women. Thus, it is very important to have comprehensive for all other associated possible comorbid conditions which can independently affect the sleep.

Further, sleep disorders and insomnia still largely remain a clinical diagnosis based on the subjective complaints of patients. The most commonly used tools for the evaluation of associated depression and anxiety are Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale.

Careful assessment be made by taking proper history not to establish clinical diagnosis of insomnia or sleep disorder but also to have an assessment regarding common comorbid condition. An accurate and detailed history from the patient, patient's partner, or family member combined with a sleep questionnaire can help in eliciting critical information. Most sleep-related complaints fall into three categories: insomnia, excessive sleepiness, or abnormal behaviors during sleep. First, the chief complaint is to be carefully evaluated like when symptom(s) started, any particular pattern of symptoms since onset, and other contributing factors (medical, environmental, occupational, psychological/stress, lifestyle choices) that may have predisposed to or precipitated the illness. Assess the impact of the sleep complaint on patient's life, and inquire about his or her meal and sleep schedules, sleep hygiene, restless legs sensation, snoring, witnessing of any apneic episodes, sweating, coughing, gasping/choking/snoring, dryness of the mouth, bruxism, excessive movements during sleep, periodic limb movements, any abnormal behaviors during sleep, daytime sleepiness, presence of cataplexy, sleep paralysis, and hypnagogic or hypnapompic hallucinations. Then, evaluate about the caffeine intake, alcohol and nicotine use, as well as use of illicit drugs. Review the pertinent medical/surgical/psychiatric history and past treatments, and their efficacy or lack thereof. Carefully evaluate if there is any family history of sleep disorders (snoring, OSAS, narcolepsy, RLS). Laboratory tests rarely performed to assess and therefore treat sleep disorders include the polysomnogram (PSG), multiple sleep latency test, maintenance of wakefulness test, actigraphy, video-PSG, and electroencephalography (EEG), including 24-h ambulatory EEG.

PSG is a complete, nocturnal, laboratory-based monitoring, which simultaneously records numerous variables during sleep. It includes various modalities such as electrocardiogram, sleep staging (EEG), electro-oculogram, submental electromyogram (EMG), nasal or oral airflow, respiratory efforts, oximetry, anterior tibialis EMG, and position monitoring. Depending upon the clinical diagnosis, additional parameters may be added: transcutaneous CO2 monitoring or end-tidal gas analysis; extremity muscle activity; motor activity movement; extended video-EEG; penile tumescence; esophageal pressure; gastroesophageal reflux; snoring; and continuous blood pressure recording.[24]

Management

Benzodiazepine hypnotics and the newer agents zolpidem, zopiclone, and zaleplon are preferred over barbiturates. Benzodiazepine compounds with a shorter half-life are favored in patients with sleep-onset insomnia. These compounds are considered appropriate for the elderly population

because of a decreased risk of accidental falls and respiratory depression.

Benzodiazepines which have longer half-lives are favored for patients who have significant daytime anxiety and who might be able to tolerate the next-day sedation but would otherwise be impaired further by rebound daytime anxiety. These benzodiazepines also are appropriate for patients receiving treatment for major depressive episodes because the short-acting agents can worsen early-morning awakening. However, longer-acting benzodiazepines can be associated with next-day cognitive impairment or delayed daytime cognitive impairment (after 2 to 4 weeks of treatment) as a result of drug accumulation with repeated administration.

Still Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic insomnia. Treatment of associated anxiety, depression, or pscychosis is important and sedatives being used as adjunct and be discontinued gradually after 3 to 6 months is the main line of treatment. However, risk of tolerance and abuse is maximum among chronic insomniacs. A slowly eliminated drug is preferable because of the rebound insomnia and withdrawal symptoms associated with such drugs.

Fort the management of short-term insomnia, lowest effective dose of Benzodiazepines, 30 minute before sleep after three night acceptable sleep, skip few doses and then use 2 to 4 time a week not more than 3 weeks is the treatment strategy recommended these days.

Similarly, for the transient insomnia, use of low dose Benzodiazepines, with short duration of action for 2 to 3 nights preferably newer non-BZD hypnotics has increased due to their rapid onset of action, minimal next-day impairment, and absence of cumulation or minimum possibility of rebound insomnia on stopping.[18]

However, it is also to understand that sedative and hypnotic are absolute safe in elderly. Clinician should always try to look for other associated factors like anxiety depression, dementia, loneliness, and loss of family support while treating sleep disorders. Smaller than usual dose of short acting BDZ, e.g., Oxazepam are to be preferred. If BDZ not tolerated, then use of non-Benzodiazepines like Zolpidem and Zoleplon are recommended.

Further, clinician must remember that among this venerable population there is high possibility of drug interactions, if already on other drugs. The risk of fall and fractures increases in elderly on the long-term hypnotic therapy. Thus, fall and fracture prevention techniques should be encouraged to those patients and planned to start short-term benzodiazepines preferably. Treatment of associated anxiety, depression, or psychosis is important and for this use of sedatives as adjunct and discontinue gradually after 3 to 6 months should always be the approach in such cases. Risk of tolerance and chances of abuse are maximum among the chronic insomniacs. A slowly eliminated drug is preferable because rebound insomnia and withdrawal symptoms are least marked with such drugs.

For the management of other Sleep disorders Mono-therapy or in combination following drugs can be used very effectively, i.e., Tricyclic antidepressant, SSRI, Melatonin, Duloxetine, fluoxetine, Imipramine, Nortriptyline or amitriptyline.

Other drugs which may be useful are Eszopiclone, escitalopram, gabapentin, isoflavones, valerian, quiteiapine XL, citalopram, mirtazapine followed by long-acting melatonin, ramelteon, Pycnogenol, may also be considered depending on the additional requirement.[25-28]

Menopausal hormone therapy improves the quality of sleep in women along with improvement in concomitant VMS.[25] Women suffering from insomnia related to VMS can be treated with hormone replacement therapy (HRT). Oestrogen itself may also have an antidepressant as well as a direct sleep effect.[26]

Welton *et al*.,[29] Sarti *et al*.,[30] in their respective studies suggested that hormone therapy to be superior over placebo in improvising sleep disorders among postmenopausal women.

Gambacciani *et al*.[31] in their study reported that low estrogen dose may have a value in the treatment of menopausal women in which sleep disturbances may be a symptom of estrogen deprivation. Low-dose estrogen associated with low-dose micronized progesterone may especially benefit women who complain of disturbed sleep.

Kagan *et al*.[32] in their study suggested that a single-capsule 17β-estradiol-progesterone significantly improved MOS-Sleep parameters from baseline to week 12, which was sustained for up to 12 months, and was associated with a very low incidence of somnolence.

Similarly, Ensrud *et al*.[33] suggested that among perimenopausal and postmenopausal women with hot flashes, both low dose oral estradiol and low-dose venlafaxine compared with placebo modestly reduced insomnia symptoms and improved subjective sleep quality.

However, few contrary results were also reported by Lindberg *et al*.[34] Mirer *et al*.[35] which failed to establish any superiority of hormonal therapy over placebo in sleep disorders both in premenopausal or postmenopausal women's.

Lindberg *et al.* in their study also reported that there is no evidence that female sex hormone changes during menopause per se are able to explain the increase in SDB in midlife women and HRT may not have any beneficial effect on SDB.[34]

Mirer *et al*.[35] in their study suggested that hormone therapy was negatively associated with SDB. The association of hormone therapy and SDB was heterogeneous ($P < 0.01$); apnea-hypopnea index among users was 15% lower in the early period but similar to nonusers in the late.

The study of Shahar *et al*.[36] also reported the inverse association between hormone use and SDB, particularly among women 50 to 59 years old.

In another recent study, estradiol levels were significantly elevated in non-OSA than in OSA patients ($P < 0.05$). Reduced estradiol levels were correlated with an increased risk of OSA among depressed perimenopausal and postmenopausal women. However, study did not evaluate any effect of HRT on OSA.[37]

Manber *et al*.[38] in their pilot study to evaluate the impact of estrogen and estrogen plus progesterone HRT on mild-to-moderate SDB in postmenopausal women suggested that estrogen to have a substantial beneficial effect on measures of SDB in postmenopausal women. Overall, no additional benefit was seen with the addition of progesterone. In fact, progesterone attenuated the beneficial effects of estrogen in 4 out of the 6 participants.

Since there is lack of consistency in studies partly due to difference in preparations of hormone, age, symptomatology, type of menopause and in light of few recent studies concluding HT to offer no significant advantage in sleep disorders and further due to recent debate surrounding use of HT in menopause due to established risk of breast cancer, cardiovascular risk, ovarian cancers etc., presently HT is not recommended as line of treatment for sleep disorders among postmenopausal women's by the current guidelines of Indian Menopause society.[39]

Nonpharmacological Treatment

Self-Hypnosis is a non-pharmacological treatment for poor sleep and hot flashes in menopausal women. The goal of hypnosis is to help educate and train the subjects to perform self-hypnosis to alleviate the underlying symptoms.

The use of hypnosis as a treatment for poor sleep has shown benefits for both acute and chronic insomnia. There were clinically meaningful improvements in reducing the perception of poor sleep quality in 50%–77% of women across time.[40]

Cognitive therapy is aimed at changing patients belief and attitude about insomnia. Combined cognitive and behavioral technique beside changing patients beliefs, have the behavioral component which may include stimulus control and or sleep restriction therapy with or without the use of relaxation therapy helps majority of postmenopausal women's suffering from chronic insomnia. Progressive muscle relaxation training also helps in some of the patients dramatically. Further, stimulus control therapy, sleep restriction therapy are also some important techniques which help many patients successfully.

Beside this, sleep hygiene preventive practices need to be advocated for overall benefit to postmenopausal patients of sleep disorders. Sleep only when sleepy, if you can't fall asleep within 20 minutes, get up and do something boring until you feel sleepy, don't take naps. Stay away from caffeine, nicotine, and alcohol at least 4–6 h before bed; Have a light meal before bed; Avoid sleep in day; Stimulus control; Establish regular bedtime; Make sure your bed and bedroom are quiet and comfortable; Avoid too much of water before sleep; Wear comfortable clothes; Switch off mobile phones; Don't try to recall events of the day; Don't worry for the next day; Dead man position-good sleep; Develop a regular bed time; Moderate exercise help in good sleep; Warm milk is useful as it contain d-tryptophan which decrease onset time of sleep; Training in relaxation and meditation help.

Conclusion

Women are likely to suffer from sleep disorders more in comparison to men during menopause and with advancing age. Insomnia with or without associated anxiety or low lying depression is most common manifestation. Sleep disorders and insomnia still largely remain a clinical diagnosis based on the subjective complaints of patients. Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic insomnia. Treatment of associated anxiety, depression, or psychosis is most important. HRT presently lacks concrete evidence to be used in menopausal women for sleep disorder. Sleep hygiene preventive practices, self hypnosis, medication, and exercise play a very important role.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Pengo MF, Won CH, Bourjeily G. Sleep in women across the life span. Chest 2018;154:196-206.
2. Brown AM, Gervais NJ. Role of ovarian hormones in the modulation of sleep in females across the adult lifespan. Endocrinology 2020;161:bqaa128.
3. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: A community survey of sleep and the menopausal transition. Menopause 2003;10:19-28.
4. Hsu HC, Lin MH. Exploring quality of sleep and its related factors among menopausal women. J Nurs Res 2005;13:153-64.
5. Baker FC, Lampio L, Saaresranta T, Polo-Kantola P. Sleep and sleep disorders in the menopausal transition. Sleep Med Clin 2018;13:443-56.
6. Dias RC, Kulak Junior J, Ferreira da Costa EH, Nisihara RM. Fibromyalgia, sleep disturbance and menopause: Is there a relationship? A literature review. Int J Rheum Dis 2019;22:1961-71.
7. Morssinkhof MW, van Wylick DW, Priester-Vink S, van der Werf YD, den Heijer M, van den Heuvel OA, *et al.* Associations between sex hormones, sleep problems and depression: A systematic review. Neurosci Biobehav Rev 2020;118:669-80.
8. Zhou Y, Yang R, Li C, Tao M. Sleep disorder, an independent risk associated with arterial stiffness in menopause. Sci Rep 2017;7:1904.
9. Perger E, Mattaliano P, Lombardi C. Menopause and sleep apnea. Maturitas 2019;124:35-8.
10. Rissling MB, Gray KE, Ulmer CS, Martin JL, Zaslavsky O, Gray SL, *et al.* Sleep disturbance, diabetes, and cardiovascular disease in postmenopausal veteran women. Gerontologist 2016;56 Suppl 1:S54-66.
11. Im EO, Yang YL, Liu J, Chee W. Sleep-related symptoms of midlife women with and without type 2 diabetes mellitus. Menopause 2019;26:1178-84.
12. Naufel MF, Frange C, Andersen ML, Girão MJ, Tufik S, Beraldi Ribeiro E, *et al.* Association between obesity and sleep disorders in postmenopausal women. Menopause 2018;25:139-44.
13. Matsumoto T, Murase K, Tabara Y, Minami T, Kanai O, Takeyama H, *et al.* Sleep disordered breathing and metabolic comorbidities across sex and menopausal status in East Asians: The Nagahama study. Eur Respir J 2020;56:1902251.
14. Krishnan V, Collop NA. Gender differences in sleep disorders. Curr Opin Pulm Med 2006;12:383-9.
15. Zolfaghari S, Yao C, Thompson C, Gosselin N, Desautels A, Dang-Vu TT, *et al.* Effects of menopause on sleep quality and sleep disorders: Canadian longitudinal study on aging. Menopause 2020;27:295-304.
16. Kalleinen N, Polo-Kantola P, Himanen SL, Alhola P, Joutsen A, Urrila AS, *et al.* Sleep and the menopause – Do postmenopausal women experience worse sleep than premenopausal women? Menopause Int 2008;14:97-104.
17. Pines A. Circadian rhythm and menopause. Climacteric 2016;19:551-2.
18. Jehan S, Jean-Louis G, Zizi F, Auguste E, Pandi-Perumal SR, Gupta R, *et al.* Sleep, melatonin, and the menopausal transition: What are the links? Sleep Sci 2017;10:11-8.
19. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. Melatonin in perimenopausal and postmenopausal women: Associations with mood, sleep, climacteric symptoms, and quality of life. Menopause 2014;21:493-500.
20. Vakkuri O, Kivelä A, Leppäluoto J, Valtonen M, Kauppila A. Decrease in melatonin precedes follicle-stimulating hormone increase during perimenopause. Eur J Endocrinol 1996;135:188-92.
21. Guidozzi F. Sleep and sleep disorders in menopausal women. Climacteric 2013;16:214-9.
22. Proserpio P, Marra S, Campana C, Agostoni EC, Palagini L, Nobili L, *et al.* Insomnia and menopause: A narrative review on mechanisms and treatments. Climacteric 2020;23:539-49.
23. Kalmbach DA, Cheng P, Arnedt JT, Anderson JR, Roth T, Fellman-Couture C, *et al.* Treating insomnia improves depression, maladaptive thinking, and hyperarousal in postmenopausal women: Comparing cognitive-behavioral therapy for insomnia (CBTI), sleep restriction therapy, and sleep hygiene education. Sleep Med 2019;55:124-34.
24. Abad VC, Guilleminault C. Diagnosis and treatment of sleep disorders: A brief review for clinicians. Dialogues Clin Neurosci 2003;5:371-88.
25. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, *et al.* Efficacy of menopausal hormone therapy on sleep quality: Systematic review and meta-analysis. Endocrine 2017;55:702-11.
26. Caretto M, Giannini A, Simoncini T. An integrated approach to diagnosing and managing sleep disorders in menopausal women. Maturitas 2019;128:1-3.
27. Eichling PS, Sahni J. Menopause related sleep disorders. J Clin Sleep Med 2005;1:291-300.
28. Attarian H, Hachul H, Guttuso T, Phillips B. Treatment of chronic insomnia disorder in menopause: Evaluation of literature. Menopause 2015;22:674-84.
29. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, *et al.* Health related quality of life after combined hormone replacement therapy: Randomised controlled trial. BMJ 2008;337:a1190.
30. Sarti CD, Chiantera A, Graziottin A, Ognisanti F, Sidoli C, Mincigrucci M, *et al.* Hormone therapy and sleep quality in women around menopause. Menopause 2005;12:545-51.
31. Gambacciani M, Ciaponi M, Cappagli B, Monteleone P, Benussi C, Bevilacqua G, *et al.* Effects of low-dose, continuous combined hormone replacement therapy on sleep in symptomatic postmenopausal women. Maturitas 2005;50:91-7.
32. Kagan R, Constantine G, Kaunitz AM, Bernick B, Mirkin S. Improvement in sleep outcomes with a 17β-estradiol-progesterone oral capsule (TX-001HR) for postmenopausal women. Menopause 2018;26:622-8.
33. Ensrud KE, Guthrie KA, Hohensee C, Caan B, Carpenter JS, Freeman EW, *et al.* Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. Sleep 2015;38:97-108.
34. Lindberg E, Bonsignore MR, Polo-Kantola P. Role of menopause and hormone replacement therapy in sleep-disordered breathing. Sleep Med Rev 2020;49:101225.
35. Mirer AG, Peppard PE, Palta M, Benca RM, Rasmuson A, Young T. Menopausal hormone therapy and sleep-disordered breathing: Evidence for a healthy user bias. Ann Epidemiol 2015;25:779-84.e1.

36. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, *et al.* Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med 2003;167:1186-92.
37. Cai LQ, Huang L, Wei LL, Yao JS, Xu LY, Chen W. Reduced plasma estradiol levels are associated with sleep apnea in depressed peri- and post-menopausal women. Neuropsychiatr Dis Treat 2021;17:3483-8.
38. Manber R, Kuo TF, Cataldo N, Colrain IM. The effects of hormone replacement therapy on sleep-disordered breathing in postmenopausal women: A pilot study. Sleep 2003;26:163-8.
39. Vaze N, Kumar A. Sleep disorder. In: Meeta M, Digumartii L, Agarwal N, Vaze N, Shah R, Malik S, editors. Clinical Practice Guidelines on Menopause. Indian Menopause society: Indian Menoapuse Society; 2020. p. 140-50.
40. Otte JL, Carpenter JS, Roberts L, Elkins GR. Self-hypnosis for sleep disturbances in menopausal women. J Womens Health (Larchmt) 2020;29:461-3.