REVIEW ARTICLE

COMMON SLEEP DISORDERS IN WOMEN – REVIEW

Elsa Matthew[1], Shekar Raman[1],Antony Fernandez[1],Leslee Hudgins[1]

1- Hunter Holmes McGuire Veterans Affairs Medical Center

ABSTRACT:

Sleep disturbances contribute to a high frequency of mental health and cardiovascular diseases with significant gender differences. Women have a higher incidence of insomnia than men, and are more likely than men to complain of insomnia, headache, irritability, and fatigue than the ‘‘typical’’ symptoms of loud snoring and apneas during sleep. Reproductive hormones play an important role in sleep in women. In the premenopausal age these hormones have a protective effect on sleep apnea, while during pregnancy there is a higher prevalence of sleep apnea and restless leg syndrome. Cardiovascular mortality is high in women with obstructive sleep apnea and continuous positive airway pressure therapy improves outcomes in most cases of obstructive sleep apnea. The epidemiology, risk factors, diagnostic criteria, and therapies for the three most common sleep disorders (insomnia, obstructive sleep apnea and restless leg syndrome), along with effects of menopause, pregnancy, and social factors on sleep in women, are discussed.

Key Words: insomnia, obstructive sleep apnea, restless leg syndrome, sleep disorders, women

INTRODUCTION

Sleep disturbances result in neurological, cardiovascular and psychiatric sequelae, and as such there are significant gender differences among these disorders. [1–3] Owing to the role of reproductive hormones, this may have a significant impact on sleep pathophysiology. Menarche, pregnancy and menopause contribute to varied manifestations of the most common sleep disorders, namely, insomnia, obstructive sleep apnea (OSA) and restless leg syndrome (RLS).[2,4] Physiological changes that occur during a woman's life, spanning puberty, pregnancy and menopause, have significant effects on sleep, daytime functioning and quality of life. In this article, we describe some of the common sleep disorders in women, particularly insomnia, OSA and RLS.

Address for correspondence:
Elsa Mathew, MD
Integrated Sleep Disorders Center
Hunter Holmes McGuire Veterans Affairs Medical Center
1201 Broad Rock Boulevard, Building 513
Richmond, VA 23249
U.S.A.
Email: elsa.mathew@va.gov

Methods

Pubmed was searched using the terms "women AND common sleep disorders" using the limits 1 January 2008 to 1 Nov 2018 & peer reviewed publications. Articles on sleep apnea, restless leg syndrome and insomnia were included, and the others excluded as indicated in the flowchart.

Influence of Menstrual Cycle and Hormoness on Sleep

The menstrual cycle averages 28 days and is divided into a pre-ovulatory follicular phase and post-ovulatory luteal phase. Ovulation occurs on day 14 and is considered the midpoint between the two phases. Estrogen is at the highest level towards the latter half of the follicular phase and progesterone levels rise in the luteal phase. If pregnancy does not occur, estrogen and progesterone levels decrease, and menstruation occurs. The female reproductive cycle's influence on sleep quality is well documented yet remains complex.[5] Progesterone, known for its soporific and thermogenic effects, is present in negligible levels prior to ovulation and in high levels after ovulation. In a study to describe and compare sleep patterns in relation to ovulatory cycles and premenstrual

mood state, healthy women's sleep patterns were monitored during both phases of the menstrual cycle. Results indicated that rapid eye movement (REM) latency was significantly shorter during post-ovulatory phase compared to the pre-ovulatory phase. However, no significant difference was observed either in latency to sleep onset or in the percentage of REM sleep. While there were no menstrual cycle phase differences in the percentages of various sleep stages, the women with negative affect symptoms during the pre-menstrual period demonstrated significantly less delta sleep during both menstrual cycle phases compared to the asymptomatic subjects.[6] Also documented is an increase in subjective sleep complaints, with decreased sleep efficiency and worsening daytime functioning, during the late luteal phase. This may be due to the declining levels of progesterone as well as premenstrual symptoms that can herald the onset of menstruation.[7]

Sleep disturbances are not uncommon during pregnancy. The National Sleep Foundation's *Women and Sleep* poll, carried out in 1998, showed that 78% of the women reported more disturbed sleep during pregnancy than at other times. The hormonal and physiological changes that take place during pregnancy may contribute to a variety of sleep disorders. The spectrum of association between pregnancy and sleep disturbances ranges from an increased incidence of insomnia, nocturnal awakenings and parasomnias (especially restless leg syndrome), to snoring, excessive sleepiness and OSA. Furthermore, hormonal changes have an inhibitory effect on muscles, which can result in snoring and possible development of sleep apnea. A combination of these factors, along with the anxiety that accompanies motherhood, can result in significant sleep disruption and daytime functioning. Although the timing and occurrence of different sleep disorders vary, they are most prevalent during the third trimester.[8,9]

Poor sleep quality is a common complaint among perimenopausal women. Hormonal shifts with a decrease in estrogen and progesterone levels, along with the social changes that accompany this age group can interfere with sleep quality. Another study noted a low prevalence of OSA among premenopausal women (0.6%) and postmenopausal women receiving HRT (0.5%) compared with postmenopausal women not receiving hormone replacement therapy or HRT (2.7%).[10] Vasomotor symptoms (VMS), particularly hot flashes, correlate strongly with subjective sleep complaints.[11] Declining estradiol levels during menopause demonstrates an association with increased VMS, trouble sleeping, and diminished sexual response.[12]

Insomnia

According to the American Academy of Sleep Medicine (AASM), the diagnostic criteria for insomnia include difficulty initiating and/or maintaining sleep, with significant daytime function impairment and mental health disturbances.[13] In one large scale study examining the economic impact of insomnia, the prevalence of insomnia was significantly higher in women than in men, at 27% and 19% respectively.[3] Among the general population, 10-15% complain of insomnia.[14] At different reproductive stages women report a high frequency of insomnia with a prevalence as high as 50% reported during the perimenopausal period.[15,16] The gender differences are also apparent among different racial groups and socioeconomic status.[17]

Also noteworthy is the high prevalence of insomnia in women with breast cancer.[18,19] Psychiatric disorders such as depression and anxiety contribute to a higher rate of insomnia in women and insomnia in itself can exacerbate major depression.[19]

Treatment

Psychological and behavioral interventions are effective in treating insomnia and recommended too. AASM has developed a practice parameter for these treatments.[20] Thirty percent of patients with insomnia have contributory poor sleep hygiene. Good sleep hygiene practices should be prescribed for all patients, in addition to other treatments, since sleep hygiene education alone is ineffective.[21] In a study of insomnia in women with breast cancer, cognitive behavioral therapy demonstrated improvement.[22]

The current Food and Drug Administration approved pharmacological treatments for insomnia include benzodiazepine receptor agonists and melatonin receptor agonists. Potential adverse effects of the former include residual sedation, memory and performance impairment, falls, undesired behaviors during sleep, somatic symptoms and drug interactions. Several other prescription medications (e.g., sedating antidepressants, antiepileptics) as off-label treatment, nonprescription drugs (e.g., sedating antihistamines) and naturopathic agents (e.g., melatonin, valerian) also are used to treat insomnia, although safety and efficacy data are limited.[21] Postmenopausal women had longer sleep latency, less slow-wave sleep, and less deep sleep compared to premenopausal subjects. Postmenopausal women not receiving HRT had

longer sleep latency than did those on treatment, suggesting that estrogens may exert a protective effect on sleep integrity.[23,24]

There is no consensus on sex-specific insomnia treatment strategies for women.[25] In general, symptom pattern, previous treatment failure, comorbid conditions, adverse effects and medication costs should be considered before starting a hypnotic regimen. Short to intermediate-acting benzodiazepine receptor agonists or melatonin receptor agonists can be started initially. Medications can be changed or dosages increased based upon the degree of symptom improvement and adverse effects experienced.[21] Since depression and insomnia are present more frequently in women than in men, selective serotonin reuptake inhibitors appear to be uniquely effective in their treatment.[25]

Obstructive Sleep Apnea (OSA)

Based on the third edition of International Classification of Sleep Disorders (ICSD-3), the diagnostic criteria for obstructive sleep apnea (OSA) includes clinical complaints of snoring, gasping, witnessed apneas, along with evidence of five or more obstructive respiratory events per hour on sleep testing. Associated manifestations commonly include daytime sleepiness and cardiovascular and cerebrovascular diseases.[13] General population studies have revealed that the prevalence of OSA with daytime sleepiness is 2-5% in adult women and 3-7% in adult men. In the absence of hypersomnia, the disease prevalence is likely greater (24% in men and 9% in women).[26]

The estimated prevalence of OSA is 9% in women and 24% in men.[27] The *Wisconsin Sleep Cohort Study* estimated that sleep apnea was undiagnosed in 90% of women with moderate to severe sleep apnea and suggested that under-diagnosis related to atypical symptomatology may explain much of the perceived disparity.[28] Several investigators have suggested that OSA may be common in pregnant women. However, the exact incidence and prevalence of sleep apnea in pregnant women is uncertain.[8,9] Loud snoring, breathing pauses during sleep and excessive daytime sleepiness are classic symptoms seen in most men with OSA, whereas atypical symptoms such as insomnia, morning headache, fatigue, tiredness, depression, and anxiety are more common presentations in women. Other less typical symptoms in women include memory loss, poor concentration, decreased libido, irritability, worsening unexplained fatigue, and tiredness which are often misdiagnosed and treated inappropriately as depression.[29] Obesity may be the most important risk factor for OSA. Women with OSA are more likely to be obese than are men with OSA of similar severity.[30] In a study of women with body mass index (BMI) >30 kg/m2, one-third of asymptomatic women were found to have OSA by polysomnographic criteria, and a significant correlation was identified between Apnea-Hypopnea Index (AHI) and BMI in this cohort.[31]

Treatment:

OSA is a chronic disease requiring long-term, multidisciplinary management. Several treatment options are available and patients should be active participants in the treatment decision process. Positive Airway Pressure therapy (PAP) is the treatment of choice for all degrees of OSA and may be delivered in Continuous Positive Airway Pressure (CPAP), bilevel PAP, or auto titrating PAP modes.[32] An in-laboratory polysomnography is the preferred approach to titrate to optimal PAP parameters.[33] In a prospective study of 1,116 women for 88 months, adequate CPAP therapy administered after controlling for age, BMI, previous cardiovascular history, hypertension and diabetes, reduced the relative risk from 3.50 (95% confidence interval 1.23 - 9.98) to 0.55 (95% confidence interval 0.17 - 1.74). These data strongly suggest that CPAP therapy may reduce cardiovascular death in patients with severe OSA.[34] Oral appliances (mandibular repositioning or tongue retaining devices) may improve upper airway patency. To date, most treatment trials have been conducted in male patients and few trials have included sufficient number of women to define differences in the efficacy of various modalities in female patients.[32]

Compliance is a major challenge and there is no consensus on the findings. In contrast to prior studies indicating no significant gender differences in regards to CPAP compliance[35], more recent population-based prospective studies indicate that female patients used CPAP more frequently than their male counterparts.[36] However another recent study reported that compliance was not different between women and men.[37]

In a prospective crossover study, postmenopausal women with OSA were treated with estrogen alone, and with an estrogen-progestin combination. Both treatment strategies reduced OSA, with a 50% reduction of AHI following estrogen-progesterone treatment and a 25% reduction following estrogen-only therapy.[38] Estrogen effects were further studied in two groups of postmenopausal women (one receiving HRT and the other untreated); treated women had

better polysomnographic sleep parameters than untreated subjects.[39] Women with established cardiovascular disease experience greater mortality when prescribed HRT[40] and with the higher incidence of major cardiovascular events in OSA patients overall, the potential for harm is significant. Further long-term outcome studies are needed to evaluate the net effect of HRT on postmenopausal women with OSA. Despite its demonstrated efficacy, HRT is not a recommended treatment for perimenopausal OSA at this time.[38,39]

Behavioral therapy, including sleep hygiene, weight reduction, exercise, alcohol avoidance, and bedtime sedatives are important adjuncts to PAP.

Restless Leg Syndrome

This movement disorder is characterized by an urge to move the leg, typically during rest, which is relieved by activity.[13] The prevalence ranges from 4% to 29% in the general population and increases with age.[41,42] Prevalence is higher among women at 13.9% , compared to. 6.1% among men in another cohort analysis.[43] RLS often is underdiagnosed. In a large multinational primary care population of 23,052 patients, 68% of women had RLS; however, only 12.9% received the diagnosis, despite 64.8% reporting their RLS symptoms to a physician. Published data on women with RLS are few and more research focusing on the symptoms and treatment options for women is needed to tailor both diagnostic and treatment strategies.[42] Although the mechanism of this disease is unknown, iron deficiency and dopaminergic dysfunction is thought to be an underlying component.[44–46] The current consensus theory on the pathophysiology of RLS is the ''iron dopamine hypothesis''.[47] Iron is a cofactor for the enzyme tyrosine hydroxylase, which performs a rate-limiting enzymatic step in the formation of dopamine.

In a cohort study of women studied during and after pregnancy, 26% were found to have RLS during pregnancy (with symptoms being most common during the third trimester), which tended to disappear after delivery. Affected women had lower hemoglobin concentrations compared to non-affected women,[48] supporting the theory that iron status may contribute to RLS.

RLS is also associated with increased morbidity and mortality in women. In a prospective study involving greater than 70,000 women, a positive correlation between RLS and coronary artery disease was found. An elevated risk for cardiac disease was appreciated in women with RLS for more than a 3-year duration.[49] Iron-deficiency anemia, pregnancy, smoking, neuropathy, rheumatoid arthritis, multiple sclerosis, diabetes, kidney disease, caffeine and alcohol consumption, use of H2-receptor blockers and some antidepressant medications have been linked to RLS.[33,44,46]

Treatment

The management of RLS is multimodal and encompasses both pharmacological and non-pharmacological treatments. The non-pharmacologic management of RLS includes behavior modification and lifestyle changes as well as cognitive-behavioral treatments which are discussed in greater detail elsewhere.[50] Avoidance of certain foods (e.g., caffeine, alcohol) and drugs (e.g., antihistamines, neuroleptics, some dopamine antagonists) can be helpful. Selective serotonin receptor blockers, tricyclic antidepressants, and lithium may worsen RLS symptoms and should be avoided whenever possible.[51] AASM has developed recommendations for pharmacotherapy which range from iron supplementation, dopamine agonists, membrane stabilizing agents, benzodiazepines to opioids.[52] These include levodopa, ropinirole, pramipexole, rotigotine, cabergoline, pergolide, gabapentin, gabapentin enacarbil, pregabalin, clonazepam, oxycodone, tramadol, methadone. Iron supplementation is beneficial solely when ferritin levels and iron studies indicate a deficiency. Appropriate clinical evaluation is important in patients who report worsening of symptoms while on dopamine agonists as this may suggest augmentation. Moreover, drugs such as cabergoline, pergolide along with opioids require special monitoring.[54]

Conclusion

Sleep is essential for women to live a functional, productive life. Sleep disorders are far more common in women than previously appreciated and presenting symptoms often differ from those in men. Although insomnia is more prevalent among women, it can constitute an atypical presentation of other sleep disorders such as OSA in them. Postmenopausal women carry a higher risk of OSA and should receive PAP therapy; if they fail to improve with optimal PAP therapy other treatment options should be discussed. RLS is common among women of all ages, but it is more frequent during pregnancy. Correction of iron deficiency and use of dopaminergic medications can be helpful for treatment.

This article is a brief overview of common sleep disorders in women and does not encompass many other sleep disorders seen in women. Women

are often under-represented in studies and more research involving women is required to further understand the unique needs in this population.

References

1. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, Inflammatory, and Metabolic Consequences of Sleep Deprivation. Prog Cardiovasc Dis. 2009;51(4):294-302. doi:10.1016/j.pcad.2008.10.003

2. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. Otolaryngol Clin North Am. 1999;32(2):303-331. http://www.ncbi.nlm.nih.gov/pubmed/10385539.

3. Kessler RC, Berglund PA, Coulouvrat C, et al. Insomnia and the Performance of US Workers: Results from the America Insomnia Survey. Sleep. 2011;34(9):1161-1171. doi:10.5665/SLEEP.1230

4. Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. Chest. 1998;114(3):697-703. doi:10.1378/chest.114.3.697

5. Romans SE, Kreindler D, Einstein G, Laredo S, Petrovic MJ, Stanley J. Sleep quality and the menstrual cycle. Sleep Med. 2015;16(4):489-495. doi:10.1016/j.sleep.2014.12.001

6. Lee K a, Shaver JF, Giblin EC, Woods NF. Sleep patterns related to menstrual cycle phase and premenstrual affective symptoms. Sleep. 1990;13(5):403-409. http://www.ncbi.nlm.nih.gov/pubmed/2287852.

7. Krystal AD. Depression and Insomnia in Women. Clin Cornerstone. 2004;6((Suppl 1B)):S19-28.

8. Oyiengo D, Louis M, Hott B, Bourjeily G. Sleep disorders in pregnancy. Clin Chest Med. 2014;35(3):571-587. doi:10.1016/j.ccm.2014.06.012

9. Sahota PK, Jain SS, Dhand R. Sleep disorders in pregnancy. Curr Opin Pulm Med. 2003;9(6).

10. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: Effects of gender. Am J Respir Crit Care Med. 2001;163(3 I):608-613. doi:10.1164/ajrccm.163.3.9911064

11. 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. doi:10.1016/S0029-7844(03)00374-0

12. Dennerstein L, Lehert P, Guthrie JR, Burger HG. Modeling women's health during the menopausal transition: A longitudinal analysis. Menopause. 2007;14(1):53-62. doi:10.1097/01.gme.0000229574.67376.ba

13. American Academy of Sleep Medicine. International classification of sleep disorders—third edition (ICSD-3). AASM Resour Libr. 2014;281(9):2313. doi:10.1111/febs.12678

14. Ohayon MM, Bixler E, Kales A, et al. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002;6(2):97-111. doi:10.1053/SMRV.2002.0186

15. Krystal AD, Edinger J, Wohlgemuth W, Marsh GR. Sleep in peri-menopausal and post-menopausal women. Sleep Med Rev. 1998;2(4):243-253. doi:S1087079298900119 [pii]

16. Hachul H, Bittencourt LRA, Soares JM, Tufik S, Baracat EC. Sleep in post-menopausal women: Differences between early and late post-menopause. Eur J Obstet Gynecol Reprod Biol. 2009;145(1):81-84. doi:10.1016/j.ejogrb.2009.03.019

17. Lauderdale DS, Knutson KL, Yan LL, et al. Objectively measured sleep characteristics among early-middle-aged adults: The CARDIA study. Am J Epidemiol. 2006;164(1):5-16. doi:10.1093/aje/kwj199

18. Palesh OG, Roscoe JA, Mustian KM, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-community clinical oncology program. J Clin Oncol. 2010;28(2):292-298. doi:10.1200/JCO.2009.22.5011

19. Zhang B, Wing YK. Sex differences in insomnia: A meta-analysis. Sleep. 2006;29(1):85-93. doi:10.1093/sleep/29.1.85

20. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006;29(11):1415-1419. doi:10.1093/sleep/29.11.1415

21. American Academy of Sleep Medicine, 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. doi:10.5664/jcsm.6470

22. Epstein DR, Dirksen SR. Randomized Trial of a Cognitive-Behavioral Intervention for Insomnia in Breast Cancer Survivors. Oncol Nurs Forum. 2007;34(5):E51-E59. doi:10.1188/07.ONF.E51-E59

23. Bei B, Coo S, Baker FC, Trinder J. Sleep in Women: A Review. Aust Psychol. 2015;50(1):14-24. doi:10.1111/ap.12095

24. Bixler EO, Papaliaga MN, Vgontzas AN, et al. Women sleep objectively better than men and the sleep of young women is more resilient to external stressors: Effects of age and menopause. J Sleep Res. 2009;18(2):221-228. doi:10.1111/j.1365-2869.2008.00713.x

25. Krystal AD. Insomnia in women. Clin Cornerstone. 2003;5(3):41-48. doi:10.1016/S1098-3597(03)90034-2

26. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-689. doi:10.1093/sleep/22.5.667

27. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. N Engl J Med. 1993;328(17):1230-1235. doi:10.1056/NEJM199304293281704

28. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997;20(9):705-706. doi:10.1093/sleep/20.9.705

29. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28(3):309-314. http://www.ncbi.nlm.nih.gov/pubmed/16173651.

30. Walker RP, Durazo-Arvizu R, Wachter B, Gopalsami C. Preoperative differences between male and female patients with sleep apnea. Laryngoscope. 2001;111(9):1501-1505. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11568595.

31. Richman RM, Elliott LM, Burns CM, Bearpark HM, Steinbeck KS, Caterson ID. The prevalence of obstructive sleep apnoea in an obese female population. Int J Obes Relat Metab Disord. 1994;18(3):173-177.

32. Campos-Rodríguez F, Martínez-García MA, Montserrat JM. Gender differences in treatment recommendations for sleep apnea. Clin Pract. 2012;9(5):565-578. doi:10.2217/cpr.12.49

33. Berry R. Fundamentals of Sleep Medicine.; 2012. doi:10.1016/C2009-0-38997-7

34. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012;156:115-122. doi:10.1059/0003-4819-156-2-201201170-00006

35. Nino-Murcia G, McCann CC, Bliwise DL, Guilleminault C, Dement WC. Compliance and side effects in sleep apnea patients treated with nasal continuous positive airway pressure. West J Med. 1989;150:165-169.

36. Sin DD. Long-term Compliance Rates to Continuous Positive Airway Pressure in Obstructive Sleep Apnea : A Population-Based Study. Chest. 2002;121(2):430-435. doi:10.1378/chest.121.2.430

37. Ye L, Pien GW, Ratcliffe SJ, Weaver TE. Gender differences in obstructive sleep apnea and treatment response to continuous positive airway pressure. J Clin Sleep Med. 2009;5(6):512-518. /pmc/articles/PMC2792965/?report=abstract.

38. Keefe DL, Watson R, Naftolin F. Hormone

replacement therapy may alleviate sleep apnea in menopausal women: a pilot study. Menopause. 1999;6(3):196-200.

39. Prinz P, Bailey S, Moe K, Wilkinson C, Scanlan J. Urinary free cortisol and sleep under baseline and stressed conditions in healthy senior women: Effects of estrogen replacement therapy. J Sleep Res. 2001;10(1):19-26. doi:10.1046/j.1365-2869.2001.00236.x

40. Hulley S, Grady D, Bush T, et al. Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. JAMA. 1998;280(7):605-613. doi:10.1001/jama.280.7.605

41. Berger K, Kurth T. RLS epidemiology - Frequencies, risk factors and methods in population studies. In: Movement Disorders. Vol 22. ; 2007. doi:10.1002/mds.21589

42. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless leg syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med. 2004;5(3):237-246. doi:10.1016/j.sleep.2004.03.006

43. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: The MEMO study. Neurology. 2000;54(5):1064-1068. doi:10.1212/WNL.54.5.1064

44. Paulus W, Dowling P, Rijsman R, Stiasny-Kolster K, Trenkwalder C, De Weerd A. Pathophysiological concepts of restless leg syndrome. Mov Disord. 2007;22(10):1451-1456. doi:10.1002/mds.21533

45. Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of restless leg syndrome. J Neurosci Res. 2000;62(5):623-628. doi:10.1002/1097-4547(20001201)62:5<623::AID-JNR1>3.0.CO;2-H

46. Allen RP. Race, iron status and restless leg syndrome. Sleep Med. 2002;3(6):467-468. doi:10.1016/S1389-9457(02)00108-9

47. Allen R. Dopamine and iron in the pathophysiology of restless leg syndrome (RLS). Sleep Med. 5(4):385-391.

48. Manconi M, Ferini-Strambi L. Restless Leg Syndrome and Pregnancy. In: Restless Leg Syndrome. ; 2009:173-177. doi:10.1016/B978-075067518-5.10023-0

49. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless leg syndrome and coronary heart disease among women. Circulation. 2012;126(14):1689-1694. doi:10.1161/CIRCULATIONAHA.112.112698

50. Sharon D. Nonpharmacologic Management of Restless Leg Syndrome (Willis-Ekbom Disease) Myths or Science. Sleep Med Clin. 2015;10(3):263-278. doi:10.1016/j.jsmc.2015.05.018

51. Picchietti D, Winkelman J. Restless leg syndrome, periodic limb movements in sleep, and depression. Sleep. 2005;28(7):891-898. doi:10.1017/CBO9781139061056.014

52. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless leg syndrome and periodic limb movement disorder in adults - An update for 2012: Practice parameters with an evidence-based systematic review and meta-analyses. Sleep. 2012;35(8):1039-1062. doi:http://dx.doi.org/10.5665/sleep.1988

53. Littner MR, Kushida C, Anderson WM, et al. Practice parameters for the dopaminergic treatment of restless leg syndrome and periodic limb movement disorder. Sleep. 2004;27(3):557-559.

54. Winkelmann J, Allen R, Högl B, et al. Treatment of Restless Leg Syndrome: Evidence-Based Review and Implications for Clinical Practice (Revised 2017) §: Treatment of RLS.; 2018. doi:10.1002/mds.27260