INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Medicines to Promote Sleep*
-August 2021-

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) last reviewed pharmacotherapy for insomnia in 2015. This review draws on more recent evidence related to this topic, as well as on professional society guidelines released since that time. Restless legs syndrome (RLS) is included insofar as disrupted sleep is its most onerous consequence. Following the current clinical review, the NPTC voted to **ADD pramipexole** to the National Core Formulary.

Insomnia is defined as difficulty falling or staying asleep despite adequate opportunity at least 3 nights per week associated with daytime dysfunction. Chronic insomnia lasts 3 months or more, affects up to 10% of adults and is more common in women and older patients. Associated adverse outcomes include hypertension, cardiovascular disease, and mood disorders, as well as work absenteeism and motor vehicle accidents.[1] Chronic insomnia accounts for as much as $18 billion annually in healthcare costs for insured workers and up to $100 billion if indirect costs are included.[2]

The 2009-2010 Behavioral Risk Factor Surveillance Survey data showed a higher unadjusted prevalence of frequent insufficient sleep among AI/AN persons (34.2%; 95% CI: 32.1–36.4) compared to non-Hispanic whites (27.4%; 95% CI: 27.1–27.6). The difference disappeared when adjusted for frequent stress.[3] Short sleep duration (<6h) in an American Indian population was shown to correlate with high degree of native ancestry, age>30, and having a high-school diploma.[4]

Discussion:

There is guideline consensus that multi-component cognitive behavioral therapy (CBTi) for insomnia (but not sleep hygiene counseling alone) offers more effective and durable treatment for chronic insomnia than do medications.[1,5,6] Access to these modalities is often limited and they do not have a role for RLS.

Five classes of medication are included among FDA-approved agents for insomnia:

Benzodiazepines (BZDs) bind to the $GABA_A$ receptor and mediate an inhibitory effect on hypothalamic wakefulness centers. Benzodiazepine receptor agonists (Z drugs) bind a specific subunit of this receptor, theoretically narrowing the spectrum of adverse effects.[7] BZDs reduce wakefulness after sleep onset and increase total sleep time, but are associated with physiologic dependence which can lead to a well-described and potentially fatal withdrawal syndrome with long term use.[8,9] A 2017 meta-analysis showed a clear association with an increased risk of hip fracture in nursing home patients, consonant with a previous study showing an association with fall recurrence.[10,11] They may increase risk for dementia in proportion to their duration of use.[12] A 2019 VA/DoD clinical practice guideline addressing the management of chronic insomnia disorder recommends against their use.

Z-drugs (zolpidem formulations, zaleplon, and eszopiclone) reduce sleep latency and improve sleep quality, total sleep time, and sleep efficiency.[1,13] A 2019 Cochrane meta-analysis of its effects showed eszopiclone (approved in 2004) reduces time to sleep onset and improves total sleep time. Serious adverse effects in elderly patients appeared minimal, though data was limited.[14] Z-drug use has been shown to double the risk of being involved in a motor vehicle accident, and can cause dependence and next-day cognitive, memory, psychomotor and balance impairments.[15] The FDA added a boxed warning in 2019 for all Z-drugs due to an association with potentially dangerous complex sleep behaviors (e.g., sleep driving and sleep walking). However, a 2017 review of FDA data concluded that an epidemiologic association with suicide is difficult to disentangle from comorbid psychiatric diagnoses, and a more recent study of data abstracted from the South Korean National Health Insurance Claims database suggests that suicide attempts peaked just *before* receiving a prescription for zolpidem and gradually declined thereafter.[16,17]

Doxepin is a strong **H1 antagonist** with relatively mild anticholinergic effects. A 2020 review of 3 RCTs which excluded studies of BZDs and Z-drugs concluded that doxepin provided sustained sleep improvement with safety comparable to placebo.[18] The American Academy of Sleep Medicine (AASM) 2017 clinical practice guideline cites evidence from 5 studies demonstrating clinically significant improvements in sleep latency, total sleep time, and sleep efficiency. Headache and somnolence were common. The 2019 VA/DoD guideline lists it as one of two recommended agents (the other being any Z-drug) for insomnia.[1,6]

Ramelteon, a **melatonin receptor agonist** confers a statistically significant improvement in time to sleep onset, but authors of the 2019 VA/DoD clinical practice guideline found insufficient evidence to recommend for or against its use, and it has not been approved by the European Medicines Agency due to lack of evidence for efficacy.[15,6]

In 2019, lemborexant was FDA-approved, joining suvorexant in the newest pharmacotherapeutic class for insomnia, the **dual orexin receptor antagonists**. They exert their effect at OX1 and OX2 receptors for a class of neuropeptides which promote wakefulness. Lemborexant improved subjective time to sleep onset by about 10 minutes and reduced awake time after sleep onset by 22 minutes. This effect was sustained over 6 months. The VA/DoD guideline authors found insufficient evidence to make a recommendation for or against suvorexant, while AASM guideline authors weakly favor its use based on low quality evidence.[19,6,1]

Many drugs are used off label for treatment of insomnia. A Cochrane 2018 systematic review of 23 studies of the use of antidepressants for insomnia concluded that data to support a benefit for SSRIs was lacking, and that short term use of trazodone or doxepin may improve sleep quality.[20] However, a different 2018 meta-analysis found no evidence that trazodone improved total sleep time, time to sleep onset, or wakefulness after sleep onset.[21] Moreover, a 2019 VA-based case-control study indicated trazodone is associated with a 61% greater risk of suicide than is zolpidem, and others have shown that fall-related injury in nursing home patients occurs as often with trazodone as with benzodiazepine use.[22,23] The VA/DoD and AASM guidelines recommend against trazodone's use.

FDA-approved OTCs for insomnia include diphenhydramine and doxylamine, however the VA/DoD and AASM guidelines recommend against the use of diphenhydramine for chronic insomnia, and both drugs appear on the Beers Criteria list of potentially inappropriate medicines for elders given their high level of anticholinergic activity.[24]

Many supplements and herbal remedies are promoted for insomnia. A 2021 systematic review of herb-related liver injury bolstered a 2002 FDA consumer advisory warning of liver injury leading to transplantation associated with use of kava.[25] Most guidelines discourage using melatonin for chronic insomnia, citing a lack of evidence of benefit.[1,6] Melatonin has been shown to be helpful for jet lag.[26]

Restless Legs Syndrome (RLS) is characterized by an urge to move the limbs associated with paresthesias or dysesthesias, starting at rest, partially relieved with physical activity, and worsening at night. It affects 2.5% of persons in North America and Northern Europe, increases in incidence with age, and is more common in pregnancy, end-stage renal disease, and iron deficiency.[27]

Iron supplementation in patients with RLS was shown to improve symptom scores to a clinically significant degree on a 40-point scale (Mean Difference: -3.78, 95% CI: -6.25 to -1.31; I^2 = 66%, 7 studies, 345 participants) in a 2019 Cochrane review. Subgroup analysis showed greater benefit for hemodialysis patients and no difference based on iron level at entry.[28] Dopamine agonists (DAs) and gabapentin enacarbil are FDA approved for RLS. Compared to placebo, more patients taking DAs experienced a clinically important response (61% vs 41%, RR 1.60; 95% CI: 1.38 to 1.86) in a 2013 meta-analysis including 7 trials, consistent with the results of 2011 Cochrane meta-analysis of 38 studies.[29,30]

DA use is associated with impulse control disorders and a risk of accelerated symptoms occurring progressively earlier in the day termed augmentation. Augmentation can be avoided by using the smallest effective dose of an DA and considering an initial trial of a gabapentinoid.[31,32] The American Academy of Neurology 2016 clinical practice guidelines found that strong evidence supports the efficacy of pramipexole, rotigotine (a transdermal formulation), gabapentin enacarbil, and cabergoline.

Findings:

Insomnia is common and associated with both adverse health outcomes and reduced quality-of-life measures. Medication improves measures of sleep quality, though harms include falls, motor vehicle accidents, dependence, abnormal sleep behaviors and an association with suicide in depressed patients. Evidence is lacking to show a clearly favorable balance between long-term benefits and harms for any specific agent for chronic insomnia. Off-label use of medicines is common, and **trazodone continues to be widely used despite substantial evidence of harm and diminishing effectiveness after a relatively short period of use.** Dopamine agonists are clearly beneficial for RLS, though augmentation is a major concern. Use of gabapentin enacarbil is also supported by strong evidence.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References

1. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017; 15;13(2):307-49.
2. Kleinman NL, Brook RA, Doan JF, et al. Health benefit costs and absenteeism due to insomnia from the employer's perspective: a retrospective, case-control, database study. *J Clin Psychiatry.* 2009; 70(8):1098-104.
3. Chapman DP, Croft JB, Liu Y, et al. Excess frequent insufficient sleep in American Indians/Alaska natives. *J Environ Public Health.* 2013; 2013:259645.
4. Ehlers CL, Wills DN, et al. Sleep Quality in an Adult American Indian Community Sample. *J Clin Sleep Med.* 2017; 13(3):385-391.
5. Qaseem A, Kansagara D, Forciea MA, et al. Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med.* 2016; 165(2):125-33.

6. Mysliwiec V, Martin JL, Ulmer CS, et al. The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guidelines. *Ann Intern Med*. 2020;172(5):325-336.
7. Chawla J. Insomnia. *Medscape Emedicine.* Accessed on July 18 2021.
8. Chiu HY, Lee HC, Liu JW, et al. Comparative efficacy and safety of hypnotics for insomnia in older adults: a systematic review and network meta-analysis. *Sleep.* 2021; 44(5):zsaa260.
9. Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000; 162:225-33.
10. Donnelly K, Bracchi R, et al. Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis. *PLoS One.* 2017; 27;12(4).
11. Rossat A, Fantino B, et al. Association between benzodiazepines and recurrent falls: a cross-sectional elderly population-based study. *J Nutr Health Aging.* 2011;15(1):72-7.
12. He Q, et al. Risk of Dementia in Long-Term Benzodiazepine Users: Evidence from a Meta-Analysis of Observational Studies. *J Clin Neurol.* 2019 Jan;15(1):9-19.
13. Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ.* 2012; 345:e8343.
14. Rösner S, Englbrecht C, Wehrle R, et al. Eszopiclone for insomnia. *Cochrane Database Syst Rev*. 2018, Issue 10. Art. No.: CD010703.
15. Atkin T, Comai S, Gobbi G. Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery. *Pharmacol Rev.* 2018; 70(2):197-245.
16. McCall WV, Benca RM, Rosenquist PB, et al. Hypnotic Medications and Suicide: Risk, Mechanisms, Mitigation, and the FDA. *Am J Psychiatry.* 2017; 174(1):18-25.
17. Kim H, Kim Y, et al. Risks of suicide attempts after prescription of zolpidem in people with depression: a nationwide population study in South Korea. *Sleep.* 2020; 43(3):zsz235.
18. Sys J, Van Cleynenbreugel S, et al. Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review. *Eur J Clin Pharmacol.* 2020; 76(3):363-381.
19. Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep.* 2020; 43(9): zsaa123.
20. Everitt H, Baldwin DS, et al. Antidepressants for insomnia in adults. *Cochrane Database Syst Rev.* 2018; 5(5):CD010753.
21. Yi XY, Ni SF, et al. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials. *Sleep Med.* 2018; 45:25-32.
22. Lavigne JE, Hur K, et al. Prescription Medications for the Treatment of Insomnia and Risk of Suicide Attempt: a Comparative Safety Study. *J Gen Intern Med.* 2019; 34(8):1554-1563.
23. Bronskill SE, Campitelli MA, et al. Low-Dose Trazodone, Benzodiazepines, and Fall-Related Injuries in Nursing Homes: A Matched-Cohort Study. *J Am Geriatr Soc.* 2018; 66(10):1963-71.
24. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019; 67(4):674-694.
25. Ballotin VR, Bigarella LG, et al. Herb-induced liver injury: Systematic review and meta-analysis. *World J Clin Cases.* 2021; 9(20):5490-5513.
26. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev.* 2002;(2):CD001520.
27. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016; 87(24):2585-93.
28. Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. *Cochrane Database Syst Rev.* 2012; 5(5):CD007834. Update in: Cochrane Database Syst Rev. 2019 Jan 04;1:CD007834.
29. Wilt TJ, MacDonald R, et al. Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis. *JAMA Intern Med.* 2013;173(7):496-505.
30. Scholz H, Trenkwalder C, et al. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev.* 2011; (3):CD006009.
31. Gossard TR, Trotti LM, Videnovic A, et al. Restless Legs Syndrome: Contemporary Diagnosis and Treatment. *Neurotherapeutics*. 2021; 18(1):140-155.
32. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med.* 2016; 21:1-11.