Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Treatment of Insomnia*
-October 2015-

Background

Insomnia is a common problem. Intermittent insomnia is estimated to affect about 50% of the population, and chronic insomnia affects approximately 10% of adults. Insomniacs are known to have a higher rate of suicide. Insomnia coexists with mental disorders at rates of up to 50%. Observed across all races and cultures, insomnia seems to occur more frequently with advancing age and within the female gender (Schutte-Rodin, et al, 2008).

According to the International Classification of Sleep Disorders, Third Edition, insomnia is defined as the difficulty initiating sleep, maintaining sleep, or waking up too early. To meet the definition of insomnia, the sleep impairment must occur despite an adequate opportunity for sleep, and it must result in impairments in daytime functioning. Insomnia can be classified as acute, chronic or other. Chronic insomnia is defined as a persistent difficulty in falling asleep lasting 30 minutes or longer, a persistent difficulty waking up after falling asleep that lasts 30 minutes or longer, or waking up 30 minutes before the desired time. Such difficulties occur at least 3 times per week, for at least 3 months to be classified as chronic insomnia.

Discussion

Prescription medications used to treat insomnia can be divided into two general categories: those that have the FDA indication, and those that are used off-label. Among the FDA approved categories are the benzodiazepines, benzodiazepine receptor agonists ("Z" drugs), melatonin receptor agonists, histamine receptor antagonists, and orexin receptor antagonists. According to a 2015 publication in *Sleep Medicine*, clinical trials comprise less than 20% of all insomnia publications, thus, research on drugs used to treat the condition is limited and head-to-head trials are lacking (Ma, et al, 2015).

Benzodiazepines act at the gamma-aminobutyric acid A ($GABA_A$) receptor. They decrease duration to the onset of sleep by about 10 minutes and increase total sleep time by about 30 to 50 minutes (Buscemi, et al, 2007). Their side effect profile includes falls and memory impairment. Of chronic users, it is estimated that 10 to 30% are physically dependent, and 50% of users experience withdrawal symptoms. Efficacy declines after 30 days of use (Zisapel, 2012).

"Z" drugs are selective GABA agonists and tend to have shorter half-lives than benzodiazepines. The FDA has indicated the importance of using the lowest possible dose of these drugs, and initial doses should be lower in women than in men. Side effects include complex sleep related behaviors including sleep walking/driving, dependence, and a high fall risk. According to a systematic review and meta-analysis, "Z" drugs decreased the time to sleep onset by about 20 minutes by polysomnographic measurements, and 7 minutes by subjective patient measurements. The placebo response was considered to be a major contributor to the effectiveness of "Z" drugs (Huedo-Medina, et al, 2012).

Ramelteon affects melatonin (MT_1) receptors in the suprachiasmatic nucleus and seems to work by regulating the sleep-wake cycle rather than as a central nervous system depressant. Its FDA indication is for sleep initiation insomnia. A 2014 meta-analysis of over 5800 patients in 13 studies showed a less than 5 minute improvement in subjective sleep onset with ramelteon (Kuriyama, et al, 2014). It does not

cause physical dependence, and is not a scheduled drug. Ramelteon was recommended as one of several first line drugs by the American Academy of Sleep Medicine in its 2008 recommendations for the treatment of insomnia (Schutte-Rodin, 2008).

Doxepin (Silenor®) has sleep effects at very low doses (3mg, 6mg) secondary to histamine (H1) blockade. At higher doses of up to 300 mg, doxepin has antidepressant predominant actions. Doxepin is marketed for sleep maintenance and duration. It is not a controlled substance and has a favorable side effect profile. There are no controlled studies directly comparing doxepin with hypnotics for insomnia treatment. In a randomized, double-blind trial published in 2011, doxepin reduced subjective estimates of wake time spent after sleep onset by 10 to 14 minutes, and increased total sleep time by 12 to 17 minutes (Krystal, et al, 2011).

The newest agent marketed for the treatment of insomnia is suvorexant, which was approved in February 2015. It binds with orexin receptors, inhibiting arousal. Like BZDs and the "Z" drugs, suvorexant is a controlled (Schedule IV) drug. In a systematic review, high dose suvorexant was found to reduce the measured time patients fell asleep by up 6 to 16 minutes compared with placebo, and to increase subjective total sleep time by 22 to 24 minutes compared to placebo (Citrome, 2014).

Many drugs are used off-label for the treatment of insomnia including trazodone, antipsychotics, mirtazapine, gabapentin and amitriptyline. Some of these agents may be appropriate when insomnia overlaps with other clinical conditions.

Trazodone is the second most prescribed medication for insomnia in the United States. Drop-out rates for use of the drug are as high as 30 percent due to its side effect profile which includes next morning grogginess and priapism. In a study comparing trazodone 50 mg with zolpidem 10 mg and placebo in 589 patients, after 2 weeks of therapy, the effectiveness of trazodone did not differ from placebo (Zisapel, 2014). Studies have shown that trazodone may have effectiveness in improving the sleep quality in patients with fibromyalgia and in demented patients (McCall et al, 2012).

Over-the-counter agents and herbal remedies are also utilized for the treatment of insomnia. The 2008 American Academy of Sleep Medicine guidelines did not recommend utilizing OTC antihistamines for the treatment of insomnia due to lack of safety and efficacy data (Schutte-Robin, 2008). Use of OTC sleep aids, however, has been found in some studies to exceed prescription drug use (Minkel and Krystal, 2013).

Alternative therapies such as Cognitive Behavioral Therapy (CBT) have been shown to be highly effective for the long-term treatment of insomnia. A randomized controlled trial showed that CBT interventions were superior to zopiclone for short and long term insomnia treatment (Sivertsen, et al, 2006). A 2015 meta-analysis showed that CBT is an effective treatment for adults with insomnia with sustained improvements in sleep and no adverse outcomes (Trauer, et al, 2015).

Findings

The NPTC noted the limited efficacy and high risk profile of medications used to treat insomnia. While some medications are shown to have a significant statistical benefit on the treatment of insomnia, their measured clinical benefits are mild at best. In particular, the **NPTC removed trazodone** from the IHS National Core Formulary due to limited evidence supporting its use in insomnia as well as concerns about safety and tolerance. Cognitive Behavioral Therapy should be considered a safe, long lasting alternative to medications. If medications are prescribed to treat insomnia, great caution should be exercised and the length of treatment should be limited to 2 weeks, whenever possible.

Insomnia Tools & Resources
Centers for Disease Control and Prevention: Sleep Disorders
http://www.cdc.gov/sleep/about_sleep/index.html
National Institute of Health: Your Guide to Healthy Sleep
http://www.nhlbi.nih.gov/files/docs/public/sleep/healthysleepfs.pdf
Center for Deployment Psychology: Insomnia tools
http://deploymentpsych.org/content/insomnia-tools

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.

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