PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #105
INSOMNIA: DRUG THERAPIES
Robert Arnold MD, Michael Miller, and Rohtesh Mehta MD MPH

Introduction *Fast Facts* #101 and #104 reviewed assessment of insomnia and its non-pharmacological therapy. This *Fast Fact* focuses on the pharmacological treatment of insomnia. Prior to pharmacological treatment, it is important to improve sleep hygiene and treat any contributing underlying medical conditions (e.g. depression, pain, worsening CHF or COPD).

Non-Specific Drug Treatment:

I. **Benzodiazepines** have been successfully used for short term insomnia as they improve sleep quality, total sleep time and reduce night-time awakenings, although there are no systematic studies on long-term use and rare studies in palliative care. All drugs are dosed orally, at bedtime. Most commonly used (and FDA approved) are temazepam (start 7.5 mg), estazolam (0.5 mg), triazolam (0.125 mg), quazepam (7.5 mg) and flurazepam (15 mg). The first two are medium half-life benzodiazepines (10-24 hours); triazolam has a shorter half-life (< 6 hours), quazepam and flurazepam are longer lasting (half-life up to 3-7 days in elderly). All of these undergo hepatic metabolism via cytochrome P450 system (except temazepam which is cleared renally) and thus have numerous drug-drug interactions. Flurazepam and triazolam have active metabolites. Benzodiazepines have a high incidence of amnesia and rebound insomnia, particularly in anxious patients, and may cause paradoxical agitation, increased risk of falls, hip fractures and cognitive impairment, especially in the elderly. Other side effects include tolerance and dependence with long-term use and additive CNS and respiratory side effects when used with other drugs.

II. **Benzodiazepine receptor agonists**. These are rapidly absorbed, metabolized by the liver, do not have active metabolites, have low abuse potential and do not cause rebound insomnia upon abrupt discontinuation. Zolpidem (5-10 mg) and Zaleplon (10-20 mg), both dosed at bedtime, are ultra-short acting agents (half-life 1-2 hours) that restore sleep in patients with nocturnal awakenings, while eszopiclone (1-2 mg) has a half-life of 6-9 hours. Zolpidem is available in a controlled-release formulation.

III. **Antidepressants** such as trazodone (25-100 mg), doxepin (10-50 mg), amitriptyline (10 -50 mg), imipramine (10-75 mg), and mirtazapine (5-15 mg) are commonly used for insomnia due to their sedative properties, however the evidence for their use is less convincing.

IV. **Atypical antipsychotics.** Most of the atypical antipsychotics (quetiapine, olanzapine and ziprasidone), except for risperidone, improve total sleep time and/or sleep efficiency in healthy subjects and schizophrenic patients. These may be beneficial in patients with insomnia who do not respond to front-line treatment or insomnia in medically ill patients with delirium.

V. **Miscellaneous sedative hypnotic**s. Choral Hydrate has moderate short term efficacy but is more toxic than benzodiazepines. Barbiturates are effective in short term treatment, but tolerance develops rapidly. Once commonly used for insomnia, these drugs are no longer used except in rare circumstances.

VI. **Antihistamines and over-the-counter drugs.** Diphenhydramine or other classical anti-histamines have sedative properties, but they are generally not preferred in the elderly due to anticholinergic properties and drug interactions. Diphenhydramine (25-100 mg) has been shown to increase sleep duration but not quality (as it does not affect sleep architecture). Its half-life is ~5-10 hours, but is much longer in elderly. Most over the counter products contain diphenhydramine or a similar sedating antihistamine, including products such as Unisom, Tylenol PM, and Nyquil.

VII. **Melatonin** is used for circadian rhythm sleep disorders and is less effective for chronic insomnia. It has short half-life (45-60 min), has been used in doses ranging from 0.3 to 20 mg, is not FDA approved, and does not have any significant effects on either sleep onset latency or sleep efficiency.

VIII. **Melatonin receptor agonists** include ramelteon, tasimelteon and agomelatine. Ramelteon (8 mg) is FDA approved, has a half-life of 1–2.6 hours; has been shown to reduce sleep latency and increased total sleep time in patients more than 65 years old with chronic insomnia. Side effects are similar to that of placebo and include headache, somnolence and sore throat. Its primary advantage is that there is no evidence of abuse and dependence, rebound insomnia, or withdrawal effects.

IX. **Herbal remedies.** Preliminary and conflicting evidence suggest that valerian (oral extract 400-900 mg QHS) may be as effective as mild hypnotics. The major side effects are hepatotoxicity, cardiotoxicity and delirium. Evidence is lacking for other medications like kava kava, L-tryptophan, chamomile, St. John's wort and Jamaican dogwood.

Drugs for specific sleep disorders: See *Fast Fact* #217 for treatment of Restless leg syndrome. Discussion of therapies for narcolepsy and nocturnal myoclonus or periodic leg movements is beyond the scope of this *Fast Fact.*

References

1. Hirst A, Sloan R. Benzodiazepines and related drugs for insomnia in palliative care. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD003346. DOI: 10.1002/14651858.CD003346.
2. Schenck CH, Mahowald MW, Sack RL. Assessment and management of insomnia**.** *JAMA.* 2003; 289:2475-2479.
3. Cohrs S. Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. CNS Drugs. 2008; 22(11):939-62.
4. Wine JN, Sanda C, Caballero J. Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. *Ann Pharmacother.* 2009; 43(4):707-13.
5. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ*. 2006; 332(7538):385-93.
6. Roth T, Seiden D, Sainati S, et al. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Med.* 2006; 7(4):312-8.
7. Meolie AL, Rosen C, Kristo D. Oral nonprescription treatment for insomnia: an evaluation of products with limited evidence. *J Clin Sleep Med.* 2005; 1(2):173-87.

Author Affiliations: University of Pittsburgh Medical Center, Pittsburgh, PA.

Version History: This *Fast Fact* was originally written by Michael Miller and Robert Arnold, edited by David E Weissman MD, and published in November 2003. Re-copy-edited in April 2009. 2nd Edition was updated by Robert Arnold and Rohtesh Mehta and published in September 2011.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's* content. The full set of *Fast Facts* are available at Palliative Care Network of Wisconsin with contact information, and how to reference *Fast Facts.*

new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.