Pharmacotherapy for Insomnia in Primary Care

Emily Smith, MD[a]; Puneet Narang, MD[b]; Manasa Enja, MD[c]; and Steven Lippmann, MD[c,*]

ABSTRACT

Pharmacotherapy for insomnia in primary care settings can be challenging. Frequently, there are multiple coexisting medical and psychiatric conditions, drug interactions, concern regarding use of habit-forming sleep aids, and paucity of time in office visits to discuss management of sleep difficulties. This article reports the results of a literature search related to pharmacotherapy for insomnia and presents 4 clinical vignettes with corresponding treatment options.

Prim Care Companion CNS Disord
2016;18(2):doi:10.4088/PCC.16br01930

[a]Department of Family Medicine, North Memorial Hospital, University of Minnesota, Minneapolis
[b]University of Minnesota and Regions Hospital, Minneapolis-St Paul
[c]Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky
**Corresponding author:* Steven Lippmann, MD, University of Louisville School of Medicine, 401 E Chestnut St, Ste 610, Louisville, KY 40202 (sblipp01@louisville.edu).

Adequate sleep is necessary for normal function and is essential for physical and psychological health. Chronic insomnia is associated with impairments in many aspects of interpersonal difficulties, quality of life, substance abuse, cognition, risk of psychiatric disease, work-related problems, and accident proneness. Approximately one-third of all people will suffer from chronic insomnia at some point in their lifetime, and one-tenth of them will have significant daytime impairment as a result.[1] Risk factors for insomnia include older age, female gender, shift work, and comorbid medical or psychiatric conditions. Problem sleep is a prominent symptom of many somatic and emotional illnesses.

The definitions and diagnoses of insomnia vary widely. The term *insomnia* has various medical meanings, as either a symptom or a specific disorder. According to *DSM-5* criteria,[2] insomnia is concern about poor sleep quantity or quality with 1 or more of the following: difficulty getting to and staying asleep, early awakenings followed by trouble returning to sleep, and personal distress or daytime dysfunction. Insomnia cannot be attributed to a substance abuse or primary sleep disorder and is not explained by a coexisting medical or psychiatric disorder. The sleep difficulty must be present despite adequate opportunity for sleep, must occur at least 3 nights per week, and must be present for at least 3 months.

The most important aspect of an insomnia evaluation is to obtain a thorough sleep history. A complete evaluation for insomnia includes assessing the physical and psychiatric conditions associated with sleep difficulties, as well as environmental and social factors or personal concerns. Always consider substance use, coexisting pathology, other sleep disorders, and medications or other agents (eg, caffeine) that cause insomnia. Subsequently, there must be an individualized management plan to address the patient's symptoms or impairment.

Sleep hygiene might be one consideration, which includes teaching habits and behaviors that aim to induce a better nighttime sleep.[3] Sleep hygiene begins with recommendations for encouraging regularized bedtimes and maintaining a quiet, comfortable, and dark atmosphere in the bedroom. Recommendations also include avoiding caffeine after lunch, avoiding alcohol consumption after the evening meal, minimizing daytime naps, and not doing exercise in the hours just before going to bed. Unfortunately, sleep hygiene is not consistently an effective, stand-alone treatment for insomnia.[4]

This article reports the results of a literature search related to pharmacotherapy for insomnia and presents 4 clinical vignettes with corresponding treatment options.

LITERATURE SEARCH

A PubMed search using the clinical query function was conducted using the following terms: *insomnia pharmacotherapy*, *insomnia and gabapentin*, *hydroxyzine*, and *insomnia treatment*. Also searched were the US Preventative Services Taskforce web site, UpToDate, National Guideline Clearinghouse, and DynaMed. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. The search results consisted of about 8,500

Clinical Points

- Insomnia is a common clinical issue and one that can impair normal daily functioning.
- Sleeplessness calls for a complete evaluation of patients to determine an etiologic diagnosis.
- Besides managing medical and psychiatric conditions, treatment of insomnia includes a variety of sleep hygiene, behavioral interventions, and pharmacotherapies.

references from all of the search modalities. Of these, 15 references[1,3–15] were identified and used in this report. The searches were restricted to human English-language studies published between 1990 and March 20, 2015 (date of search).

CLINICAL VIGNETTES

Vignette 1

Mr A, a 45-year-old man new to your practice, presents with the complaint "I do not sleep well." Which of the choices below are appropriate for your initial evaluation?

1. Obtain a thorough history, including sleep or daytime impairments, a medical and psychiatric assessment, an occupational/social review, and a list of medications or substances used
2. Refer for polysomnography
3. Refer for cognitive-behavioral therapy
4. Initiate short-term pharmacotherapy
5. Ask the patient to complete a sleep record for the next 2 weeks.

Any of these choices may be reasonable strategies depending on the presentation. It is crucial to first obtain a complete history from the patient. It is important to assess for coexisting medical or psychiatric conditions, as well as for medications or substance use that may be contributing to the sleep difficulties, and always inquire about caffeine consumption. Polysomnography is rarely indicated in initial insomnia evaluation; however, if the presentation yields concern for sleep apnea (eg, loud snoring), then such referral is most appropriate. Sleep apnea can be confused with primary insomnia. Clinicians should maintain a high index of suspicion for sleep apnea in all patients with a sleep-related complaint, since otherwise it can exert a dramatic negative impact on health and quality of life. Referral for polysomnography and a sleep specialist consultation is also indicated if an overt sleep disorder is suspected (eg, central sleep apnea) or past treatments have been unsuccessful. Loud snoring, apneic spells while asleep, and daytime fatigue are common presentations of sleep apneas.

Cognitive-behavioral therapy is an effective treatment for primary and secondary insomnia, sleep dysfunction in the elderly, and chronic users of hypnotic drugs.[4–6] Long-term sedative pharmacologic treatment for insomnia is not recommended due to risk of drug dependence, abuse, medication side effects, and rebound-emergent insomnia. Short-term use of benzodiazepine-receptor agonists (ie, "Z-drugs": zolpidem, zaleplon, eszopiclone), sedating antidepressant medicines, and other pharmacologic options are often especially reasonable if the sleep problem is expected to be temporary or if medications are being prescribed for short-term augmentation of nonpharmacologic treatments or other medicinal therapies.

Vignette 2

Ms B, a 32-year-old woman, presents for evaluation of nightmares and anxiety at bedtime. She has a history of depression, anxiety, and posttraumatic stress disorder (PTSD). She is being treated with a selective serotonin reuptake inhibitor (SSRI) and her depression has improved, but she continues to have significant anxiety and panic attacks and is afraid to sleep because of nightmares. In addition to cognitive-behavioral psychotherapy, which of these choices is a reasonable adjunct pharmacotherapy to consider for Ms B's sleep disturbance?

1. Prazosin 2 mg at bedtime
2. Gabapentin 300 mg at bedtime
3. A long-acting benzodiazepine at bedtime.

The increased central nervous system noradrenergic state documented in PTSD patients yields disruption of rapid eye movement sleep, in turn contributing to nightmares. Prazosin is a lipid-soluble, α_1-adrenergic receptor antagonist that crosses the blood-brain barrier and decreases the sympathetic outflow in the brain. This blockage is believed to be the mechanism for mitigating PTSD symptoms, especially nightmares. The use of prazosin for nightmares is not an approved indication, yet there is support for its effectiveness.[7] Prazosin is an antihypertensive medication, with potential induction of clinically significant orthostatic hypotension, falling, and syncope. Nightmares often return following discontinuation of prazosin. Common dosing to counter PTSD nightmares is 1 to 16 mg before bedtime on a gradually titrated basis, with therapeutic benefit sometimes beginning at 1 mg nightly.

Gabapentin, a calcium channel/γ-aminobutyric acid–modulating medication, exhibits promise as another off-label pharmacotherapy for insomnia, especially effective for patients with underlying anxiety, chronic pain, or coexisting alcohol dependence.[8–10] Gabapentin has advantages as a hypnotic medication: few adverse drug interactions, a favorable side effect profile, a wide therapeutic index, and no known evidence for abuse potential or hepatic interference. One common dosing strategy is to begin at 300 mg by mouth before bedtime and increase gradually up to a conventional maximum dose of 1,800 mg in a single nocturnal regimen.

Prescribing benzodiazepines for insomnia is controversial but can be undertaken with caution to avoid misuse. Especially with long-term exposure, clinicians should be wary of tolerance and dependence, potential for abuse or overdose, and altered sleep physiology. Nevertheless, benzodiazepines may be safe and reasonable to initiate a

Prim Care Companion CNS Disord
2016;18(2):doi:10.4088/PCC.16br01930

short-term, intermittent, and well-monitored course in individually selected cases. Despite concerns about long-term benzodiazepine use, many patients successfully use this pharmacotherapy without abuse or misuse.

Vignette 3

Mr C, a 55-year-old man, presents for an insurance physical. He reports no medical problems, and his examination is unremarkable. He drinks 2–3 glasses of whiskey before bed each night "to relax" and denies other substance use. He takes no medications. He easily initiates sleep at around 11 PM but usually awakens too early each morning (at around 3 AM) and is unable to fall back to sleep. This early awakening has led to significant daytime fatigue and low energy, for which he indulges in a nap each afternoon. What should you do to treat Mr C's insomnia?

1. Gradually taper off of nocturnal alcohol
2. Begin doxepin 6 mg at bedtime
3. Evaluate further for signs of coexisting psychiatric conditions, especially depression and substance use
4. Consider obstructive sleep apnea
5. Start hydroxyzine 25 mg at bedtime.

Alcohol consumption at bedtime is an extremely common self-medication strategy. Ethanol use in the evening decreases sleep latency, making it an attractive option for sleep-onset insomnia; however, it results in more restless sleep, difficulty with sleep maintenance, and decreased and delayed rapid eye movement sleep.[11] Abuse of alcohol is strongly associated with chronic sleep disturbances—even small amounts of alcohol can interfere with sleep quality. In addition to improving sleep hygiene and recommending the gradual cessation of nocturnal alcohol, Mr C should be evaluated for coexisting medical or psychiatric conditions, especially depression and sleep apnea.

Low-dose (3 or 6 mg) doxepin, a tricyclic drug, is an approved antidepressant medication that is an effective, safe pharmacotherapy for sleep maintenance insomnia, ie, waking up frequently or waking too early and not being able to fall back asleep. A commonly recommended hypnotic doxepin dose is 6 mg administered 30 minutes before bedtime for patients younger than 65 years. For patients over 65 years, begin with 3 mg 30 minutes before bedtime and consider increasing to 6 mg if indicated. While higher doses (10–150 or even up to 300 mg) of doxepin are prescribed as antidepressant agents, at low doses, doxepin acts as a selective H_1 antagonist, and this mechanism is thought to be responsible for a hypnotic effect. Doxepin is available in pill and liquid forms. While higher doses are associated with significant anticholinergic side effects, hypotension, and cardiotoxicity, the quantities approved for insomnia have a benign side effect profile. There is no addiction, withdrawal, or rebound phenomena associated with doxepin usage.[12]

Hydroxyzine is an antihistaminic drug with selective H_1 antagonism and significantly less affinity for acetylcholine receptors than diphenhydramine; this results in H_1-receptor blockade with less anticholinergic effects. There is no evidence for tolerance with antihistaminergic medications, and they are economical compared to other hypnotics. However, while hydroxyzine (25 to 100 mg at bedtime) is commonly prescribed for insomnia, there are few data to support its efficacy or safety for this indication.[13] Moreover, there is concern of electrocardiographic QTc interval prolongation, especially if coprescribed with certain QT-prolonging medications or in individuals with cardiac risk factors. A shorter half-life offers an advantage over prescribing diphenhydramine, which sometimes yields daytime sedation.

Vignette 4

Ms D, a 23-year-old woman, presents to your office with 2 months of worsening sadness, hopelessness, anhedonia, and guilt. She has no significant medical or psychiatric history and is normally a happy person. Recently, however, she has been depressed "for no good reason." Unable to sleep more than 4 hours per night, she also has lost 10 lb due to poor appetite. Physical examination is unremarkable, but her affect is flat and she is overweight. While not suicidal, she admits to passive thoughts of death. In addition to recommending psychotherapy, which of the following options is appropriate for Ms D?

1. Paroxetine 20 mg nocturnally
2. Trazodone 150 mg before bedtime
3. Mirtazapine 15 mg before bedtime
4. Venlafaxine 37.5 mg each morning
5. Zolpidem 5 mg before bedtime.

Selection of a medication that addresses depression and insomnia is ideal. Sleep disturbances are commonly reported by people with depression, and treatment of Ms D's depression most likely will improve her insomnia. A common first step could be to begin with an SSRI such as paroxetine, which yields antidepressant and sedating properties. When initiating pharmacotherapy for depression, many people with insomnia benefit from an option with sedating properties. Several SSRIs also have the potential to worsen sleep disturbances. (eg, fluoxetine).

Trazodone is an antidepressant medication commonly prescribed off-label for insomnia, with typical initial dosing at 25–100 mg before bedtime. In depressed patients, 150 mg is often the initial nocturnal dose. The dosage used in depression can be titrated upward, even up to 600 mg nightly, while closely observing blood pressure. Trazodone has a favorable safety profile; however, its side effects include prominent hypotension, fainting or falling, priapism, cardiac arrhythmias, and weight gain. Trazodone is sometimes associated with daytime somnolence and psychomotor impairment.[14]

Mirtazapine is an antidepressant drug that works on noradrenergic and serotonergic receptors. While doses from 15 to 45 mg daily are effective at treating depression and insomnia, mirtazapine may stimulate significant weight gain.[15] Therefore, mirtazapine is best selected for patients

who would benefit from sedation and increased appetite, particularly in chronically ill or cachectic persons. As Ms D is overweight, it is not an ideal first drug of choice for her. Venlafaxine is another antidepressant drug option to consider.

The benzodiazepine receptor agonists or Z-drugs (eg, zolpidem, zaleplon, eszopiclone) are approved for the treatment of insomnia. These sleep-aid medications are effective at reducing sleep-onset latency and increasing total sleep time. However, they also may be associated with adverse events, including daytime somnolence, rebound insomnia, anterograde amnesia, and bizarre or dangerous sleep-related behaviors (ie, inappropriate eating, sexual behavior, or driving). They also might be able to induce dependence, tolerance, and withdrawal, although abuse is uncommon. Zaleplon has the advantage of a short half-life, allowing ingestion following early morning awakenings, if not close to arousal time. Prescription of these medications is controversial; they should be applied with close monitoring and are best only for short durations. Addiction issues and rebound insomnia can be minimized by slowly tapering the dosing regimen.[16] Intermittent use and the lowest effective dosage are recommended.

Otherwise, some alternate sleep aids such as melatonin, useful at correcting jetlag or sleep pattern changes in shift workers, and the new antialertness medication, suvorexant, can be considered.

CONCLUSION

The management of sleep problems can be difficult, given the coexistence of medical and psychiatric conditions, various drug interactions, and concern about developing sleep medication dependence. Evaluation of insomnia should include a complete history and physical examination focusing on different medical and psychiatric causes of sleep disturbances including substance use history and proper counseling about sleep hygiene. Depending on the cause of sleep disturbance, behavioral therapy with or without adjunctive medications is the mainstay of treatment for insomnia. There are several off-label pharmaceutical options such as doxepin, gabapentin, prazosin, and hydroxyzine available for management of insomnia with coexisting disorders. Despite physicians understanding the importance of sleep, it may be difficult to adequately manage insomnia amid addressing multiple conditions and in a brief appointment. This is particularly true when education about sleep hygiene fails and coexisting conditions or pharmacotherapies complicate the clinical status.

Drug names: doxepin (Silenor and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), gabapentin (Neurontin, Gralise, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), prazosin (Minipress and others), suvorexant (Belsomra), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

Submitted: January 1, 2016; accepted January 29, 2016.

Published online: March 17, 2016.

Potential conflicts of interest: None reported.

Funding/support: None reported.

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