

Insomnia: Pharmacologic Therapy

ERIC MATHESON, MD, and BARRY L. HAINER, MD, *Medical University of South Carolina, Charleston, South Carolina*

Insomnia accounts for more than 5.5 million visits to family physicians each year. Although behavioral interventions are the mainstay of treatment, pharmacologic therapy may be necessary for some patients. Understanding the risks and benefits of insomnia medications is critical. Controlled-release melatonin and doxepin are recommended as first-line agents in older adults; the so-called z-drugs (zolpidem, eszopiclone, and zaleplon) should be reserved for use if the first-line agents are ineffective. For the general population with difficulty falling asleep, controlled-release melatonin and the z-drugs can be considered. For those who have difficulty staying asleep, low-dose doxepin and the z-drugs should be considered. Benzodiazepines are not recommended because of their high abuse potential and the availability of better alternatives. Although the orexin receptor antagonist suvorexant appears to be relatively effective, it is no more effective than the z-drugs and much more expensive. Sedating antihistamines, antiepileptics, and atypical antipsychotics are not recommended unless they are used primarily to treat another condition. Persons with sleep apnea or chronic lung disease with nocturnal hypoxia should be evaluated by a sleep specialist before sedating medications are prescribed. (*Am Fam Physician*. 2017;96(1):29-35. Copyright © 2017 American Academy of Family Physicians.)

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 21. Author disclosure: No relevant financial affiliation.

► Patient information: A handout on this topic is available at <http://www.aafp.org/afp/2015/1215/p1058-s1.html>.

Scan the QR code below for easy access to the patient information handout on the *AFP* mobile site.



Insomnia is among the most common problems encountered by the family physician, accounting for more than 5.5 million visits annually.¹ The American Academy of Sleep Medicine defines insomnia as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment.² The recommended first-line therapies for insomnia are nonpharmacologic, such as stimulus control, relaxation training, or sleep restriction. However, this article focuses on pharmacologic treatment of insomnia; nonpharmacologic methods were discussed in an earlier review.³

Women are more likely than men to experience insomnia and twice as likely to be diagnosed with insomnia.^{4,5} The prevalence of insomnia in women increases with hormonal changes, such as in the third trimester of pregnancy and after menopause.⁵ Insomnia can occur at any age but is particularly common in older adults, with symptoms present in as many as 65% of persons 65 years or older.⁵⁻⁷ Patients with comorbidities such as pulmonary disease, heart failure, neurologic disease, and painful conditions are at increased risk.⁸ An increased prevalence of insomnia is also associated with psychiatric disorders, including depression, anxiety, substance abuse, and posttraumatic stress

disorder.^{9,10} Population studies suggest that insomnia is more prevalent in persons who have experienced the death of a family member or are unemployed, divorced, widowed, separated, or of lower socioeconomic status.^{11,12} Persons withdrawing from alcohol or opiates also report high levels of insomnia.

The number of prescriptions written for insomnia skyrocketed from 5.3 million in 1999 to 20.8 million in 2010.¹ Given the widespread use of medications for insomnia, understanding the benefits and risks of these agents is critical. Numerous classes of medications have been used for insomnia; the most commonly prescribed are reviewed in *Table 1*.¹³

GABA Agonists BENZODIAZEPINES

Benzodiazepines work through the modulation of the γ -aminobutyric acid (GABA)_A receptor in neurons, resulting in hyperpolarization of the cell.¹⁴ GABA serves as an inhibitory neurotransmitter in the central nervous system, decreasing neuronal excitability. Through stimulation of GABA receptors, benzodiazepines cause sedation, decreased anxiety, muscle relaxation, and retrograde amnesia.^{15,16}

Although many benzodiazepines are used to treat insomnia, only five are approved by the U.S. Food and Drug Administration (FDA) for this indication. Several important

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Although benzodiazepines improve short-term sleep outcomes, they have significant adverse effects and may be addictive.	B	18
The z-drugs (zolpidem [Ambien], eszopiclone [Lunesta], and zaleplon [Sonata]) improve sleep outcomes in the general population.	A	18
Ramelteon (Rozerem) is only modestly effective compared with placebo, but it has few adverse effects.	B	18
Low-dose doxepin (Silenor) improves sleep outcomes and has no significant adverse effects compared with placebo.	A	18

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

differences must be taken into account when prescribing a benzodiazepine for insomnia, including onset and duration of action, and metabolism. Rate of metabolism is particularly important in patients with impaired liver and/or kidney function or advanced age because these agents can bioaccumulate, resulting in adverse effects such as memory impairment, loss of coordination, and daytime somnolence. Beyond the immediate effects, chronic benzodiazepine use disrupts the quality of sleep by distorting sleep architecture and diminishing deep sleep time, which may account for the fact that persons who take long-term benzodiazepines report much greater fatigue than self-reported good sleepers.¹⁷

The risk of developing physical dependence to benzodiazepines is high¹⁸; 15% to 40% of long-term users report severe withdrawal symptoms after cessation.¹⁹ Even after only a few weeks of benzodiazepine therapy, patients often have rebound insomnia and increased anxiety.²⁰ Benzodiazepines are contraindicated during pregnancy and breastfeeding (category D or X). They should not be used in patients with sleep apnea and/or chronic pulmonary disease because they may suppress respiratory drive. Because of their abuse potential, benzodiazepines are classified as schedule IV drugs.

NONBENZODIAZEPINE HYPNOTICS

The most commonly prescribed class of medication for insomnia is the so-called z-drugs, zaleplon (Sonata), zolpidem (Ambien), and eszopiclone (Lunesta).²¹ Numerous trials have demonstrated the effectiveness of these drugs, including a recent meta-analysis that showed that they decreased sleep latency by an average of 42 minutes vs. 20 minutes for placebo.²² Like benzodiazepines, the z-drugs bind to the GABA_A receptor, causing hyperpolarization of the cell. However, unlike

benzodiazepines, the z-drugs bind more selectively to certain subunits of the GABA_A receptor, primarily targeting the sedative effect of the receptor rather than the anxiolytic effect.²³ Like benzodiazepines, the z-drugs have several adverse effects, particularly in higher dosages, including memory loss, dizziness, disinhibition, gastrointestinal upset, and hallucinations. Uncommonly, complex sleep-related behaviors (e.g., sleep driving, sleep eating) have been reported in patients taking high doses of z-drugs; this risk should be discussed with patients when these medications are initially prescribed.²⁴⁻²⁶ The prescriber must be aware of the abuse potential of the z-drugs

because they may cause stimulation, euphoria, and anxiety in some patients, particularly at high dosages.²⁷

The z-drugs have been used to treat a broad array of sleep problems without sacrificing sleep efficiency.¹⁸ In addition to treating insomnia related to difficulty with sleep latency and sleep maintenance, zolpidem, an imidazopyridine agent, has been used to treat circadian rhythm misalignment and high-altitude insomnia.²⁸⁻³⁰ Eszopiclone is a cyclopyrrolone drug that has been used to improve sleep latency, and it is particularly well suited for sleep maintenance given its long half-life.³¹ One unique adverse effect of eszopiclone is unpleasant taste that affects nearly one-third of patients at the maximum recommended dosage. Zaleplon, a pyrazolopyrimidine drug, has an extremely short half-life and is indicated for improving sleep latency but not sleep maintenance. Each of the z-drugs has a slightly different pharmacologic profile, indications, effectiveness, and adverse effect profile (*Tables 1¹³ and 2³²*). These agents should be used during pregnancy only if the benefits outweigh the risks. Because of their abuse potential, eszopiclone, zaleplon, and zolpidem are classified as schedule IV drugs.

Melatonin Agonists

Melatonin has a key role in regulating the sleep-wake cycle, and disruption of the timing of melatonin release or decreased melatonin production can contribute to insomnia. The problem is particularly pronounced when changing time zones or during shift work. Melatonin production also wanes with age, which may be partially responsible for the sleep difficulties experienced by older adults.³³ Ramelteon (Rozerem) is a melatonin agonist approved by the FDA for insomnia related to sleep latency. Although the effectiveness of ramelteon is

Table 1. Comparison of Commonly Prescribed Sleep Medications

Medication	Dose (mg)	Approximate time to peak (hours)	Approximate half-life (hours)	Cost*	Recommended use
Benzodiazepines					
Estazolam	0.5 to 2	2	10 to 24	\$14	Sleep maintenance†
Flurazepam	15 to 30	1	47 to 100	\$12	Sleep maintenance†
Quazepam (Doral)	7.5 to 15	2	25 to 84	(NA) \$357	Sleep maintenance†
Temazepam (Restoril)	7.5 to 30	1.5	3.5 to 18.4	\$102 (\$600)	Sleep onset and maintenance†
Triazolam	0.125 to 0.25	2	1.5 to 5.5	\$21	Sleep onset†
Z-drugs					
Eszopiclone (Lunesta)	1 to 3	1	6	\$25 (\$437)	Sleep onset and maintenance
Zaleplon (Sonata)	5 to 10	1	1	\$17 (\$278)	Sleep onset
Zolpidem (Ambien)	5 to 10	1.6	2.6	\$8 (\$488)	Sleep onset and maintenance
Zolpidem, extended release (Ambien CR)	6.25 to 12.5	1.5	2.8	\$66 (\$488)	Sleep onset and maintenance
Zolpidem, sublingual (Intermezzo)	1.75 or 3.5	1	2.5	\$105 (\$357)	Night awakening‡
Melatonin agonists					
Melatonin, controlled release	1	1.5	3.5	\$1	Sleep onset
Ramelteon (Rozerem)	8	0.75	2.5	NA (\$351)	Sleep onset
Tricyclic/quatracyclic antidepressants					
Amitriptyline	25 to 150	4	30	\$4	Limited use§
Doxepin (Silenor)	3 to 6	3.5	15	NA (\$383)	Sleep maintenance
Mirtazapine (Remeron)	7.5 to 15	2	30	\$28 (\$185)	Not recommended
Nortriptyline (Pamelor)	25 to 150	8	30	\$4 (\$1,024)	Limited use§
Trazodone	50 to 100	1	10	\$4	Not recommended
Orexin receptor antagonist					
Suvorexant (Belsomra)	5 to 20	2	15	\$314	Sleep onset and maintenance
Antihistamines					
Diphenhydramine (Benadryl)	25 to 50	2.5	8.5	\$3 (\$5)	Not recommended
Doxylamine	25 to 50	2.4	10	\$5	Not recommended
Hydroxyzine	50 to 100	2	20	\$4	Not recommended
Antipsychotics					
Olanzapine (Zyprexa)	2.5 to 20	6	30	\$13 (\$325)	Limited use¶
Quetiapine (Seroquel)	50 to 400	1.5	6	\$12 (\$205)	Limited use¶
Risperidone (Risperdal)	0.25 to 6	1	20	\$11 (\$246)	Limited use¶
Anticonvulsants					
Gabapentin (Neurontin)	300 to 600	2.5	6	\$6 (\$129)	Limited use**
Pregabalin (Lyrica)	50 to 300	3	6	NA (\$185)	Limited use**

NA = not available.

*—Estimated retail price of one month's treatment at the lowest dose based on information obtained at <http://www.goodrx.com> for prescription medications and <http://www.walgreens.com> for over-the-counter medications (both accessed December 16, 2016). Generic price listed first; brand name in parentheses.

†—Benzodiazepines should be avoided if possible and are recommended for use only in healthy adults for brief periods. They should be avoided entirely in older adults and in patients with a history of substance abuse or sleep apnea.

‡—Use only if three to four hours remain before planned awakening.

§—Use only for insomnia with comorbid depression, fibromyalgia, and/or chronic neuropathic pain.

||—Generic formulation is available in 10-mg capsules (\$9 for 30). Although safe, this dosage has not been approved by the U.S. Food and Drug Administration for the treatment of insomnia.

¶—Use only for insomnia with comorbid schizophrenia or bipolar disorder.

**—Use only for insomnia with comorbid seizure disorder, fibromyalgia, restless legs syndrome, or neuropathic pain.

Information from reference 13.

Table 2. Comparison of Medications for Insomnia in Adults

Medication	Dose (mg)	Difference in sleep onset latency (minutes)*	Difference in total sleep time (minutes)†	Difference in time awake after sleep onset (minutes)‡	Relative risk of withdrawal from study because of adverse events (95% confidence interval)
Benzodiazepine					
Temazepam (Restoril)	7.5 to 30	- 30.9	93.5	NR	6.7 (0.4 to 121.1)
Z-drugs					
Eszopiclone (Lunesta)	2 to 3	- 19.1	44.8	- 10.8	NS
Zaleplon (Sonata)	5 to 20	- 9.9	NR	NR	1.6 (0.7 to 3.9)
Zolpidem (Ambien)	5	- 18.3	NS	NR	0.3 (0.1 to 1.6)
	10	- 14.8	48.1	- 22.8	2.8 (1.0 to 8.0)
Zolpidem, extended release (Ambien CR)	12.5	- 9	25	- 16	1.79 (1.04 to 3.1)
Zolpidem, sublingual (Intermezzo)	3.5	- 18	NS	NR	NS
Melatonin agonist					
Melatonin, controlled release	1	- 6.0	NR	NR	0.86 (0.4 to 1.8)
Ramelteon (Rozerem)	4 to 16	NS	NS	NS	1.2 (0.47 to 3.2)
Tricyclic antidepressant					
Doxepin (Silenor)	3	NS	11.9	- 18	1.1 (0.4 to 3.9)
	6	NS	17.3	- 23	1.1 (0.4 to 3.9)
Orexin receptor antagonist					
Suvorexant (Belsomra)	15 to 20	- 6.0	16.0	- 4.7	0.6 (0.3 to 1.3)

NR = not reported; NS = not significant.

*—Mean difference in the length of time to transition from full wakefulness to sleep vs. placebo.

†—Mean difference in total sleep time vs. placebo.

‡—Mean difference in total minutes of wakefulness recorded after sleep onset vs. placebo.

Information from reference 32.

modest, it has few adverse effects and is not habit forming.¹⁸ One small study found that ramelteon decreased the risk of hospital-associated delirium in older adults, lowering the incidence from 32% to 3% compared with placebo.³⁴ Ramelteon should be used in pregnancy only if the benefits outweigh the risks.

Controlled-release melatonin is much less expensive and may work as well, if not better, than ramelteon for insomnia. A 2013 meta-analysis found that melatonin at doses of 0.1 mg to 5 mg decreased sleep latency by 7.1 minutes, increased total sleep time by 8.3 minutes, improved overall sleep quality, and had a favorable adverse effect profile.³⁵ Because melatonin is not regulated by the FDA and purity varies widely among products, reviewing third-party product evaluations is recommended to determine product quality.

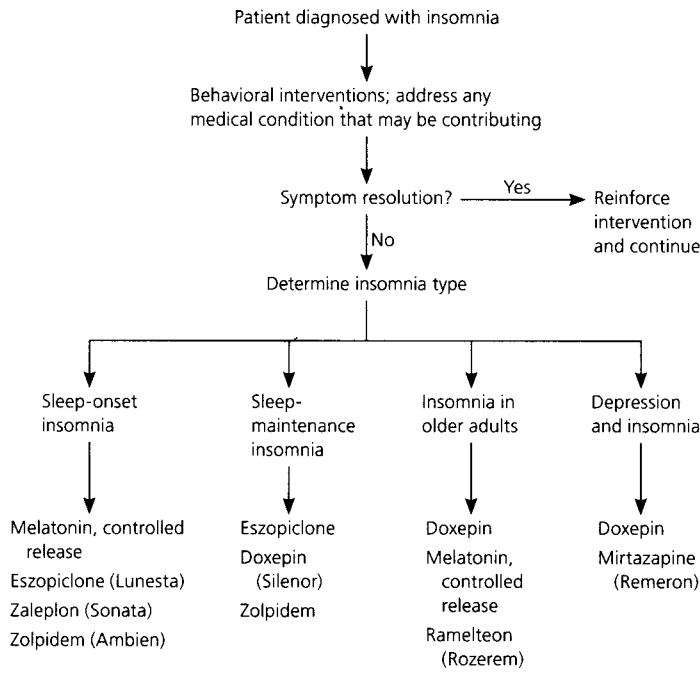
Other Hypnotic Drugs

ANTIDEPRESSANTS

Although antidepressants have been widely used for their sedative effects, only the tricyclic antidepressant doxepin (Silenor) has been FDA approved for the treatment of insomnia characterized by difficulties with sleep

maintenance. The mechanism of action is not known but is likely related to antagonism of the histamine H₁ receptor. Compared with placebo, doxepin at doses of 3 and 6 mg improves sleep efficiency and total sleep time, and a 6-mg dose improves sleep latency.³⁶ The adverse effect profile of both doses is favorable in older adults and similar to placebo, even when used long term.^{18,37} Doxepin is also available in a much less expensive generic formulation in 10-mg capsules. Although safe, this dosage has not been approved by the FDA for the treatment of insomnia. Doxepin should be used during pregnancy only if the benefits outweigh the risks. Several other antidepressants are also used off-label to treat insomnia, especially trazodone, which is typically prescribed at dosages of 50 to 100 mg at bedtime. However, the evidence for trazodone is weak, and it should not be considered as first-line therapy.³⁸ In addition to trazodone, mirtazapine (Remeron), amitriptyline (Elavil), and nortriptyline (Pamelor) are used off-label for the treatment of insomnia. The evidence for these medications is also limited, and they should be considered only if there is another indication besides insomnia. These medications have anticholinergic effects and should not

Treatment of Insomnia



NOTE: Medications are listed in order of preference for each indication.

Figure 1. Recommended treatment algorithm for insomnia.

be used in patients with glaucoma or difficulty with urinary retention.

ANTIHISTAMINES

Diphenhydramine (Benadryl) and doxylamine are available over the counter for the treatment of insomnia, but they are recommended only for the treatment of pregnancy-related insomnia. Although these medications are effective, the evidence for their use is limited compared to that for doxepin.^{39,40} Doxylamine (category A) and diphenhydramine (category B) are first-line therapies for insomnia in pregnant women because they may be effective for nausea and insomnia and are generally considered safe during pregnancy. Hydroxyzine is another antihistamine with sedating qualities, but evidence for its use in the treatment of insomnia is lacking. Sedating antihistamines have significant anticholinergic effects and should be avoided in patients with glaucoma or difficulty with urinary retention.

ANTIPSYCHOTICS

Several antipsychotic medications are used off-label to treat insomnia, including olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal). As with trazodone, the evidence for their use is weak, and these medications should be used only if the patient has some other indication, such as bipolar disorder.⁴¹

OREXIN RECEPTOR ANTAGONIST

Suvorexant (Belsomra) is the first orexin receptor antagonist approved for the treatment of insomnia. The orexin system regulates the sleep arousal cycle that promotes wakefulness.⁴² Compared with placebo, suvorexant in doses of 10 and 20 mg decreased first-night sleep latency by an average of 3.4 and 9.4 minutes, respectively, but these times did not reach statistical significance.⁴³⁻⁴⁵ At one month, the 10-mg dose still did not significantly improve sleep latency, but the 20-mg dose did (22.3 minutes compared with placebo). Both dosages reduced awakening after sleep by 21 and 25 minutes, respectively, on the first night of testing and continued during the entire four-week trial.⁴⁶ The most common adverse effect was daytime somnolence, but otherwise the medication was well tolerated. Suvorexant is thought to have moderate potential for addiction and is classified as a schedule IV drug. Given its high cost and addictive potential, suvorexant is not recommended as

a first-line treatment for insomnia.

ANTIPILEPTICS

Gabapentin (Neurontin) and pregabalin (Lyrica) have been found to improve sleep, but the mechanism of action is not clear.^{47,48} A randomized, double-blind, placebo-controlled trial of adults who reported occasional sleep disturbance found that taking 250 mg of gabapentin at bedtime improved total sleep time by 64 minutes on day 1 of the trial and 46 minutes on day 28.⁴⁶ Other trials found similar benefits in healthy participants with sleep disturbances and in those with depression and sleep disturbances.^{48,49} Gabapentin is particularly useful for persons with insomnia due to restless legs syndrome.⁵⁰ Pregabalin may also improve sleep quality, but the evidence is too limited to recommend it for this indication.⁵¹⁻⁵³

Approach to the Patient

Behavioral interventions are the mainstay of treatment for insomnia. If pharmacologic intervention becomes necessary, a tailored approach based on the type of insomnia is suggested (Figure 1). If the initial intervention is ineffective, a different agent in the same class or a different class of medication should be considered. Although some persons can tolerate multiple sedating agents, such as a sedating tricyclic antidepressant and a z-drug, extreme caution should be used when

BEST PRACTICES IN SLEEP MEDICINE: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	Sponsoring organization
Do not use benzodiazepines or other sedative-hypnotics in older adults as a first choice for insomnia, agitation, or delirium.	American Geriatrics Society
Avoid the use of hypnotics as primary therapy for chronic insomnia in adults; instead, offer cognitive behavior therapy and reserve medication for adjunctive treatment when necessary.	American Academy of Sleep Medicine
Do not routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults.	American Psychiatric Association

Source: For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <http://www.aafp.org/afp/recommendations/search.htm>.

prescribing such combinations. Because of the risk of respiratory depression, patients at risk of sleep apnea or nocturnal hypoxia due to lung disease should be evaluated by a sleep specialist before sedating medication is prescribed. Benzodiazepines are generally not recommended because of their high risk of abuse. If benzodiazepines are prescribed, they should be used for the shortest possible time at the lowest possible dose. Benzodiazepines, z-drugs, atypical antipsychotics, and tricyclic antidepressants (other than low-dose doxepin and nortriptyline) should be avoided in older adults, patients with untreated sleep apnea, and those with chronic nocturnal hypoxia. Herbal medications have not been proven effective for the treatment of insomnia.¹³

This article updates previous articles on this topic by Ramakrishnan and Scheid²⁴; Rajput and Bromley⁵⁵; and Eddy and Walbroehl.⁵⁶

Data Sources: A PubMed search was completed in Clinical Queries using the key terms insomnia, medications, and pharmacological. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, Banelier, Clinical Evidence, the Cochrane database, Database of Abstracts of Reviews of Effects, Essential Evidence Plus, the Institute for Clinical Systems Improvement, the National Guideline Clearinghouse database, the Trip database, and UpToDate. Search dates: December 15, 2015, and March 2017.

The Authors

ERIC MATHESON, MD, is an associate professor in the Department of Family Medicine at the Medical University of South Carolina, Charleston.

BARRY L. HAINER, MD, is a professor in the Department of Family Medicine at the Medical University of South Carolina.

Address correspondence to Eric Matheson, MD, Medical University of

South Carolina, 9228 Medical Plaza Dr., Charleston, SC 29406 (e-mail: matheson@muscc.edu). Reprints are not available from the authors.

REFERENCES

1. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999-2010. *Sleep*. 2014;37(8):1283-1293.
2. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 2nd ed. Westchester, Ill.: American Academy of Sleep Medicine; 2005.
3. Maness DL, Khan M. Nonpharmacologic management of chronic insomnia. *Am Fam Physician*. 2015;92(12):1058-1064.
4. Masters PA. In the clinic. Insomnia. *Ann Intern Med*. 2014;161(7):ITC1-ITC15.
5. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6(2):97-111.
6. Morphy H, Dunn KM, Lewis M, Boardman HF, Croft PR. Epidemiology of insomnia: a longitudinal study in a UK population. *Sleep*. 2007;30(3):274-280.
7. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep*. 1995;18(6):425-432.
8. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems [published correction appears in *Sleep*. 2007;30(7):table of contents]. *Sleep*. 2007;30(2):213-218.
9. Spiegelhalder K, Regen W, Nanovska S, Baglioni C, Riemann D. Comorbid sleep disorders in neuropsychiatric disorders across the life cycle. *Curr Psychiatry Rep*. 2013;15(6):364.
10. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;135(1-3):10-19.
11. Gellis LA, Lichstein KL, Scarinci IC, et al. Socioeconomic status and insomnia. *J Abnorm Psychol*. 2005;114(1):111-118.
12. Paine SJ, Gander PH, Harris R, Reid P. Who reports insomnia? Relationships with age, sex, ethnicity, and socioeconomic deprivation. *Sleep*. 2004;27(6):1163-1169.
13. 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.
14. Griffin CE III, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J*. 2013;13(2):214-223.
15. Rudolph U, Crestani F, Benke D, et al. Benzodiazepine actions mediated by specific gamma-aminobutyric acid(A) receptor subtypes [published correction appears in *Nature*. 2000;404(6778):629]. *Nature*. 1999;401(6755):796-800.
16. Rudolph U, Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of GABA_A receptor subtypes. *Nat Rev Drug Discov*. 2011;10(9):685-697.
17. Bastien CH, LeBlanc M, Carrier J, Morin CM. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep*. 2003;26(3):313-317.
18. Brasure M, MacDonald R, Fuchs E, et al. Management of insomnia disorder. Comparative effectiveness reviews no. 159. Rockville, Md.: Agency for Healthcare Research and Quality; 2015.

19. Hood SD, Norman A, Hince DA, Melichar JK, Hulse GK. Benzodiazepine dependence and its treatment with low dose flumazenil. *Br J Clin Pharmacol*. 2014;77(2):285-294.
20. Kales A, Scharf MB, Kales JD, Soldatos CR. Rebound insomnia. A potential hazard following withdrawal of certain benzodiazepines. *JAMA*. 1979;241(16):1692-1695.
21. Bartholomew M. Top 200 drugs of 2012. *Pharm Times*. 2013;79(7):42, 44. <http://www.pharmacytimes.com/publications/issue/2013/july2013/top-200-drugs-of-2012>. Accessed January 18, 2017.
22. Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. 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.
23. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnotics: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet*. 2004;43(4):227-238.
24. Tsai MJ, Tsai YH, Huang YB. Compulsive activity and anterograde amnesia after zolpidem use. *Clin Toxicol (Phila)*. 2007;45(2):179-181.
25. Tsai JH, Yang P, Chen CC, et al. Zolpidem-induced amnesia and somnambulism: rare occurrences? *Eur Neuropsychopharmacol*. 2009;19(1):74-76.
26. Praplan-Pahud J, Forster A, Gamulin Z, Tassonyi E, Sauvanet JP. Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo. *Br J Anaesth*. 1990;64(6):670-674.
27. Victorri-Vigneau C, Dailly E, Veyrac G, Joliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol*. 2007;64(2):198-209.
28. Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. *Sleep*. 1995;18(4):246-251.
29. Asnis GM, Chakraborty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. *J Clin Psychiatry*. 1999;60(10):668-676.
30. Beaumont M, Batéjat D, Piérard C, et al. Zaleplon and zolpidem objectively alleviate sleep disturbances in mountaineers at a 3,613 meter altitude. *Sleep*. 2007;30(11):1527-1533.
31. Gunja N. The clinical and forensic toxicology of z-drugs. *J Med Toxicol*. 2013;9(2):155-162.
32. Micromedex Solutions [subscription required]. <http://www.micro-medexsolutions.com>. Accessed February 25, 2016.
33. Wetterberg L, Bratlid T, von Knorring L, Eberhard G, Yuwiler A. A multinational study of the relationships between nighttime urinary melatonin production, age, gender, body size, and latitude. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(5):256-262.
34. Hatta K, Kishi Y, Wada K, et al.; DELIRIA-J Group. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry*. 2014;71(4):397-403.
35. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One*. 2013;8(5):e63773.
36. Roth T, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep*. 2007;30(11):1555-1561.
37. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep*. 2011;34(10):1433-1442.
38. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM III-R primary insomnia. *Hum Psychopharmacol Clin Exp*. 1998;13(3):191-198.
39. Glass JR, Sproule BA, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *J Clin Psychopharmacol*. 2008;28(2):182-188.
40. Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep*. 2005;28(11):1465-1471.
41. Tassniyom K, Paholpak S, Tassniyom S, Kiewyoo J. Quetiapine for primary insomnia: a double blind, randomized controlled trial. *J Med Assoc Thai*. 2010;93(6):729-734.
42. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013;36(2):259-267.
43. Phase IIB 2-period crossover polysomnography study in participants with primary insomnia (MK-4305-006). <https://clinicaltrials.gov/ct2/show/NCT00792298>. Accessed January 18, 2017.
44. Center for Drug Evaluation and Research. Application number 204569 Orig1s000: medical review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204569Orig1s000MedR.pdf. Accessed January 18, 2017.
45. Herring WJ, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012;79(23):2265-2274.
46. Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca²⁺ channel alpha2delta ligands: novel modulators of neurotransmission [published correction appears in *Trends Pharmacol Sci*. 2007;28(4):151]. *Trends Pharmacol Sci*. 2007;28(2):75-82.
47. Furey SA, Hull SG, Leibowitz MT, Jayawardena S, Roth T. A randomized, double-blind, placebo-controlled, multicenter, 28-day, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *J Clin Sleep Med*. 2014;10(10):1101-1109.
48. Foldvary-Schaefer N, De Leon Sanchez I, Karafa M, Mascha E, Dinner D, Morris HH. Gabapentin increases slow-wave sleep in normal adults. *Epilepsia*. 2002;43(12):1493-1497.
49. Mowla A, Ahmadzadeh L, Razeghian Jahromi L, Dastgheib SA. Comparing gabapentin with clonazepam for residual sleeping problems following antidepressant therapy in patients with major depressive disorder: a randomized clinical trial. *Clin Drug Investig*. 2015;35(8):513-517.
50. Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, DeRossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. *Mov Disord*. 2011;26(11):2065-2072.
51. Bazil CW, Dave J, Cole J, Stalvey J, Drake E. Pregabalin increases slow-wave sleep and may improve attention in patients with partial epilepsy and insomnia. *Epilepsy Behav*. 2012;23(4):422-425.
52. Russell JJ, Crofford LJ, Leon T, et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. *Sleep Med*. 2009;10(6):604-610.
53. Cho YW, Song ML. Effects of pregabalin in patients with hypnotic-dependent insomnia. *J Clin Sleep Med*. 2014;10(5):545-550.
54. Ramakrishnan K, Scheid DC. Treatment options for insomnia. *Am Fam Physician*. 2007;76(4):517-526.
55. Rajput V, Bromley SM. Chronic insomnia: a practical review. *Am Fam Physician*. 1999;60(5):1431-1438.
56. Eddy M, Walbroehl GS. Insomnia. *Am Fam Physician*. 1999;59(7):1911-1916.