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Comparison of Insomnia Treatments

Insomnia is a very common disorder that can present in a number of different ways. Patients may have difficulty falling asleep (**sleep latency**), difficulty staying asleep (**sleep maintenance**), or may not feel rested by a night's sleep (**sleep quality**).[1] Insomnia can be transient (lasting days to weeks) or chronic (occurring at least three times per week for at least three months).[1] Approximately 30% to 50% of Americans have symptoms of insomnia at some time in their lives, with distress or impairment in about 10% to 15%.[1] First-line treatment of chronic insomnia should focus on nonpharmacologic interventions (e.g., sleep hygiene).[2-4] Pharmacologic treatments are added only if necessary.[2-4] Studies show medications are only modestly effective, helping patients fall asleep about five to 15 minutes faster and/or stay asleep about 30 to 60 minutes longer.[1] In general, benzodiazepines have more side effects and a higher potential for dependence, tolerance, and rebound insomnia than the newer nonbenzodiazepine hypnotics.[5] Hypnotics have a risk of complex sleep-related behaviors (e.g., sleepwalking, sleep driving) with amnesia; however they appear to be more common with the nonbenzodiazepine "Z" drugs (e.g., zolpidem, eszopiclone, zaleplon).[6] For most patients, medications should be started at the low end of the dose range and increased as necessary based on effect. The chart below provides a comparison of medications that are commonly used to treat insomnia. See our patient education handout, *Strategies for a Good Night's Sleep*, which provides information about sleep hygiene. See our *Benzodiazepine Toolkit*, for more information on the comparison of benzodiazepines. Also see our commentary, *Melatonin for Insomnia*, and our CE, *Natural Medicines in the Clinical Management of Insomnia Disorder*, for information on melatonin, valerian, and other supplements.

-Information pertains to U.S. products-

Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Nonprescription Antihistamines					
Diphenhydramine (*Benadryl*, *Sleep Tabs*, *ZzzQuil*, etc; generics)	Avoid[1,4,5]/ 25-50[7]	~$0.10/25 mg	15-30[8]	2-8[8]	• Anticholinergic side effects can occur.[4] • Not recommended due to poor evidence of efficacy.[1]
Doxylamine (*Unisom*, generics)	Avoid[1,4,5]/ 25[9]	~$0.13/25 mg	30[8,f]	10[8]	• Anticholinergic side effects can occur.[1] • Not recommended due to poor evidence of efficacy.[1]

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Antidepressants					
Doxepin (*Silenor*, generics)	3/ 6	$12.59/3 mg, 6 mg	30[10]	15 31 (primary metabolite)	• Approved for insomnia, to improve sleep maintenance. • Maximum dose is 3 mg in patients taking cimetidine. • Dose-dependent anticholinergic adverse effects.[10] • Do not take within three hours of a meal due to delayed onset and potential for next day drowsiness. • Little evidence of rebound insomnia. • Dispense with a MedGuide.
Mirtazapine (*Remeron*, *Remeron Soltab*, generics)	15/ 15[11]	Tablet: ~$0.38/15 mg Disintegrating tablet: ~$1.78/15 mg	Not available	20-40	• Off-label use. • Some evidence on reducing insomnia in patients with depression, especially early in treatment.[12] • Increased risk of restless legs syndrome and periodic limb movements in sleep.[12] • Low anticholinergic activity compared to doxepin.[13] • Dispense with a MedGuide.
Trazodone (generics)	Start with 25[14]/ 25-100[3]	~$0.06/50 mg ~$0.11/100 mg	30[15,f]	6.4 in younger patients, 11.6 in elderly[10]	• Off-label use. • Limited efficacy data, especially in primary insomnia.[2,12] • Not recommended for insomnia as harms outweigh the benefits.[1,3] • Low anticholinergic effects compared to doxepin.[11,12] • Anticholinergic effects can be significant in the elderly.[3] • Can cause priapism, even at low doses.[10,16] • Dispense with a MedGuide.
Benzodiazepines					
Estazolam (generics)	0.5-1/ 1-2	$0.54/1 mg $0.60/2 mg	60-120[10]	10-24	• Approved for the short-term[d] treatment of insomnia, to improve sleep onset and maintenance. • Concurrent administration with strong CYP450 3A4 inhibitors such as the azole antifungals is contraindicated. • Duration six to ten hours.[17] • Dispense with a MedGuide.

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Benzodiazepines, *continued*					
Flurazepam (generics)	15/ 15-30 (start with 15 in women)	~$0.29/15 mg ~$0.35/30 mg	<60[5,18]	>100 (including active metabolite)[10]	• Approved for insomnia, to improve sleep onset and maintenance. • Avoid in elderly due to active metabolite with long half-life.[10] • Duration ten to 20 hours.[17] • Risk of daytime drowsiness and impaired functioning. • Dispense with a MedGuide.
Lorazepam (*Ativan*, generics)	0.25-1/ 0.5-4[19,20]	~$0.06/0.5 mg ~$0.08/1 mg ~$0.15/2 mg	30-60[20]	12 18 (primary metabolite)	• Off-label use. • Generally used for secondary insomnia (e.g., due to anxiety).[21] • Useful to improve sleep maintenance, not sleep onset.[21] • Dispense with a MedGuide.
Oxazepam (generics)	10-15/ 15-30[10]	~$1.38/10 mg ~$1.58/15 mg ~$2.20/30 mg	45-60[20]	5.7-10.9	• Off-label use. • May be effective for sleep-onset insomnia.[19]
Quazepam (*Doral*, generics)	7.5-15/ 7.5-15	~$21.07/15 mg	30-60[10]	39-73 (including active metabolites)	• Approved for insomnia, to improve sleep onset and maintenance. • Avoid in the elderly due to long half-life.[10] • Duration ten to 20 hours.[17] • Risk of daytime drowsiness and impaired functioning. • Dispense with a MedGuide.
Temazepam (*Restoril*, generics)	Start with 7.5/ 7.5-30	~$4.21/7.5 mg ~$0.10/15 mg ~$6.23/22.5 mg ~$0.12/30 mg	60-120[10]	3.5-18.4	• Approved for short-term[d] treatment of insomnia. • No cytochrome P450 interactions. • Improves sleep onset and sleep maintenance.[1,10] • If a benzodiazepine is to be used in the elderly, temazepam may be one of the better options if appropriately dosed.[22] • Duration six to ten hours.[17] • Dispense with a MedGuide.
Triazolam (*Halcion*, generics)	0.125-0.25/ 0.125-0.5	$2.93/0.125 mg ~$2.32/0.25 mg	15-30[10]	1.5-5.5	• Approved for short-term[d] treatment of insomnia. • Contraindicated with CYP3A4 inhibitors such as azole antifungals and HIV protease inhibitors. • Avoid in elderly due to risk of cognitive and behavioral side effects.[22] • Duration two to five hours.[17] • Dispense with a MedGuide.

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Nonbenzodiazepine Hypnotics ("Z" Drugs)					
Eszopiclone (*Lunesta*, generics)	1-2/ 1-3 (start with 1 in all patients)	~$0.52/1 mg, 2 mg, 3 mg	30[10]	6	• Approved for insomnia, to improve sleep onset and maintenance. • Not limited to short-term use, studies up to six months duration. • Nonbenzodiazepine benzodiazepine receptor agonist. • Dose should not exceed 2 mg in patients with severe hepatic impairment or those taking strong CYP3A4 inhibitors. • Do not take with or immediately after a meal due to delayed onset. • Can cause a dose-dependent unpleasant taste. • Duration about seven to eight hours. • Dispense with a MedGuide.
Zolpidem immediate-release (*Ambien*, generics)	5/ 5-10 (start with 5 in women)	~$0.08/5 mg, 10 mg	30[10]	1.4-4.5	• Approved for the short-term[d] treatment of insomnia, to improve sleep onset. • Nonbenzodiazepine benzodiazepine receptor agonist. • Rebound insomnia is not associated with stopping zolpidem. • Reports of withdrawal after rapid dose reduction or abruptly stopping. • May have a lower risk of dependence than benzodiazepines.[10] • Taking with CYP3A4 inducers can reduce effects. • Taking with or immediately after a meal results in delayed onset. • Dose is 5 mg in patients with mild to moderate hepatic impairment. • Duration about seven to eight hours. • Dispense with a MedGuide.

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Nonbenzodiazepine Hypnotics ("Z" Drugs), *continued*					
Zolpidem controlled-release (*Ambien CR*, generics)	6.25/ 6.25-12.5 (start with 6.25 in women)	~$0.98/ 6.25 mg, 12.5 mg	30[10]	1.62-4.05	• Approved for insomnia, to improve sleep onset and maintenance. • Not limited to short-term use. • Biphasic absorption with rapid initial absorption similar to immediate-release tablet, but with extended plasma concentration beyond three hours. • No clear clinical advantage of controlled-release zolpidem vs immediate-release zolpidem.[10] • Taking with CYP3A4 inducers can reduce effects. • Taking with or immediately after a meal results in delayed onset. • Dose is 6.25 mg in patients with mild to moderate hepatic impairment. • Duration about seven to eight hours. • Dispense with a MedGuide.
Zolpidem sublingual (*Edluar*)	5/ 5-10 (start with 5 in women)	~$12.47/5 mg, 10 mg	30[10]	1.57-6.73 (for 5 mg dose) 1.75-3.77 (for 10 mg dose)	• Approved for the short-term[d] treatment of insomnia, to improve sleep onset. • To be dissolved under the tongue. Should not be swallowed whole or taken with water. • Taking with or immediately after a meal results in delayed onset. • Dose is 5 mg in patients with hepatic impairment. • Duration about seven to eight hours. • Dispense with a MedGuide.
Zolpidem sublingual (*Intermezzo*, generics)	1.75/ 1.75 (women) 3.5 (men)	~$7.90/1.75 mg ~$7.90/3.5 mg	20-38[10]	1.4-3.6	• Approved for insomnia associated with middle-of-the-night awakening. • Take only if there are at least four hours remaining before planned wake time. • To be dissolved under the tongue, not to be swallowed whole • Taking with or immediately after a meal results in delayed onset • Duration about four hours.[24] • Dispense with a MedGuide.

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Nonbenzodiazepine Hypnotics ("Z" Drugs), *continued*					
Zolpidem oral spray (*Zolpimist*)	5/ 5-10 (start with 5 in women)	$10.98/5 mg	10[10]	1.7-5 (for 5 mg dose) 1.7-8.4 (for 10 mg dose)	• Approved for the short-term[d] treatment of insomnia, to improve sleep onset. • Do not take with or immediately after a meal due to delayed onset. • Dose is 5 mg in patients with hepatic impairment. • Duration about seven to eight hours. • Dispense with a MedGuide.
Zaleplon (*Sonata* [brand discontinued], generics)	5-10/ 10-20	~$0.43/5 mg ~$0.50/10 mg	30[10]	1	• Approved for the short-term[d] treatment of insomnia, to improve sleep onset. • Nonbenzodiazepine benzodiazepine receptor agonist. • No apparent withdrawal symptoms, daytime anxiety, next-day sedation, or psychomotor impairment. • Mild dose-dependent rebound insomnia. • May have a lower risk of dependence than benzodiazepines.[10] • Taking with or immediately after a heavy, high-fat meal may decrease absorption and delay onset. • Dose is 5 mg in patients taking cimetidine, with mild to moderate hepatic impairment, and low-weight patients. • Duration about two to four hours.[17] • Dispense with a MedGuide.
Melatonin Receptor Agonist					
Ramelteon (*Rozerem*, generics)	8/ 8	~$6.13/8 mg	30[10]	1-2.6 2-5 (active metabolite)	• Approved for insomnia, to improve sleep onset. • Not limited to short-term use, studies up to six months duration. • Melatonin receptor agonist. • Not a controlled substance. • Metabolized by CYP1A2. Use with fluvoxamine is contraindicated. • Do not take with or immediately after a high-fat meal due to delayed onset. • Duration about six to eight hours.[17] • Dispense with a MedGuide.

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Generic (Brand)	Usual Dose (mg/day)[a,g] Elderly[e]/ Adult	Cost[b]	Onset (min)[c]	Half-life (hours)[a,c]	Comments[a]
Orexin Receptor Antagonists					
Lemborexant (*Dayvigo*)	5-10/ 5-10 (use caution with doses over 5 in the elderly)	Not yet available.	<30[f]	17-19	• Approved for insomnia, to improve sleep onset and maintenance. • Orexin receptor antagonist. • Taking with or immediately after a meal results in delayed onset. • Not associated with rebound insomnia when stopped. • No apparent withdrawal symptoms. • Risk of sleep paralysis. • Avoid taking with moderate or strong CYP3A inhibitors and inducers. • The max dose is 5 mg in patients taking weak CYP3A inhibitors and with moderate hepatic impairment. • Duration about seven hours. • Dispense with a MedGuide.
Suvorexant (*Belsomra*)	Not specified/ 10-20	$12.19/5 mg, 10 mg, 15 mg, 20 mg	30[10]	12	• Approved for insomnia, to improve sleep onset and maintenance. • Orexin receptor antagonist. • Taking with or immediately after a meal results in delayed onset. • Not associated with rebound insomnia when stopped. • No apparent withdrawal symptoms. • Risk of sleep paralysis. • Taking with strong CYP3A inhibitors is not recommended. • Dose is 5 to 10 mg with moderate CYP3A inhibitors. • Duration about seven hours. • Dose-related adverse effects are greater in obese patients and women. Use caution if increasing dose above 10 mg. • Dispense with a MedGuide.

a. The following U.S. product labeling was used for the above chart unless otherwise noted: *Ambien* (August 2019), *Ambien CR* (August 2019), *Ativan* (September 2018), *Belsomra* (March 2020), *Dayvigo* (December 2019), *Doral* (April 2019), estazolam (Actavis, October 2019), *Edluar* (May 2017), flurazepam (Mylan, December 2018), *Halcion* (October 2019), *Intermezzo* (August 2019), *Lunesta* (August 2019), oxazepam (Actavis, September 2016), trazodone (Teva, May 2019), *Remeron*/*Remeron Soltab* (March 2020), *Restoril* (September 2017), *Rozerem* (December 2018), *Silenor* (August 2019), zaleplon (Teva, August 2015), *Zolpimist* (August 2019).

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b. Pricing based on the average wholesale acquisition cost (WAC) per dose for generic (if available), by Elsevier, accessed April 2020.
c. Administration of a drug with a fast onset and short half-life decreases the risk of adverse daytime effects such as falls.[23]
d. Generally, should not be used for more than seven to ten consecutive days.
e. In general, when dosing sedatives in elderly patients, some experts recommend starting with half the usual adult dose and titrating up as necessary.[19]
f. Based on recommendations on the timing of the bedtime dose.
g. For otherwise healthy individuals with normal hepatic/renal function.

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