

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 This disorder can be transient (lasts days to weeks) or chronic (defined as occurring nightly for greater than six months).¹ It is estimated that one third of Americans experience insomnia nightly.² The first-line treatments for chronic insomnia tend to focus on nonpharmacologic interventions, and then include pharmacologic treatments if necessary. In general, the benzodiazepines have more side-effects and have a higher potential for dependence, tolerance, and rebound insomnia. The newer nonbenzodiazepines have a better side effect profile.³ In general, pharmacologic agents 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. Also see our *PL Patient Education Handout, Strategies for a Good Night's Sleep*, which provides information about sleep hygiene. See our *PL Detail-Document, Benzodiazepine Toolkit*, for more information on the comparison of benzodiazepines. Also see our *PL Detail-Document, Insomnia in the Elderly*, for more information on insomnia management in the elderly population.

(Information pertains to U.S. products)

Drugs Commonly Used to Treat Insomnia^d					
Generic Name (Brand name)	Dosage Range (mg/day)^a Usual Elderly Dose^f/Adult Dose	Price^b	Onset (min)^c	Half-life (hr)^{a,c}	Comments
Nonprescription Drugs					
Diphenhydramine ² (Benadryl, Nytol, Sominex, Unisom)	25 mg/25-50 mg	\$0.06/25 mg	60-120 min ²	2.4-9.3 hr	<ul style="list-style-type: none"> • Anticholinergic side effects can occur • Minimally effective • Consider an "off" night after three days of use to reduce tolerance² • Avoid using more than ten days without consulting a health care professional² • >10 days consecutive use can lead to tolerance to sleep-inducing effect, but not side effects² • Not suitable for older adults due to side effects such as hangover effect, urinary retention, constipation, blurred vision, cognitive impairment, and other anticholinergic effects³

More . . .

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Nonprescription Drugs, continued					
Doxylamine ² (Unisom Nighttime)	25 mg/25 mg	\$0.22/25 mg	30 min ¹⁵	10 hr ^{2,15}	<ul style="list-style-type: none"> • Anticholinergic side effects can occur • Minimally effective • Not suitable for older adults due to side effects such as hangover effect, urinary retention, constipation, blurred vision, cognitive impairment, and other anticholinergic effects³
Prescription Drugs: <u>Antidepressants</u> *Tricyclics have occasionally been used as hypnotics; conventional hypnotics are safer and more efficacious.²					
Doxepin (Sinequan) ^{1,3,4}	10 mg ⁸ /10 mg ⁸	\$0.32/10 mg	N/A	15-20 hr ⁶ 80 hr ⁶ (active metabolite)	<ul style="list-style-type: none"> • Not FDA-approved for treatment of insomnia • Increased risk of cardiovascular problems and anticholinergic side effects¹⁹ • Narrow therapeutic window³ • Low dose (subtherapeutic for depression) typically used⁴
Doxepin (Silenor)	3 mg/6 mg	\$6.16/3 mg ^h \$6.16/6 mg ^h	N/A	15 hr 31 hr (primary metabolite)	<ul style="list-style-type: none"> • FDA-approved in 2010 for insomnia, to improve sleep maintenance • Does not improve sleep latency⁵ • Not to be taken within three hours of a meal due to delayed absorption and potential for next day drowsiness • Improved sleep maintenance is expected the first night. Consult prescriber if improved sleep maintenance is not evident within one week⁵ • Does not cause rebound insomnia • Duration about 7 to 8 hours⁵

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Prescription Drugs: <u>Antidepressants</u> *Tricyclics have occasionally been used as hypnotics; conventional hypnotics are safer and more efficacious.²					
Mirtazapine (Remeron)	15 mg/15 mg ⁶	\$2.37/15 mg	N/A	20-40 hr	<ul style="list-style-type: none"> Not FDA-approved for insomnia Increases the risks of restless leg syndrome and periodic limb movements in sleep⁴ Some evidence on reducing insomnia in depression, especially early in treatment⁴
Trazodone (Desyrel) ³	25-100 mg ¹⁴ / 50-150 mg ^{3,18}	\$0.40/50 mg \$0.47/100 mg	30 ¹⁸ -60 min	5-9 hr ³	<ul style="list-style-type: none"> Not FDA-approved for the treatment of insomnia Limited efficacy data, especially in primary insomnia⁴ Little or no anticholinergic activity as compared to doxepin^{4,6,7} Caution men that trazodone, even at low doses, can cause priapism^{9,13}
Prescription Drugs: <u>Benzodiazepines</u>					
Estazolam	0.5-1 mg/1-2 mg	\$0.83/1 mg \$0.93/2 mg	60-120 min ⁹	10-24 hr	<ul style="list-style-type: none"> FDA-approved for insomnia, to improve sleep onset and maintenance Concurrent administration with CYP450 3A4 inhibitors such as the azole antifungals is contraindicated Duration about 6 to 10 hours⁹
Flurazepam	15 mg/15-30 mg	\$0.43/15 mg \$0.47/30 mg	60-120 min ⁹ 15-45 min with chronic dosing ¹⁹	>100 hours (includes active metabolites) ²¹	<ul style="list-style-type: none"> FDA-approved for insomnia, to improve sleep onset and maintenance Clinically active metabolite Avoid in elderly due to long half-life⁸ Potential for daytime drowsiness Metabolized by CYP3A4¹⁹ Duration about 10 to 20 hours⁹
Lorazepam (Ativan)	0.25-1 mg /0.5-1 mg ¹⁴ (2 to 4 mg for insomnia due to anxiety [adults])	\$0.50/0.5 mg \$0.50/1 mg \$0.73/2 mg	20-30 min ⁹	About 18 hr	<ul style="list-style-type: none"> Not FDA-approved for insomnia Generally used for insomnia due to anxiety Rebound insomnia can appear after a week of therapy

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Prescription Drugs: Benzodiazepines, continued					
Oxazepam	10-15 mg/ 15-30 mg	\$0.60/10 mg \$1.53/15 mg \$1.93/30 mg	30-60 min ⁹	5.7-10.9 hr	<ul style="list-style-type: none"> Not FDA-approved for insomnia
Quazepam (Doral)	7.5-15 mg/ 7.5-15 mg	\$3.37/7.5 mg \$4.27/15 mg	60-120 min ⁹	47-100 hr ²¹ (includes active metabolites)	<ul style="list-style-type: none"> FDA-approved for insomnia, to improve sleep onset and maintenance Clinically active metabolite Avoid in elderly due to long half-life⁹ Duration about 10 to 20 hours⁹
Temazepam (Restoril)	7.5-15 mg/ 7.5-30 mg	\$5.19/7.5 mg \$0.43/15 mg \$0.50/30 mg	60-120 min ⁹	3.5-18.4 hr	<ul style="list-style-type: none"> FDA-approved for short-term^e treatment of insomnia Improves sleep onset and sleep maintenance^{8,18} More likely to cause hangover effect with its intermediate half-life²⁰ Not eliminated by the cytochrome P450 system Duration of 6 to 10 hours⁹
Triazolam (Halcion)	0.125-0.25 mg/ 0.125-0.5 mg	\$0.63/0.25 mg	15-30 min ⁹	1.5-5.5 hr	<ul style="list-style-type: none"> FDA-approved for short-term^e treatment of insomnia Concurrent administration with azole antifungals or other CYP3A4 inhibitors is contraindicated Tolerance develops sooner than with other benzodiazepines Increased daytime anxiety is a potential side effect Rebound insomnia can occur after discontinuation of therapy Higher rate of antegrade amnesia than other benzodiazepines Avoid in elderly due to risk of cognitive/behavioral disturbance²⁰ Duration about 2 to 5 hours⁹

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Generic Name (Brand name)	Dosage Range (mg/day) ^a Usual Elderly Dose ^f /Adult Dose	Price ^b	Onset (min) ^c	Half-life (hr) ^{a,c}	Comments
Prescription Drugs: Others					
Eszopiclone (Lunesta)	1-2 mg/2-3 mg	\$7.63/1 mg \$7.53/2 mg \$7.70/3 mg	30 min ^g	6 hr	<ul style="list-style-type: none"> FDA-approved for insomnia, to improve sleep onset and maintenance Not limited to short-term use 3 mg dose may be better for sleep maintenance 1 mg for elderly having difficulty falling asleep, 2 mg for elderly having difficulty staying asleep Metabolized by CYP450 3A4 and 2E1 Tolerance did not develop after six months Taken with or immediately after a meal results in delayed onset Causes metallic aftertaste in up to one-third of patients, especially at higher doses¹² Duration about 8 hours⁹
Ramelteon (Rozerem)	8 mg/8 mg	\$5.86/8 mg	30 min ^g	1-2.6 hr 2-5 hr (active metabolite)	<ul style="list-style-type: none"> FDA-approved for insomnia to improve sleep onset Not limited to short-term use Melatonin receptor agonist Not a controlled substance Metabolized by CYP450 1A2 Coadministration with fluvoxamine is contraindicated Taken with or immediately after a meal results in delayed onset Duration about 8 hours⁹
Zolpidem (Ambien)	5 mg/5 mg (women) and 5-10 mg (men) ²²	\$6.79/5 mg \$7.00/10 mg	30 min ^g	1.4-4.5 hr	<ul style="list-style-type: none"> FDA-approved for short-term treatment of insomnia, to improve sleep onset No objective rebound insomnia associated with discontinuation of <i>Ambien</i> Lower risk of dependence than benzodiazepines Metabolized by CYP450 3A4 Taken with or immediately after a meal results in delayed onset Duration about 8 hours⁹

Drugs Commonly Used to Treat Insomnia ^d					
Generic Name (Brand name)	Dosage Range (mg/day) ^a Usual Elderly Dose ^f /Adult Dose	Price ^b	Onset (min) ^c	Half-life (hr) ^{a,c}	Comments
Prescription Drugs: Others, continued					
Zolpidem controlled-release (Ambien CR)	6.25 mg/6.25 mg (women) and 6.25-12.5 mg (men) ²²	\$6.47/6.25 mg \$6.33/12.5 mg	30 min ^g	1.62-4.05 hr	<ul style="list-style-type: none"> FDA-approved for insomnia, to improve sleep onset and maintenance Not limited to short-term use Metabolized by CYP450 3A4 Biphasic absorption with rapid initial absorption similar to conventional tablet following oral administration, but with extended plasma concentration beyond three hours Although approved for improved sleep maintenance, no comparative trials have shown distinct clinical advantage of controlled-release zolpidem vs immediate-release zolpidem⁸ Taken with or immediately after a meal results in delayed onset Duration about 8 hours⁹
Zolpidem sublingual (Edluar)	5 mg/5 mg (women) and 5-10 mg (men) ²²	\$5.99/5 mg \$5.99/10 mg	30 min ^g	1.57-6.73 hr (for 5 mg dose) 1.75-3.77 hr (for 10 mg dose)	<ul style="list-style-type: none"> FDA-approved for the short-term insomnia, to improve sleep onset Metabolized by CYP450 3A4 Duration about 8 hours⁹
Zolpidem sublingual (Intermezzo)	1.75 mg/1.75 mg (women) and 3.5 mg (men)	\$7.33/1.75 mg \$7.33/3.5 mg	20-38 min ^{16,17,g}	1.4-3.6 hr	<ul style="list-style-type: none"> FDA-approved for insomnia associated with middle-of-the-night awakening Take only if there are four hours remaining before planned wake time Metabolized by CYP450 3A4 To be dissolved under the tongue, not to be swallowed whole Use 1.75 mg dose for patients using other CNS depressants such as opioids or TCAs Concomitant use with other sedative-hypnotics not recommended Duration about 4 hours¹⁷

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Prescription Drugs: Others, continued					
Zolpidem oral spray (ZolpiMist)	5 mg/5 mg (women) and 5-10 mg (men) ²²	\$1.32/5 mg ^h \$2.64/10 mg ^h	30 min ¹⁰	1.5-4.5 hr	<ul style="list-style-type: none"> FDA-approved for short-term insomnia, to improve sleep onset Metabolized by CYP450 3A4 Lower dose version of <i>ZolpiMist</i> is being developed for use in the middle of the night for patients with sleep maintenance problems¹⁰ Duration about 8 hours⁹
Zaleplon (Sonata)	5-10/10-20 mg	\$0.58/5 mg \$0.43/10 mg	30 min ^g	1 hr	<ul style="list-style-type: none"> FDA-approved for the short-term treatment of insomnia, to improve sleep onset Low-weight patients may respond to 5 mg Partially metabolized by CYP450 3A4 No apparent withdrawal symptoms, daytime anxiety, sedation, or psychomotor impairment Rebound insomnia is more likely with higher doses Can be used four to five hours before arising Lower risk of dependence than benzodiazepines Taken with or immediately after a meal results in delayed onset Duration about 4 hours⁹
<p>a. The following product labeling was used for the above chart unless otherwise indicated: <i>Ambien</i> (August 2010), <i>Ambien CR</i> (October 2010), <i>Ativan</i> (October 2009), <i>Doral</i> (August 2009), Estazolam, Watson (September 2008), <i>Edluar</i> (October 2010), Flurazepam, Mylan (May 2010), <i>Intermezzo</i> (December 2011), <i>Lunesta</i> (November 2010), Oxazepam, Teva (December 2008), Trazodone, Mylan (January 2012), Estazolam, Watson (September 2008), <i>Remeron</i> (June 2010), <i>Restoril</i> (November 2010), <i>Rozerem</i> (November 2010), <i>Silenor</i> (March 2010), <i>Sonata</i> (February 2009), Triazolam, Greenstone (February 2012), <i>ZolpiMist</i> (December 2008).</p> <p>b. Price is from drugstore.com (unless otherwise indicated) at time of writing. Cost is for generic if available.</p> <p>c. Administration of a drug with a fast onset and short half-life decreases the risk of adverse daytime effects such as falls.¹¹</p> <p>d. Prescription products approved for the treatment of insomnia should be dispensed with a MedGuide.</p> <p>e. Generally seven to ten days.</p> <p>f. In general, when dosing sedatives in elderly patients, some experts recommend starting with half the usual adult dose and titrating up as necessary.¹⁴</p> <p>g. Onset time confirmed with manufacturer.</p> <p>h. Pricing is AWP.</p> <p>i. Generic doxepin 10 mg dose has not been studied for insomnia. However, it is likely effective for insomnia based on <i>Silenor</i> data.</p>					

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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