SAMPLE CHAPTER

CTC 7

Compendium of Therapeutic Choices

Seventh Edition

Canada's Trusted Reference for Primary Care Therapeutics

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The *Compendium of Therapeutic Choices*, formerly *Therapeutic Choices*, is a trusted Canadian source for evidence-based treatment information for all health care practitioners involved in therapeutic decision-making. Practical, bottom-line, clinical information covering more than 200 common medical conditions is referenced and organized in a concise format by therapeutic condition. More than 72 chapters cover drug therapy during pregnancy and breastfeeding. The content is based on the best available evidence, subject to a rigorous peer review process.

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Chapter 8
Insomnia

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Insomnia is defined as dissatisfaction with sleep quality or quantity that is associated with one or more of the following features: difficulty falling asleep, difficulty staying asleep or early morning awakening without being able to return to sleep. The diagnosis requires that the sleep disturbance causes distress or impairment in functioning, occurs at least 3 nights per week for at least 3 months, and is not substance related.[1] Insomnia is a common symptom of a number of psychiatric and medical conditions including depression, anxiety and pain.

Goals of Therapy

- Promote subjectively sound and restorative sleep when external (e.g., stress, noise, jet lag) or internal (e.g., pain, anxiety) factors disrupt natural sleep
- Reduce subjective daytime impairment (e.g., dysphoria, fatigue, decreased alertness) associated with sleep loss
- Potentiate the effectiveness of behavioural interventions in managing patients with chronic insomnia[2]

Investigations

- A complete sleep history (Table 1) is *essential:*
  - to quantify current sleep performance and daytime impairment
  - to determine the outcome of previous interventions
  - to rule out other sleep pathologies including those for which hypnotics are contraindicated and potentially lethal, e.g., obstructive sleep apnea
- Completion of a sleep diary (Table 3) for one week, to quantify sleep performance and variability
- Psychiatric workup to rule out associated mental disorders (especially mood and anxiety disorders, drug and alcohol use)
- Medical workup to rule out associated medical disorders (especially those associated with nocturnal discomfort or pain such as arthritis, Parkinson's disease)
- Thorough drug history including prescription and nonprescription medications, herbal or other natural remedies, caffeine, nicotine, alcohol and recreational drugs
- Self-rating scales for depression and anxiety symptoms (such as the PHQ-9 available from www.ncbi.nlm.nih.gov/pmc/articles/PMC1495268/#app1 or the GAD-7 available from www.mpho.org/resource/d/34008/GAD708.19.08Cartwright.pdf) are useful screening tools for identifying depressive or anxiety disorders causing insomnia

  Note: Insomnia can be both an early symptom and a cause of depression.

Therapeutic Choices

Nonpharmacologic Choices

- Instruct patient in sleep hygiene, emphasizing the importance of rising at the same time 7 days a week, even when taking hypnotics (Figure 1, Table 2); monitor and encourage adherence throughout treatment and follow-up (important to success of *any* intervention).

- Suggest relaxation exercises (available as free downloads for home use, e.g., www.allaboutdepression.com/relax).
- Consider sleep restriction, stimulus control (avoidance of sensory arousal) or other behavioural approaches such as cognitive behavioural therapy (CBT-I),[3] either alone or in conjunction with pharmacologic interventions. Online CBT-I self-help programs are available for a fee from www.sleepio.com or cbtforinsomnia.com.
- Aerobic exercise, a useful modifier of stress and dysphoric moods, also promotes deeper and more restful sleep; encourage patients with insomnia to eliminate daytime rest periods and increase exercise, just as brisk walking (Table 2).

Pharmacologic Choices

Short courses of hypnotics (Figure 1, Table 4) are useful combined with good sleep hygiene (Table 2). A comprehensive evaluation, education stressing the importance of sleep hygiene (especially preventing extended sleeping such as naps or nocturnal sleep periods of more than 8 hours) and careful monitoring of progress are important. With these measures, use of the preferred agents (short-acting benzodiazepines or benzodiazepine receptor agonists) is usually straightforward in patients with insomnia.

It is inappropriate to use the sedative side effect of another medication (e.g., antidepressants, antihistamines, antipsychotics such as quetiapine[4]) to avoid using a benzodiazepine or benzodiazepine receptor agonist, in cases where the latter agents are the treatment of choice.

Generally, self-medication with nonprescription agents such as diphenhydramine is not recommended. For distressing insomnia lasting more than a few days, patients should see their physician for an accurate diagnosis of symptoms and monitoring of the treatment plan.

Table 1: **The Sleep History**

1. Time data (can also be collected as part of a sleep diary—Table 3)
Did you nap or lie down to rest today? If yes, when and for how long?
What time did you go to bed last night?
What time did you put out the lights?
How long did it take you to fall asleep?
How many times did you awaken last night?
How long was your longest awake period; when was it? What time did you finally awaken?
What time did you get out of bed?
How many hours of sleep did you get last night?
2. Questions about the sleep period
Do physical symptoms, such as pain, prevent you from falling asleep?
Do mental or emotional symptoms (e.g., worry or anxiety) prevent you from falling asleep?
When you awaken during the night, what awakens you? (Snoring? Gasping for air? Dreams/nightmares? Noise?)
When you get up for the day, do you have any symptoms? (Headache? Confusion? Sleepiness?)
3. Questions for the patient's bed partner
Does your partner snore, gasp or make choking sounds during the night?
Does your partner stop breathing during the night?
Do your partner's legs twitch, jerk or kick during the night?
Has your partner's use of alcohol, nicotine, caffeine or other drugs changed recently?
Has your partner's mood or emotional state changed recently?
What do you think is the cause of your partner's sleep problem?

Benzodiazepines

All benzodiazepines have sedative and hypnotic properties, but differ significantly in potency and pharmacokinetics. All may cause confusion and ataxia, especially in the elderly and the medically ill. Benzodiazepines also confer a significant risk of dependence and withdrawal symptoms with long-term use, and judicious therapeutic trials for insomnia involve use for up to 2 weeks.

Benzodiazepines that have been studied in sleep-disturbed patients are generally preferred over other agents. When insomnia is secondary to prominent anxiety symptoms, a long-acting benzodiazepine (such as **clonazepam**) given at night may promote sleep and also manage daytime anxiety. It is inappropriate to use one benzodiazepine to manage anxiety during the day and a different one as a bedtime hypnotic agent, in the same patient.

Figure 1: **Management of Insomnia**

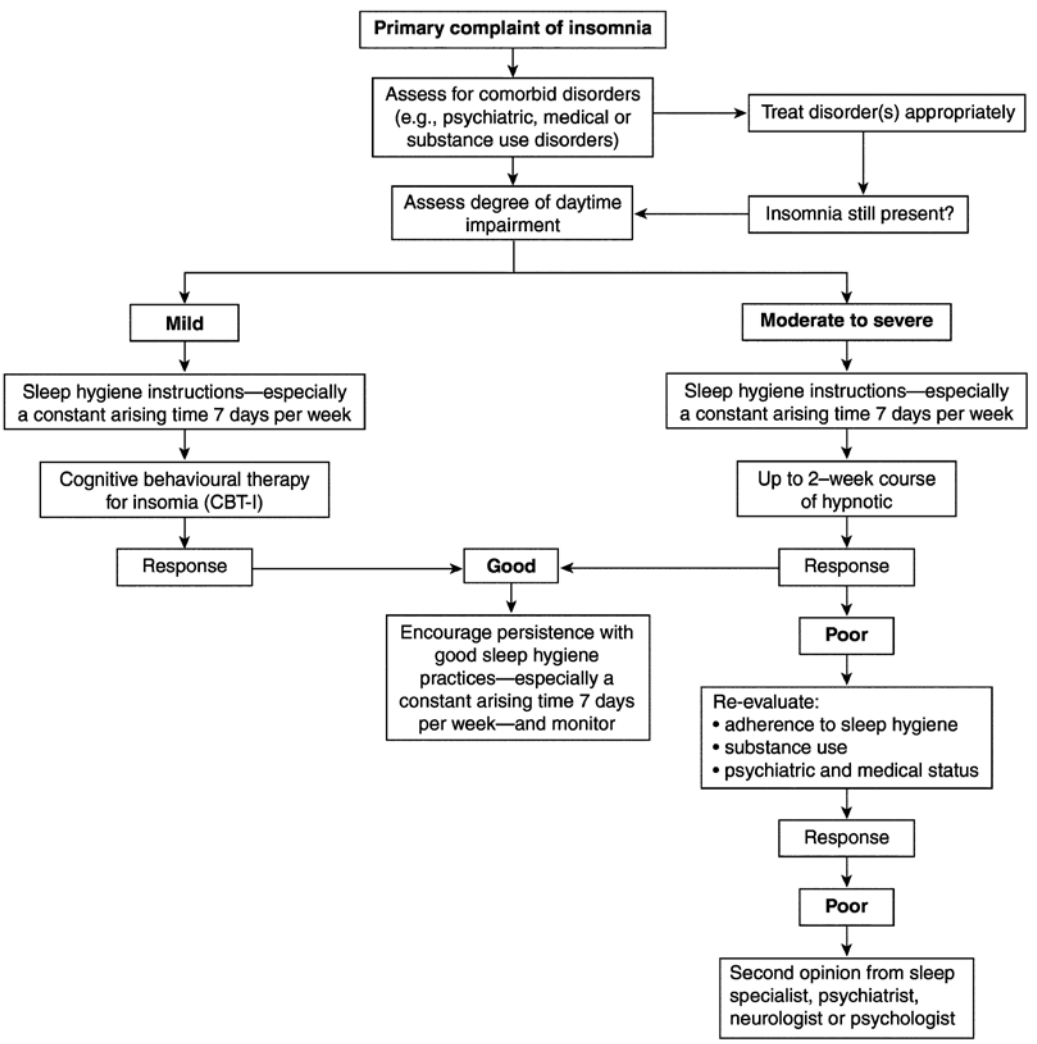

Table 2: **Sleep Hygiene Guidelines**

1. Keep a regular sleep-wake schedule, with a consistent arising time 7 days per week.
2. Restrict the sleep period to the average sleep time you have obtained each night over the preceding week.
3. Avoid sleeping in, extensive periods of horizontal rest or daytime napping; these activities usually affect the subsequent night's sleep.
4. Get regular exercise every day: about 40 minutes of an activity with sufficient intensity to cause sweating. If evening exercise prevents sleep, schedule the exercise earlier in the day.
5. Avoid caffeine, nicotine, alcohol and other recreational drugs, all of which disturb sleep. If you must smoke do not do so after 7:00 p.m.
6. Plan a quiet period before lights out; a warm bath may be helpful.
7. Avoid large meals late in the evening; a light carbohydrate snack (e.g., crackers and warm milk) before bedtime can be helpful.
8. Turn the clock face away and always use the alarm. Looking at the clock time on awakening can cause emotional arousal (performance anxiety or anger) that prevents return to sleep.
9. As much as possible, keep the bedroom dark and soundproofed. If you live in a noisy area, consider ear plugs.
10. Use the bedroom only for sleep and intimacy; using the bed as a reading place, office or media centre conditions you to be alert in a place that should be associated with quiet and sleep. If you awaken during the night and are wide awake, get up, leave the bedroom and do something quiet until you feel drowsy-tired, then return to bed.

Note: Pharmacologic (or any) interventions will be less effective if these guidelines are not followed. In mild cases of insomnia, sleep hygiene strategies, practised consistently and together, may be sufficient to reinstate a normal sleep pattern.

In Canada, 4 benzodiazepines (flurazepam, nitrazepam, temazepam and triazolam) are officially indicated for insomnia. However, **flurazepam** and **nitrazepam** are not recommended, particularly in the elderly.[5] Because of their longer half-lives, flurazepam and nitrazepam accumulate with repeated dosing and are associated with more hangover effects than shorter-acting agents. In the elderly, they cause higher cortical impairment resulting in confusion and falls.

Temazepam is a good all-purpose hypnotic with a half-life sufficient to cover the sleep period without causing hangover effects. However, few hypnotics have proven tolerability in the elderly, and temazepam may be associated with falls in this population.[6] It causes less rebound insomnia than more potent agents such as lorazepam.

Triazolam has a fast onset and short duration of action, which makes it more suited to use in *initial insomnia* (first third of the night) than *maintenance insomnia* (last third of the night). Because these pharmacokinetic properties may confer a higher risk of abuse and dependence, a shorter treatment course (5–7 days) is recommended for triazolam. In addition to causing rebound insomnia, triazolam has a unique, dose-related adverse effect profile (confusion, agitation and amnesia) making it unsuitable for use in the elderly.[7] Some experts recommend against use of triazolam in any patient.

Although the number of comparative studies is relatively small, **oxazepam** is as effective as the benzodiazepines that are officially indicated for insomnia.[8,9] In patients with initial insomnia, oxazepam should be given 60–90 minutes before bedtime because of its slow absorption, although patients should be aware that some sedation/impairment could occur before this time. Conversely, patients who have no difficulty falling asleep but experience maintenance insomnia can take oxazepam when getting into bed.

There are few trials studying the effects of **lorazepam** on insomnia. Lorazepam may cause significant rebound effects such as anxiety and tension.[10]

Table 3: **Sleep Diary**

Date							
Daytime							
Caffeine intake (what, when)							
Alcohol intake (what, when)							
Nicotine use (what, when)							
Naps (start time, end time)							
Exercise (what, when)							
Overall daytime functioning, on a scale of 1 to 5 (1 = alert, energetic; 5 = fatigued, sleepy)							
Nighttime							
What time did you go to bed?							
Did you watch television in bed?							
Did you read in bed?							
How long did it take to fall asleep?							
For each time you woke up during the night, record the following: 1. Time you were awake (e.g., 1:10–2:30 a.m.) 2. What woke you up (e.g., snoring, gasping for air, bad dreams, pet, noise)?							
What time did you *wake up* for the day?							
What time did you *get out of bed* for the day?							
How many hours of sleep did you get?							
How did you feel when you woke up this morning, on a scale of 1 to 5? (1 = refreshed, alert; 5 = fatigued, sleepy)							

Benzodiazepine Receptor Agonists

Although not a benzodiazepine, the cyclopyrrolone **zopiclone** acts at the benzodiazepine receptor and so has similar therapeutic and side effects. Although psychomotor impairment associated with combined use of zopiclone and small amounts of alcohol has been shown to be minor, zopiclone can have residual or hangover effects that could impair morning driving, when used with or without alcohol.[11] Compared with benzodiazepines, tolerance to zopiclone's hypnotic effect may be delayed and rebound insomnia may be reduced.[12] **Eszopiclone**, the active (S+) isomer of zopiclone, shares similar pharmacologic properties to the racemic compound but is more potent.[13] Several studies have demonstrated efficacy in transient and chronic insomnia. One study showed continued efficacy over 12 months of use with no evidence of tolerance or a withdrawal syndrome or rebound insomnia on discontinuation.[14] Eszopiclone in not available in Canada.

Zolpidem is an imidazopyrine with preferential affinity to benzodiazepine type I receptors. Memory disturbances and complex sleep behaviours (night eating, somnambulism) have been reported in patients using zolpidem. Gender and age-based differences in metabolic clearance of zolpidem and incidence of complex sleep behaviours have led to lower dosing recommendations for women and elderly patients.[15,16] As with all hypnotics, zolpidem must not be combined with alcohol.

Other Hypnotics

The toxicity and drug interaction profile of **chloral hydrate** make it less safe than benzodiazepines. Tolerance to its hypnotic effect typically develops within 2 weeks. Its use is not recommended.[17] **Barbiturates** are contraindicated in the management of insomnia due to their unacceptable safety profile.[18]

In high dosages (>1 g), **L-tryptophan** has a hypnotic effect, but it is not as predictable as that seen with traditional hypnotics.[19] It may be useful when one wishes to avoid benzodiazepines.

Use of **melatonin** (1–5 mg) in the management of insomnia remains controversial.[20] A meta-analysis of nineteen studies on the effects of melatonin on insomnia showed a decrease in the time to onset of sleep (weighted mean difference 7.06 minutes), an increase in total sleep time (weighted mean difference 8.25 minutes) and an improvement in overall sleep quality.[21] Improvement increased with dose and treatment duration; trials with higher dosages and longer duration had greater effects on shortening sleep onset latency and increasing total sleep time. Though the effect size is smaller than for other pharmacologic treatments for insomnia, melatonin may have a role in the management of insomnia given its relatively benign side effect profile.

Ramelteon, a novel compound with chronohypnotic properties (causing phase shifts in circadian rhythm) and high selectivity for MT_1 and MT_2 melatonin receptors, is available in the US but not in Canada. In various animal models, ramelteon has demonstrated hypnotic properties[22] with no effect on learning, memory or motor coordination. Human studies in young adults and elderly patients show it is effective and well tolerated.[23]

Choices during Pregnancy and Breastfeeding

Insomnia and Pregnancy

Disrupted sleep is one of the most frequently reported complaints of pregnant women, and tends to worsen as the pregnancy progresses.[24] Multiple endogenous factors, such as endocrine changes, physical discomfort and bladder distention, contribute to this common complaint. In the postpartum period, exogenous factors, e.g., the child's sleep-wake and feeding schedules, further disrupt sleep. Additionally, psychological factors, e.g., anxiety, or the emergence of psychiatric disorders during the pregnancy or after the birth can add to the insomnia burden with persistent sleep complaints increasing the risk of postpartum mood disorders.[25] Two sleep disorders, sleep apnea[26] and restless legs

syndrome (see Chapter 24),[27] are known to worsen during pregnancy and may present as insomnia in the pregnant patient.

There has been little research on the effects of insomnia during pregnancy on maternal functioning and no randomized controlled studies of any intervention in this population. Regardless of cause, it is likely that significantly disrupted sleep during pregnancy and in the postpartum period will impair the mother's quality of life by causing similar daytime impairments to those seen in the nonpregnant population,[28] and that this impairment may adversely affect the mother-child bond.

When insomnia is severe, carefully consider the risk-benefit ratio to both the mother and developing fetus when using a pharmacologic intervention.[29] Although lacking empirical evidence, intermittent dosing using the safest medication, at the lowest effective dose, combined with behavioural strategies is reasonable.

Management of Insomnia during Pregnancy and Postpartum Period

Although not well studied, clinical experience suggests that behavioural techniques are effective in pregnant patients with insomnia and are the treatments of choice when distress and impairment are mild to moderate.

Evidence for the safety of psychotropics in human pregnancy is derived from patients who have been inadvertently exposed to these medications at conception. Orofacial malformations were the most feared consequence of **benzodiazepine** exposure but the risk appears small (0.1% vs. 0.06%) and in some studies, nonexistent.[30]

Benzodiazepines are associated with more prenatal and perinatal risks than **zopiclone**.[31] Neonatal flaccidity, hypothermia, respiratory depression and feeding difficulties have been reported in infants whose mothers received benzodiazepines late in pregnancy; these infants may also be at risk of experiencing withdrawal symptoms during the postnatal period. **Zolpidem** has been associated with a higher risk of preterm deliveries, delivery of small-for-gestational-age infants and cesarean delivery, and is not recommended in pregnancy.[32]

Although derived from limited data, available evidence suggests the preferred hypnotic for use in pregnancy is zopiclone.[33,34]

Diphenhydramine, an antihistamine commonly used as a nonprescription hypnotic (though not recommended), may cause neonatal depression if used during labour, and whether it enters breast milk is unknown.[35]

Insomnia and Breastfeeding

A review of hypnotic drug use during breastfeeding suggests that with respect to **benzodiazepines**,[36] **zolpidem**[37] and **zopiclone**,[36] the amount of active drug excreted in breast milk is generally quite low, and they can be used safely with appropriate monitoring. Behavioural interventions to manage insomnia are preferred, but should medications be required, low doses of short-acting benzodiazepines or benzodiazepine receptor agonists (used intermittently or for short periods) appear relatively safe.

When long-acting benzodiazepines are used during pregnancy, they should be switched to short-acting agents before delivery, to minimize effects on the fetus. There is a risk of inducing a withdrawal syndrome, particularly if high-potency benzodiazepines (such as **alprazolam**) are withdrawn abruptly. When there is marked functional impairment in the mother, supportive assistance from a relative, nanny or nurse, may improve coping. Regulating the sleep period as much as possible and ensuring regular exercise (such as walking) will help both mood and sleep performance. Monitor the baby for signs of sedation (e.g., lethargy, drowsiness, poor suckling, weight loss) or other adverse effects, and to ensure appropriate thriving.

A discussion of general principles on the use of medications in these special populations can be found in Appendix II and Appendix III. Other specialized reference sources are also provided in these appendices.

Therapeutic Tips

- Sleep diaries (Table 3) are often helpful in delineating the initial complaint, monitoring progress and facilitating withdrawal.
- The degree of daytime impairment directs the intervention: if there is an acute change in daytime functioning, a short course of hypnotics may be indicated; if the daytime impairment is mild or chronic, try a behavioural intervention (e.g., sleep restriction) first.
- Always start hypnotics at the lowest dose and use them for the shortest possible time.
- Set realistic treatment goals with the patient, mainly to minimize daytime impairment; a chronic poor sleeper will not be turned into a good sleeper overnight.
- Warn patients about combined effects when hypnotics are used with other CNS depressants. They should never be combined with alcohol.
- If a short course of a hypnotic has been used, plan to withdraw it at a low-stress time, e.g., a weekend. Two nights before the planned withdrawal, the patient should shorten the sleep time (while staying on the medication) by 20 minutes. This modest degree of sleep deprivation will promote physiological sleepiness, which should counterbalance any sleep disruption associated with withdrawal. This shortened sleep period should be maintained for one week.
- Insomnia often occurs as a symptom, comorbid condition or prodrome of other psychiatric conditions such as depression and/or anxiety disorders.[38,39] Chronic sleep disturbance of at least 1 year in duration increases the risk of a mood disorder in subsequent years.[40,41] Vigilance is required for the emergence of a mood disorder, which should be managed with appropriate specific therapy. Short-term use of adjunctive hypnotic agents such as benzodiazepines or benzodiazepine receptor agonists may be appropriate and beneficial in select patients with depression [Evidence: SORT B*].[42,43]

* SORT (Strength of Recommendation Taxonomy) is a rating system (A, B or C) that addresses the quality of available evidence. For more information consult **How to Use *Compendium of Therapeutic Choices*** on page xxv.

Table 4: **Drugs Used to Manage Insomnia**

Class	Drug	Dose (bedtime PRN)	Adverse Effects	Drug Interactions	Comments	Cost[a]
Benzodiazepines	*lorazepam* Ativan, generics	Initial: 0.5 mg po Maximum: 1 mg po	*Benzodiazepines:* dose-dependent ataxia, dizziness; dependence/withdrawal symptoms. *Lorazepam:* may cause more rebound insomnia on withdrawal than temazepam or oxazepam; may cause amnesia with higher dosages.	Additive sedation with CNS depressants such as alcohol.	Widely used as a hypnotic although not officially indicated.	$
	oxazepam generics	Initial: 10–15 mg po Maximum: 30 mg po	See benzodiazepines.	See lorazepam.	Slowly absorbed; should be taken 60–90 min before bedtime for *initial* insomnia, but some sedation/impairment may occur earlier; no hangover effects. Not officially indicated as a hypnotic.	$
	temazepam Restoril, generics	Initial: 15 mg po Maximum: 30 mg po	See benzodiazepines.	Substrate of CYP3A4; metabolism could be increased by inducers (e.g., carbamazepine, phenytoin) or decreased by inhibitors (e.g., cimetidine, clarithromycin, efavirenz, erythromycin, grapefruit juice, itraconazole, ketoconazole, ritonavir) of the enzyme.	Good all-purpose hypnotic; does not accumulate.	$
	triazolam generics	Initial: 0.125 mg po Maximum: 0.25 mg po	See benzodiazepines. *Triazolam:* anterograde amnesia (especially with higher dosages, concurrent use of alcohol) and other potency and dose-related side effects (rebound insomnia, daytime anxiety) have limited its use; useful for *initiating* sleep.	See temazepam.	Absence of hangover effects is an advantage (does not affect daytime alertness). Higher risk of abuse/dependence than other benzodiazepines. Avoid in elderly patients, especially in doses >0.125 mg.	$$

Class	Drug	Dose (bedtime PRN)	Adverse Effects	Drug Interactions	Comments	Cost[a]
Benzodiazepine Receptor Agonists	*zolpidem* Sublinox	Men (<65 y): 5–10 mg po Women: 5 mg po Elderly patients (≥65 y): 5 mg po	Complex sleep behaviours such as night eating, somnambulism, with no recollection of such activities. Discontinue immediately if such reactions occur.	Do not combine with alcohol. Additive sedation with other CNS depressants. Increased risk of complex sleep behaviours in combination with other CNS-active drugs. Avoid zolpidem in patients taking moderate to strong inhibitors of CYP3A4 such as clarithromycin, erythromycin, grapefruit juice, itraconazole, ketoconazole, metronidazole, sertraline, verapamil, due to risk of decreased zolpidem clearance.	Use only when there is a period of at least 7–8 h before planned awakening. Avoid in patients with a history of somnambulism.	$$$
	zopiclone Imovane, Rhovane, generics	Initial: 3.75 mg po (geriatric) Usual adult dose: 7.5 mg po Maximum: 7.5 mg po	Major adverse effect is bitter/metallic taste.	Minimal additive effects with low doses of alcohol.	Does not accumulate; minimal cognitive effects;[44] may cause less rebound on withdrawal.	$$
Serotonin Precursors	*L-tryptophan* Tryptan, generics	1–3 g 20 min before bedtime po	May cause serotonin syndrome (shivering, diaphoresis, hypomanic behaviour and ataxia) alone (rarely) or when combined with other serotonergic drugs.	Combined therapy with serotonergic drugs such as triptans, SSRIs, SNRIs or MAOIs can increase the risk of serotonin syndrome.	Alternative to benzodiazepines and benzodiazepine receptoragonists; erratic response.	$$$

[a] Cost of 14-day supply; includes drug cost only.
Abbreviations: MAOI = monamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor
Legend: $ < $2 $$ $2–15 $$$ $15–30

Suggested Readings

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