

Pharmacological treatment of insomnia

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Sleep changes with aging

Box 1: Typical sleep changes with aging

- Decreased total nocturnal sleep time
- Delayed onset of sleep
- Advanced circadian phase: early to bed, early to rise
- Reduced slow-wave sleep
- Reduced rapid-eye-movement (REM) sleep
- Reduced threshold for arousal from sleep
- Fragmented sleep with multiple arousals
- Daytime napping

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Insomnia

- Primary insomnia
 - Sleeplessness that is not attributable to a medical, psychiatric or environmental cause
- Secondary insomnia
 - Sleeplessness secondary to another medical condition

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Causes of secondary insomnia

- Pain
- Nocturia
- COPD
- Gastroesophageal reflux
- Cardiac insufficiency
- Depression
- Dementia
- Inappropriate medication

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Sleep hygiene

Box 1: Fundamentals of good sleep hygiene

What to do

- Use your bed only for sleep and sexual activities
 - If you cannot sleep, get out of bed and read or do other relaxation activities before attempting to sleep again
- Make the quality of your sleep a priority
 - Go to bed and get up at the same time every day
 - Ensure a restful environment:
 - A comfortable bed in a cool, well-ventilated room
 - Protection from light and noise
- Develop and maintain bedtime “rituals” that make going to sleep a familiar routine; for example,
 - Prepare for sleep with 20-30 minutes of relaxation (e.g., soft music, meditation, breathing exercises, yoga)
 - Take a warm bath
 - Have a light snack, which could include:
 - Warm milk
 - Foods high in tryptophan, such as bananas
 - Carbohydrates, which can help induce sleep (whereas proteins promote wakefulness)

What to avoid

- In general, refrain from:
 - Napping, especially after 3:00 pm
 - Going to sleep too early in the evening (this can lead to phase advance syndrome)
- Before bedtime (or late in the day), avoid:
 - Heavy eating
 - Consumption of caffeine or alcohol
 - Smoking (nicotine interferes with sleep)
 - Exercise, which is a stimulant (although daytime activity will promote later sleep)
- While you try to fall asleep, avoid:
 - Thinking about life issues
 - Problem-solving
 - Rehashing the events of the day

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Harmful medications or substances

Table 2: Medications and other substances that can contribute to insomnia in older patients

Substance	Effects and points of advice
Alcohol	Sleep induction Subsequent sleep disruption
Anticholinesterase inhibitors	Insomnia Disturbing dreams
β-blockers	Sleep physiology altered Nightmares possible
Caffeine, decongestants	Stimulant effects • Advise patient to avoid evening use
Carbadopa, levadopa	Nightmares; insomnia
Corticosteroids	Stimulant effect; may cause agitation • Prescribe lowest possible dose
Diuretics	Nocturia • Avoid late in day
Nicotine	• Encourage smoking cessation
Phenytoin (e.g., Dilantin)	Frequent insomnia
SSRIs	Frequent insomnia
Theophylline	Stimulant effect • Substitute metered-dose bronchodilators
Thyroid hormone	• Check thyroid function

Note: SSRIs = selective serotonin reuptake inhibitors.

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Risks of sleeplessness

- Sleeplessness itself, or situations behind that, increased risks for falls in a study of 34163 NH-patients (Avidan et al. 2005)
- When use of benzodiazepines were restricted in New York (60% decrease in use), and compared with New Jersey with no restrictions 1989, there were no difference in the amount of hip fractures (Wagner et al.2007)
- May the situations behind the need for benzodiazepines (anxiety, depression, fears, other psychiatric disorders), if untreated, cause even more risk for falls than a well-coordinated use of benzodiazepines?

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Benzodiazepines

Table 1: Sedative or hypnotic medications in common use

Drug	Usual adult dose,* mg
Benzodiazepines	
Short-acting (half-life < 10 h)	
Oxazepam	15-30
Triazolam	0.125-0.25
Intermediate-acting (half-life about 10-20 h)	
Alprazolam	0.25-0.5
Estazolam (unavailable in Canada)	0.5-2
Lorazepam	0.5-1
Temazepam	15
Long-acting (half-life > 20 h)	
Chlordiazepoxide	5
Clonazepam	0.25-0.5
Diazepam	2-10
Flurazepam	15-30
Non-benzodiazepines†	
Eszopiclone	1-3
Ramelteon	8
Zaleplon	5-10
Zolpidem	5-10
Zopiclone‡	5-7.5

*For elderly patients, start with about half the average adult starting dose and adjust if necessary.
 †Of the non-benzodiazepines, only zopiclone is available in Canada (as of this writing).

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Others

- Amitriptyline
 - anticholinergic side-effects: tachycardia, urinary retention, constipation, cognitive impairment, confusion, sedation, delirium
 - most commonly used inappropriate medication (Curtis et al. 2004)
- Trazodone
 - little objective data, no RCT:s (James and Mendelson 2004)
 - may be efficacious with agitation or depression (Kaynak et al. 2004)
- Antihistamines
 - may cause excessive somnolence: should be avoided among elderly
- Testosterone
 - may offer hypogonadal men benefit, but long-term studies of its efficacy and safety are lacking (Sternbach, 1998)

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Melatonin

- Concentration peak is about half the plasma levels of younger people (Pandi-Perumal et al. 2005)->may promote insomnia
- Modestly effective in improving sleep quality among elderly (Olde and Rigaud, 2001)
- Although safe, only of limited value in treating most sleep disorders (Buscemi et al. 2005 and 2006)
- Short-term melatonin was useful in treating delayed sleep-phase syndrome, a disorder of sleep timing (Buscemi et al. 2005)
- Ramelteon, a selective agonist for melatonin receptors, has been shown to reduce sleep latency and increase total sleep time, is approved for the treatment of insomnia in US (McGeehan and Wellington, 2005)

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REM-sleep behaviour disorder

- Safe sleep environment
- Removal of medication that promotes REM-sleep behavior disorder activity, such as SSRI's
- When associated with Parkinson, MS or Alzheimer's disease, treatment of the primary disorder
- Clonazepam 0.5-1 mg at bedtime
- Long-term therapy is usually needed, since symptoms tend to persist

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Narcolepsy and cataplexy

- 7-8 h of sleep nightly with daytime naps
- Central stimulants, such as methylphenidate and modafinil are effective (Mignot and Nishino, 2005)
- Tricyclic antidepressants decrease the frequency of cataplexy (but have side-effects)
- SSRIs in combination with stimulants
- Sodium oxybate approved in US can be effective (US Xyrem Multicenter Study Group 2003 and 2004)

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Sleep-related movement disorders

Table 3: Characteristics of sleep-related movement disorders – restless legs and periodic leg movements

Aspect	Restless legs syndrome	Periodic leg-movement disorder								
Clinical features	<ul style="list-style-type: none"> • Unpleasant sensations in legs, usually at night <ul style="list-style-type: none"> – Described as “creeping,” “crawling” or painful – Improved by movement • Sleep-onset insomnia • Daytime fatigue 	<ul style="list-style-type: none"> • Involuntary limb movements that recur at regular intervals (20-40 s) during the non-rapid-eye-movement stages of sleep • Patient often unaware of movements • Frequent arousal or awakening during sleep • Daytime fatigue 								
Prevalence	<ul style="list-style-type: none"> • 2%-15% of general population • 10%-35% among people 65 years or older • More common in women than in men 	<ul style="list-style-type: none"> • 5% among people aged 30-50 yr; up to 45% among those ≥ 65 yr • Equally common in women and men 								
Diagnosis	Clinical	Polysomnography showing repetitive muscle contractions								
Associated factors	<ul style="list-style-type: none"> • Accompanied by periodic leg-movement disorder in about 85% of cases • Family history (about half of affected people) <table border="0"> <tr> <td style="text-align: center;">More common</td> <td style="text-align: center;">Less common</td> </tr> <tr> <td> <ul style="list-style-type: none"> • Iron deficiency • Peripheral neuropathy • Renal failure </td> <td> <ul style="list-style-type: none"> • Diabetes • Parkinson's disease • Cigarette smoking • Use of alcohol, caffeine • Some medications </td> </tr> </table>	More common	Less common	<ul style="list-style-type: none"> • Iron deficiency • Peripheral neuropathy • Renal failure 	<ul style="list-style-type: none"> • Diabetes • Parkinson's disease • Cigarette smoking • Use of alcohol, caffeine • Some medications 	Accompanied by restless legs syndrome in around 25% of cases				
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Treatments	<table border="0"> <tr> <td style="text-align: center;">In frequent use</td> <td style="text-align: center;">Less frequently used</td> </tr> <tr> <td> <ul style="list-style-type: none"> • Dopaminergic agents • Dopamine agonists </td> <td> <ul style="list-style-type: none"> • Benzodiazepines • Anticonvulsants • Opioids </td> </tr> </table>	In frequent use	Less frequently used	<ul style="list-style-type: none"> • Dopaminergic agents • Dopamine agonists 	<ul style="list-style-type: none"> • Benzodiazepines • Anticonvulsants • Opioids 	<table border="0"> <tr> <td style="text-align: center;">In frequent use</td> <td style="text-align: center;">Less frequently used</td> </tr> <tr> <td> <ul style="list-style-type: none"> • Dopaminergic agents • Dopamine agonists </td> <td> <ul style="list-style-type: none"> • Benzodiazepines • Anticonvulsants • Muscle relaxants </td> </tr> </table>	In frequent use	Less frequently used	<ul style="list-style-type: none"> • Dopaminergic agents • Dopamine agonists 	<ul style="list-style-type: none"> • Benzodiazepines • Anticonvulsants • Muscle relaxants
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Snoring and obstructive sleep apnea

- Weight reduction
- Smoking cessation
- Abstinence from alcohol
- Nasal humidifiers or steroids
- Counseling to sleep on their side, not on the back
- Surgical options
 - uvulopalatopharyngoplasty (Kyrnizakis et al. 2003)
 - considerable postoperative morbidity among elderly (Jones et al.2005)
- CPAP or nasal CPAP (Shochat and Pillar 2003, Quinzel and Smith 2004)

Summary

- Sleep disturbances are common among elderly
- Also sleeplessness may increase the risk for falls
- Medications may be highly efficacious, but because of side-effects, they must be administered judiciously and in conservative doses
- Start low, go slow, but go