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Treatment of Insomnia

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Insomnia is a highly pervasive condition. Approximately one-third to one-fourth of the population in industrialized nations report sleep disturbance problems at some point in their lives and approximately 10% suffer from persistent insomnia.[1] Consequences of insomnia can be measured by both societal economic consequences and health-related consequences. From the standpoint of societal cost, insomnia is estimated to have direct and indirect costs exceeding $100 billion annually in the U.S. alone.[2]

Due to its significant impact, the recognition and treatment of insomnia is important. The definition of insomnia from the International Classification of Sleep Disorders is provided in Figure 1.[3] In general most clinicians and investigators consider ≥30 minutes to fall asleep and/or ≥30 minutes of wakefulness after sleep onset and total sleep time of ≤ 6.5 hours per night to represent the threshold between normal and abnormal sleep.

Figure 1. Definition of Insomnia (International Classification of Sleep Disorders)[3]

Diagnostic Criteria for Primary Insomnia Requires:

(i) A predominant complaint of difficulty in initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month;

(ii) That the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning;

(iii) That the sleep disturbance does not occur exclusively during the course of another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, etc.); and

(iv) That the disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another psychiatric or general medical condition.

In general, the approach to the treatment of acute insomnia includes the following considerations[4]:

1. The elimination of causative factors (e.g. caffeine, certain medications, etc.)
2. The treatment of comorbid diagnoses (e.g. depression, sleep apnea)
3. Nonpharmacologic treatment
4. Pharmacologic interventions

Ideally, treatment for insomnia would improve sleep quantity and quality, improve daytime function (greater alertness and concentration), and cause minimal adverse drug effects. Many experts support the implementation of nonpharmacologic treatment methods prior to the initiation of a sedative/hypnotic.[4]

Nonpharmacologic Management. Nonpharmacologic treatment options include sleep hygiene, stimulus control, sleep restriction, relaxation training, and cognitive behavioral therapy (CBT). Research has shown that behavioral therapies may produce similar effects on sleep latency, waking after sleep onset, total sleep time, and quality of sleep when compared to pharmacotherapy. [5] In addition, a recent study found that subjects treated with a combination of zolpidem and CBT achieved better long term outcomes after the zolpidem was discontinued than those treated with zolpidem alone. [6] The following are helpful patient resources related to nonpharmacologic treatment options:

- http://www.cci.health.wa.gov.au/docs/Info-sleep%20hygiene.pdf
- http://heretohelp.bc.ca/skills/module6
- http://www.mayoclinic.com/health/insomnia-treatment/SL00013

Pharmacologic Management. A number of pharmacologic treatment options exist including: benzodiazepines, nonbenzodiazepine hypnotics, and sedating antidepressants. Benzodiazepines decrease the time to onset of sleep and prolong the first two stages of sleep. They slightly reduce the relative amount of deep non-rapid-eye-movement sleep. The primary difference between the available benzodiazepines is their duration of action.

Zaleplon (Sonata), zolpidem (Ambien) and eszopiclone (Lunesta) are not structural benzodiazepines but appear to bind to benzodiazepine receptors. Their exact mechanism of action is not known but they are believed to act through an agonist effect on GABA-A receptor complexes located close to or coupled with benzodiazepine receptors. All non-benzodiazepines act quickly to improve sleep latency. Both zaleplon and zolpidem are available as generics, making them lower cost alternatives.

Ramelteon (Rozerem), a melatonin agonist, is FDA approved for sleep-onset insomnia. Studies have shown a small reduction in sleep latency, but have not demonstrated improvement in sleep maintenance.[7] Comparative studies with other hypnotics are lacking.

A wide variety of other medications, although not FDA indicated, are commonly prescribed for insomnia. The most common are antidepressants such as trazodone (Desyrel), mirtazapine (Remeron) or amitriptyline (Elavil). With the exception of one study with low dose doxepin (Sinequan), there are no well-controlled trials demonstrating that antidepressant medications are efficacious in treating insomnia that is not associated with depression. In addition, while certain atypical antipsychotics have sedating properties, their use, even at low dose, is associated with significant adverse effects and cost.[8] Unless psychiatric comorbidities support their initiation, evidence does not support the use of atypical antipsychotics in the treatment of insomnia.

Two first-generation antihistamines — diphenhydramine (Nytol, Benadryl, others) and doxylamine (Unisom, others) — are approved by the FDA as "sleep-aids" over-the-counter. Tolerance to the sedative effects of antihistamines may develop rapidly. They can cause next-day sedation, impairment of performance skills such as driving, and anticholinergic effects such as dry mouth and urinary retention. Alcohol is also a poor hypnotic. Alcohol causes initial CNS depression followed by rebound excitation, which disrupts sleep. Melatonin supplementation taken 3-5 hours before the desired time of sleep onset has been reported to be effective in some patients with insomnia[9,10], but adequate controlled trials are lacking. It does not appear to be effective when taken at bedtime. The hypnotic dose and purity of melatonin have not been established. Valerian root is claimed to be a mild hypnotic, but studies have not demonstrated any objective improvement in sleep compared to placebo.[11] As with other herbal products, optimal dosage is unclear and purity is a concern.

The perception of good sleep does not often correlate with objective sleep measures. In fact, the objective benefit of sedative treatment (from polysomnography) is often far more limited than people subjectively perceive (from sleep journals). Buscemi et al. provided an indirect comparison of subjective and objective measures of sleep improvement, specifically improvement in sleep latency, sleep duration, and amount of time spent awake after sleep onset (WASO).[12] In this study, the subjective and objective improvements varied significantly, and often the objective

improvement with the newer drugs is limited. A patient's perception of their current sleep quality and their treatment expectations from sedative use should be thoroughly discussed.

Table 1. Objective versus subjective findings with sedative/hypnotics[12]

Class	Sleep Latency Subjective / Objective	Sleep Duration Subjective / Objective	WASO Subjective / Objective
BZs	-20 min / - 10 min	+53 min / +33 min	-40 min / -17 min
Non BZs	-17 min / -13 min.	+32 min / +11min	-15 min / - 7 min
ATDs	-12 min/ -7 min	-54 min/ +80 min	-7 min / -12 min

BZs=Benzodiazepines, Non BZs=Non-Benzodiazepines (e.g. zolpidem, zaleplon, eszopiclone), ATDs=Sedating Antidepressants, WASO=Wakefulness after sleep onset,

The findings from the Drug Effectiveness Review Project review on newer drugs for insomnia found few differences in terms of effectiveness and safety between the newer agents (with the exception that ramelteon appears to be somewhat less effective).[13] A summary of key findings is included in Table 2.

To minimize side effects, potential toxicity and dependence, it is preferable to prescribe benzodiazepines and non-benzodiazepines for as short of duration as possible and evaluate their benefit versus risk in elderly patients. The potential for tolerance, dependence and withdrawal is common to all benzodiazepines and non-benzodiazepines. The National Institute for Clinical Excellence lists the following as factors that can increase the risk of developing dependence: short duration of action, long-term use, high dose, high potency, alcoholism and other drug dependency, personality disorders and use without medical supervision.[14] In addition, findings from a meta-analysis of risks and benefits of hypnotics in older people suggested that although improvements in sleep with hypnotics are statistically relevant, the extent is small. Data from this study also suggested an increased risk of falls and cognitive-related side effects associated with these agents did not justify their use in older adults.[15]

In summary, the consequences of untreated insomnia can be significant. Successful treatment approaches should include nonpharmacologic methods with or without the addition of a sedative/hypnotic. Newer sedatives are generally equally effective, but the patient's expectations for meaningful improvement in sleep should not be over exaggerated.

Table 2. Summary of Sedative/Hypnotic Findings[13]

Drug	Sleep onset vs. placebo (min)*	Sleep duration vs. placebo (min)**	Dose / Dose in Elderly
Non-benzodiazepine Sedative Hypnotics[16]			
Zolpidem (Ambien, generics)	20	34	10 mg / 5 mg
Zaleplon (Sonata, generics)	14	20	10 mg / 5 mg
Zolpidem CR (Ambien CR)[17]	7-10+	26-43+	12.5 mg / 6.25mg
Eszopiclone (Lunesta)	13-19	24-46	2-3 mg / 1-2 mg
Ramelteon (Rozerem)	8	3-10	8 mg / 8 mg
Sublingual Zolpidem (Edluar)[18]	5-10 (v. IR)	not different than IR	10 mg / 5 mg
Benzodiazepine[19,20] (half life in hours)			
Triazolam	14-20#	48-53#	0.125-0.25 mg / 0.125 mg
Temazepam			15-30 mg / 7.5-15 mg

*Minutes faster relative to placebo based on self reported sleep diary assessments
** Minutes longer of sleep relative to placebo based on self reported sleep diary assessments
+Sleep onset determined by polysomnography; sleep duration exact data not given
Patient estimates of sleep latency and duration (estimates show ranges from two meta-analyses)

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