The Medical Letter®
On Drugs and Therapeutics

Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, N.Y. 10801 • A Nonprofit Publication

Vol. 42 (W1084C)
August 7, 2000

HYPNOTIC DRUGS

Many drugs are used to treat insomnia, but for some patients nonpharmacological treatments such as changing sleep habits, relaxation training and cognitive therapy may be more effective than drugs (J Wagner et al, Ann Pharmacother, 32:680, 1998; CM Morin et al, JAMA, 281:991, 1999).

NONPRESCRIPTION HYPNOTICS — Two **antihistamines**—diphenhydramine (*Nytol, Benadryl* and others) and doxylamine (*Unisom*, and others)—are currently approved by the FDA for sale as "sleep-aids" without a prescription. They can cause daytime sedation, impairment of performance skills such as driving, and troublesome anticholinergic effects such as dry mouth and urinary retention. **Alcohol** causes initial CNS depression followed by rebound excitation, disrupting sleep. **Melatonin** has shown some promise, but adequate controlled trials are lacking, and the purity, hypnotic dose and adverse effects of melatonin products have not been established (D Avery et al, Ann Med, 30:122, 1998; J Pepping, Am J Health Syst Pharm, 56:2520, 1999). **Valerian root** is a mild hypnotic that may improve the quality of sleep and appears to have few adverse effects, but as with other herbal products, optimal dosage is unclear and purity is a concern (SL Plushner, Am J Health Syst Pharm, 57:328, 2000).

OLDER PRESCRIPTION HYPNOTICS — Chloral hydrate (*Noctec*, and others) is an effective hypnotic when used for a few nights to treat transient insomnia. Within two weeks, however, its effectiveness can wane, and continued use often leads to physical dependence. Withdrawal of the drug can cause disrupted sleep and intense nightmares. The usual hypnotic dose of chloral hydrate is 0.5 to 1 gram; fatalities have occurred following ingestion of as little as 4 grams. **Barbiturates** have the disadvantages of a narrow therapeutic ratio, lethality in overdosage, rapid development of tolerance, high liability for physical dependence and abuse, and many drug interactions (*The Medical Letter Handbook of Adverse Drug Interactions*, 2000, page 122). **Ethchlorvynol** (*Placidyl*, and others), which also has been associated with dependence and abuse, has some serious adverse effects and is lethal in overdosage.

BENZODIAZEPINE RECEPTOR AGONISTS — Benzodiazepines decrease the time to onset of sleep (sleep latency), prolong the first two stages of sleep, and suppress stages 3 and 4 (deep sleep) and REM sleep. Although all benzodiazepines have hypnotic activity, only triazolam, estazolam, temazepam, flurazepam and quazepam are labeled for use as hypnotics in the USA. Zaleplon and zolpidem, which are not benzodiazepines but bind selectively to benzodiazepine receptors, decrease sleep latency with little effect on sleep stages. Zaleplon is a

rapid-acting hypnotic that is less potent and has a shorter duration of action than zolpidem. Zaleplon does not decrease premature awakenings or increase total sleep time, but appears to have a low risk of next-day residual effects, even with middle-of-the-night use (Medical Letter, 38:60, 1996; 41:93, 1999; JK Walsh et al, Clin Neuropharmacol, 23:17, 2000).

Adverse Effects – Fatal overdosage is rare with any oral benzodiazepine receptor agonist unless it is taken with alcohol or other central-nervous-system depressants. The effectiveness of these drugs as hypnotics can persist for weeks or even several months, but all probably can produce physical dependence, especially with higher doses and longer duration of treatment. All benzodiazepine agonists can cause anterograde amnesia and psychiatric effects. Those with a short duration of action may be the most likely to cause daytime anxiety and rebound insomnia. Drugs with a long duration of action may cause daytime sedation and motor impairment. Benzodiazepines with an intermediate duration of action theoretically could avoid both rebound and hangover effects, but both can occur with these drugs as well (MM Mitler, Sleep, 23 suppl 1:S39, 2000). Use of benzodiazepines in elderly patients has been associated with an increased incidence of falls and hip fractures, and impairment of memory (RM Leipzig et al, J Am Geriat Soc, 47:30, 1999; JT Hanlon et al, Clin Pharmacol Ther, 64:684, 1998). Some Medical Letter consultants believe that zolpidem and zaleplon will prove safer than older, longer-acting benzodiazepines, but direct comparisons are lacking.

SOME BENZODIAZEPINE RECEPTOR AGONISTS USED TO TREAT INSOMNIA

Drug	Duration	Onset of action	Hypnotic dose	Dose in Elderly	Cost[1]
Zaleplon[2] – *Sonata* (Wyeth-Ayerst)	ultra-short	rapid 15-30 min.	10-20 mg	5 mg	$14.84
Zolpidem[2] – *Ambien* (Searle)	short	rapid 30 min.	10 mg	5 mg	14.97
Triazolam – generic price	short	rapid 15-30 min	0.125-0.25 mg	0.125 mg	3.39
Halcion (Pharmacia & Upjohn)					7.71
Oxazepam[3] – average generic price	short to intermediate	intermediate to slow 45-60 min	15-30 mg	10-15 mg	5.56
Estazolam – average generic price	intermediate	rapid to intermediate 15-60 min	1-2 mg	0.5-1 mg	6.23
ProSom (Abbott)					8.73
Lorazepam[3] – generic price	intermediate	intermediate 30-60 min	1-2 mg	0.25-1 mg	4.68
Ativan (Wyeth-Ayerst)					7.34
Temazepam – average generic price	intermediate	intermediate to slow 45-60 min	15-30 mg	7.5-15 mg	3.23
Restoril (Novartis)					6.44
Clonazepam[3] – generic price	long	intermediate 30-60 min	0.5 mg	0.25 mg	2.90
Klonopin (Roche)					5.44
Diazepam[3] – generic price	long	rapid 15-30 min	5-10 mg	2.5-5 mg	.33
Valium (Roche)					5.62
Flurazepam – generic price	long	intermediate 30-60 min	30 mg	7.5 mg	.47
Dalmane (Roche)					10.83
Quazepam – *Doral* (Wallace)	long	intermediate 20-45 min	15 mg	7.5 mg	18.67

1. Cost to the pharmacist for 7 doses at the lowest recommended hypnotic dosage, according to AWP or HCFA listings in *Drug Topics Red Book* 2000 and July 2000 *Update*. Retail prices may be higher or lower, depending on the pharmacy and the patient's insurance coverage.
2. Not a benzodiazepine, but binds to benzodiazepine receptors.
3. Insomnia is not an FDA-approved indication.

ANTIDEPRESSANTS — Trazodone (*Desyrel*, and others) a non-tricyclic, non-SSRI antidepressant, has been used effectively in a single 25- to 150-mg dose at bedtime to relieve insomnia in depressed and non-depressed patients, including some taking a selective serotonin reuptake inhibitor (SSRI) or bupropion *(Wellbutrin)*. Orthostatic hypotension can occur, and male patients should be warned about the rare occurrence of priapism. Nefazodone *(Serzone)* and mirtazapine *(Remeron)* have also been used in a single dose at bedtime to produce somnolence (ME Thase, J Clin Psychiatry, 60 suppl 17:28, 1999).

CONCLUSION — All drugs available for treatment of insomnia have some drawbacks, especially with prolonged use. Short-term use of a short-acting benzodiazepine receptor agonist is generally effective and safe, but may not prevent early morning awakening. When this occurs, a benzodiazepine with an intermediate duration of action may be more helpful.

THE MEDICAL LETTER® (ISSN 1523-2859) is published and printed in the USA bi-weekly by The Medical Letter, Inc., a non-profit corporation. Second-class postage paid at New Rochelle, NY, and at additional mailing offices. POSTMASTER: Send address changes to THE MEDICAL LETTER at 1000 Main Street, New Rochelle, NY 10801-7537. Subscription fees: 1 year, $49.00; 2 years, $82.00; 3 years, $114.00 ($24.50—U.S. Funds—per year for individual subscriptions to students, interns, residents, and fellows in the USA and Canada; special fees for bulk orders). Major credit cards accepted. Subscriptions are accepted with the understanding that no part of the material may be reproduced or transmitted by any process in whole or in part without prior permission in writing.
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