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Abstract Potential of Sleeping Agents: Liability Varies Among Agents

Introduction

Roland R. Griffiths, PhD

The treatment of insomnia is a challenging undertaking, and many physicians hesitate to prescribe pharmacologic therapy for this condition, preferring to avoid the risk of exposing patients to the abuse and dependence potential of sedative/hypnotic drugs. The result is that patients with insomnia may be untreated or undertreated. However, the risk of abuse or dependence is not great in all individuals and not all sedative/hypnotics carry the same liability for abuse or toxicity. For patients judged to be vulnerable to abuse or toxicity, these possible problems can be minimized by administering low-risk drugs.

A study analyzing the currently available sedatives/hypnotics is reviewed on page 3.

TOPIC HIGHLIGHTS

FACULTY AND UNAPPROVED USE DISCLOSURES

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Dr Griffiths has disclosed that he is Principal Investigator of two grants from the National Institute on Drug Abuse (NIDA) (R01 DA03889 and R01 DA03890) and co-investigator on a contract and several other grants from NIDA. During the past 5 years, on issues about drug abuse liability, he has been a consultant to or received grants from the following pharmaceutical companies: Abbott Laboratories, Forest Laboratories Inc., Merck & Co., Inc., Neurocrine Biosciences, Inc., Novartis Pharmaceuticals Corporation, Orphan Medical, Pharmacia Corporation, Pfizer Inc., Takeda Pharmaceuticals, TransOral Pharmaceuticals, Inc., Somaxon Pharmaceuticals Inc., and Wyeth Pharmaceuticals. He has disclosed that he will be discussing non-medical use (ie, abuse) of various hypnotic drugs.

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Insomnia: A Brief Review

Primary insomnia is the complaint of sleeplessness that is not attributable to a medical, psychiatric, or environmental cause. Its diagnosis is based on a patient's subjective report of sleep patterns, including complaints of nonrestful sleep and difficulty with sleep onset or maintenance. *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IVR®*)[1] criteria for primary insomnia is shown in the **Table**. A detailed discussion of insomnia and other sleep disorders is available in the *International Classification of Sleep Disorders Revised, Diagnostic and Coding Manual*.[2]

Individuals with insomnia typically have one or more common complaints: difficulty initiating sleep, waking up often during the night and having trouble going back to sleep, waking up too early in the morning, or unrefreshing sleep. Unsatisfactory sleep quality is perceived by the patient as inadequate or nonrestorative, despite ample opportunity to sleep.

In a 1998 survey of patients enrolled in five managed care organizations, Hatoum and colleagues[3] found that, of the 3,447 patients who responded (46% of the enrollees), 33% endorsed insomnia with daytime dysfunction. An international survey of insomnia published recently showed that 27% of American respondents reported having insomnia.[4] In France and Italy, the rate was 37%; in Japan, 7% of respondents reported insomnia. In the entire sample of respondents, the mean number of symptoms reported was two. The three most commonly reported symptoms were difficulty maintaining sleep (73%), difficulty initiating sleep (61%), and poor sleep quality (48%).

Effects of Insomnia

Chronic insomnia may be associated with a variety of adverse effects on quality of life, including impaired social functioning and work problems (for example, time missed from work and impaired job performance). In addition, chronic sleep loss may result in subjective reports of memory impairment and next day functional impairment.[5,6] Insomnia is also associated with an increased risk for comorbid psychiatric and medical illness and is a strong predictor of future development of depression.[7,8]

Stoller[9] calculated that the cost of lost productivity and accidents related to insomnia is approximately $80 billion each year. These estimated expenses likely result from insomnia-related effects on daytime alertness and behavior. [6]

For individuals who experience daytime sleepiness and impaired performance related to transient insomnia, the use of sleeping agents usually provides rapid relief of symptoms and may improve sleep and next-day alertness.

Pharmacologic Treatment of Insomnia

Until the late 1960s, barbiturates such as pentobarbital and secobarbital were widely used in the treatment of insomnia. However, the use of these drugs declined with the recognition that barbiturates were associated with abuse and could produce clinical dependence, including severe withdrawal symptoms with abrupt cessation of use.

The discovery of the benzodiazepine anxiolytic chlordiazepoxide and subsequent development of numerous analogs with similar pharmacologic profiles rapidly led to replacement of barbiturates by benzodiazepines for the treatment of anxiety and sleep disorders. Compared with barbiturates, benzodiazepines caused fewer unwanted side effects, were relatively safer in overdose, were less likely to produce severe withdrawal symptoms, and were less likely to be abused. Currently, 14 benzodiazepine drugs are marketed in the United States and all possess sedative-hypnotic properties to varying degrees; these properties are extensively exploited clinically, especially to facilitate sleep.[10]

By binding to specific receptor sites, benzodiazepines potentiate the effects of gamma-aminobutyric acid (GABA) and facilitate inhibitory GABA neurotransmission. The discovery of selective binding sites led to the discovery and development of other drugs with sedative/hypnotic properties that differ structurally from benzodiazepines but that also interact with the benzodiazepine receptor (eg, zolpidem, zaleplon, eszopiclone). Thus, the term "benzodiazepine receptor agonist" is useful for denoting any drug, regardless of chemical structure, that acts on a benzodiazepine receptor to increase GABAergic inhibitory transmision.

For individuals who experience daytime sleepiness and impaired performance related to transient insomnia, the use of sleeping agents usually provides rapid relief of symptoms and may improve sleep and next-day alertness.

Benzodiazepine receptor agonists are safe and effective, but risks associated with their use include memory impairment, withdrawal syndrome, and increased frequency of accidents, falls, and hip fractures in the elderly. Concern about overuse and abuse has also dampened prescribing. Recently the less efficacious and possibly less safe antidepressant trazodone has became the most commonly prescribed medication for insomnia in the United States.[11,12]

Patterns of Sedative/ Hypnotic Abuse

Dating to the introduction of barbiturates and benzodiazepines, physicians and patients have been concerned about abuse potential of drugs used to treat insomnia. Two patterns of nonmedical use are recognized. One is described as chronic quasitherapeutic abuse (ie, long-term drug taking by patients for a duration

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Table. Primary Insomnia DSM-IV Diagnostic Criteria

A. The predominant complaint is difficulty initiating or maintaining sleep, or having nonrestorative sleep, for at least 1 month.
B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The sleep disturbance does not occur exclusively during the course of narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep disorder, or a parasomnia.
D. The disturbance does not occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, a delirium).
E. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

Source: American Psychiatric Association.[1]

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Summary of a Key Study

Abuse Potential of Hypnotic Agents: Study Evaluates Relative Abuse Liability

Possible recreational abuse, inappropriate chronic use, and withdrawal symptoms may discourage the appropriate use of sedative/hypnotic agents. However, it should be recognized that the risk of abuse or problematic use of hypnotics varies with the characteristics of the patient (it is increased in patients with histories of drug or alcohol abuse, as well as with elderly patients and individuals with chronic pain) and with the characteristics of the hypnotic drug (hypnotic drugs vary widely in their abuse liability).

Recently, Griffiths and Johnson [*J Clin Psychiatry.* 2005;66 (suppl 9):31-41] conducted an analysis of hypnotic drugs and concluded that differences exist among these agents, in terms of both the likelihood of abuse and toxicity. They note that wide variations are found among these drugs and range from high to no abuse potential and/or toxicity.

Defining Relative Abuse Liability and Toxicity

The authors use Balster and Bigelow's definition of abuse liability as the likelihood that a drug with central nervous system effects will sustain patterns of nonmedical self-administration that result in disruptive or undesirable effects.[1] The likelihood that a drug will be abused is primarily influenced by its reinforcing effects, which can be examined using drug self-administration methods in both animal and human studies.[2,3] In clinical trials, the gold standard for determining the potential for abuse of a novel hypnotic compound is to compare three or more dose levels of the test drug with those of a known drug of abuse in a double-blind manner among subjects with histories of sedative drug abuse.[4] Outcome measures that reflect degree of behavioral reinforcement include subjective ratings of liking/disliking, positive/negative drug effects, and disposition to take the drug again.[5-7]

A defining characteristic of drugs of abuse is their ability to reinforce behavior (ie, sustain nonmedical self-administration). In addition to reinforcing effects, drugs of abuse produce adverse effects that also contribute to the overall liability or toxic consequences of nonmedical use. These two factors—the reinforcing effects and the toxic effects—served as the authors' basis for characterizing the relative abuse liability of a variety of compounds used in the treatment of insomnia (**Table,** page 3).

Relative Abuse Liability Table

The comprehensive **Table** is divided into three main categories: pharmacology, likelihood of abuse, and other toxic consequences. The three columns under the category heading of pharmacology provide information about each drug's molecular site of action, half-life, and peak time.

Under the heading of likelihood of abuse, the authors present information that was used in estimating the likelihood of abuse of each agent. In the first two columns under this heading, the results of studies of drug self-administration conducted in nonhuman primates and humans form the basis of ratings of the degree to which the various drugs function as reinforcers. The third column (actual abuse) uses epidemiologic data to estimate the amount of nonmedical use and recreational abuse. The ratings in each of these columns range from 0 to 4 (designated as 0 or with one to four "plus" signs). A "likelihood of abuse" score was derived from these three types of data and is expressed as a mean percentage across the three columns.

Four columns contain information used to estimate the other toxic consequences of use of each of the compounds: the relative severity of withdrawal symptoms after cessation of chronic supratherapeutic doses; the degree of behavioral or cognitive impairment after acute supratherapeutic doses; and the likelihood that an overdose would be fatal. The mean percentage across the four columns in this category represents an overall toxicity score for each compound.

Results of Analysis

Based on this analysis, the likelihood of abuse scores of 19 hypnotic drugs (**Figure**) range from 100% (pentobarbital) to 0% (trazodone and ramelteon). The benzodiazepines (diazepam, flunitrazepam, lorazepam, temazepam, triazolam, flurazepam, oxazepam, estazolam, and quazepam) and nonbenzodiazepines with activity at the benzodiazephine receptor binding site (zaleplon, eszopiclone, zopiclone, and zolipdem) vary widely in likelihood of abuse scores, despite the fact that all of these compounds are active at the same receptor sites. The scores range from highs of 67% for diazepam and flunitrazepam to 13% for quazepam.

The three drugs that do not have GABA-mediated activity (diphenhydramine, trazodone, and ramelteon) had low abuse liability scores and produce atypical profiles of subjective effects. Diphenhydramine and trazodone were associated with some unpleasant subjective side effects greater than those of classical hypnotics, whereas ramelteon produced no detectable subjective effects at supratherapeutic doses of up to 20 times the recommended therapeutic dose.[8]

The relative toxicity scores ranged from 94% (pentobarbital) to 0% (ramelteon). The analysis also showed that, at supratherapeutic doses, pentobarbital, methaqualone, and gamma-hydroxybutyrate are more likely to be lethal than are the other hypnotics. Ramelteon is the exception: at 20 times the recommended therapeutic dose, it produced no detectable motor or cognitive impairment.[8]

Conclusion

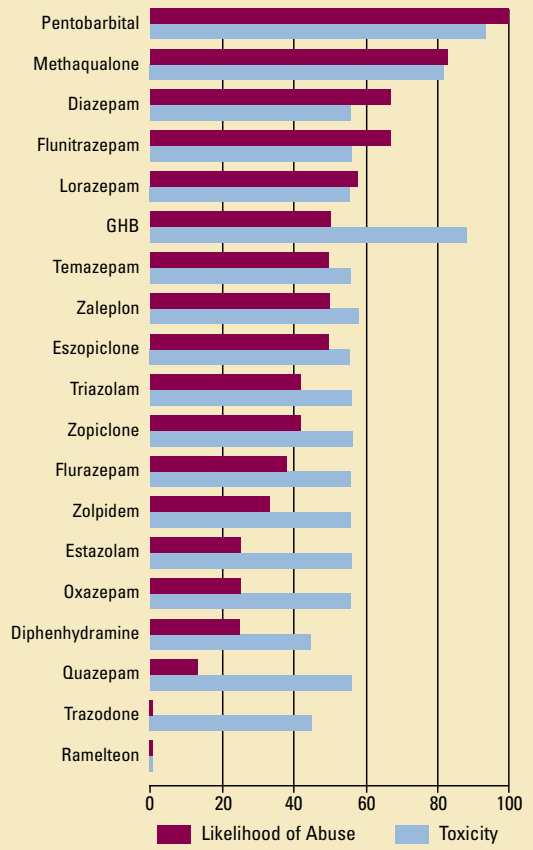
Concern about recreational abuse, the development of inappropriate long-term use, or adverse effects should not deter physicians from prescribing hypnotics when clinically indicated. After clinical evaluation, physicians may choose from a range of compounds that differ in their potential for problematic use and toxicity. Choice among specific compounds should depend on the clinician's assessment of the vulnerability of the patient for nonmedical use, as well as other drug characteristics that may be important for optimal treatment of the individual patient (eg, speed of onset, duration of action). Available hypnotic agents range from compounds with virtually no likelihood of abuse (eg, ramelteon, trazodone) to those with varying degrees of both likelihood of abuse and other toxicity. The **Table** reprinted on page 3 provides evidence-based information about the potential for recreational abuse, the development of inappropriate long-term use, or adverse effects of sedative/hypnotic agents.

References

1. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend.* 2003;70:S13–S40.
2. Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. *Drug Alcohol Depend.* 2003;70(3 suppl):S55–S72.
3. Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animal and human drug-taking behavior. In: *Advances in Substance Abuse, Behavioral and Biological Research,* vol 1. Greenwich, Conn: JAI Press, Inc; 1980:1–90.
4. Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. *Drug Alcohol Depend.* 2003;70(3 suppl):S41–S54.
5. Griffiths RR, Wolf B. Relative abuse potential of different benzodiazepines in drug abusers. *J Clin Psychopharmacol.* 1990;10:237–243.
6. Iguchi MY, Handelsman L, Bickel WK, Griffiths RR. Benzodiazepine and sedative use/abuse by methadone maintenance clients. *Drug Alcohol Depend.* 1993;32:257–266.
7. Jaffe JH, Bloor R, Crome I, et al. A post-marketing study of relative abuse liability of hypnotic sedative drugs. *Addiction.* 2004;99:165–173.
8. Johnson MW, Suess PE, Griffiths RR. Dose effect comparison of ramelteon and triazolam: Abuse potential and behavioral effects. Presented at the 67th annual meeting of the College on Problems of Drug Dependence; 18–23 June 2005; Orlando, Fla.

Based on Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: A conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry.* 2005;66(suppl 9): 31–41.

Figure. Relative Abuse Liability of Hypnotic Drugs.[a]



[a]As discussed in text, relative abuse liability comprises an assessment of both the likelihood of abuse (dark bars) and the toxicity (light bars). Scores show the mean percentage of maximum possible score (see text and **Table** [on page 3] footnotes for details).

GHB = γ-hydroxybutyrate (also known as sodium oxybate)

Source: Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: A conceptual framework and algorithm for differentiating among compounds.

Table. Relative Abuse Liability of Hypnotic Drugs (a)

Drug	Pharmacology (b)			Likelihood of Abuse (b)			Other Toxic Consequences (b)				Likelihood of Abuse Score, % of Maximum (c)	Toxicity Score, % of Maximum (c)
	Receptor Site (d)	Half-Life, h (e)	Peak Time, h (f)	Animal Drug Self-Administration (g)	Human Liking/ Reinforcement (h)	Actual Abuse (i)	Animal Withdrawal (j)	Human Withdrawal (j)	Acute Sedation/ Memory Impairment (k)	Lethality in Overdose (l)		
Pentobarbital *Nembutal*	Barb/$GABA_A$	33 (1)	2–3 (2)	++++ (3,4)	++++ (5–7)	++++ (8–10)	++++ (11)	++++ (12,13)	+++ (2)	++++ (14,15)	100	94
Methaqualone* *Quaalude* (aa)	$GABA_A$ (presumed) (16)	30 (14)	2 (14)	++ (17)	++++ (18–20)	++++ (18,21)	++ (22,23) (o)	++++ (14)	+++ (14)	++++ (14)	83	81
Diazepam *Valium and others* (bb)	BZ/$GABA_A$	43 (1)	1.3 (1)	++ (3)	+++ (6,7,24)	+++ (24–27)	++ (m)	++ (m)	+++ (27)	++ (y)	67	56
Flunitrazepam* *Rohypnol*	BZ/$GABA_A$	14 (28)	2 (28)	++ (3)	+++ (29,30)	+++ (30,31)	++ (31) (m)	++ (31) (m)	+++ (30)	++ (y)	67	56
Lorazepam *Ativan and others*	BZ/$GABA_A$	14 (1)	2 (28)	++ (3)	+++ (24,32–37)	++ (24,26,32,37,38)	++ (m)	++ (m)	+++ (35)	++ (y)	58	56
GHB (γ-*hydroxybutyrate*, also known as sodium oxybate) *Xyrem*	GHB and $GABA_B$	0.75 (39)	0.9 (39)	+ (40,41)	++ (42)	+++ (43,44)	++ (45)	++++ (46)	++++ (42) (u)	++++ (43,47) (cc)	50	88
Temazepam *Restoril and others*	BZ/$GABA_A$	11 (1)	1.2 (48)	++ (49)	++ (25)	++ (25,50,51)	++ (m)	++ (m)	+++ (52)	++ (y)	50	56
Zaleplon *Sonata*	BZ/$GABA_A$ α_1 selective	1 (53)	1 (53)	++ (54)	++ (55)	… (v)	++ (56)	…	+++ (39)	++ (y)	50	58
Eszopiclone *Lunesta*	BZ/$GABA_A$	6 (57)	1 (57)	++ (x)	++ (57) (x)	… (v)	++ (x)	++ (x)	+++ (58) (x)	++ (x)	50	56
Triazolam *Halcion and others*	BZ/$GABA_A$	2.9 (1)	1.3 (1)	++ (3)	++ (55,59)	+ (24,60–62) (q)	++ (m)	++ (m)	+++ (2)	++ (y)	42	56
Zopiclone* *Imovane*	BZ/$GABA_A$	5 (63)	1 (63)	++ (64)	++ (65,66)	+ (25,67)	++ (64)	++ (67)	+++ (63)	++ (68)	42	56
Flurazepam *Dalmane and others*	BZ/$GABA_A$	74 (1)	1 (28)	++ (3)	…	+ (24,37,38,62)	++ (m)	++ (m)	+++ (69)	++ (y)	38	56
Zolpidem *Ambien*	BZ/$GABA_A$ α_1 selective	2.5 (53)	1.6 (53)	++ (3,70)	+ (25,59,71,72) (r)	+ (25,67,73)	++ (70,74)	++ (73)	+++ (59,71,72)	++ (y)	33	56
Estazolam *ProSom and others*	BZ/$GABA_A$	17 (48)	3 (48)	++ (3)	…	o (w)	++ (75)	++ (m)	+++ (z)	++ (y)	25	56
Oxazepam	BZ/$GABA_A$	8.0 (1)	2–4 (28)	…	+ (24,27,32,76,77) (p)	+ (24,27,78)	++ (m)	++ (m)	+++ (76)	++ (y)	25	56
Diphenhydramine *Benadryl and others*	H_1	8.5 (1)	2.3 (1)	++ (79)	+ (25,33,34) (s)	o (25,33,80)	…	+ (81)	++ (33)	++ (82–84)	25	42
Quazepam *Doral*	BZ/$GABA_A$ α_1 selective	39 (1)	2.5 (48)	+ (85)	…	o (w)	++ (m)	++ (m)	+++ (86)	++ (y)	13	56
Trazodone *Desyrel and others* (n)	5-HT and adrenergic α_1	6 (1)	2.0 (1)	…	o (72)	o (25,87)	…	++ (88,89)	+ (72)	++ (87,90)	0	42
Ramelteon *Rozerem*	MT_1 and MT_2	1–5 (91)	0.8 (91)	o (92)	o (93)	… (v)	o (94)	o (95,96)	o (93)	o (t)	0	0

*Methaqualone, flunitrazepam, and zopiclone are not approved by the US Food and Drug Administration for use in the United States.

Source: Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: A conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry*. 2005;66(suppl 9):31–41. Reprinted with permission.

a. Throughout the table, the number of "+" symbols indicates the degree to which the rated dimension was positive; "…" indicates no information available for that drug. Within a column, scores can vary from "**o**" (none) to "++++." A score of "++++" is assigned to the drug(s) that is judged, on the basis of available evidence, to be greatest on that dimension within a column. References and footnotes provide the rationale for the relative ratings of the dimensions as well as key citations to other relevant literature.

b. Pharmacologic and behavioral dimensions relevant to the relative abuse and toxicity of hypnotic drugs.

c. Likelihood of Abuse Score: For each drug in each of the 3 columns summarizing likelihood of abuse (columns 4–6), a numerical value of +1 for each "+" symbol was assigned; the percentage of the maximum score (ie, 4) was then calculated for each drug in each column. The overall Likelihood of Abuse Score is the mean score across the 3 columns for that drug, excluding columns for which no information was available for that drug. The Toxicity Score is calculated similarly for the 4 columns summarizing toxicity information.

d. Barb/$GABA_A$ = barbiturate site on the γ-aminobutyric acid-A ($GABA_A$) receptor complex; BZ/$GABA_A$ = benzodiazepine site on the $GABA_A$ receptor complex; BZ/$GABA_A$ α_1-selective = preferential binding at the benzodiazepine site of α_1-containing subtypes of the $GABA_A$ receptor complex; H_1 = histamine-1 receptor (antagonist); 5-HT = serotonin; MT_1 and MT_2 = melatonin 1 and 2 receptor subtypes.

e. Half-life = $t_{1/2}$ (elimination half-life) of drug or active metabolite; when only a range was available, the mean of the minimum and maximum values of the range is provided.

f. Peak time = t_{max} (time to peak blood concentration); when only a range was available, the mean of the minimum and maximum values of the range is provided.

g. Based on intravenous drug self-injection in nonhuman primates.[97]

h. Summarizes results from prospective double-blind studies in subjects with histories of drug abuse (see reference 98) with outcome measures of drug self-administration, choice, or subjective ratings of liking/disliking or positive/negative drug effects. Also summarized are retrospective questionnaire studies of drug abusers and drug abuse clinicians.

i. Provides an estimate of relative recreational abuse and nonmedical use based on drug abuse epidemiology data as well as from the frequency of case reports of recreational abuse in the medical literature. A ranking of "**o**" does not necessarily indicate a total absence of reports of abuse but indicates that the rate, relative to drug availability and to abuse of other drugs, is very low.

j. An estimate of the relative severity of withdrawal signs after abrupt termination of chronic dosing at supratherapeutic doses.

k. Indicates the relative behavioral or cognitive impairment after acute drug administration at supratherapeutic doses.

l. Indicates the relative likelihood of death after overdose with the drug alone or in combination with other sedatives.

m. Animal and human withdrawal from benzodiazepines is rated as intermediate based on numerous studies evaluating withdrawal from different benzodiazepines and the well-documented pharmacologic similarities among benzodiazepines. Reviews of this literature generally do not differentiate among benzodiazepines[69,99]; however, some reviews of human research have concluded that withdrawal severity and frequency and rebound insomnia are greater with rapidly eliminated benzodiazepines than with slowly eliminated benzodiazepines.[100,101]

n. Trazodone appears to have low efficacy as a hypnotic.[102]

o. Methaqualone produced severe physical dependence, although species and sex differences have been noted.[17,22,23]

p. Although oxazepam produces drug-liking and some drug reinforcement, in the table it is ranked lower among benzodiazepines because in prospective studies it produced less liking and choice than diazepam[27,76]; in prospective studies, high doses produced peak liking ratings that were delayed up to 8 hours after drug administration[76]; in retrospective studies of polydrug abusers, it was the benzodiazepine that was least likely to be used "to get high or to sell"[24,32]; and drug abuse clinicians identify its liking or abuse liability as particularly low among the benzodiazepines.[24,77]

q. Although triazolam was, for a time, the most widely prescribed hypnotic in the world, there are only a few reports documenting abuse.[24,60–62]

r. Although zolpidem produces drug-liking similar to triazolam, in the table it is ranked lower because in prospective studies it also produced a profile of somatic symptoms (queasy, emesis, dizzy)[59,71,72] that may decrease its likelihood of abuse, and in a retrospective study of polydrug abusers it was less likely than diazepam and nitrazepam to be liked.[25]

s. Although, like lorazepam, diphenhydramine produced liking and reinforcement,[33,34] it did so less reliably[33] and also produced a profile of unpleasant somatic symptoms.[33,34] In retrospective questionnaires, it produced less liking than zolpidem and temazepam.[25]

t. In an oral escalating-dose acute toxicity study in monkeys, the lethal oral dose of ramelteon was greater than 2000 mg/kg (Takeda Chemical Industries, personal communication, July 2005).

u. The dose-effect function with GHB appears steeper than that for other hypnotics, including pentobarbital, thus increasing the risk of inadvertent overdose.[42]

v. Although there are apparently no reports of recreational abuse of this compound, a meaningful estimate of relative abuse is not possible because of the relatively short duration of clinical availability of this compound.

w. To our knowledge, there are no published reports of abuse of quazepam or estazolam.

x. This rating for eszopiclone [which is the (*S*)-isomer of zopiclone] is estimated to be identical to that for zopiclone on the basis of strikingly similar behavioral profiles of eszopiclone and zopiclone.[103,104]

y. Animal and human studies of benzodiazepine receptor agonists indicate a remarkable safety profile when administered alone, with the lethal dose being hundreds or thousands of times the therapeutic dose.[99,105–107]

z. The acute sedative and memory impairing effects of estazolam are assumed to be identical to classic benzodiazepine hypnotics on the basis of the common mechanism of action.

aa. Methaqualone was first marketed in the United States in 1965. In the United States, in response to significant abuse, it was moved to Schedule II in 1973 and to Schedule I in 1984. Methaqualone abuse remains a significant public health problem in some countries.[108]

bb. Although diazepam is not officially approved for use as a hypnotic, it is included as a comparator because it is a frequently abused benzodiazepine sedative, it is efficacious as a hypnotic, and off-label use as a hypnotic occurs.[109,110]

cc. Although respiration is well-maintained in GHB anesthesia, deaths attributable to GHB, most often in combination with other drugs, have been reported.[43,47] It seems likely that the steep dose-effect profile with GHB[42] and the variability of the dose concentration of GHB on the illicit market contribute to the risk of inadvertent overdose death.

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Abuse Potential of Sleeping Agents: Liability Varies Among Agents *Continued from page 1*

that is inconsistent with accepted medical practice and demonstrated therapeutic efficacy). Although recent studies suggest that some hypnotics may have long-term efficacy, the benefits and risks (eg, memory impairment, increased risks of accidents and falls) of such chronic use have not been adequately explored.[13] With chronic use, patients may report that the hypnotic is ameliorating their symptoms; however, it is important to recognize that patients are unlikely able to distinguish between their original symptoms versus the emergence of phenomenologically similar withdrawal symptoms (ie, rebound insomnia). Patients may be unable to quit and may continue to use the medication to relieve or avoid withdrawal symptoms. This type of use often occurs at therapeutic doses, but it can involve dose escalation and visits to multiple physicians to obtain prescriptions. Quasitherapeutic abuse of sedative/hypnotic drugs occurs in patients with and without histories of alcohol or drug abuse, but it is more likely to develop among substance abusers, elderly patients, or patients treated for chronic pain.[14]

A 1990 survey by Balter and Ulenhuth in the United States revealed that 14% of people taking hypnotic agents during the previous year had taken these agents daily for longer than a year,[15] despite product labeling indicating that these hypnotics should be prescribed only on a short-term basis. Similarly, surveys in western Europe showed that 72% of current users of hypnotic agents had been taking their medications for longer than a year.[16]

A second pattern of hypnotic abuse is referred to as recreational abuse. Typically, recreational users are males between 18 and 25 years of age who use drugs obtained illegally for the purpose of becoming intoxicated ("high").[14] Recreational abuse of benzodiazepines, especially diazepam and flunitrazepam among abusers of multiple drugs, is well documented.[13] This type of abuse usually involves individuals in the illicit drug culture (with attendant legal and health hazards) and is associated with overdose, memory impairment, risk of accidents, and withdrawal syndrome.[14]

Although this type of abuse is less common than the quasitherapeutic abuse, a US survey showed that 10% and 11% of high school seniors illicitly used barbiturates and tranquilizers, respectively, a slightly higher rate of abuse than that for MDMA ("Ecstasy") or cocaine.[17] Another survey found that 19% of Americans 18 years of age and older who used sedatives during the previous year fulfilled diagnostic criteria for dependence (addiction) or abuse; this rate of abuse is higher than that for marijuana, stimulants, pain killers, alcohol, tranquilizers, hallucinogens, and inhalants.[18]

Conclusion

Insomnia is a prevalent condition associated with significant morbidity, and the potential for dependence and abuse should not dissuade clinicians from prescribing sedative/hypnotic drugs when clinically indicated. A range of compounds that differ in their potential for problematic use and toxicity are available, now ranging from agents with virtually no likelihood of abuse (eg, ramelteon, trazodone) to those with varying degrees of likelihood of abuse and/or toxicity. A complete review of these characteristics is provided in the **Table** on page 3.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994;557.
2. American Academy of Sleep Medicine. *International Classification of Sleep Disorders Revised: Diagnostic and Coding Manual*. Westchester, Ill: American Academy of Sleep Medicine; 2001.
3. Hatoum HT, Kania CM, Kong SX, Wong JM, Mendelson WB. Prevalence of insomnia: A survey of the enrollees at five managed care organizations. *Am J Man Care*. 1998;4:79-86.
4. Leger D, Poursain B. An international survey of insomnia: Under-recognition and under-treatment of a polysymptomatic condition. *Curr Med Res Opin*. 2005;21:1785-1792.
5. Roth T, Roehrs T. Insomnia: Epidemiology, characteristics, and consequences. *Clin Cornerstone*. 2003;5:5-15.
6. Thase ME. Correlates and consequences of chronic insomnia. *Gen Hosp Psychiatry*. 2005;27:100-112.
7. Benca RM. Consequences of insomnia and its therapies. *J Clin Psychiatry*. 2001; 62(suppl 10):33-38.
8. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Med Rev*. 2002;6: 97-111.
9. Stoller MK. Economic effects of insomnia. *Clin Ther*. 1994;16:873-897.
10. Charney DS, Mihic SJ, Harris RA. Hypnotics and sedatives. In Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, ed 10*. New York, NY: McGraw-Hill; 2001; pp 399-428.
11. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry*. 2005;66:469-476.
12. National Institutes of Health. National Heart, Lung, and Blood Institute. Insomnia. NIH Publication No. 95-3801. October 2005. Available at: http://www.nhlbi.nih.gov/health/public/sleep/insomnia.pdf. Accessed January 15, 2006.
13. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: A conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry*. 2005;66(suppl 9):31-41.
14. Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals: Implications for problems of long-term use and abuse. *Psychopharmacology (Berl)*. 1997;134:1-37.
15. Woods JH, Katz JL, Winger G. Benzodiazepines: Use, abuse, and consequences. *Pharmacol Rev*. 1992;44:151-347.
16. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. *J Clin Psychiatry*. 2002;63:817-825.
17. Johnston LD, O'Malley PM, Bachman JG, et al. Overall teen drug use continues gradual decline, but use of inhalants rises. University of Michigan News and Information Services; Ann Arbor, Mich; December 21, 2004. Available at: www.monitoringthefuture.org. Accessed Aug 5, 2005.
18. Substance Abuse and Mental Health Services Administration. Results from the 2003 National Survey on Drug Use and Health: National Findings. (DHHS Publication No. 04 3964). Rockville MD: Department of Human and Health Services, 2004.

Table. Relative Abuse Liability of Hypnotic Drugs *Continued from page 3*

References

1. Hardman GJ, Limbird LE. Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY:McGraw-Hill; 2001.
2. Roache JD. *J Pharmacol Exp Ther*. 1985; 234:120–133.
3. Griffiths RR. *Psychopharmacology* (Berl) 1997;134:1–37.
4. Yanagita T. *J Pharmacol Exp Ther*. 1973;185:307–316.
5. de Wit H. *Drug Alcohol Depend*. 1991;28:83–111.
6. Griffiths RR. *J Pharmacol Exp Ther*. 1979;210:301–310.
7. Griffiths RR. *J Pharmacol Exp Ther*. 1980;215:649–661.
8. Isbell H. *J Pharmacol Exp Ther*. 1950; 99:355–397.
9. Griffiths RR. In: *Advances in Substance Abuse, Behavioral and Biological Research*, vol 1. Greenwich, Conn: JAI Press; 1980:1–90.
10. Essig CF. In: *The Addictive States*. Baltimore, Md: Williams & Wilkins; 1968:188–198.
11. Yanagita T. *J Pharmacol Exp Ther*. 1970;172:163–169.
12. Fraser HF. In: Martin WR, ed. *Drug Addiction-I Morphine, Sedative/Hypnotic and Alcohol Dependence*. New York, NY: Springer-Verlag; 1977:589–612.
13. Fraser HF. *AMA Arch Intern Med*. 1954; 94:34–41.
14. Harvey SC. In: Gilman AG, Goodman LS, eds. *The Pharmacological Basis of Therapeutics*. 6th ed. New York, NY: MacMillan Publishing;1980:339–375.
15. Fraser HF. *Ann Intern Med*. 1953;38: 1319–1325.
16. Hicks TP. *Can J Neurol Sci*. 1990;17: 30–34.
17. Yanagita T. *CIEA Preclin Rep*. 1976;2: 63–68.
18. Ionescu-Pioggia M. *Int Clin Psychopharmacol*. 1988;3:97–109.
19. Orzack MH. *Int J Addict*. 1988;23: 449–467.
20. Jasinski DR. In: US Dept Health, Education and Welfare Public Health Service. Alcohol, Drug Abuse and Mental Health Administration. Proceedings of the 39th Annual Scientific Meeting (CPDD);1977:133–168.
21. Falco M. *Int J Addict*. 1976;11: 597–610.
22. Suzuki T. *Pharmacol Biochem Behav*. 1988;30:483–488.
23. Yutrzenka GJ. *Drug Alcohol Depend*. 1990;26:9–17.
24. Griffiths RR. *J Clin Psychopharmacol*. 1990;10:237–243.
25. Jaffe JH. *Addiction*. 2004;99:165–173.
26. Fleischhacker WW. *Acta Psychiatr Scand*. 1986;74:80–83.
27. Griffiths RR. *J Pharmacol Exp Ther*. 1984;229:501–508.
28. Schutz H. In: *A Handbook. Basic Data, Analytical Methods, Pharmacokinetics and Comprehensive Literature*. New York, NY: Springer-Verlag; 1982.
29. Farre M. *Psychopharmacology (Berl)*. 1998;140:486–495.
30. Mintzer MZ. *Drug Alcohol Depend*. 1998;53:49–66.
31. Woods JH. J *Clin Psychopharmacol*. 1997;17(3 suppl 2):1S–57S.
32. Iguchi MY. *Drug Alcohol Depend*. 1993; 32:257–266.
33. Preston KL. *J Pharmacol Exp Ther*. 1992; 262:707–720.
34. Mumford GK. *Exp Clin Psychopharmacol*. 1996;4:421–430.
35. Roache JD. *J Pharmacol Exp Ther*. 1987; 243:978–988.
36. Funderburk FR. *Drug Alcohol Depend*. 1988;22:215–222.
37. Wolf B. In: Harris LS, ed. *Problems of Drug Dependence*, 1989. Washington, DC: Government Printing Office; 1990. NIDA Research Monograph No. 95.
38. Ladewig D. *Pharmacopsychiatry*. 1988; 21:104–108.
39. *Physicians' Desk Reference*. 58th ed. Montvale, NJ: Thompson PDR; 2004.
40. Beardsley PM. *Psychopharmacology (Berl)*. 1996;127:315–322.
41. Woolverton WL. *Drug Alcohol Depend*. 1999;54:137–143.
42. Richards BD. Presented at the 67th Annual Meeting of the College of Problems on Drug Dependence; June 18–23, 2005;Orlando, Fla.
43. Nicholson KL. *Drug Alcohol Depend*. 2001;63:1–22.
44. Gonzalez A. *J Psychopharmacol*. 2005;19: 195–204.
45. Weerts EM. *Psychopharmacology (Berl)*. 2005;179:678–687.
46. McDonough M. *Drug Alcohol Depend*. 2004;75:3–9.
47. Timby N. *Am J Med*. 2000;108: 518–519.
48. Schutz H. In: *A Handbook. Basic Data, Analytical Methods, Pharmacokinetics and Comprehensive Literature*. New York, NY: Springer-Verlag; 1989.
49. Johanson CE. *NIDA Res Monogr*. 1986; 67:98–104.
50. Breen CL. *Med J Aust*. 2004;181:300–304.
51. Farrell M. *BMJ*. 1988;297:1402.
52. Rush CR. *J Clin Psychopharmacol*. 1996;16:146–157.
53. *Physicians' Desk Reference*. 59th ed. Montvale, NJ: Thompson PDR; 2005.
54. Ator NA. *Drug Alcohol Depend*. 2000;61:55–68.
55. Rush CR. *Psychopharmacology (Berl)*. 1999;145:39–51.
56. Ator NA. *Drug Alcohol Depend*. 2000; 61:69–84.
57. *Physicians' Desk Reference*. 59th ed. Supplement A. Montvale, NJ: Thompson PDR; 2005.
58. Lunesta [package insert]. Malborough, Mass: Sepracor; 2005. Available at: http://www.lunesta.com/postedapprovedlabelingtext.pdf. Accessed August 22, 2005.
59. Evans SM. *J Pharmacol Exp Ther*. 1990; 255:1246–1255.
60. Martinez-Cano H. *Acta Psychiatr Scand*. 1993;88:286–288.
61. Fleming JA. *Can Med Assoc J*. 1983; 129:324–325.
62. Substance Abuse and Mental Health Services Administration. Results from the 2003 National Survey on Drug Use and Health: National Findings. Rockville, Md; 2004. Office of Applied Studies, NSDUH Series H-25, DHHS Publication SMA 04-3964.
63. Goa KL. *Drugs*. 1986;32:48–65.
64. Yanagita T. *Int Pharmacopsychiatry*. 1982;17(suppl 2):216–227.
65. Bechelli LP. *Pharmacology*. 1982;27 (suppl 2):235–241.
66. Boissl K. *Pharmacology*. 1982;27(suppl 2): 242–247.
67. Hajak G. *Addiction*. 2003;98:1371–1378.
68. Reith DM. *J Toxicol Clin Toxicol*. 2003; 41:975–980.
69. Woods JH. *Pharmacol Rev*. 1987;39: 251–413.
70. Weerts EM. *Behav Pharmacol*. 1998;9: 285–297.
71. Mintzer MZ. *Behav Pharmacol*. 1998;9: 545–559.
72. Rush CR. *Psychopharmacology (Berl)*. 1999;144:220–233.
73. Soyka M. *Pharmacopsychiatry*. 2000;33: 138–141.
74. Weerts EM. *J Pharmacol Exp Ther*. 1998;285:41–53.
75. Yanagita T. *CIEA Preclin Rep*. 1976;2: 35–39.
76. Griffiths RR. *Psychopharmacology (Berl)*. 1984;84:147–154.
77. Bliding A. *Acta Psychiatr Scand Suppl*. 1978;274:111–116.
78. Bergman U. *Drug Alcohol Depend*. 1986; 16:293–301.
79. Sannerud CA. *Exp Clin Psychopharmacol*. 1995;3:26–32.
80. Halpert AG. *Neurosci Biobehav Rev*. 2002;26:61–67.
81. de Nesnera AP. *J Clin Psychiatry*. 1996; 57:136–137.
82. Koppel C. *J Toxicol Clin Toxicol*. 1987; 25:53–70.
83. Karch SB. *Am J Forensic Med Pathol*. 1998;19:143–147.
84. Radovanovic D. *Hum Exp Toxicol*. 2000;19:489–495.
85. Yanagita T. *Clin Neuropharmacol*. 1985; 8(suppl 1):S118–S122.
86. Rush CR. *Exp Clin Psychopharmacol*. 1999;7:257–265.
87. James SP. *J Clin Psychiatry*. 2004;65: 752–755.
88. Otani K. *Int Clin Psychopharmacol*. 1994;9:131–133.
89. Wolfe RM. *Am Fam Physician*. 1997;56:455–462.
90. Gamble DE. *J Clin Psychiatry*. 1986;47: 544–546.
91. Rozerem [package insert]. Lincolnshire, Ill: Takeda Pharmaceuticals America; 2005. Available at: http://www.rozerem.com/images/PI.pdf. Accessed February 10, 2006.
92. Nishida N. *Sleep*. 2005;28(suppl):A45.
93. Johnson MW. Presented at the 67th Annual Meeting of the College of Problems on Drug Dependence; June 18–23, 2005; Orlando, Fla.
94. France CP. *Sleep*. 2005;28(suppl):A45.
95. Roth T. *J Am Geriatr Soc*. 2005;53(suppl 4):S25.
96. Zammit G. Presented at the 158th Annual Meeting of the American Psychiatric Association; May 21–26, 2005; Atlanta, Ga. Abstract NR613.
97. Ator NA. *Drug Alcohol Depend*. 2003; 70:S55–S72.
98. Griffiths RR. *Drug Alcohol Depend*. 2003;70:S41–S54.
99. Woods JH. *Pharmacol Rev*. 1992;44: 151-347.
100. Wolf B. *Drug Alcohol Depend*. 1991;29: 153–156.
101. Kales A. *Clin Pharmacol Ther*. 1986; 40:378–386.
102. Mendelson WB. *J Clin Psychiatry*. 2005; 66:469–476.
103. McMahon LR. *Psychopharmacology (Berl)*. 2003;165:222–228.
104. Carlson JN. *Eur J Pharmacol*. 2001;415: 181–189.
105. Haefely W. In: Smith DE, Wesson DR, eds. *The Benzodiazepines: Current Standards for Medical Practice*. Boston, Mass: MTP Press Limited; 1985:7–41.
106. Buckley NA. *Drug Saf*. 2004;27: 135–141.
107. Garnier R. *J Toxicol Clin Toxicol*. 1994; 32:391–404.
108. McCarthy G. *Cochrane Database Syst Rev*. 2005;18:CD004146.
109. Kales A. *J Clin Psychopharmacol*. 1988; 8:340–346.
110. Nicholson AN. *Br J Clin Pharmacol*. 1979;7:463–468.

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