

Relative Abuse Liability of Hypnotic Drugs: A Conceptual Framework and Algorithm for Differentiating Among Compounds

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Hypnotic drugs, including benzodiazepine receptor ligands, barbiturates, antihistamines, and melatonin receptor ligands, are useful in treating insomnia, but clinicians should consider the relative abuse liability of these drugs when prescribing them. Two types of problematic hypnotic self-administration are distinguished. First, recreational abuse occurs when medications are used purposefully for the subjective “high.” This type of abuse usually occurs in polydrug abusers, who are most often young and male. Second, chronic quasi-therapeutic abuse is a problematic use of hypnotic drugs in which patients continue long-term use despite medical recommendations to the contrary. Relative abuse liability is defined as an interaction between the relative reinforcing effects (i.e., the capacity to maintain drug self-administration behavior, thereby increasing the likelihood of nonmedical problematic use) and the relative toxicity (i.e., adverse effects having the capacity to harm the individual and/or society). An algorithm is provided that differentiates relative likelihood of abuse and relative toxicity of 19 hypnotic compounds: pentobarbital, methaqualone, diazepam, flunitrazepam, lorazepam, GHB (γ -hydroxybutyrate, also known as sodium oxybate), temazepam, zaleplon, eszopiclone, triazolam, zopiclone, flurazepam, zolpidem, oxazepam, estazolam, diphenhydramine, quazepam, trazodone, and ramelteon. Factors in the analysis include preclinical and clinical assessment of reinforcing effects, preclinical and clinical assessment of withdrawal, actual abuse, acute sedation/memory impairment, and overdose lethality. The analysis shows that both the likelihood of abuse and the toxicity vary from high to none across these compounds. The primary clinical implication of the range of differences in abuse liability is that concern about recreational abuse, inappropriate long-term use, or adverse effects should not deter physicians from prescribing hypnotics when clinically indicated.

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Insomnia is a common medical condition that is associated with significant morbidity and public health burden.¹ Although hypnotic medications have proven quite useful in the treatment of insomnia, the issues of abuse (i.e., nonmedical use) and toxicity (e.g., withdrawal, falls, motor/cognitive impairment, and lethality in overdose) have been of concern to prescribing physicians as well as to patients. This article describes 2 types of problematic

self-administration of hypnotic drugs and a conceptual framework for understanding relative abuse liability. An analysis is then provided that differentiates the relative likelihood of abuse and relative toxicity of 19 hypnotic compounds. A final section discusses the clinical implications of differences in abuse liability.

TWO TYPES OF PROBLEMATIC SELF-ADMINISTRATION OF HYPNOTICS

Table 1² outlines and contrasts the distinguishing features of 2 types of problematic self-administration of hypnotics: recreational abuse and quasi-therapeutic abuse. Although the term “abuse” is most commonly applied to the former, it is important to recognize that both represent inappropriate (i.e., outside of accepted medical practice) drug self-administration significantly determined by the common mechanism of drug reinforcement. Thus in the current article, the term *abuse* is defined as nonmedical use, which is different from the definition of *substance abuse* provided by the American Psychiatric Association for diagnostic purposes.³

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Table 1. Characteristics of 2 Types of Problematic Self-Administration of Hypnotic Drugs^a

Characteristic	Recreational Abuse	Chronic Quasi-Therapeutic Abuse
Description	Intermittent or chronic use of high doses, often in a pattern of polydrug abuse	Long-term use by patients that is inconsistent with accepted medical practice
Example	Large doses of diazepam or flunitrazepam used in combination with opioids or alcohol	Nightly use of triazolam as hypnotic for years despite physician's recommendation to the patient that the medication be stopped
Population	Polydrug abusers; often young and male	Patients with and without histories of alcohol or drug abuse, with the former being over-represented; elderly and chronic pain patients are also over-represented
Motive for use	To get "high" (alcohol-like intoxication)	Patients often report that a motive for use is to treat insomnia; patients may report unsuccessful efforts to cut down use and use to relieve or avoid withdrawal
Route of administration	Usually oral, but sometimes intranasal or intravenous	Oral
Dose level	Higher than usual therapeutic doses	Therapeutic doses
Pattern of use	Intermittent or chronic, but most often intermittent	Chronic
Source of drug	Often illicit	Often licit, however may involve deception of prescriber to obtain drug (eg, multiple physicians)
Incidence	Relatively rare compared to the rate of prescription, but similar to abuse of other illicit substances such as opioids or cocaine	Relatively prevalent compared to the rate of prescription
Problems	Involvement in illicit drug culture with associated legal and health risks; overdose; memory impairment; risk of accidents; withdrawal syndrome	Memory impairment; risk of accidents; falls and hip fractures in elderly; withdrawal syndrome

^aAdapted with permission from Griffiths and Weerts.²

Recreational Abuse

Recreational abuse of hypnotics is nonmedical use for purposes of becoming intoxicated or "high."² An example of this type of abuse would be the use of a large dose of pentobarbital, flunitrazepam, or diazepam, perhaps in combination with opioids or alcohol. Recreational abusers are typically young males between 18 and 25 years old who usually obtain their hypnotics illicitly. Popular abused hypnotics are readily available for illicit purchase "on the street." The problems associated with recreational abuse include involvement in the illicit drug culture (with the attendant legal and health risks), overdose, memory impairment, risk of accidents, and a withdrawal syndrome.

Recreational abuse of sedatives, particularly the benzodiazepines diazepam and flunitrazepam, has been a particular problem in selected populations such as methadone maintenance patients and intravenous drug abusers.^{2,4,5} Furthermore, there have been localized outbreaks of significant abuse of specific hypnotics such as GHB (γ -hydroxybutyrate, also known as sodium oxybate)^{6,7} and flunitrazepam (see reference 8) in recent years. On a population basis, the incidence of recreational abuse of sedatives/hypnotics and related drugs is relatively rare, but it is similar to the incidence of abuse of other illicit substances. For example, in a 2004 survey of high school seniors in the United States, 10% and 11% of students reported illicit use of sedatives (barbiturates) and tranquilizers, respectively.⁹ For comparison, this rate of abuse is somewhat higher than that reported for either MDMA (3,4-methylenedioxymethamphetamine [ecstasy]) or cocaine in the same survey. The 2003 National Survey on Drug Use and Health¹⁰ found that 4.4% and 9.1% of individuals 18 years or older in the

United States reported lifetime illicit use of sedatives and tranquilizers, respectively. This same survey showed 19% of past year sedative users fulfilled diagnostic criteria for dependence (i.e., addiction) or abuse, which is a rate higher than that for marijuana, stimulants, pain relievers, alcohol, tranquilizers, hallucinogens, or inhalants.

Chronic Quasi-Therapeutic Abuse

Table 1 also outlines a second type of problematic self-administration of hypnotics (i.e., chronic quasi-therapeutic abuse) that is characterized by long-term drug-taking by patients for a duration that is inconsistent with accepted medical practice.² An example would be nightly use of triazolam for years as a hypnotic despite the physician's recommendation that medication be stopped. Although patients may insist that the drug is continuing to function as an excellent hypnotic, it is important to recognize that they are unlikely to be able to distinguish between the reemergence of their original symptoms versus the emergence of phenomenologically similar withdrawal symptoms (i.e., rebound insomnia). This type of problematic use occurs in patients with and without histories of alcohol or drug abuse, but it is more likely in substance abusers. The elderly and patients being treated for pain also have elevated rates of chronic quasi-therapeutic abuse. This form of problematic use is associated with memory impairment; an increased risk of accidents, falls, and hip fractures in the elderly; and a withdrawal syndrome.

In contrast to recreational abuse, chronic quasi-therapeutic abuse is relatively prevalent in the general population. A 1990 survey in the United States^{11(p270)} found that 14% of past-year hypnotic users had taken the medica-

tion daily for more than 12 months. Notably, surveys during the 1990s¹² from France, Germany, Italy, and United Kingdom showed that 72% of *current* hypnotic users had been taking their medications for more than 12 months. Long-term users of hypnotics also account for most of the hypnotics consumed.²

Until recently, the U.S. Food and Drug Administration (FDA) required labeling of prescription hypnotics to indicate that hypnotics be used only on a short-term basis (e.g., 7 to 10 days). Recent studies^{13,14} suggest that some hypnotics may have long-term efficacy, but more research examining the risks and benefits of long-term use is needed.^{1,15,16}

DETERMINANTS OF RELATIVE ABUSE LIABILITY

Abuse liability refers to the likelihood that a drug with central nervous system effects will sustain patterns of non-medical self-administration that result in disruptive or undesirable consequences.¹⁷ It is important to recognize that the commonly used concept of relative abuse liability¹⁸ refers to both the liability *for* abuse (i.e., the likelihood that a drug will be abused) and the liability *of* abuse (i.e., the untoward or toxic effects of using the drug nonmedically).

These 2 senses of the term *abuse liability* correspond to 2 major characteristics of drugs of abuse. First, all drugs of abuse have reinforcing effects. That is, they have the capacity to maintain drug self-administration behavior, thereby increasing the likelihood of nonmedical problematic use. Second, in addition to maintaining self-administration, drugs of abuse produce adverse or toxic effects and thus they have the capacity to harm the individual and/or society.

Both the likelihood of abuse and the toxicity are inextricably intertwined in the lay understanding of relative abuse liability as well as embedded within the guidelines by which regulatory agencies such as the FDA, the Drug Enforcement Administration, and the World Health Organization formulate decisions about relative abuse potential and scheduling of drugs. The relative abuse liability of a compound is an interactive function of the degree of reinforcing effects and adverse effects.

Reinforcing Effects

Reinforcing effects are the primary determinant of abuse liability because they are a major determinant of whether a drug will be used in some socially unapproved fashion (i.e., abused). A nontherapeutic drug devoid of reinforcing effects but producing significant adverse effects should be considered to be a poison, not a drug of abuse (e.g., cyanide).

For hypnotic drugs, the reinforcing effects or likelihood of abuse can be assessed both in laboratory animals and in humans using drug self-administration procedures. Pre-clinical drug self-administration models¹⁹ have been widely investigated and are well validated. These models

provide replicable data about whether or not a drug can function as a reinforcer. In general, there is a good correspondence between those drugs self-administered by laboratory animals and those that are self-administered and abused by humans.^{2,19,20}

Although human drug self-administration and choice methods have been used to differentiate among hypnotics, this time-consuming approach may be impractical for comparing drugs over a range of doses. A more efficient and common approach is to thoroughly characterize under double-blind conditions the subjective effects profile of single administrations of a drug in subjects with histories of sedative drug abuse.²¹ Typically, a known drug of abuse and a novel compound are compared over a range of doses. Subjective effect measures that are used to infer the degree of behavioral reinforcement include ratings of liking/disliking, good/bad effects, disposition to take the drug again, amount of money that the subject would be willing to pay for the drug, and estimated monetary value that the drug would be worth on the street.²¹

A less rigorous but nonetheless useful indirect source of information about reinforcing effects is retrospective survey studies of polydrug abusers. Drawing on their past experience with the drugs, subjects are typically asked to rate subjective liking, "high," street value, and disposition to take again.²²⁻²⁴

Adverse or Toxic Effects

Adverse effects are of secondary importance in determining abuse liability. Common adverse effects associated with many hypnotics include a withdrawal syndrome, overdose toxicity, psychomotor impairment and risk of falls, memory and cognitive impairment, and interactions with alcohol. For hypnotics, a withdrawal syndrome after termination of chronic dosing is often considered an important secondary determinant of abuse liability because, in addition to the discomfort and health risks of withdrawal, some withdrawal symptoms (e.g., insomnia, anxiety) can potentiate the reinforcing effects. For example, chronic self-administration of a hypnotic may be maintained because the individual experiences significant rebound insomnia if he/she does not take the drug. Symptoms of withdrawal following therapeutic doses of benzodiazepines and other hypnotics include anxiety, insomnia, irritability, tremor, muscle twitching, headache, gastrointestinal disturbance (anorexia and nausea), depersonalization, perceptual changes (paresthesias and hypersensitivity to light and noise), and, in rare cases, psychosis or seizure.²⁵⁻²⁸

COMPARATIVE LIKELIHOOD OF ABUSE AND TOXICITY AMONG HYPNOTICS

Table 2 (appears at the end of this article) summarizes information on pharmacology, relative likelihood of abuse, and relative toxicity for 19 hypnotic compounds, most of

which are available in the United States. The first 3 columns provide basic pharmacologic information about molecular site of action, half-life, and peak time. Columns 4–10 provide relative ratings of several dimensions proposed as definitional of likelihood of abuse and toxicity for hypnotics. The footnotes and references in the table provide the rationale and algorithm for calculating the relative ratings of the dimensions and an explanation of derived scores. It is beyond the scope of this article to provide detailed explanations for ratings in each table cell; however, the cited references provide key citations to relevant literature.

Likelihood of Abuse

Columns 4–6 provide information relevant to estimating the likelihood of abuse. Specifically, column 4 (animal drug self-administration) rates the degree to which a compound functions as a reinforcer in drug self-administration studies conducted in nonhuman primates (cf. preceding section: Reinforcing Effects).

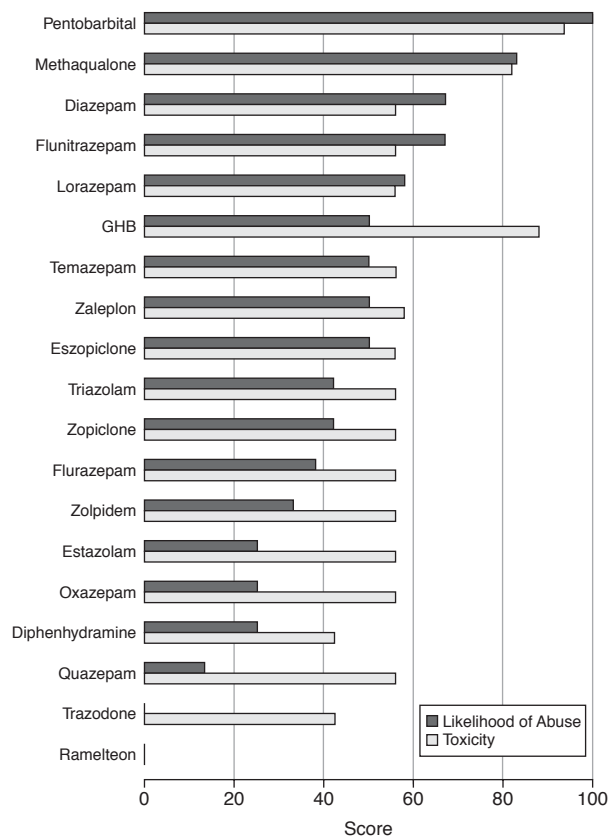
Column 5 (human liking/reinforcement) summarizes results from 2 types of human studies that reflect drug reinforcement and/or subjective drug liking: (1) prospective double-blind studies conducted in subjects with histories of drug abuse and assessing drug self-administration, drug choice, or ratings of liking/disliking or positive/negative subjective effects²¹ and (2) retrospective questionnaire studies of drug abusers and drug abuse clinicians who rate relative liking or preference for hypnotics based on abusers' past histories of exposure to these compounds.

Column 6 (actual abuse) provides an estimate of the relative rate of nonmedical use and recreational abuse of the individual hypnotics based on epidemiologic survey data and on case reports of abuse in the medical literature.

The second to last column in Table 2 provides an overall likelihood of abuse score for each of the hypnotic drugs based on the information in column 4 (animal drug self-administration), column 5 (human liking/reinforcement), and column 6 (actual abuse). For each drug in each of the 3 columns, the percentage of the maximum score (+4) was calculated. The overall mean likelihood of abuse score is the mean percentage across the 3 columns (see table footnote).

Based on this analysis, Figure 1 shows that the relative likelihood of abuse scores of the 19 hypnotic compounds range from 100 for pentobarbital to 0 for trazodone and ramelteon. Interestingly, despite sharing a common molecular site of action, the 9 benzodiazepine compounds (diazepam, flunitrazepam, lorazepam, temazepam, triazolam, flurazepam, oxazepam, estazolam, quazepam) and the 4 nonbenzodiazepine compounds (zaleplon, eszopiclone, zopiclone, zolpidem) with activity at the benzodiazepine receptor binding site show a wide range of abuse liability scores, ranging from highs of 67 for diazepam and flunitrazepam to 13 for quazepam.

Figure 1. Relative Abuse Liability of 19 Hypnotic Drugs^a



^aAs 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 2 footnotes for details).

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

Also of interest is that the 3 compounds with actions not mediated through a GABA (γ -aminobutyric acid) receptor site are associated with a low likelihood of abuse (diphenhydramine, trazodone, and ramelteon). All 3 of these compounds produce an atypical profile of subjective effects, with diphenhydramine and trazodone producing greater adverse side effects than the classic hypnotics^{29,30} and ramelteon producing no detectable subjective effects at up to 20 times the recommended therapeutic dose.³¹

Other Toxic Consequences of Use

Columns 7–10 of Table 2 provide information for estimating the degree of drug-associated toxicity in addition to the self-administration itself. Specifically, columns 7 and 8 provide an estimate of the relative withdrawal severity after termination of chronic supratherapeutic doses. Column 9 indicates the relative degree of behavioral or cognitive impairment after acute administration of supratherapeutic doses, and column 10 indicates the relative likelihood of death after overdose.

Figure 1 and the last column in Table 2 provide an overall toxicity score for each of the hypnotic compounds based on the information from columns 7–10. Calculation of this overall toxicity score is analogous to that for the likelihood of abuse score. The relative toxicity scores range from 94% for pentobarbital to 0% for ramelteon. Pentobarbital, methaqualone, and GHB (also known as sodium oxybate) are notable because supratherapeutic doses are more likely to be lethal with these drugs than with any of the other hypnotics. Most of the other hypnotics produce intermediate toxicity. Ramelteon is the notable exception in that it produced no detectable motor or cognitive impairment at up to 20 times the recommended therapeutic dose.³¹

CLINICAL IMPLICATIONS OF DIFFERENCES IN ABUSE LIABILITY AMONG HYPNOTICS

Concern about possible recreational abuse, inappropriate chronic use, and withdrawal are major deterrents to physicians prescribing hypnotics and to patients. Because the risk of abuse or problematic use of hypnotic drugs is significantly elevated among patients with histories of drug or alcohol abuse or dependence,² physicians are strongly discouraged from prescribing hypnotics to these patients. This caution is repeated throughout the pharmacologic and medical scholarly literature.^{32–34} For example, the *Physicians' Desk Reference* entry for zolpidem recommends that, "Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or *any other hypnotic*"^{35(p2982)} (italics added). Jindal and colleagues³⁶ "recommend[ed] that benzodiazepine receptor agonists be used very cautiously, if at all, in patients with any history of substance abuse." The advice to deny hypnotic treatment to patients with histories of substance abuse is impractical given that patients may be unwilling to disclose such information and the large number of people in the population who have such histories. For example, the 2003 National Survey on Drug Use and Health³⁷ found that, among individuals 12 years or older in the United States, 46% had lifetime use of illicit drugs and 9% fulfilled a diagnosis of abuse of or dependence on illicit drugs or alcohol within the past year. In addition to a history of substance abuse or dependence, groups at risk for the development of problematic hypnotic use include the elderly and patients with chronic pain.²

Given the large portion of the general population at risk for development of problematic hypnotic use, it is understandable that physicians are hesitant to readily prescribe such compounds. However, insomnia is a prevalent condition associated with significant morbidity.¹ The primary implication of the wide differences in abuse liability among hypnotic drugs (as illustrated in Figure 1) is that

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 and a thorough medical history, physicians may choose from a range of compounds that differ in their potential for problematic use and toxicity. Choice among specific compounds not only should depend on the clinician's assessment of the vulnerability of the patient for nonmedical use, but also should take into account other drug characteristics that may be important for optimal treatment of the individual patient (e.g., speed of onset, duration of action, likelihood of next-day carry-over effects).

Available hypnotics range from compounds with virtually no likelihood of abuse (e.g., ramelteon, trazodone) to those with varying degrees of both likelihood of abuse and other toxicity. If a compound is selected that has some likelihood of abuse and if the clinician is concerned about the vulnerability of the particular patient to problematic use, then limited amounts of hypnotic medication should be dispensed to reduce the possibility of dose escalation or diversion into the illicit market. Such prescriptions should be restricted to the lowest effective dose for a limited duration. Intermittent use of hypnotics may also be an option³⁸ to help limit the amount of hypnotic prescribed.

Drug names: diazepam (Valium and others), diphenhydramine (Benadryl and others), estazolam (ProSom), eszopiclone (Lunesta), flurazepam (Dalmene and others), lorazepam (Ativan and others), pentobarbital (Nembutal), quazepam (Doral), ramelteon (Rozerem), temazepam (Restoril and others), trazodone (Desyrel and others), triazolam (Halcion), zaleplon (Sonata), and zolpidem (Ambien).

Disclosure of off-label usage: The authors have determined that substantial information is provided in this article about the abuse of drugs, which is outside U.S. Food and Drug Administration–approved labeling, and trazodone is not approved for the treatment of sleep disorders.

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Table 2 appears on page 37.

Table 2. 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 <i>Nembutal</i>	Barb/GABA _A	33 (1)	2-3 (2)	++++ (3,4)	++++ (5-7)	++++ (8-10)	++++ (11)	++++ (12,13)	+++ (2)	++++ (14,15)	100	94	
Methaqualone* <i>Quaalude</i> (aa)	GABA _A (presumed) (16)	30 (14)	2 (14)	++ (17)	++++ (18-20)	++++ (18,21)	++ (22,23) (c)	++++ (14)	+++ (14)	++++ (14)	83	81	
Diazepam <i>Valium and others</i> (bb)	BZ/GABA _A	43 (1)	1.3 (1)	++ (3)	+++ (6,7,24)	+++ (24-27)	++ (m)	++ (m)	+++ (27)	++ (y)	67	56	
Flunitrazepam* <i>Rohypnol</i>	BZ/GABA _A	14 (28)	2 (28)	++ (3)	+++ (29,30)	+++ (30,31)	++ (31) (m)	++ (31) (m)	+++ (30)	++ (y)	67	56	
Lorazepam <i>Ativan and others</i>	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) <i>Xyrem</i>	GHB and GABA _B	0.75 (39)	0.9 (39)	+ (40,41)	++ (42)	+++ (43,44)	++ (45)	++++ (46)	++++ (42)	++++ (43,47)	50	88	
Tenazepam <i>Restoril and others</i>	BZ/GABA _A	11 (1)	1.2 (48)	++ (49)	++ (25)	++ (25,50,51)	++ (m)	++ (m)	+++ (52)	++ (y)	50	56	
Zaleplon <i>Sonata</i>	BZ/GABA _A α ₁ selective	1 (53)	1 (53)	++ (54)	++ (55)	... (v)	++ (56)	... (v)	+++ (39)	++ (y)	50	58	
Eszopiclone <i>Lunesta</i>	BZ/GABA _A	6 (57)	1 (57)	++ (8)	++ (57)	... (v)	++ (8)	++ (8)	+++ (58)	++ (x)	50	56	
Triazolam <i>Halcion and others</i>	BZ/GABA _A	2.9 (1)	1.3 (1)	++ (3)	++ (55,59)	+ (24,60-62) (q)	++ (m)	++ (m)	+++ (2)	++ (y)	42	56	
Zopiclone* <i>Imovane</i>	BZ/GABA _A	5 (63)	1 (63)	++ (64)	++ (65,66)	+ (25,67)	++ (64)	++ (67)	+++ (63)	++ (68)	42	56	
Flurazepam <i>Dalmane and others</i>	BZ/GABA _A	74 (1)	1 (28)	++ (3)	... (69)	+ (24,37,38,62)	++ (m)	++ (m)	+++ (69)	++ (y)	38	56	
Zolpidem <i>Ambien</i>	BZ/GABA _A α ₁ selective	2.5 (53)	1.6 (53)	++ (3,70)	+ (25,59,71,72) (f)	+ (25,67,73)	++ (70,74)	++ (73)	+++ (59,71,72)	++ (y)	33	56	
Estazolam <i>ProSom and others</i>	BZ/GABA _A	17 (48)	3 (48)	++ (3)	... (71)	○ (w)	++ (75)	++ (m)	+++ (z)	++ (y)	25	56	
Oxazepam	BZ/GABA _A	8.0 (1)	2-4 (28)	... (72)	+ (24,27,32,76,77) (p)	+ (24,27,78)	++ (m)	++ (m)	+++ (76)	++ (y)	25	56	
Diphenhydramine <i>Benadryl and others</i>	H ₁	8.5 (1)	2.3 (1)	++ (79)	+ (25,33,34) (s)	○ (25,33,80)	... (81)	+	++ (33)	++ (82-84)	25	42	

continued

Table 2. Relative Abuse Liability of Hypnotic Drugs (a), cont.

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 (k)	Acute Sedation/Memory Impairment (l)	Lethality in Overdose (m)			
Quazepam <i>Doral</i>	BZ/GABA _A α ₁ selective	39 (1)	2.5 (48)	+	...	0	++	++	+++	++	++	13	56
Trazodone <i>Desyrel and others</i> (n)	5-HT and adrenergic α ₁	6 (1)	2.0 (1)	...	0	0	...	++	+	++	++	0	42
Ramelteon <i>Rozeren</i>	MT ₁ and MT ₂	1-5 (91)	0.8 (91)	0	0	...	0	0	0	0	0	0	0

*Methaqualone, flunitrazepam, and zopiclone are not approved by the U.S. Food and Drug Administration for use in the United States. 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 "0" (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.

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 "0" 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 benzo-

diazepines because in prospective studies it produced less liking and choice than diazepam^{77,76}; in prospective studies, high doses produced peak liking ratings that were delayed up to 8 hours after drug administration⁷⁶; 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)^{99,72} 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 reliably³³ 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

continued

Table 2. Relative Abuse Liability of Hypnotic Drugs (a), cont.

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 GHB⁴² 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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Table 2. Relative Abuse Liability of Hypnotic Drugs (a), cont.

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