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

Roland R. Griffiths, Ph.D., and Matthew W. Johnson, Ph.D.

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.

(J Clin Psychiatry 2005;66[suppl 9]:31–41)

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.

From the Department of Psychiatry (Drs. Griffiths and Johnson) and the Department of Neuroscience (Dr. Griffiths), Johns Hopkins University School of Medicine, Baltimore, Md.

This article is derived from the planning roundtable "Sleep: New Frontiers in Psychiatry and Primary Care," which was held March 18, 2005, in Chicago, Ill., and supported by an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc. Preparation of this article was supported in part by National Institute on Drug Abuse grant R01 DA03889.

The authors thank Nancy Ator, Ph.D., and Lawrence Carter, Ph.D., for helpful comments on the manuscript.

Corresponding author and reprints: Roland R. Griffiths, Ph.D., Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224 (e-mail: rgriff@jhmi.edu).

TWO TYPES OF PROBLEMATIC SELF-ADMINISTRATION OF HYPNOTICS

Table 1[2] 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]

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

[a]Adapted 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 Health[10] 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 1990s[12] 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 nonmedical self-administration that result in disruptive or undesirable consequences.[17] It is important to recognize that the commonly used concept of relative abuse liability[18] 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. Preclinical drug self-administration models[19] 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).

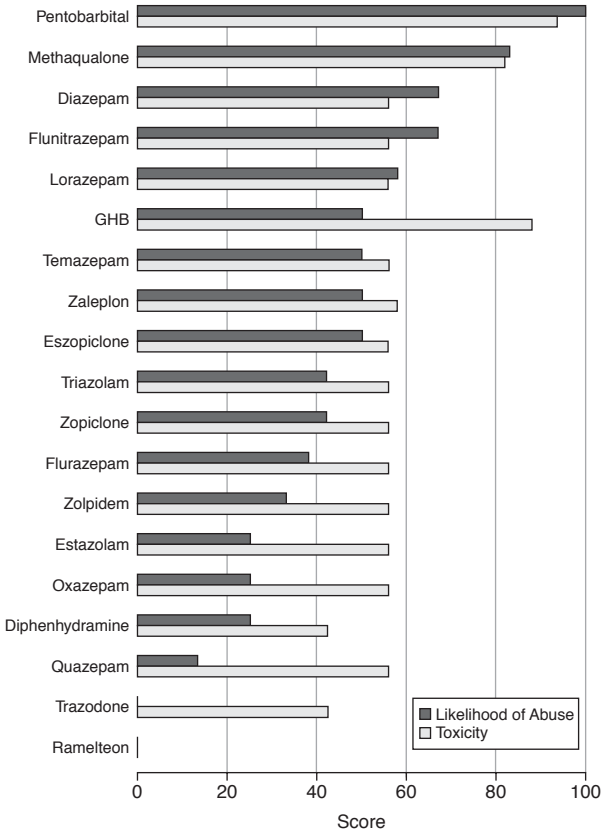
Column 5 (human liking/reinforcement) summarizes results from 2 types of human studies that reflect drug reinforcement and/or subjective drug liking: (1) prospective double-blind studies conducted in subjects with histories of drug abuse and assessing drug self-administration, drug choice, or ratings of liking/disliking or positive/negative subjective effects[21] 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]



[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 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 colleagues[36] "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 Health[37] 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 carryover 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 option[38] to help limit the amount of hypnotic prescribed.

Drug names: diazepam (Valium and others), diphenhydramine (Benadryl and others), estazolam (ProSom), eszopiclone (Lunesta), flurazepam (Dalmane 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.

REFERENCES

1. National Institutes of Health, NIH Consensus Development Program. NIH state-of-the-science conference statement on manifestations and management of chronic insomnia in adults. June 13–15, 2005. Available at: http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm. Accessed Sept 28, 2005
2. 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
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
4. Barnas C, Rossmann M, Roessler H, et al. Benzodiazepines and other psychotropic drugs abused by patients in a methadone maintenance program: familiarity and preference. J Clin Psychopharmacol 1992;12:397–402
5. Gelkopf M, Bleich A, Hayward R, et al. Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. Drug Alcohol Depend 1999;55:63–68
6. Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. Drug Alcohol Depend 2001;63:1–22
7. Gonzalez A, Nutt DJ. Gamma hydroxy butyrate abuse and dependency.

J Psychopharmacol 2005;19:195–204
8. Mintzer MZ, Griffiths RR. Flunitrazepam and triazolam: a comparison of behavioral effects and abuse liability. Drug Alcohol Depend 1998;53: 49–66
9. 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. Dec 21, 2004. Available at: www.monitoringthefuture.org. Accessed Aug 5, 2005
10. 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 No. SMA 04-3964
11. Balter MB, Uhlenhuth EH. Unpublished survey results. Cited by: Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse, and consequences. Pharmacol Rev 1992;44:151–347
12. 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
13. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep 2003;26: 793–799
14. Ancoli-Israel S, Richardson GS, Mangano RM, et al. Long-term use of sedative hypnotics in older patients with insomnia. Sleep Med 2005;6: 107–113
15. Lader MH. Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? Eur Neuropsychopharmacol 1999;9(suppl 6): S399–S405
16. Jindal RD, Buysse DJ, Thase ME. Maintenance treatment of insomnia: what can we learn from the depression literature? Am J Psychiatry 2004; 161:19–24
17. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend 2003;70: S13–S40
18. Griffiths RR, Lamb RJ, Ator NA, et al. Relative abuse liability of triazolam: experimental assessment in animals and humans. Neurosci Biobehav Rev 1985;9:133–151
19. Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. Drug Alcohol Depend 2003;70:S55–S72
20. 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
21. Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend 2003; 70:S41–S54
22. Griffiths RR, Wolf B. Relative abuse potential of different benzodiazepines in drug abusers. J Clin Psychopharmacol 1990;10:237–243
23. Iguchi MY, Handelsman L, Bickel WK, et al. Benzodiazepine and sedative use/abuse by methadone maintenance clients. Drug Alcohol Depend 1993;32:257–266
24. Jaffe JH, Bloor R, Crome I, et al. A postmarketing study of relative abuse liability of hypnotic sedative drugs. Addiction 2004;99:165–173
25. Fraser HF, Jasinski DR. The assessment of the abuse potentiality of sedative/hypnotics (depressants) (methods used in animals and man). In: Martin WR, ed. Drug addiction-I Morphine, Sedative/Hypnotic and Alcohol Dependence. New York: Springer-Verlag; 1977:589–612
26. Woods JH, Katz JL, Winger G. Abuse liability of benzodiazepines. Pharmacol Rev 1987;39:251–413
27. Schweizer E, Rickels K. Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. Acta Psychiatr Scand Suppl 1998;393:95–101
28. Gatzonis SD, Angelopoulos EK, Daskalopoulou EG, et al. Convulsive status epilepticus following abrupt high-dose benzodiazepine discontinuation. Drug Alcohol Depend 2000;59:95–97
29. Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. Psychopharmacology (Berl) 1999;144:220–233
30. Preston KL, Wolf B, Guarino JJ, et al. Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: evaluation of abuse liability. J Pharmacol Exp Ther 1992;262:707–720
31. 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 of Problems on Drug Dependence; June 18–23, 2005; Orlando, Fla
32. American Psychiatric Association Task Force on Benzodiazepine Dependency. Benzodiazepine Dependence, Toxicity, and Abuse. Washington, DC: American Psychiatric Association; 1990
33. Longo LP, Johnson B. Addiction, pt 1: benzodiazepines—side effects, abuse risk and alternatives. Am Fam Physician 2000;61. Available at: http://www.aafp.org/afp/20000401/2121.html. Accessed Aug 9, 2005
34. Clark RE, Xie H, Brunette MF. Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. J Clin Psychiatry 2004;65:151–155
35. Physicians' Desk Reference. 59th ed. Montvale, NJ: Thompson PDR; 2005
36. Jindal RD, Buysse DJ, Thase ME. Dr. Jindal and colleagues reply [letter]. Am J Psychiatry 2004;161:1723
37. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health, 2002 and 2003. Rockville, Md; 2005. Office of Applied Studies, NSDUH. Available at: http://oas.samhsa.gov/nhsda/2k3tabs/toc.htm#DU. Accessed Aug 8, 2005
38. Hajak G, Bandelow B, Zulley J, et al. "As needed" pharmacotherapy combined with stimulus control treatment in chronic insomnia—assessment of a novel intervention strategy in a primary care setting. Ann Clin Psychiatry 2002;14:1–7

Table 2 appears on page 37.

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

	Pharmacology (b)			Likelihood of Abuse (b)			Other Toxic Consequences (b)				Likelihood of Abuse Score, % of maximum (c)	Toxicity Score, % of maximum (c)
Drug	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

continued

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

	Pharmacology (b)			Likelihood of Abuse (b)			Other Toxic Consequences (b)					
Drug	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)	Likelihood of Abuse Score, % of maximum (c)	Toxicity Score, % of maximum (c)
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 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 "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 (i.e., 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

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 GHB[42] and the variability of the dose concentration of GHB on the illicit market contribute to the risk of inadvertent overdose death.

References

1. Hardman GJ, Limbird LE, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill; 2001
2. Roache JD, Griffiths RR. Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. J Pharmacol Exp Ther 1985;234:120–133
3. 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
4. Yanagita T, Takahashi S. Dependence liability of several sedative-hypnotic agents evaluated in monkeys. J Pharmacol Exp Ther 1973;185:307–316
5. de Wit H, Griffiths RR. Testing the abuse liability of anxiolytic and hypnotic drugs in humans. Drug Alcohol Depend 1991;28: 83–111
6. Griffiths RR, Bigelow G, Liebson I. Human drug self-administration: double-blind comparison of pentobarbital, diazepam, chlorpromazine and placebo. J Pharmacol Exp Ther 1979;210:301–310
7. Griffiths RR, Bigelow GE, Liebson I, et al. Drug preference in humans: double-blind choice comparison of pentobarbital, diazepam and placebo. J Pharmacol Exp Ther 1980;215:649–661
8. Isbell H, Fraser HF. Addiction to analgesics and barbiturates. J Pharmacol Exp Ther 1950;99:355–397
9. 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; 1980:1–90
10. Essig CF. Addiction to barbiturate and nonbarbiturate sedative drugs. In: The Addictive States. Baltimore, Md: Williams & Wilkins; 1968:188–198
11. Yanagita T, Takahashi S. Development of tolerance to and physical dependence on barbiturates in rhesus monkeys. J Pharmacol Exp Ther 1970;172:163–169
12. Fraser HF, Jasinski DR. The assessment of the abuse potentiality of sedative/hypnotics (depressants) (methods used in animals and man). In: Martin WR, ed. Drug Addiction-I Morphine, Sedative/ Hypnotic and Alcohol Dependence. New York, NY: Springer-Verlag; 1977:589–612
13. Fraser HF, Isbell H, Eisenman AJ, et al. Chronic barbiturate intoxication: further studies. AMA Arch Intern Med 1954;94:34–41
14. Harvey SC. Hypnotics and sedatives. In: Gilman AG, Goodman LS, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 6th ed. New York, NY: Macmillan Publishing; 1980:339–375
15. Fraser HF, Shaver MR, Maxwell ES, et al. Death due to withdrawal of barbiturates. Ann Intern Med 1953;38:1319–1325
16. Hicks TP, Kaneko T, Oka JI. Receptive-field size of S1 cortical neurones is altered by methaqualone via a GABA mechanism. Can J Neurol Sci 1989;17:30–34
17. Yanagita T, Miyasato K. Dependence potential of methaqualone tested in rhesus monkeys. CIEA Preclin Rep 1976;2:63–68
18. Ionescu-Pioggia M, Bird M, Orzack MH, et al. Methaqualone. Int Clin Psychopharmacol 1988;3:97–109
19. Orzack MH, Friedman L, Dessain E, et al. Comparative study of the abuse liability of alprazolam, lorazepam, diazepam, methaqualone, and placebo. Int J Addict 1988;23:449–467
20. Jasinski DR, Griffith JD, Pevnick J, et al. Progress report from the clinical pharmacology section of the NIDA Addiction Research Center. 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. Methaqualone misuse: foreign experience and United States drug control policy. Int J Addict 1976;11:597–610
22. Suzuki T, Koike Y, Misawa M. Sex differences in physical dependence on methaqualone in the rat. Pharmacol Biochem Behav 1988;30:483–488
23. Yutrzenka GJ, Patrick GA, Rosenberger W. Substitution of psychoactive drugs in pentobarbital-dependent rats. Drug Alcohol Depend 1990;26:9–17
24. Griffiths RR, Wolf B. Relative abuse potential of different benzodiazepines in drug abusers. J Clin Psychopharmacol 1990;10: 237–243
25. Jaffe JH, Bloor R, Crome I, et al. A postmarketing study of relative abuse liability of hypnotic sedative drugs. Addiction 2004;99:165–173
26. Fleischhacker WW, Barnas C, Hackenberg B. Epidemiology of benzodiazepine dependence. Acta Psychiatr Scand 1986;74:80–83
27. Griffiths RR, McLeod DR, Bigelow GE, et al. Comparison of diazepam and oxazepam: preference, liking and extent of abuse. J Pharmacol Exp Ther 1984;229:501–508
28. Schutz H. Benzodiazepines: A Handbook. Basic Data, Analytical Methods, Pharmacokinetics and Comprehensive Literature. New York, NY: Springer-Verlag; 1982
29. Farre M, Teran MT, Roset PN, et al. Abuse liability of flunitrazepam among methadone-maintained patients. Psychopharmacology (Berl) 1998;140:486–495
30. Mintzer MZ, Griffiths RR. Flunitrazepam and triazolam: a comparison of behavioral effects and abuse liability. Drug Alcohol Depend 1998;53:49–66
31. Woods JH, Winger G. Abuse liability of flunitrazepam. J Clin Psychopharmacol 1997;17(3, suppl 2):1S–57S
32. Iguchi MY, Handelsman L, Bickel WK, et al. Benzodiazepine and sedative use/abuse by methadone maintenance clients. Drug Alcohol Depend 1993;32:257–266
33. Preston KL, Wolf B, Guarino JJ, et al. Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: evaluation of abuse liability. J Pharmacol Exp Ther 1992;262: 707–720
34. Mumford GK, Silverman K, Griffiths RR. Reinforcing, subjective, and performance effects of lorazepam and diphenhydramine in humans. Exp Clin Psychopharmacol 1996;4:421–430
35. Roache JD, Griffiths RR. Lorazepam and meprobamate dose effects in humans: behavioral effects and abuse liability. J Pharmacol Exp Ther 1987;243:978–988
36. Funderburk FR, Griffiths RR, McLeod DR, et al. Relative abuse liability of lorazepam and diazepam: an evaluation in "recreational" drug users. Drug Alcohol Depend 1988;22:215–222
37. Wolf B, Iguchi MY, Griffiths RR. Sedative/tranquilizer use and abuse in alcoholics: incidence, pattern, and preference. In: Harris LS, ed. Problems of Drug Dependence, 1989. Washington, DC: Government Printing Office; 1990. NIDA Research Monograph No. 95
38. Ladewig D, Grossenbacher H. Benzodiazepine abuse in patients of doctors in domicilary practice in the Basle area. Pharmacopsychiatry 1988;21:104–108
39. Physicians' Desk Reference. 58th ed. Montvale, NJ: Thompson PDR; 2004
40. Beardsley PM, Balster RL, Harris LS. Evaluation of the discriminative stimulus and reinforcing effects of gammahydroxybutyrate (GHB). Psychopharmacology (Berl) 1996;127:315–322
41. Woolverton WL, Rowlett JK, Winger G, et al. Evaluation of the reinforcing and discriminative stimulus effects of gamma-hydroxybutyrate in rhesus monkeys. Drug Alcohol Depend

continued

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

1999;54:137–143

42. Richards BD, Mintzer MZ, Griffiths RR. Abuse liability and comparative pharmacology of GHB, triazolam and pentobarbital in sedative drug abusers. Presented at the 67th annual meeting of the College of Problems on Drug Dependence; June 18–23, 2005; Orlando, Fla
43. Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. Drug Alcohol Depend 2001;63:1–22
44. Gonzalez A, Nutt DJ. Gamma hydroxy butyrate abuse and dependency. J Psychopharmacol 2005;19:195–204
45. Weerts EM, Goodwin AK, Griffiths RR, et al. Spontaneous and precipitated withdrawal after chronic intragastric administration of gamma-hydroxybutyrate (GHB) in baboons. Psychopharmacology (Berl) 2005;179:678–687
46. McDonough M, Kennedy N, Glasper A, et al. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. Drug Alcohol Depend 2004;75:3–9
47. Timby N, Eriksson A, Bostrom K. Gamma-hydroxybutyrate associated deaths. Am J Med 2000;108:518–519
48. Schutz H. Benzodiazepines, 2: A Handbook. Basic Data, Analytical Methods, Pharmacokinetics and Comprehensive Literature. New York, NY: Springer-Verlag; 1989
49. Johanson CE. Stimulant depressant report. NIDA Res Monogr 1986;67:98–104
50. Breen CL, Degenhardt LJ, Bruno RB, et al. The effects of restricting publicly subsidized temazepam capsules on benzodiazepine use among injecting drug users in Australia. Med J Aust 2004; 181:300–304
51. Farrell M, Strang J. Misuse of temazepam [letter]. Br Med J 1988;297:1402
52. Rush CR, Griffiths RR. Zolpidem, triazolam, and temazepam: behavioral and subject-rated effects in normal volunteers. J Clin Psychopharmacol 1996;16:146–157
53. Physicians' Desk Reference. 59th ed. Montvale, NJ: Thompson PDR; 2005
54. Ator NA. Zaleplon and triazolam: drug discrimination, plasma levels, and self-administration in baboons. Drug Alcohol Depend 2000;61:55–68
55. Rush CR, Frey JM, Griffiths RR. Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. Psychopharmacology (Berl) 1999;145:39–51
56. Ator NA, Weerts EM, Kaminski BJ, et al. Zaleplon and triazolam physical dependence assessed across increasing doses under a once-daily dosing regimen in baboons. 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 Aug 22, 2005
59. Evans SM, Funderburk FR, Griffiths RR. Zolpidem and triazolam in humans: behavioral and subjective effects and abuse liability. J Pharmacol Exp Ther 1990;255:1246–1255
60. Martinez-Cano H, Vela-Bueno A. Daytime consumption of triazolam. Acta Psychiatr Scand 1993;88:286–288
61. Fleming JA. Triazolam abuse. 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, Heel RC. Zopiclone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as a hypnotic. Drugs 1986;32:48–65
64. Yanagita T. Dependence potential of zopiclone studied in monkeys. Int Pharmacopsychiatry 1982;17(suppl 2):216–274
65. Bechelli LP, Navas F, Pierangelo SA. Comparison of the reinforcing properties of zopiclone and triazolam in former alcoholics. Pharmacology 1982;27(suppl 2):235–241
66. Boissl K, Dreyfus JF, Delmotte M. Studies on the dependence-inducing potential of zopiclone and triazolam. Pharmacology 1982;27(suppl 2):242–247
67. Hajak G, Muller WE, Wittchen HU, et al. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. Addiction 2003;98:1371–1378
68. Reith DM, Fountain J, McDowell R, et al. Comparison of the fatal toxicity index of zopiclone with benzodiazepines. J Toxicol Clin Toxicol 2003;41:975–980
69. Woods JH, Katz JL, Winger G. Abuse liability of benzodiazepines. Pharmacol Rev 1987;39:251–413
70. Weerts EM, Griffiths RR. Zolpidem self-injection with concurrent physical dependence under conditions of long-term continuous availability in baboons. Behav Pharmacol 1998;9:285–297
71. Mintzer MZ, Frey JM, Griffiths RR. Zolpidem is differentiated from triazolam in humans using a three-response drug discrimination procedure. Behav Pharmacol 1998;9:545–559
72. Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. Psychopharmacology (Berl) 1999;144:220–233
73. Soyka M, Bottlender R, Moller HJ. Epidemiological evidence for a low abuse potential of zolpidem. Pharmacopsychiatry 2000;33: 138–141
74. Weerts EM, Ator NA, Grech DM, et al. Zolpidem physical dependence assessed across increasing doses under a once-daily dosing regimen in baboons. J Pharmacol Exp Ther 1998;285:41–53
75. Yanagita T, Takahashi S, Sei M. Drug dependence potential of estazolam tested in the rhesus monkey. CIEA Preclin Rep 1976; 2:35–39
76. Griffiths RR, McLeod DR, Bigelow GE, et al. Relative abuse liability of diazepam and oxazepam: behavioral and subjective dose effects. Psychopharmacology (Berl) 1984;84:147–154
77. Bliding A. The abuse potential of benzodiazepines with special reference to oxazepam. Acta Psychiatr Scand Suppl 1978;274:111–116
78. Bergman U, Griffiths RR. Relative abuse of diazepam and oxazepam: prescription forgeries and theft/loss reports in Sweden. Drug Alcohol Depend 1986;16:293–301
79. Sannerud CA, Kaminski BJ, Griffiths RR. Maintenance of H1 antagonists self-injection in baboons. Exp Clin Psychopharmacol 1995;3:26–32
80. Halpert AG, Olmstead MC, Beninger RJ. Mechanisms and abuse liability of the anti-histamine dimenhydrinate. Neurosci Biobehav Rev 2002;26:61–67
81. de Nesnera AP. Diphenhydramine dependence: a need for awareness. J Clin Psychiatry 1996;57:136–137
82. Koppel C, Ibe K, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. J Toxicol Clin Toxicol 1987;25:53–70
83. Karch SB. Diphenhydramine toxicity: comparisons of postmortem findings in diphenhydramine-, cocaine-, and heroin-related deaths. Am J Forensic Med Pathol 1998;19:143–147
84. Radovanovic D, Meier PJ, Guirguis M, et al. Dose-dependent toxicity of diphenhydramine overdose. Hum Exp Toxicol 2000;19:489–495
85. Yanagita T. Dependence potential of the benzodiazepines: use of animal models for assessment. Clin Neuropharmacol 1985;8(suppl 1):S118–S122
86. Rush CR, Ali JA. A follow-up study of the acute behavioral effects of benzodiazepine-receptor ligands in humans: comparison of quazepam and triazolam. Exp Clin Psychopharmacol 1999;7:257–265
87. James SP, Mendelson WB. The use of trazodone as a hypnotic: a critical review. J Clin Psychiatry 2004;65:752–755
88. Otani K, Tanaka O, Kaneko S, et al. Mechanisms of the development of trazodone withdrawal symptoms. Int Clin Psychopharmacol 1994;9:131–133
89. Wolfe RM. Antidepressant withdrawal reactions. Am Fam Physician 1997;56:455–462
90. Gamble DE, Peterson LG. Trazodone overdose: four years of experience from voluntary reports. J Clin Psychiatry 1986;47: 544–546
91. Rozerem [package insert]. Lincolnshire, Ill: Takeda Pharmaceuticals America; 2005. Available at: http://www.rozerem.com/PI.pdf. Accessed Aug 22, 2005
92. Nishida N, Sasaki M, Wakasa Y, et al. Reinforcing effects of ramelteon (TAK-375) assessed by intravenous self-administration experiments in rhesus monkeys [abstract]. Sleep 2005;28(suppl): A45
93. 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 of Problems on Drug Dependence; June 18–23, 2005; Orlando, Fla
94. France CP, Weltman RH, Cruz CM. Lack of primary physical dependence effects of ramelteon (TAK375) in rhesus monkeys [abstract]. Sleep 2005;28(suppl):A45
95. Roth T, Seiden D, van der Zee P, et al. Phase III outpatient trial of

continued

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

ramelteon for the treatment of chronic insomnia in elderly patients [abstract]. J Am Geriatr Soc 2005;53(suppl 4):S25

96. Zammit G, Roth T, Erman M, et al. Polysomnography and outpatient study to determine the efficacy of ramelteon in adults with chronic insomnia. In: New Research Abstracts of the 158th Annual Meeting of the American Psychiatric Association; May 21–26, 2005; Atlanta, Ga. Abstract NR613
97. Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. Drug Alcohol Depend 2003; 70:S55–S72
98. Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend 2003;70:S41–S54
99. Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse and consequences, IV: adverse behavioral consequences of benzodiazepine use. Pharmacol Rev 1992;44: 207–237
100. Wolf B, Griffiths RR. Physical dependence on benzodiazepines: differences within the class. Drug Alcohol Depend 1991;29:153–156
101. Kales A, Bixler EO, Vela-Bueno A, et al. Comparison of short and long half-life benzodiazepine hypnotics: triazolam and quazepam. Clin Pharmacol Ther 1986;40:378–386
102. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005;66:469–476
103. McMahon LR, Jerussi TP, France CP. Stereoselective discriminative stimulus effects of zopiclone in rhesus monkeys. Psychopharmacology (Berl) 2003;165:222–228
104. Carlson JN, Haskew R, Wacker J, et al. Sedative and anxiolytic effects of zopiclone's enantiomers and metabolite. Eur J Pharmacol 2001;415:181–189
105. Haefely W. The biological basis of benzodiazepine actions. In: Smith DE, Wesson DR, eds. The Benzodiazepines: Current Standards for Medical Practice. Boston, Mass: MTP Press Limited; 1985:7–41
106. Buckley NA, McManus PR. Changes in fatalities due to overdose of anxiolytic and sedative drugs in the UK (1983–1999). Drug Saf 2004;27:135–141
107. Garnier R, Guerault E, Muzard D, et al. Acute zolpidem poisoning—analysis of 344 cases. J Toxicol Clin Toxicol 1994;32:391–404
108. McCarthy G, Myers B, Siegfried N. Treatment for methaqualone dependence in adults. Cochrane Database Syst Rev 2005;18:CD004146
109. Kales A, Soldatos CR, Bixler EO, et al. Diazepam: effects on sleep and withdrawal phenomena. J Clin Psychopharmacol 1988;8:340–346
110. Nicholson AN, Stone BM. Diazepam and 3-hydroxydiazepam (temazepam) and sleep in middle age. Br J Clin Pharmacol 1979;7:463–468