The Pharmacotherapy of Insomnia: Efficacy and Rebound With Hypnotic Drugs

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Currently prescribed hypnotics (i.e., benzodiazepines and benzodiazepine-like compounds) are commonly categorized according to pharmacokinetic profile, which is primarily distinguished by long, intermediate, or short elimination half-life. Hypnotics with a long elimination half-life (flurazepam and quazepam) maintain efficacy over prolonged periods of nightly use and their discontinuation does not usually result in rebound insomnia, but they have the major drawback of causing unwanted potent daytime sedative effects. Use of intermediate half-life hypnotics (estazolam, flunitrazepam, lormetazepam, nitrazepam, and temazepam) is associated with carryover effects of moderate intensity and varying degrees of tolerance and rebound insomnia. Rapidly eliminated benzodiazepine (brotizolam, midazolam, triazolam) and nonbenzodiazepine (zaleplon, zolpidem, and zopiclone) hypnotics are practically devoid of carryover effects, making them appropriate for use in the majority of cases of insomnia, but they are generally associated with relatively rapid development of tolerance and rather frequent occurrence of rebound insomnia upon their discontinuation. Contrary to previous beliefs, tolerance and rebound insomnia vary considerably among the rapidly eliminated hypnotics: tolerance is intense with triazolam and slight with midazolam and zolpidem, while rebound insomnia is intense with triazolam, variable with midazolam, and quite mild with zolpidem. For brotizolam, zaleplon, and zopiclone, existing relevant research findings are still inconclusive; brotizolam and zopiclone, however, appear to have a marked potential for the development of tolerance and/or rebound insomnia, which does not seem to be the case with zaleplon.

(Primary Care Companion J Clin Psychiatry 2002;4[suppl 1]:27–32)

Insomnia is usually the outcome of the interplay of various biological and psychological etiologic factors and, therefore, requires a multidimensional therapeutic approach.[1–9] Consequently, hypnotic drugs should not be the sole treatment modality in the management of insomnia. Rather, they should be generally administered as a part of the overall therapeutic intervention in order to help the patient gain mastery in combating the fear of sleeplessness and facilitate the implementation of psychotherapy and other treatment methods as they may be needed.[1,5,9]

The drugs currently marketed as hypnotics (Table 1) have a much more favorable side-effect profile and a larger therapeutic margin compared with the barbiturates, which were formerly used in the treatment of insomnia.[10] The benzodiazepine receptor on the γ-aminobutyric acid receptor type A ($GABA_A$) is the site of action of hypnotic drugs; binding of the drug to this receptor facilitates the inhibitory action of GABA in the central nervous system (CNS).[11] The $GABA_A$ receptor is a multimeric membrane-spanning ion channel consisting of various combinations of more than 15 known subunits,[12] and different drugs are known to bind with varying degree of affinity to different receptor types produced by these combinations.[13] For example, most benzodiazepines show similar affinity to all types of $GABA_A$ receptors, while the benzodiazepine-like compounds generally differentiate among these types.[13,14] Additionally, compared with other nonbenzodiazepine hypnotics, zaleplon has a much lower affinity for the target receptor,[14] thereby providing effective sleep induction without significant impairment at peak plasma concentrations.[15]

All hypnotic drugs share short absorption and distribution times, which lead to a relatively short period between their intake and highest plasma concentrations. This pharmacokinetic characteristic allows for rapid sleep induction following intake of the drug and is particularly important since delayed sleep onset is often the main complaint of patients with insomnia.[16] However, based on their rate of elimination, hypnotics can be broadly distinguished in 3 categories (see Table 1): those with long elimination half-lives (40–200 hours), those with intermediate elimination half-lives (8–40 hours), and those with short elimination

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Presented at the symposium "Current Considerations for the Clinical Management of Insomnia," which was held April 15, 2000, in Athens, Greece, and supported by an unrestricted educational grant from Wyeth-Ayerst Pharmaceuticals.

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Table 1. Currently Available Hypnotics: Broad Categories and Subgroups Based on Elimination Half-Life

Benzodiazepines	Long elimination half-life	Flurazepam
		Quazepam
	Intermediate elimination half-life	Estazolam
		Flunitrazepam
		Lormetazepam
		Nitrazepam
		Temazepam
	Short elimination half-life	Brotizolam
		Midazolam
		Triazolam
Benzodiazepine-like compounds	Short elimination half-life	Zaleplon
		Zolpidem
		Zopiclone

half-lives (1–8 hours).[17–24] The benzodiazepine hypnotics initially developed had a long elimination half-life; consequently, their administration was associated with carryover effects, such as next-day sleepiness and impaired performance reflected in psychomotor and cognitive impairment.[25–36] The rapidly eliminated hypnotic drugs, which were developed subsequently, were practically devoid of carryover effects but were found to be associated with earlier and more frequent development of tolerance as well as with more intense rebound insomnia, amnesia, and other behavioral side effects than the slowly eliminated ones.[37–44]

The present review on efficacy, tolerance, and rebound with hypnotic drugs will be primarily based on sleep laboratory studies. In these studies, the quantification of the sleep parameters is accurate and objective, allowing for the identification of changes that depict initial efficacy, development of tolerance, or presence of any rebound effects. The controlled environment of the sleep laboratory and the strict experimental design provide standardized conditions that make the evaluation of even the subjective variables very reliable.[45–48] As such, subjective data from clinical trials will be used as appropriate to support findings from sleep laboratory studies.

EFFICACY

Initial Efficacy

All hypnotic drugs have been shown to be initially efficacious for the treatment of insomnia, irrespective of the length of their elimination half-lives.[41,44,49–54] Hypnotics with long elimination half-lives usually show their highest effectiveness in the second and third night of administration, after the accumulation of the parent drug and its active metabolites is achieved.[27,55,56] In contrast, the rapidly eliminated hypnotics usually demonstrate effective sleep-inducing effects on the very first night.[57–60] In fact, zaleplon, which is very rapidly eliminated, can be used as an effective sleep inducer not only at bedtime but also after a prolonged unsuccessful attempt to sleep or even following a disturbing awakening occurring in the first half of the night.[61,62]

Tolerance

The effectiveness of the slowly eliminated hypnotics, flurazepam and quazepam, is well retained into the third week of their administration.[44] A slight loss of efficacy with continued use, observed in some studies, is either merely subjective[63] or does not reach a magnitude that considerably affects hypnotic potency.[26–28,44,64,65] For the agents with intermediate elimination half-lives (estazolam, flunitrazepam, lormetazepam, nitrazepam, and temazepam), loss of efficacy with continued use was reported in some studies.[66–73] In other studies, however, development of tolerance during 2 weeks of nightly administration was not demonstrated with these drugs.[74–80]

Regarding the rapidly eliminated hypnotics, certain sleep laboratory studies showed clear-cut loss of efficacy 1 to 2 weeks following nightly use.[1,44,49,57,58,71,81–85] However, the results of other studies did not demonstrate development of tolerance with these drugs.[51,64,86–95] To resolve this controversy, we recently conducted a meta-analysis of all sleep laboratory studies of 5 hypnotics with short elimination half-lives that were published until 1997 (i.e., brotizolam, midazolam, triazolam, zolpidem, and zopiclone). The results of this meta-analysis showed that tolerance with continued use is intense for triazolam and slight for midazolam and zolpidem. For brotizolam, there were no data allowing any conclusions to be drawn; data pertaining to zopiclone, although inconclusive, provided evidence for development of tolerance with this drug.[53]

The newly marketed hypnotic zaleplon has been assessed for continued efficacy in 2 sleep laboratory studies on insomniacs who were administered the 10-mg dose for either 2[49] or 5 weeks.[51] Sleep latency was significantly shorter during initial administration of zaleplon, 10 mg, compared with placebo (by 6.1 min, $p < .04$ in the 2-week study and by 15.7 min, $p < .005$ in the 5-week study); in 1 study, the decrease of sleep latency was not statistically significant in the second (i.e., final) week,[49] yet in the other study the decrease persisted to a statistically significant degree up to 5 weeks (sleep latency was 8.2 min shorter with zaleplon, 10 mg, than with placebo for weeks 3–5, $p < .05$).[51]

REBOUND INSOMNIA

Kales and associates[42,96,97] termed the worsening of sleep difficulty above baseline levels following withdrawal of a hypnotic *rebound insomnia.* Rebound insomnia does not seem to follow the discontinuation of hypnotics with long elimination half-lives, because the majority of studies of flurazepam and quazepam actually show carryover hypnotic effects during the withdrawal period of these drugs.* A few studies provided evidence of some worsening of

*References 27, 28, 44, 55, 57, 65, 70, 77, 91, and 98–104.

sleep following withdrawal of flurazepam, but this did not appear to have clinical significance, either because it was very mild, delayed, and/or transitional[26,28] or it was not objectively substantiated in the sleep laboratory.[63]

Results of studies on discontinuation of hypnotics with intermediate elimination half-lives are variable regarding the propensity of these drugs to cause rebound insomnia. The discontinuation of nitrazepam, estazolam, and lormetazepam was followed by development of rebound insomnia in some studies[66,72,75,77,79]; yet this was not the case in a study of 0.1 mg of lormetazepam in the elderly.[78] Similarly, temazepam, 30 mg, was found to cause rebound insomnia in 3 studies,[74,76,105] but not in 2 other studies[84,106]; moreover, doses up to 20 mg were found not to be associated with the development of rebound insomnia.[70,74,84,107,108] Finally, 2 studies of flunitrazepam showed occurrence of rebound insomnia upon its discontinuation,[68,109] although in another 5 studies no rebound was evident with this drug.[67,80,110–112]

Rebound insomnia is considered to be the main drawback of the rapidly eliminated hypnotics.[37,42,43,52,96,97] Until recently, a controversy existed on whether the frequency and intensity of rebound insomnia substantially differ across these agents.[44,113–117] This controversy was addressed through a meta-analysis conducted on all published studies of brotizolam, midazolam, triazolam, zopiclone, and zolpidem.[53] Results of this meta-analysis showed that when the first withdrawal night is compared with baseline, the discontinuation of triazolam causes an average decrease in total sleep time of more than 1 hour and an increase in sleep onset latency of about 30 minutes. On the contrary, the discontinuation of zolpidem was found to cause a milder degree of rebound insomnia on the first withdrawal night, with sleep latency being on average 13 minutes longer than at baseline.[53] Mean values from individual studies of brotizolam and midazolam (for which data were inadequate for the meta-analysis) suggested that discontinuation of these drugs may cause variable degrees of rebound insomnia.[53,90,118] Although data pertaining to the withdrawal period of zopiclone were also inadequate for the meta-analysis, there is some evidence that discontinuation of this drug may result in rebound insomnia.[53,94] Zaleplon was not marketed until 1999 and was thus not included in the meta-analysis. However, the results of 2 sleep laboratory studies[49,51] have been corroborated by subjective reports in 3 clinical studies,[119–121] indicating that rebound insomnia does not seem to be a significant consequence of the discontinuation of zaleplon.

CLINICAL IMPLICATIONS

Benzodiazepine and benzodiazepine-like hypnotics can be placed in 3 categories according to their pharmacokinetic characteristics. Flurazepam and quazepam have a long elimination half-life; estazolam, flunitrazepam, lormetazepam, nitrazepam, and temazepam have an intermediate elimination half-life; and brotizolam, midazolam, triazolam, zaleplon, zolpidem, and zopiclone have a short elimination half-life.[17–24] All these hypnotics are initially efficacious, especially in terms of reduction of sleep onset latency following their administration.[27,41,44,49–56] Nonetheless, development of tolerance, occurrence of rebound insomnia, and presence of residual sedation or other behavioral side effects are clinical characteristics that distinguish among them[37–44] and should be taken into account when considering their prescription.

Hypnotics with long elimination half-lives are not characterized by early development of tolerance, and their use is not associated with the occurrence of rebound insomnia upon their discontinuation.* They have, however, the disadvantage of unwanted carryover effects, i.e., daytime somnolence and marked psychomotor and cognitive impairment,[25–36] which render them inappropriate for use in the majority of patients with insomnia. The intermediate half-life hypnotics generally present with milder carryover effects than the slowly eliminated ones[31,66,68,122–131] and a relatively moderate degree of tolerance and rebound insomnia.[66–80,84,105–112]

The main advantage of the rapidly eliminated hypnotics is that their use is practically devoid of residual sedation or next-day psychomotor impairment.[29,32,34,126,132–134] On the other hand, tolerance may develop even after the first week of nightly administration,[1,44,49,53,57,58,71,81–85] and rebound insomnia is not an unusual occurrence upon discontinuation.[37,42,43,52,53,90,94,96,97,118] Elimination half-life, however, is not the only pharmacologic characteristic leading to the development of tolerance and rebound insomnia, both of which seem to be dependent on other properties of these drugs, such as binding affinity and receptor binding site specificity.[117,135] For example, tolerance has been shown to be relatively intense with triazolam and slight with midazolam and zolpidem, while rebound insomnia was found to be quite intense with triazolam and rather mild with zolpidem.[53] For brotizolam, zaleplon, and zopiclone—the 3 other rapidly eliminated hypnotics—existing data are still inconclusive; brotizolam and zopiclone, however, may have marked propensity for the development of tolerance and/or rebound insomnia, which does not seem to be the case with zaleplon.[49,51,53,90,94,119–121]

CONCLUSION

From a practical standpoint, the following clinical recommendations can be offered for the use of hypnotics in the management of insomnia. Because unimpaired next-day performance is desirable for patients with insomnia, a rapidly eliminated hypnotic is usually appropriate as part

*References 26–28, 44, 55, 57, 63–65, 70, 77, 91, 98–101, 103, and 104.

of a multidimensional treatment approach. Individual characteristics of hypnotic drugs, such as propensity for the development of tolerance with prolonged use and occurrence of rebound insomnia upon discontinuation, invariably should be taken into consideration.

Drug names: estazolam (ProSom and others), midazolam (Versed), quazepam (Doral), temazepam (Restoril and others), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

REFERENCES

1. Kales A, Kales JD. Evaluation and Treatment of Insomnia. New York, NY: Oxford University Press; 1984
2. Kales A, Caldwell AB, Soldatos CR, et al. Biopsychobehavioral correlates of insomnia, 2: pattern specificity and consistency with the Minnesota Multiphasic Personality Inventory. Psychosom Med 1983;45:341–356
3. Kales A, Soldatos CR, Kales JD. Sleep disorders: insomnia, sleepwalking, night terrors, nightmares, and enuresis. Ann Intern Med 1987;106:582–592
4. Soldatos CR. Insomnia. In: Rakel R, ed. Conn's Current Therapy. 43rd ed. Philadelphia, Pa: WB Saunders; 1991:29–31
5. Soldatos CR, Kales A, Kales JD. Management of insomnia. Ann Rev Med 1979;30:301–312
6. Kales A, Soldatos CR, Kales JD. Taking a sleep history. Am Fam Physician 1980;22:101–107
7. Beersma DGM. Insomnia and the 2-process model of sleep regulation: etiopathogenic considerations. Primary Care Companion J Clin Psychiatry 2002;4(suppl 1):13–16
8. Hauri PJ. Psychological and psychiatric issues in the etiopathogenesis of insomnia. Primary Care Companion J Clin Psychiatry 2002;4(suppl 1): 17–20
9. Morin CM. Contributions of cognitive-behavioral approaches to the clinical management of insomnia. Primary Care Companion J Clin Psychiatry 2002;4(suppl 1):21–26
10. Soldatos CR, Kales A. Hypnotic drugs and alcohol. In: Goth A, Vesell ES, eds. Medical Pharmacology: Principles and Concepts. 11th ed. St. Louis, Mo: CV Mosby; 1984:281–303
11. Study RE, Barker JL. Diazepam and (--)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. Proc Natl Acad Sci 1981;78: 7180–7184
12. Barnard EA. The molecular biology of $GABA_A$ receptors and their structural determinants. In: Biggio G, Sanna E, Costa E, eds. $GABA_A$ Receptors and Anxiety: From Neurobiology to Treatment. New York, NY: Raven Press; 1995:1–16
13. Zorumski CF, Isenberg KE. Insights into the structure and function of GABA-benzodiazepine receptors: ion channels and psychiatry. Am J Psychiatry 1991;148:162–173
14. Dämgen K, Lüddens H. Zaleplon displays a selectivity to recombinant $GABA_A$ receptors different from zolpidem, zopiclone and benzodiazepines. Neurosci Res Commun 1999;25:139–148
15. Mangano RM. Efficacy and safety of zaleplon at peak plasma levels. Int J Clin Pract Suppl 2001;116:9–13
16. Kales JD, Kales A, Bixler EO, et al. Biopsychobehavioral correlates of insomnia, 5: clinical characteristics and behavioral correlates. Am J Psychiatry 1984;141:1371–1376
17. Greenblatt DJ, Shader RI. Clinical pharmacokinetics of the benzodiazepines. In: Smith DE, Wesson DR, eds. The Benzodiazepines: Current Standards for Medical Practice. Lancaster, England: MTP Press; 1985:43–58
18. Arendt RM, Greenblatt DJ, Liebisch DC, et al. Determinants of benzodiazepine brain uptake: lipophilicity versus binding affinity. Psychopharmacology (Berl) 1987;93:72–76
19. Mhuller WE, Erhard W. The Benzodiazepine Receptor: Drug Acceptor Only or a Physiologically Relevant Part of Our Central Nervous System? New York, NY: Cambridge University Press; 1987
20. Gustavson LE, Carrigan PJ. The clinical pharmacokinetics of single doses of estazolam. Am J Med 1990;88(suppl 3A):2S–5S
21. Beer B, Ieni JR, Wu WH, et al. A placebo-controlled evaluation of single, escalating doses of CL 284,846, a non-benzodiazepine hypnotic. J Clin Pharmacol 1994;34:335–344
22. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1990;40: 291–313
23. Fernandez C, Maradeix V, Gimenez F, et al. Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Drug Metab Dispos 1993;21:1125–1128
24. Bailey L, Ward M, Musa MN. Clinical pharmacokinetics of benzodiazepines. J Clin Pharmacol 1994;34:804–811
25. Johnson LC, Chernik DA. Sedative-hypnotics and human performance. Psychopharmacology (Berl) 1982;76:101–113
26. Mitler MM, Seidel WF, van den Hoed J, et al. Comparative hypnotic effects of flurazepam, triazolam, and placebo: a long-term simultaneous nighttime and daytime study. J Clin Psychopharmacol 1984;4:2–13
27. Kales A, Bixler EO, Scharf M, et al. Sleep laboratory studies of flurazepam: a model for evaluating hypnotic drugs. Clin Pharmacol Ther 1976;19: 576–583
28. Kales A, Bixler EO, Soldatos CR, et al. Quazepam and flurazepam: long-term use and extended withdrawal. Clin Pharmacol Ther 1982;32:781–788
29. Moskowitz H, Linnoila M, Roehrs T. Psychomotor performance in chronic insomniacs during 14-day use of flurazepam and midazolam. J Clin Psychopharmacol 1990;10(suppl 4):44S–55S
30. Oswald I, Adam K, Borrow S, et al. The effects of two hypnotics on sleep, subjective feelings and skilled performance. In: Passouant J, Oswald I, eds. Pharmacology of the States of Alertness: Proceedings of the Satellite Symposium of the 7th International Congress of Pharmacology, Montpellier. New York, NY: Pergamon Press; 1979:51–63
31. Wesnes K, Warburton DM. A comparison of temazepam and flurazepam in terms of sleep quality and residual changes in performance. Neuropsychobiology 1984;11:255–259
32. Elie R, Lavoie G, Bourgouin J, et al. Zopiclone versus flurazepam in insomnia: prolonged administration and withdrawal. Int Clin Psychopharmacol 1990;5:279–286
33. Dement WC. Objective measurements of daytime sleepiness and performance comparing quazepam with flurazepam in two adult populations using the multiple sleep latency test. J Clin Psychiatry 1991;52(9, suppl): 31–37
34. Mamelak M, Csima A, Buck L, et al. A comparative study on the effects of brotizolam and flurazepam on sleep and performance in the elderly. J Clin Psychopharmacol 1989;9:260–267
35. Aden GC, Thatcher C. Quazepam in the short-term treatment of insomnia in outpatients. J Clin Psychiatry 1983;44:454–456
36. Mendels J, Stern S. Evaluation of the short-term treatment of insomnia in out-patients with 15 milligrams of quazepam. J Int Med Res 1983;11: 155–161
37. Roehrs T, Vogel G, Roth T. Rebound insomnia: its determinants and significance. Am J Med 1990;88:39S–42S
38. Bixler EO, Kales A, Manfredi RL, et al. Next-day memory impairment with triazolam use. Lancet 1991;337:827–831
39. Scharf MB, Fletcher K, Graham JP. Comparative amnestic effects of benzodiazepine hypnotic agents. J Clin Psychiatry 1988;49:134–137
40. Lader M. Rebound insomnia and newer hypnotics. Psychopharmacology (Berl) 1992;108:248–255
41. Kales A, Kales JD. Sleep laboratory studies of hypnotic drugs: efficacy and withdrawal effects. J Clin Psychopharmacol 1983;3:140–150
42. Kales A, Soldatos CR, Bixler EO, et al. Rebound insomnia and rebound anxiety: a review. Pharmacology 1983;26:121–137
43. Gillin JC, Spinweber CL, Johnson LC. Rebound insomnia: a critical review. J Clin Psychopharmacol 1989;9:161–172
44. Kales A, Vgontzas AN, Bixler EO. Hypnotic drugs. In: Kales A, ed. The Pharmacology of Sleep. New York, NY: Springer-Verlag; 1995:345–385
45. Soldatos CR, Kales A. Role of the sleep laboratory in the evaluation of hypnotic drugs. In: Priest RG, Pletscher A, Ward J, eds. Sleep Research (Proceedings of the North-European Symposium on Sleep Research). Lancaster, England: MTP Press Ltd; 1979:181–195
46. Kales A, Scharf MB, Soldatos CR, et al. Clinical evaluation of hypnotic drugs: contributions from sleep laboratory studies. J Clin Pharmacol 1979; 19:329–336
47. Bixler EO, Kales A. Clinical and laboratory evaluation of hypnotic drugs. In: McMahon FG, ed. Principles and Techniques of Human Research and Therapeutics: Selected Topics. Mount Kisco, NY: Futura Publishing Co Inc; 1985:153–189
48. Bixler EO, Vgontzas AN, Kales A. Methodological issues in pharmacological studies of sleep. In: Kales A, ed. The Pharmacology of Sleep. New

York, NY: Springer-Verlag; 1995:323–343
49. Walsh JK, Fry J, Erwin CW, et al. Efficacy and tolerability of 14-day administration of zaleplon 5 mg and 10 mg for the treatment of primary insomnia. Clin Drug Invest 1998;16:347–354
50. Nowell PD, Mazumdar S, Buysse DJ, et al. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA 1997; 278:2170–2177
51. Walsh JK, Vogel GW, Scharf M, et al. A five week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Med 2000;1:41–49
52. Lader M, Lawson C. Sleep studies and rebound insomnia: methodological problems, laboratory findings, and clinical implications. Clin Neuropharmacol 1987;10:291–312
53. Soldatos CR, Dikeos DG, Whitehead A. Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. Int Clin Psychopharmacol 1999;14:287–303
54. Soldatos CR, Dikeos DG. Efficacy and rebound of five hypnotics in the elderly: a critical review of sleep disorders and insomnia in the elderly. L' Annee Gerontologique 1993;7(suppl):209–222
55. Roth TG, Roehrs TA, Koshorek GL, et al. Hypnotic effects of low doses of quazepam in older insomniacs. J Clin Psychopharmacol 1997;17:401–406
56. Tietz EI, Roth T, Zorick FJ, et al. The acute effect of quazepam on the sleep of chronic insomniacs: a dose-response study. Arzneimittelforschung 1981; 31:1963–1966
57. 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
58. Kales A, Soldatos CR, Bixler EO, et al. Midazolam: dose-response studies of effectiveness and rebound insomnia. Pharmacology 1983;26:138–149
59. Mamelak M, Csima A, Price V. Effects of brotizolam on the sleep of chronic insomniacs. Br J Clin Pharmacol 1983;16(suppl 2):377S–382S
60. Vela-Bueno A, Oliveros JC, Dobladez-Blanco B, et al. Brotizolam: a sleep laboratory evaluation. Eur J Clin Pharmacol 1983;25:53–56
61. Walsh JK, Pollak CP, Scharf MB, et al. Lack of residual sedation following middle-of-the-night zaleplon administration in sleep maintenance insomnia. Clin Neuropharmacol 2000;23:17–21
62. Doghramji K. The need for flexibility in dosing of hypnotic agents. Sleep 2000;23(suppl 1):S16–S20
63. Mendelson WB, Weingartner H, Greenblatt DJ, et al. A clinical study of flurazepam. Sleep 1982;5:350–360
64. Kripke DF, Hauri P, Ancoli-Israel S, et al. Sleep evaluation in chronic insomniacs during 14-day use of flurazepam and midazolam. J Clin Psychopharmacol 1990;10(4 suppl):32S–43S
65. Kales A, Scharf MB, Soldatos CR, et al. Quazepam, a new benzodiazepine hypnotic: intermediate-term sleep laboratory evaluation. J Clin Pharmacol 1980;20:184–192
66. Kales A, Bixler EO, Soldatos CR, et al. Dose-response studies of lormetazepam: efficacy, side effects, and rebound insomnia. J Clin Pharmacol 1982;22:520–530
67. Monti JM, Trenchi HM, Morales F, et al. Flunitrazepam (Ro 5–4200) and sleep cycle in insomniac patients. Psychopharmacologia 1974;35:371–379
68. Scharf MB, Bixler EO, Kales A, et al. Long-term sleep laboratory evaluation of flunitrazepam. Pharmacology 1979;19:173–181
69. Adam K, Oswald I. A comparison of the effects of chlormezanone and nitrazepam on sleep. Br J Clin Pharmacol 1982;14:57–65
70. Kales A, Bixler EO, Soldatos CR, et al. Quazepam and temazepam: effects of short- and intermediate-term use and withdrawal. Clin Pharmacol Ther 1986;39:345–352
71. Adam K, Oswald I, Shapiro C. Effects of loprazolam and of triazolam on sleep and overnight urinary cortisol. Psychopharmacology (Berl) 1984;82: 389–394
72. Vogel GW, Morris D. The effects of estazolam on sleep, performance, and memory: a long-term sleep laboratory study of elderly insomniacs. J Clin Pharmacol 1992;32:647–651
73. Vgontzas AN, Kales A, Bixler EO, et al. Temazepam 7.5 mg: effects on sleep in elderly insomniacs. Eur J Clin Pharmacol 1994;46:209–213
74. Mitler MM, Carskadon MA, Phillips RL, et al. Hypnotic efficacy of temazepam: a long-term sleep laboratory evaluation. Br J Clin Pharmacol 1979; 8:63S–68S
75. Adam K, Adamson L, Brezinova V, et al. Nitrazepam: lastingly effective but trouble on withdrawal. BMJ 1976;1:1558–1560
76. Bixler EO, Kales A, Soldatos CR, et al. Effectiveness of temazepam with short-, intermediate-, and long-term use: sleep laboratory evaluation. J Clin Pharmacol 1978;18:110–118
77. Adam K, Oswald I. Effects of lormetazepam and of flurazepam on sleep. Br J Clin Pharmacol 1984;17:531–538
78. Vogel GW. Sleep laboratory study of lormetazepam in older insomniacs. Psychopharmacology Suppl 1984;1:69–78
79. Lamphere J, Roehrs T, Zorick F, et al. Chronic hypnotic efficacy of estazolam. Drugs Exp Clin Res 1986;12:687–691
80. Rosekind MR, Seidel WF, Brown ED, et al. 28-night sleep laboratory evaluation of flunitrazepam [abstract]. Sleep Res 1979;8:104
81. Lamphere J, Roehrs T, Vogel G, et al. The chronic efficacy of midazolam. Int Clin Psychopharmacol 1990;5:31–39
82. Mamelak M, Scima A, Price V. Effects of zopiclone on the sleep of chronic insomniacs. Int Pharmacopsychiatry 1982;17(suppl 2):156–164
83. Kales A, Kales JD, Bixler EO, et al. Hypnotic efficacy of triazolam: sleep laboratory evaluation of intermediate-term effectiveness. J Clin Pharmacol 1976;16:399–406
84. Scharf MB, Sachais BA, Mayleben DW, et al. The effects of a calcium channel blocker on the effects of temazepam and triazolam. Curr Ther Res Clin Exp 1990;48:516–523
85. Besset A, Tafti M, Villemin E, et al. Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers. Drugs Exp Clin Res 1995;21:161–169
86. Roth T, Kramer M, Lutz T. Intermediate use of triazolam: a sleep laboratory study. J Int Med Res 1976;4:59–63
87. Jovanovic UJ, Dreyfus JF. Polygraphical sleep recordings in insomniac patients under zopiclone or nitrazepam. Pharmacology 1983;27(suppl 2): 136–145
88. Monti JM, Debellis J, Gratadoux E, et al. Sleep laboratory study of the effects of midazolam in insomniac patients. Eur J Clin Pharmacol 1982; 21:479–484
89. Gath I, Bar-On E, Rogowski Z, et al. Automatic scoring of polygraphic sleep recordings: midazolam in insomniacs. Br J Clin Pharmacol 1983;16 (suppl 1):89S–96S
90. Vogel GW, Vogel F. Effect of midazolam on sleep of insomniacs. Br J Clin Pharmacol 1983;16(suppl 1):103S–108S
91. Mamelak M, Csima A, Price V. A comparative 25-night sleep laboratory study on the effects of quazepam and triazolam on chronic insomniacs. J Clin Pharmacol 1984;24:65–75
92. Monti JM, Pineyro G, Alvarino F, et al. Combined effects of midazolam and ethanol on sleep and on psychomotor performance in normal subjects. Fundam Clin Pharmacol 1989;3:613–620
93. Fleming JA, Bourgouin J, Hamilton P. A sleep laboratory evaluation of the long-term efficacy of zopiclone. Can J Psychiatry 1988;33:103–107
94. Mouret J, Ruel D, Maillard F, et al. Zopiclone versus triazolam in insomniac geriatric patients: a specific increase in delta sleep with zopiclone. Int Clin Psychopharmacol 1990;5(suppl 2):47–55
95. Vogel G, Scharf M, Walsh J, et al. Effects of chronically administered zolpidem on the sleep of healthy insomniacs [abstract]. Sleep Res 1989;18: 80
96. Kales A, Scharf MB, Kales JD, et al. Rebound insomnia: a potential hazard following withdrawal of certain benzodiazepines. JAMA 1979;241: 1692–1695
97. Kales A, Scharf MB, Kales JD. Rebound insomnia: a new clinical syndrome. Science 1978;201:1039–1041
98. Kales A, Allen C, Scharf MB, et al. Hypnotic drugs and their effectiveness: all-night EEG studies of insomniac subjects. Arch Gen Psychiatry 1970;23:226–232
99. Kales A, Kales JD, Scharf MB, et al. Hypnotics and altered sleep-dream patterns, 2: all-night EEG studies of chloral hydrate, flurazepam, and methaqualone. Arch Gen Psychiatry 1970;23:219–225
100. Kales A, Scharf MB, Bixler EO, et al. Dose-response studies of quazepam. Clin Pharmacol Ther 1981;30:194–200
101. Vogel GW, Barker K, Gibbons P, et al. A comparison of the effects of flurazepam 30 mg and triazolam 0.5 mg on the sleep of insomniacs. Psychopharmacology (Berl) 1976;47:81–86
102. Dement WC, Carskadon MA, Mitler MM, et al. Prolonged use of flurazepam: a sleep laboratory study. Behav Med 1978;5:25–31
103. Mamelak M, Csima A, Price V. The effects of quazepam on the sleep of chronic insomniacs. Curr Ther Res Clin Exp 1981;29:135–147
104. Bliwise D, Seidel W, Greenblatt DJ, et al. Nighttime and daytime efficacy of flurazepam and oxazepam in chronic insomnia. Am J Psychiatry 1984; 141:191–195
105. Kales A, Manfredi RL, Vgontzas AN, et al. Rebound insomnia after only

brief and intermittent use of rapidly eliminated benzodiazepines. Clin Pharmacol Ther 1991;49:468–476
106. Roehrs T, Lamphere J, Paxton C, et al. Temazepam's efficacy in patients with sleep onset insomnia. Br J Clin Pharmacol 1984;17:691–696
107. Moja EA, Scamonatti L, Camera A, et al. Hypnotic efficacy of temazepam (TMZ) with short- and intermediate-term use: sleep laboratory evaluation [abstract]. Electroencephalogr Clin Neurophysiol 1982;54:15P
108. Wittig R, Zorick F, Roehrs T, et al. Effects of temazepam soft gelatin capsules on the sleep of subjects with insomnia. Curr Ther Res Clin Exp 1985;38:15–22
109. Bixler EO, Kales A, Soldatos CR, et al. Flunitrazepam, an investigational hypnotic drug: sleep laboratory evaluations. J Clin Pharmacol 1977;17: 569–578
110. Cerone G, Crignotta F, Coccagna G, et al. All-night polygraphic recordings on the hypnotic effects of a new benzodiazepine: flunitrazepam (Ro 5–4200, Rohypnol). Eur Neurol 1974;11:172–179
111. Jovanovic UJ. Polygraphic sleep recordings before and after the administration of flunitrazepam. J Int Med Res 1977;5:77–84
112. Hauri PJ, Silberfarb PM. Effects of R05–4200 on sleep [abstract]. Sleep Res 1976;5:65
113. Salva P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. Clin Pharmacokinet 1995;29: 142–153
114. Lobo BL, Greene WL. Zolpidem: distinct from triazolam? Ann Pharmacother 1997;31:625–632
115. Mendelson WB, Jain B. An assessment of short-acting hypnotics. Drug Saf 1995;13:257–270
116. Vogel GW, Poirrier R. Studies of effects following discontinuation of zolpidem treatment. In: Freeman H, Puech AJ, Roth T, eds. Zolpidem: An Update of Its Pharmacological Properties and Therapeutic Place in the Management of Insomnia. Amsterdam, the Netherlands: Elsevier; 1996: 149–160
117. Vgontzas AN, Kales A. Mechanisms of benzodiazepine drug dependence. In: Kales A, ed. The Pharmacology of Sleep. New York, NY: Springer-Verlag; 1995:503–536
118. Roehrs T, Zorick F, Koshorek GL, et al. Effects of acute administration of brotizolam in subjects with disturbed sleep. Br J Clin Pharmacol 1983; 16(suppl 2):371S–376S
119. Elie R, Rüther E, Farr I, et al, for the Zaleplon Clinical Study Group. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. J Clin Psychiatry 1999;60:536–544
120. Ancoli-Israel S, Walsh JK, Mangano RM, et al. Zaleplon, a novel nonbenzodiazepine hypnotic, effectively treats insomnia in elderly patients without causing rebound effects. Primary Care Companion J Clin Psychiatry 1999;1:114–120
121. Fry J, Scharf M, Mangano R, et al. Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. Int Clin Psychopharmacol 2000;15:141–152
122. Bixler EO, Kales A, Brubaker BH, et al. Adverse reactions to benzodiazepine hypnotics: spontaneous reporting system. Pharmacology 1987;35: 286–300
123. Fowler LK, Schiller M. Euhypnos forte, high dose temazepam for resistant insomnia: post-marketing surveillance in 10,057 patients unresponsive to conventional hypnotic dosage. J Int Med Res 1980;8:446–452
124. Heel RC, Brogden RN, Speight TM, et al. Temazepam: a review of its pharmacological properties and therapeutic efficacy as an hypnotic. Drugs 1981;21:321–340
125. Clark BG, Jue SG, Dawson GW, et al. Loprazolam: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in insomnia. Drugs 1986;31:500–516
126. Hindmarch I, Clyde CA. The effects of triazolam and nitrazepam on sleep quality, morning vigilance and psychomotor performance. Arzneimittelforschung 1980;30:1163–1166
127. Mattila MJ, Aranko K, Mattila ME, et al. Objective and subjective assessment of hangover during subacute administration of temazepam and nitrazepam to healthy subjects. Eur J Clin Pharmacol 1984;26:375–380
128. Stanley RO, Tiller JW, Adrian J. The psychomotor effects of single and repeated doses of hypnotic benzodiazepines. Int Clin Psychopharmacol 1987;2:317–323
129. Nicholson AN, Stone BM. Hypnotic activity and effects on performance of lormetazepam and camazepam—analogues of temazepam. Br J Clin Pharmacol 1982;13:433–439
130. Subhan Z, Hindmarch I. The effects of midazolam in conjunction with alcohol on iconic memory and free-recall. Neuropsychobiology 1983;9: 230–234
131. Pierce MW, Shu VS. Efficacy of estazolam: the United States clinical experience. Am J Med 1990;88:6S–11S
132. Ogura C, Nakazawa K, Majima K, et al. Residual effects of hypnotics: triazolam, flurazepam, and nitrazepam. Psychopharmacology (Berl) 1980;68:61–65
133. Murphy P, Hindmarch I, Hyland CM. Aspects of short-term use of two benzodiazepine hypnotics in the elderly. Age Ageing 1982;11:222–228
134. Judd LL, Ellinwood E, McAdams LA. Cognitive performance and mood in patients with chronic insomnia during 14-day use of flurazepam and midazolam. J Clin Psychopharmacol 1990;10(4, suppl):56S–67S
135. Hutchison MA, Smith PF, Darlington CL. The behavioural and neuronal effects of the chronic administration of benzodiazepine anxiolytic and hypnotic drugs. Prog Neurobiol 1996;49:73–97