A Psychiatric Perspective on Insomnia

W. Vaughn McCall, M.D., M.S.

Insomnia is a cardinal symptom for many psychiatric disorders, especially depressive disorders. Treatment of the underlying psychiatric disorder may be sufficient to relieve the accompanying insomnia. If the insomnia fails to respond, then consideration should be given to the possibility of inadequate treatment of the primary psychiatric disorder, iatrogenic insomnia, insomnia related to a medical disorder, or learned/habit insomnia. Persistent insomnia should be aggressively pursued, since it has been associated with a variety of adverse outcomes in samples of depressed patients. The physician should always inquire about and encourage healthy sleeping behaviors, even if hypnotic medication is contemplated. Benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists (BzRAs) have the best evidence for efficacy as hypnotics, although sedating antidepressants are popularly prescribed. Although all benzodiazepine hypnotics and nonbenzodiazepine BzRAs are comparably efficacious in inducing sleep, they vary markedly in their potential for residual side effects.
(J Clin Psychiatry 2001;62[suppl 10]:27–32)

At least a third of adult Americans experience insomnia every year, yet there is concern that insomnia and sleep disorders in general go largely undetected in primary care practice.[1] We conducted a study[2] of the wellness-promoting strategies of 20 seasoned primary care physicians who were interviewing simulated patients and found that none of them asked a single question about the patients' sleep. Although no data exist regarding the frequency with which psychiatrists ask about sleep in an initial evaluation, the frequency of psychiatrists' inquiring into sleep disturbance is likely very high since insomnia (or "sleep disturbance") is a criterion symptom for many psychiatric disorders.

Sleep disturbance is a diagnostic symptom for major depressive disorder, dysthymia, generalized anxiety disorder, and posttraumatic stress disorder.[3] Sleep has probably been best studied in major depression, given that at least 80% of patients with major depression have an insomnia complaint.[4] The high prevalence of insomnia in persons with psychiatric disorders may have the unexpected consequence of leading some physicians to believe that insomnia necessarily indicates that a psychiatric disorder is present. Insomnia and psychiatric disorders are dissociable, even in a psychiatric clinic, so that insomnia is neither necessary nor sufficient to make any psychiatric diagnosis. Instead, a report of insomnia in a psychiatric clinic may indicate an underlying medical cause, iatrogenesis, a learned response that occurred during the course of an acute psychiatric illness, or possibly even a primary sleep disorder.[5] This article will suggest an evaluation and management strategy for insomnia in psychiatric practice, including transient insomnia, persistent insomnia in the untreated patient, and persistent insomnia in the otherwise successfully treated psychiatric patient.

TRANSIENT INSOMNIA

The first branch point in a psychiatrist's algorithm for insomnia is the duration of the complaint. Transient insomnia lasting a few days is the most common form of insomnia in the general population, but its frequency in psychiatric practice is unknown.[1] The differential diagnosis for transient insomnia could include an acute stress or adjustment disorder, acute medication or substance effects, or, possibly, acute medical illness.[3] Examples of acute stress or adjustment disorders that may merit short-term use of hypnotics in psychiatric practice include bereavement, exposure to acute psychological trauma, acute relationship discord, and acute occupational stress. Transient insomnia usually will have a time-limited course of a number of days or weeks, but a small proportion of episodes last months or longer. For example, transient insomnia could also herald a new episode of psychiatric illness for patients with prior histories of psychiatric disorder.[6]

From the Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, N.C.
Supported in part by the National Institute of Mental Health award MH01090.
Presented at the symposium "New Developments for Treating Sleep Disorders," which was held March 24, 2000, in Chicago, Ill., and supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.
Reprint requests to: W. Vaughn McCall, M.D., M.S., Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157 (e-mail: vmccall@wfubmc.edu).

Determination of a sleep disorder is especially important for bipolar disorder, since sleep loss may represent a modifiable risk for the development of new episodes of mania.[7] Hypnotic medications are probably best justified for all sorts of transient insomnia and are indicated for short-term use. The rationale for this use of hypnotics is analogous to the use of opioid analgesics for acute pain, with the assumption that the pain will resolve over a few days and the duration of therapy will be correspondingly brief.

PERSISTENT INSOMNIA

Importance of Persistent Insomnia

We define persistent insomnia as nightly or near-nightly insomnia lasting weeks or months. Psychiatric disorders account for ≥ 40% of the underlying diagnoses in persons with persistent insomnia.[8,9] A general principle in the treatment of insomnia in the context of psychiatric disorders is that treatment of the underlying psychiatric disorder should lead to the resolution of the associated insomnia complaint. This is usually the case for anxiety and depressive disorders.[10–13]

Even when patients report improvement in their insomnia, clinicians cannot assume that objective measures of sleep are also showing improvement. For example, Gillin et al.[12] studied depressed insomniacs treated with either fluoxetine or nefazodone and compared the effect on sleep. They found both groups experienced equal improvement on measures of depression and nearly equal improvement in their insomnia complaints, but the groups had marked differences in polysomnographic measures of sleep continuity, with fluoxetine-treated patients showing a deterioration in sleep continuity. This finding begs the question, what is the desirable endpoint of treating insomnia in psychiatric disorder—improvement in the subjective complaint of insomnia or polysomnographic improvement as well?

The persistence of insomnia after the otherwise successful treatment of a psychiatric disorder is an increasingly common problem. Insomnia is the most common residual symptom among patients who have otherwise been successfully treated with fluoxetine for depression. As described by Nierenberg et al.,[13] 25% to 45% of patients who were otherwise deemed responders to antidepressant therapy (17-item Hamilton Rating Scale for Depression score < 7) reported persistent insomnia. This phenomenon may be unique to the newer antidepressant medications (e.g., fluoxetine) that have been associated with deterioration in polysomnographic sleep.[14–18] In contrast, electroencephalographic (EEG) measures of sleep continuity may improve with tricyclic antidepressants.[19]

Persistent insomnia after treatment of depression is of concern for 3 reasons. First, insomnia makes a unique contribution to poor quality of life in persons with major depression. Many prior investigations have shown that increasing levels of depression are associated with poor quality of life (for example see McCall et al.[20]), and independent lines of inquiry have reported that insomnia is associated with poor quality of life in nondepressed persons. In a new study,[4] we found that insomnia makes a unique contribution to poor quality of life in depressed patients after controlling for all other symptoms of depression. Second, severe insomnia is an independent risk factor for suicide during the first 2 years of an episode of major depression.[21,22] It is unknown whether treatment of persistent insomnia would reduce that risk. Third, residual insomnia after treatment of depression is a predictor of relapse.[23]

Assessment of Persistent Insomnia

The first step in the assessment of persistent insomnia for patients already under psychiatric care is renewal of the diagnostic interview, since the office-based interview remains the cornerstone of evaluation of insomnia. Diagnostic considerations include the following: (1) Is the residual insomnia due to incomplete response of the primary psychiatric disorder to treatment? (2) Is the insomnia possibly iatrogenesis from the effects of the prescribed treatment? (3) Has an underlying medical disorder not yet been addressed? (4) Has a primary sleep disorder not yet been addressed? (5) Has the patient adopted poor sleeping habits, including compensations such as excess caffeine? (6) Has conditioned insomnia developed during the course of an acute mental disorder?

The interview will usually be sufficient to tackle persistent insomnia, but occasionally the physician will desire additional information. Ancillary sources of information include sleep logs, psychometric testing, blood work, and polysomnography (PSG). Although a patient's single global estimate of sleep-onset latency as obtained during the interview may closely approximate the mean values documented on daily sleep logs over 2 weeks, a single global estimate cannot give an accurate sense of night-to-night variability in sleep parameters.[24] Extreme variation in night-to-night variability of sleep may be an important source of insomniacs' distress, since they cannot predict from one night to the next whether they will sleep well or poorly. Measuring, and ultimately reducing, night-to-night variability is a goal of insomnia evaluation and treatment.

Psychometric tests may be useful to screen for depression or anxiety. The Epworth Sleepiness Scale (ESS) has been validated against a physiologic measure of sleepiness (the Multiple Sleep Latency Test).[25] The ESS[26] is a self-administered scale of 8 items, with higher scores indicating greater levels of sleepiness. Surprisingly, many persons with insomnia do not manifest daytime sleepiness. Occasionally, a person with insomnia will complain of true daytime sleepiness, and a corresponding ESS score > 11 may signal the need for PSG testing for primary sleep disorders such as obstructive sleep apnea.

Blood tests are of limited use in the assessment of persistent insomnia. Common wisdom suggests that insomnia may be a sign of thyroid disease, but the evidence to support this belief is slim. In one study[27] of a nonclinical working population, persons receiving thyroid hormone with low thyroid-stimulating hormone levels (TSH) but normal T_4 thyroxine levels slept significantly less than euthyroid controls. Measurement of TSH is probably justified in persons with persistent insomnia. Measurement of thyroid indices, serum iron, and vitamin B_{12} is also indicated in insomniacs with restless legs syndrome, since a subset of this syndrome is attributable to thyroid disease, low serum iron, or vitamin B_{12} deficiency.[5]

Polysomnography is not routinely indicated in the assessment of persistent insomnia, according to practice parameters of the American Academy of Sleep Medicine.[28] Polysomnography may be of use if the patient complains of excessive daytime sleepiness or if the clinician has a high index of suspicion for sleep apnea, periodic limb movements, nocturnal hypoxemia, or refractory insomnia.[5]

Nonpharmacologic Treatment of Persistent Insomnia

Nonpharmacologic treatments include both education of the patient regarding healthy sleep practices (sleep hygiene) and specific behavioral therapies. The elements of good sleep hygiene include avoidance of stimulating substances and consistency in sleeping patterns. The specific behavioral therapies include progressive deep muscle relaxation, stimulus control, sleep restriction, and others. Evidence supports stimulus control and sleep restriction therapy as having the greatest impact on reducing sleep latency and middle-of-the-night wakefulness.[29] These treatments have a therapeutic impact that is comparable to hypnotic medications, with some evidence of greater longevity of effect for behavioral therapies compared with hypnotic medications. Obstacles to the implementation of these behavioral techniques include physician unfamiliarity and the amount of effort required on the part of the patient. A further limitation is the lack of information to support that these treatments can be effectively delivered in routine clinical settings—most of the efficacy data for behavioral therapy are derived from tertiary care research clinics in persons with primary insomnia. Some reports[30] suggest that behavioral therapies may mitigate insomnia secondary to psychiatric disorders.

Pharmacologic Treatment of Persistent Insomnia

Pharmacologic therapy of insomnia may be guided by the following principles. First, treatment should be specific for any underlying psychiatric or medical disorders. Second, successful treatment should include relief of the daytime consequences, promote daytime functioning, and not focus exclusively on reducing sleep latency or increasing total sleep time. At a minimum, treatment of insomnia should not diminish daytime functioning. Third, the physician should inquire about the patient's sleep habits throughout the course of pharmacologic therapy of persistent insomnia, with the expectation that the patient will continue to follow good sleep practices.

Choices of adjunctive sleep-promoting agents include melatonin, sedating antihistamines, sedating antidepressants, benzodiazepines, and nonbenzodiazepine BzRAs. Melatonin is a dietary supplement, one of many "alternative medicine" regimens popular in the United States. Alternative medicine accounts for health care expenditures comparable with or in excess of mainstream medicine, yet the value of these therapies is largely obscure and not subject to the same standards of purity as prescription medication.[31] Melatonin, in particular, is not a convincing hypnotic.[32] Some evidence supports valerian as a hypnotic, but controlled clinical trials have not consistently shown efficacy.[33]

Sedating antihistamines and antidepressants (in particular, trazodone) represented the fastest-growing class of prescription medications used to treat sleeplessness in the 1990s[34]; however, no convincing clinical trial data have demonstrated their efficacy as hypnotics. Most of the available studies are limited by nonhomogeneous patient samples, short duration of treatment (2–4 days), and a lack of objective measures of efficacy (e.g., PSG).[5] One of the rare studies of sedating antidepressants[16] to include PSG measures actually showed objective worsening rather than improvement. These medications may have gained favor as hypnotics based upon the belief that they are innocuous compared with standard hypnotics, but sedating antidepressants and antihistamines are burdened with their own side effects.

The efficacy of benzodiazepine hypnotics, in contrast with that of sedating antidepressants, is supported by numerous rigorously conducted clinical trials.[35] The principal limitation of these trials is that the sample populations usually included only primary insomniacs (i.e., persons without a psychiatric disorder). It is unknown whether the results from samples of primary insomniacs directly translate to samples of psychiatric insomniacs. Another concern is that benzodiazepines have been linked to tolerance and dependence, daytime sleepiness, delayed reaction time, memory problems, falls, and accidents.[36–40] These adverse events are probably more common for patients taking other psychotropic medications in addition to hypnotics.

Zaleplon and zolpidem represent a new class of nonbenzodiazepine BzRAs that has advantages over standard benzodiazepine hypnotics. Although they are structurally dissimilar from benzodiazepines, the action of the nonbenzodiazepine BzRAs is mediated through the benzodiazepine receptor.[41] Zolpidem and zaleplon have serum half-lives shorter than any benzodiazepine hypnotics.[41,42] Furthermore, zolpidem and zaleplon are selective for the $GABA_A$/benzodiazepine type 1 receptors, in particular, subtype $\alpha_1\beta_2\gamma_2$, a receptor that may play a role in hypnotic

efficacy.[43] Zaleplon binds less tightly to this receptor than does zolpidem.[43] Differences in pharmacokinetics and receptor binding may explain observed differences in therapeutic and residual side effects.

The hypnotic efficacy of nonbenzodiazepine BzRAs, as is that of benzodiazepine hypnotics, is established in samples of primary insomniacs.[44–49] Data supporting the efficacy of nonbenzodiazepine BzRAs in psychiatric insomniacs are less complete but are suggestive of a beneficial effect.[50–52] In general, clinical trials of nonbenzodiazepine BzRAs show superior hypnotic efficacy compared with placebo in samples of primary insomniacs, maintained over 4 weeks of continuous dosing with no evidence of tolerance. Equally interesting is the finding of a strong placebo effect—placebo-treated patients usually show steady reductions in sleep latency throughout clinical trials.[44,49] This may be explained as part of the spontaneous waxing and waning of the insomnia symptom or perhaps as a response to the behavioral constraints placed upon the subjects as part of their participation in a clinical trial. This strong placebo effect has an important implication: anecdotal reports and uncontrolled trials suggesting hypnotic efficacy for sedating antidepressants could be explained as a placebo response.[53]

Dosing recommendations for hypnotics have traditionally included the stipulation that the medication be taken at bedtime, with the intent of discouraging dosing later in the night at a time that would predictably lead to daytime residual impairment. Adherence to this recommendation necessarily means taking the medication before it is clear that it will be needed, thus encouraging nightly use in anticipation of a poor sleep experience. Intermittent dosing of hypnotics would theoretically result in a reduced total consumption of hypnotics and an increased sense of self-efficacy. Intermittent bedtime administration of zolpidem has already been shown to provide global improvement in daytime functioning comparable with nightly administration.[54] However, the use of zolpidem should be followed by 7 to 8 hours of inactivity due to its potential for residual symptoms.[55] Zaleplon is the most rapidly eliminated hypnotic, opening the possibility that this hypnotic could be taken as needed even after bedtime. Growing evidence supports the safety of middle-of-the-night dosing of zaleplon. Anterograde memory performance and reaction time 4 hours after middle-of-the-night ingestion of zaleplon, 10 mg, are no different than after placebo.[56] Actual driving performance 5 hours after ingestion of zaleplon was as proficient as after placebo.[57]

INSOMNIA IN PSYCHIATRIC PATIENTS

Most of the clinical trials of hypnotic medication are derived from samples of persons with primary insomnia. By definition, these subjects have less psychological distress than psychiatric patients. Furthermore, persons who volunteer for clinical trials of insomnia treatment have even less psychological disturbance than that seen in a routine clinical presentation.[58]

A second concern is the need to continue hypnotics beyond 5 weeks in some psychiatric patients, yet few controlled clinical trials proceed beyond 5 weeks, and no hypnotic is approved for more than a few weeks of continuous use. The long-term investigations of hypnotic efficacy[52,59,60] generally do not include PSG measurement. There are some available 6-month and 1-year data for zaleplon in the form of open-label studies that show a lack of withdrawal effects.[61] Zaleplon was not distinguishable from placebo at doses of 5, 10, or 20 mg as assessed by the Benzodiazepine Withdrawal Symptom Questionnaire or spontaneously reported withdrawal emergent adverse effects.[61]

Since many patients who have chronic insomnia need to use medication long term, clinicians should press for the conduct of studies that would address these concerns. In the meantime, these 2 concerns may be met as follows: the physician should directly reexamine each patient every few months to ascertain whether (1) the hypnotic is still efficacious and necessary, (2) the patient has escalated the dose, (3) there are any late-emergent side effects, (4) the general medical history has changed, and (5) the primary psychiatric disorder has changed. The physician should also advise the patient that prescriptions extended beyond 4 weeks of therapy constitute off-label use. Finally, the use of a hypnotic medication does not relieve the patient of the responsibility to follow good sleep practices. Therefore, the physician should use each visit to prescribe sharp limits on caffeine, alcohol, and nicotine, while encouraging regular bedtime hours and exercise.

Sleep-inducing agents are often used as add-on therapy with other psychotropics, especially antidepressants. A review of 239 patients receiving either sertraline or fluoxetine[62] found that 60% were concurrently receiving an additional medication for sleep, usually trazodone or a low-dose tricyclic antidepressant. In a sample of highly treatment-resistant patients, Nolen et al.[63] found that coadministration of a short-acting hypnotic (lormetazepam) at the outset of antidepressant treatment with either nortriptyline or maprotiline resulted in a higher response rate for nonsleep depressive symptoms as compared with coadministration of placebo. Dominguez et al.[64] and Cohn[65] examined the effect of adding triazolam to depressed patients who continue to experience insomnia despite imipramine treatment. Both studies found a nonsignificant reduction in the dropout rate among the patients receiving triazolam versus placebo, and Cohn[65] found that the addition of triazolam was associated with superior global improvement. A recent study[52] compared the nonbenzodiazepine BzRA zolpidem and placebo in depressed patients with continuing insomnia despite otherwise successful treatment with a selective serotonin reuptake inhibitor (SSRI) and found that the addition of zolpidem was associated with an im-

proved sense of well-being during the daytime. Thus, the use of nonbenzodiazepine BzRAs with SSRIs could be helpful for patients whose insomnia persists.

The combination of newer antidepressants and hypnotics is appealing but theoretically could result in drug-drug interactions. Cytochrome P450 3A4 has been reported to play an important role in the degradation of triazolam and zolpidem.[42,66,67] Some antidepressants, specifically, fluoxetine, sertraline, fluvoxamine, and nefazodone, are metabolized through 3A4 cytochrome enzymes.[68] Nevertheless, reports of possible drug interactions between hypnotics and SSRIs are sparse. Zaleplon is extensively metabolized by aldehyde oxidase.[69]

SUMMARY

Insomnia is a cardinal symptom for many psychiatric disorders, especially depressive disorders. Treatment of the underlying psychiatric disorder may be sufficient to relieve the accompanying insomnia. If the insomnia fails to respond, then consideration should be given to the possibility of inadequate treatment of the primary psychiatric disorder, iatrogenic insomnia, insomnia related to a medical disorder, or a learned/habit insomnia. Persistent insomnia should be aggressively pursued since it has been associated with a variety of adverse outcomes in depressed patients. Treatment should always include inquiring about and encouraging healthy sleeping behaviors even if hypnotic medication is contemplated. Benzodiazepines and nonbenzodiazepine BzRAs have the best evidence for efficacy as hypnotics, although sedating antidepressants are popularly prescribed. Although all benzodiazepine hypnotics and nonbenzodiazepine BzRAs are comparably efficacious in inducing sleep, they vary markedly in their potential for residual side effects. Benzodiazepines are generally administered every night. Intermittent bedtime administration of the nonbenzodiazepine BzRA zolpidem has been shown to provide global improvement in daytime functioning,[54] and growing evidence supports the safety of middle-of-the-night dosing of the nonbenzodiazepine BzRA zaleplon.[56] Finally, every few months the patient should be reassessed to see if the need for treatment still exists.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), nortriptyline (Pamelor and others), sertraline (Zoloft), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, trazodone has not been approved by the U.S. Food and Drug Administration for insomnia, and zaleplon and zolpidem are not approved for long-term use in insomnia.

REFERENCES

1. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey, I. Sleep 1999;22 (suppl 2):S347–S353
2. Haponik EF, Frye AW, Richards B, et al. Sleep history is neglected diagnostic information: challenges for primary care physicians. J Gen Intern Med 1996;11:759–761
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
4. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. J Sleep Res 2000;9:43–48
5. McCall WV. A Practical Guide to Insomnia. Minneapolis, MN: McGraw-Hill Companies; 1999
6. Dryman A, Eaton WW. Affective symptoms associated with the onset of major depression in the community: findings of the US National Institute of Mental Health Epidemiologic Catchment Area Program. Acta Psychiatr Scand 1991;84:1–5
7. Wehr TA, Sack DA, Rosenthal NE. Sleep reduction as a final common pathway in the genesis of mania. Am J Psychiatry 1987;144:201–204
8. Buysse DJ, Reynolds CF III, Hauri PJ, et al. Diagnostic concordance for DSM-IV sleep disorders: a report from the APA/NIMH DSM-IV field trial. Am J Psychiatry 1994;151:1351–1360
9. Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. J Psychiatr Res 1997;31:333–346
10. Cohn JB, Bowden CL, Fisher JG, et al. Double-blind comparison of buspirone and clorazepate in anxious outpatients. Am J Med 1986;80 (suppl 3B):10–16
11. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234–241
12. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. J Clin Psychiatry 1997;58:185–192. Correction 1997;58:275
13. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999; 60:221–225
14. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colín R, et al. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry 1997;58:348–350
15. Bemmel AL, Hoofdakker RH, Beersma DG, et al. Changes in sleep polygraphic variables and clinical state in depressed patients during treatment with citalopram. Psychopharmacology 1993;113:225–230
16. Nowell PD, Reynolds CF III, Buysse DJ, et al. Paroxetine in the treatment of primary insomnia: preliminary clinical and electroencephalogram sleep data. J Clin Psychiatry 1999;60:89–95
17. Armitage R, Emslie G, Rintelmann J. Effects of fluoxetine on sleep EEG in childhood depression [abstract]. Sleep Res 1997;26:369
18. Buysse DJ, Monahan JP, Cherry CR, et al. Persistent effects on sleep EEG following fluoxetine discontinuation [abstract]. Sleep Res 1997;26:370
19. Kupfer DJ, Spiker DG, Coble PA, et al. Amitriptyline and EEG sleep in depressed patients, I: drug effect. Sleep 1978;1:149–159
20. McCall WV, Cohen W, Reboussin B, et al. Effects of mood and age on quality of life in depressed inpatients. J Affect Disord 1999;55:107–114
21. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
22. Agargün MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatry 1997;58:249–251
23. Reynolds CF III, Frank E, Houck PR, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? Am J Psychiatry 1997; 154:958–962
24. Johns MW. Validity of subjective reports of sleep latency in normal subjects. Ergonomics 1997;20:683–690
25. Chervin RD, Aldrich MS, Pickett R, et al. Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. J Psychosom Res 1997;42:145–155
26. Johns MW. A new method for measuring sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–545
27. Schlote B, Schaaf L, Schmidt R, et al. Mental and physical state in subclinical hyperthyroidism: investigations in a normal working population. Biol Psychiatry 1992;32:48–56
28. Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of polysomnography in the evaluation of insomnia. Sleep 1995;18:55–57

29. Morin CM, Culbert JP, Schwartz SM. Nonpharmacologic interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry 1994; 151:1172–1180
30. Dashevsky BA, Kramer M. Behavioral treatment of chronic insomnia in psychiatrically ill patients. J Clin Psychiatry 1998;59:693–699
31. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 1997;278:32–37
32. Mendelson WB. Efficacy of melatonin as a hypnotic agent. J Biol Rhythms 1997;12:651–656
33. Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. Sleep Med 2000;1:91–99
34. Walsh JK, Schweitzer PK. Ten-year trends in the pharmacological treatment of insomnia. Sleep 1999;22:371–375
35. 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
36. Dealberto MJ, McAvay GJ, Seeman T, et al. Psychotropic drug use and cognitive decline among older men and women. Int J Geriatr Psychiatry 1997;12:567–574
37. Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 1997;278:27–31
38. Leveille SG, Buchner DM, Hoepsell TD, et al. Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 1994;5:591–598
39. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA 1989;262: 3303–3307
40. Tonne U, Hiltunen AJ, Vikander B, et al. Neuropsychological changes during steady-state drug use, withdrawal, and abstinence in primary benzodiazepine-dependent patients. Acta Psychiatr Scand 1995;91:299–304
41. Wagner J, Wagner ML, Hening WA. Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. Ann Pharmacother 1998;32:680–691
42. Greenblatt DJ, Wright CE, von Moltke LL, et al. Ketoconazole inhibition of triazolam and alprazolam clearance: differential kinetic and dynamic consequences. Clin Pharmacol Ther 1998;64:237–247
43. Damgen K, Luddens H. Zaleplon displays a selectivity to recombinant $GABA_A$ receptors different from zolpidem, zopiclone, and benzodiazepines. Neuroscience Res Comm 1999;25:139–148
44. Elie R, Rüther E, Farr I, et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. J Clin Psychiatry 1999;60:536–544
45. 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
46. Monti JM. Effect of zolpidem on sleep in insomnia patients. Eur J Clin Pharmacol 1989;36:461–466
47. 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. Correction 1999;1:193
48. Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. Sleep 1995;18: 246–251
49. Scharf MB, Roth T, Vogel GW, et al. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry 1994;55:192–199
50. Shaw SH, Curson H, Coquelin JP. A double-blind, comparative study of zolpidem and placebo in the treatment of insomnia in elderly psychiatric in-patients. J Int Med Res 1992;20:150–161
51. Kummer J, Linden J, Eich FX, et al. Long-term polysomnographic efficacy and safety of zolpidem in elderly psychiatric in-patients with insomnia. J Int Med Res 1993;21:171–184
52. Asnis GM, Chakraburtty A, Duboff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999;60: 668–676
53. Hajak G, Adler L, Bandelow B, et al. Nocturnal melatonin secretion and sleep after doxepin administration in chronic primary insomnia. Pharmacopsychiatry 1996;29:187–192
54. Cluydts R, Peeters K, Bouyalsky I, et al. Comparison of continuous versus intermittent administration of zolpidem in chronic insomniacs: a double-blind, randomized pilot study. J Int Med Res 1998;26:13–24
55. Zolpidem. Physicians Desk Reference. Montvale, NJ: Medical Economics 2001:2627
56. Danjou P, Paty I, Fruncillo R, et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 and 2 h before awakening. Br J Clin Pharmacol 1999;48:367–374
57. Vermeen A, Danjou PE, O'Hanlon JF. Residual driving effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. Hum Psychopharmacology 1998; 13(suppl):98–107
58. Stepanski E, Korshorek G, Zorick F, et al. Characteristics of individuals who do or do not seek treatment for chronic insomnia. Psychosomatics 1989;30:421–427
59. Schlich D, L'Heritier C, Coquelin JP, et al. Long-term treatment of insomnia with zolpidem: a multicentre general practitioner study of 107 patients. J Int Med Res 1991;19:271–279
60. Maarek L, Cramer P, Coquelin JP, et al. The safety and efficacy of zolpidem in insomnia patients: a long-term open study in general practice. J Int Med Res 1991;20:162–170
61. Zaleplon. Physicians Desk Reference. Montvale, NJ: Medical Economics 2001: 3451
62. Cook MD, Conner J. Retrospective review of hypnotic use in combination with fluoxetine and sertraline. Clin Drug Invest 1995;9:2112–2116
63. Nolen WA, Haffmans PMJ, Bouvy PF, et al. Hypnotics as concurrent medication in depression. J Affect Disord 1993;28:179–188
64. Dominguez RA, Jacobson AF, Goldstein BJ, et al. Comparison of triazolam and placebo in the treatment of depressed patients. Curr Ther Res 1984; 36:856–865
65. Cohn JB. Triazolam treatment in depressed patients taking tricyclics. J Clin Psychiatry 1983;44:401–406
66. Chouinard G, Lefko-Singh K, Teboul E. Metabolism of anxiolytics and hypnotics: benzodiazepines, buspirone, zopiclone, and zolpidem. Cell Mol Neurobiol 1999;19:533–552
67. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs 2000;59: 865–889
68. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153:311–320
69. Kawashima K, Hosoi K, Naruke T, et al. Aldehyde oxidase–dependent marked species differences in hepatic metabolism of the sedative-hypnotic, zaleplon, between monkeys and rats. Drug Metab Dispos 1999;27: 422–428