A Physiologic Basis for the Evolution of Pharmacotherapy for Insomnia

Thomas Roth, Ph.D.

Insomnia is a highly prevalent disorder with consequences for the patient's physical and mental health, daily function, and job performance. Although the exact pathophysiology of insomnia is unknown, recent research has demonstrated that normal sleep and wakefulness are controlled by reciprocal inhibition by different brain regions. This sleep-wake control system offers multiple therapeutic targets for the treatment of insomnia; currently, most research and available hypnotic agents target γ-aminobutyric acid (GABA) on the sleep side of the switch. Historically, drugs have evolved from benzodiazepine receptor agonists to nonbenzodiazepines to, most recently, selective extrasynaptic $GABA_A$ receptor agonists. However, these drugs have a differential impact on characteristics of sleep. Among the compounds that modulate the benzodiazepine-sensitive $GABA_A$ receptors, benzodiazepines suppress stage 3–4 sleep, whereas nonbenzodiazepines have no substantial effect on these stages of sleep. Recently, work on GABA agonists indicates that they increase stage 3–4 sleep. This has been demonstrated via sleep-stage scoring as well as with spectral analysis. Further, this increase in stage 3–4 sleep is associated with a decrease in stage 1 sleep and arousals from sleep. Thus, the GABA agonists may not simply promote sleep, but consolidate it as well. The clinical utility of the increase in slow-wave sleep and the sleep consolidation it produces warrants further investigation.

(J Clin Psychiatry 2007;68[suppl 5]:13–18)

Insomnia is a highly prevalent disorder with consequences for the individual's physical and mental health, daily function, and job performance. According to the 2005 Sleep in America poll of more than 1500 randomly selected adults conducted by the National Sleep Foundation, three fourths of Americans have at least 1 sleep problem symptom, such as difficulty falling asleep, multiple awakenings during the night, waking up too early and not being able to fall back asleep, waking up feeling unrefreshed, snoring, restless legs syndrome, or pauses in breathing, a few nights a week.[1] More than half of study participants had experienced a symptom of insomnia, such as difficulty falling asleep, waking in the middle of the night, waking early, or feeling unrefreshed in the morning, several nights a week, whereas a full third of participants reported having such symptoms on a near-nightly basis. The most common symptoms of insomnia were feeling unrefreshed after sleeping (38%) and waking in the middle of the night (32%).[1]

Half of the individuals who participated in the Sleep in America poll reported feeling tired, fatigued, or below par at least 1 day per week. These respondents were far more likely than those who rarely or never feel this way to also report having missed work or events or to have made errors at work at least 1 day in the previous 3 months (43% vs. 14%, respectively).[1] Clearly, sleep disturbances have implications for the day-to-day lives of affected individuals. Individuals who have insomnia are more likely than their well-rested peers to get into industrial or automotive accidents[2]; have work-related problems, such as decreased job performance and increased absenteeism[3]; have neurocognitive impairment in the realms of vigilance, working memory, and motor control[4]; and report mood problems, concentration problems, fatigue, and sleepiness.[4] Insomnia has a complex relationship with depression and many other psychiatric disorders, but the available evidence suggests it represents a 5-fold risk for the subsequent

From the Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, Mich.

This article is derived from the symposium "Understanding Neuronal Pathways: Novel Targets for the Management of Insomnia," a satellite symposium of SLEEP 2006, the 20th Anniversary Meeting of the Associated Professional Sleep Societies (APSS), which was held June 19, 2006, in Salt Lake City, Utah, and supported by an educational grant from Merck and Lundbeck.

Dr. Roth is a consultant for Abbott, Acadia, Acoglix, Actelion, Alchemers, Alza, Ancil, Arena, AstraZeneca, Aventis, Bristol-Myers Squibb, Cephalon, Cypress, Dove, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Jazz, Johnson and Johnson, King, Lundbeck, McNeil, MediciNova, Merck, Neurim, Neurocrine, Neurogen, Novartis, Orexo, Organon, Orginer, Prestwick, Proctor and Gamble, Pfizer, Purdue, Resteva, Roche, Sanofi, Schering-Plough, Sepracor, Servier, Shire, Somaxon, Syrex, Takeda, TransOral, Vanda, Vivometrics, Wyeth, Yamanuchi, and Xenoport; has received grant/research support from Aventis, Cephalon, GlaxoSmithKline, Neurocrine, Pfizer, Sanofi, Schering-Plough, Sepracor, Somaxon, Syrex, Takeda, TransOral, Wyeth, and Xenoport; and is a member of the speakers/advisory boards for Sanofi and Takeda.

Corresponding author and reprints: Thomas Roth, Ph.D., Sleep Disorders and Research Center, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202 (e-mail: troth1@hfhs.org).

development of depression and that treating the insomnia helps alleviate comorbid psychiatric disorders.[5] Hypnotic agents commonly used to facilitate sleep and treat insomnia include zolpidem, zaleplon, eszopiclone, and ramelteon. In some cases, benzodiazepines may also be used.

INSOMNIA, THE SLEEP-WAKE CYCLE, AND HYPNOTIC AGENTS

Wakefulness is thought to be the result of activation in the thalamus and cerebral cortex; when these systems are shut off by the hypothalamus, sleep results.[6] Sleep induction is centered in the ventrolateral preoptic nucleus (VLPO), which innervates neurons thought to influence transitions between wakefulness and non–rapid eye movement (NREM) sleep.[6] The wake- and sleep-promoting centers are mutually inhibitory. During waking periods, the VLPO is inhibited by monoaminergic inputs, whereas during sleep, VLPO projections dampen the firing of these same neurons. This is known as a "flip-flop switch" and has the advantage that it can produce quick and stable transitions from wake to sleep and sleep to wake.[6]

Sleep can be divided into 2 states: NREM sleep, which is further subdivided into stages 1–4, and rapid eye movement (REM) sleep. In stage 2, the individual's brain waves begin to slow and eye movements stop. Stages 3 and 4 comprise deep sleep and are characterized by slow delta waves.[7] Slow-wave sleep originates in the thalamocortical pathways and only begins once hypothalamic signals dampen activating inputs to these pathways.[8] When an individual transitions from NREM to REM sleep, ascending cholinergic activation shuts off the thalamocortical oscillations associated with NREM sleep.[8] REM sleep, in which dreaming occurs, is characterized by rapid, irregular breathing and eye movements. In normal human sleep, several of these NREM-REM cycles occur nightly, each lasting approximately 90–110 minutes.[7]

Insomnia is defined as difficulty initiating or maintaining sleep, or nonrestorative sleep associated with some negative daytime consequence or daytime distress.[9] The pathophysiology of insomnia is not fully understood. Many cases, however, are thought to have their origins in poorly timed central nervous system arousal. Substances such as caffeine or activities such as stressful nighttime work that result in central nervous system arousal may interfere with sleep, dominated by parasympathetic nervous system activity. This cycle of stress-induced arousal and consequent sleeplessness may become self-reinforcing; individuals who have difficulty sleeping may develop anxiety surrounding falling asleep that takes the place of the original stressor.[10] Behavioral treatments for insomnia may focus on teaching the sleepless individual to avoid stimulating activities near bedtime and/or changing the thought patterns that contribute to sleep-related anxiety.

Hypnotic medications facilitate sleep by acting directly on pathways involved in sleep. Most hypnotic medications are GABAergic and promote sleep by directly dampening the arousal system. At low doses, these agents are thought to facilitate the GABAergic dampening of the arousal system by the VLPO, whereas at higher doses these agents act as general central nervous system depressants. Available benzodiazepine receptor agonists (BZRAs) vary in their selectivity: benzodiazepines bind all benzodiazepine receptors containing γ and α-1, -2, -3, or -5 subunits, whereas nonbenzodiazepine agents such as zolpidem and eszopiclone bind preferentially to benzodiazepine receptors with both γ and α-1 subunits. Gaboxadol, a new hypnotic agent under development, differs from these other agents in that it binds to receptors with δ and α-4 subunits, which are located primarily in the thalamus, limbic system, and cerebral cortex.[6] Although hypnotic agents all promote sleep, they have different effects on stages of sleep, particularly slow-wave sleep, which may have implications for the quality of the sleep they produce.

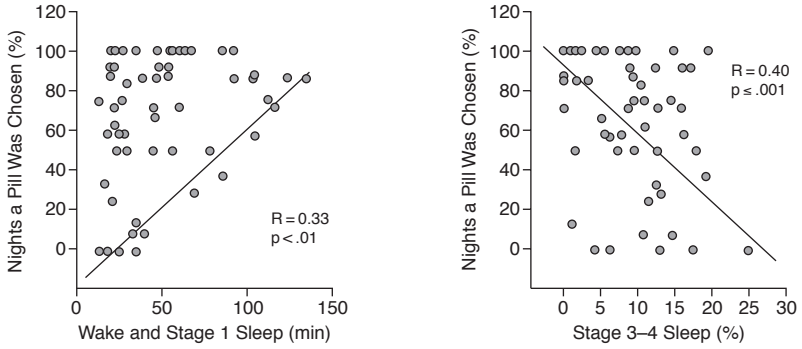
IMPORTANCE OF SLOW-WAVE SLEEP

The exact function of slow-wave (stage 3–4) sleep is not known. It is thought that slow-wave sleep serves to maintain synaptic homeostasis by downscaling synaptic strength, which increases during waking cortical activity, thus maintaining overall synaptic weight while preserving relative changes in synaptic strength. If there were not some sort of synaptic downscaling system, the brain's already heavy energy requirements would steadily increase, and there would be small increases in synaptic volume that may have the potential to be dangerous.[11] In addition, the lower a patient's proportion of stage 3–4 sleep to stage 1 sleep and wakefulness, the more likely a patient is to self-administer a sleep-promoting agent (Figure 1).[12] Thus, although its exact function is not known, slow-wave sleep seems to play a key role in determining sleep quality.

As a class, benzodiazepines usually decrease slow-wave sleep.[13] For example, in volunteer participants (N = 8) without a history of sleep disturbances who received 15, 26, or 45 mg of flurazepam or placebo in double-blind crossover fashion over the course of four 3-day study visits (1 placebo and 2 treatment nights), all doses of flurazepam resulted in significantly less stage 3–4 sleep than was seen with placebo ($p < .001$ overall, $p < .05$ for each dose).[14] In contrast, phenobarbital has no effect on the proportion of time spent in stage 3–4 sleep relative to placebo.[15]

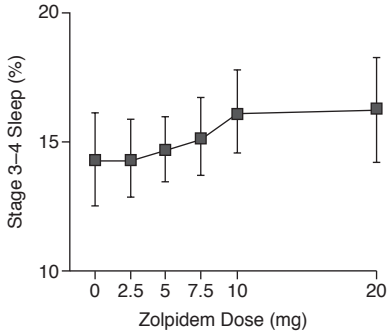
In normal sleepers undergoing a model of transient insomnia, the BZRA hypnotics zolpidem[16] and eszopiclone[17] have no effects on stage 3–4 sleep relative to placebo (Figure 2). Zaleplon, in contrast, increases stage 3–4 sleep.

Figure 1. Slow-Wave Sleep and Self-Administration of a Sleep-Promoting Agent[a]



[a]Adapted with permission from Roehrs et al.[12]

Figure 2. Effects of Zolpidem on Slow-Wave Sleep[a]



[a]Adapted with permission from Merlotti et al.[16]

Normal sleepers attempting to sleep during the day experienced significantly more sleep with zaleplon compared with placebo (54 vs. 37.4 minutes, respectively; p = .034).[18]

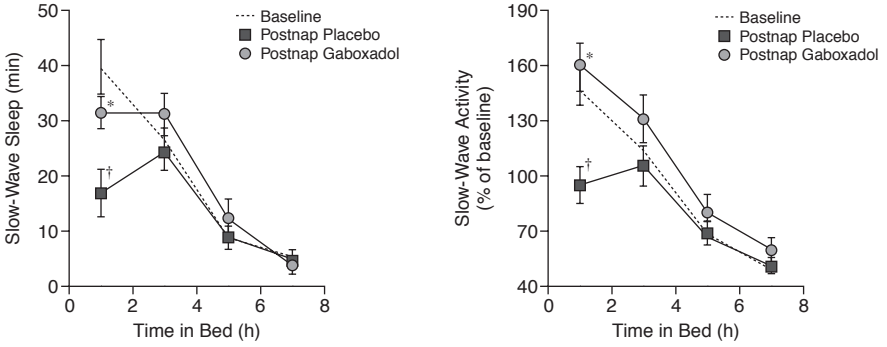
Gaboxadol, a selective extrasynaptic $GABA_A$ agonist, has been shown to consistently increase slow-wave sleep in terms of both sleep stages and slow-wave activity. The effects of gaboxadol 20 mg on sleep were assessed in healthy young individuals without sleep disturbances who had had a 2-hour nap on the day of testing.[19] Because naps reduce sleep drive, postnap sleep is an effective means of modeling disrupted sleep in healthy individuals who do not routinely have problems with their sleep quality. Patients who received gaboxadol experienced significantly more slow-wave sleep than did patients who received placebo (78.4 vs. 54.2 minutes, respectively; p < .05) and experienced an amount of slow-wave sleep not statistically different from the amount achieved when these healthy sleepers slept without having napped (79.6 minutes). The effect of gaboxadol on slow-wave sleep was particularly marked on stage 4 sleep during the first 2 hours of sleep (Figure 3).[19] An increase in slow-wave sleep has also been demonstrated in healthy elderly subjects.[20]

In a separate study, gaboxadol improved polysomnograph sleep measures, including slow-wave measures, and demonstrated distinct differences from zolpidem in slow-wave sleep.[21] Healthy volunteers (N = 109) first had a placebo-controlled night of normal sleep and then, on a second night on which they went to bed 4 hours early to mimic the effects of transient insomnia, were randomly assigned to receive either gaboxadol (5, 10, or 15 mg) or zolpidem (10 mg). Gaboxadol increased the power density of low-frequency brain waves (delta and theta frequencies) in a dose-dependent manner, but had no effect on high frequencies. In addition, higher doses of gaboxadol (10 and 15 mg) both increased the power density of slow-wave bands and decreased that of the high alpha band. In contrast, zolpidem (10 mg) suppressed the power density of low-frequency brain waves and had no significant effect on the slow-wave activity range. Finally, like gaboxadol, it decreased the alpha band.[21]

As in previous studies with models of transient insomnia, gaboxadol improved slow-wave sleep in a group of patients with primary insomnia. Patients who received 15 mg of gaboxadol experienced significantly more slow-wave sleep than did patients who received placebo (114 vs. 93.9 minutes; p < .001) and also reported their quality of sleep and ability to get to sleep as being significantly better than with placebo.[22]

There is growing evidence that agents that increase slow-wave sleep can reverse some of the cognitive deficits that result from decreased total sleep time. Healthy adults (N = 38) underwent 4 nights in which their sleep was restricted to 5 hours per night and received either tiagabine 8 mg or placebo prior to bedtime.[23] Prior experiments had demonstrated that tiagabine, a selective GABA-reuptake inhibitor, increases slow-wave sleep in primary insomnia,[24] and slow-wave sleep was also increased in the normal but sleep-restricted patients in this sample. After 4

Figure 3. Gaboxadol Promotes Slow-Wave Sleep During Postnap Sleep[a]



[a]Adapted with permission from Mathias et al.[19]
*p < .05 vs. postnap placebo.
†p < .05 vs. baseline.

Table 1. Performance on Wisconsin Card-Sorting Task in Sleep-Restricted Individuals Receiving Tiagabine or Placebo[a,b]

Group	Total Trials	Total Errors	Perseverative Errors	Trials to Complete First Category	Percentage Correct
Tiagabine (N = 17)	82.2 (15.1)	13.7 (8.9)	6.8 (3.8)	11.5 (1.0)	84.2 (6.3)
Placebo (N = 18)	95.7 (20.9)	21.7 (13.3)	10.9 (7.1)	14.8 (4.5)	79.0 (8.9)
p Value	.036	.047	.044	.007	.049

[a]Adapted with permission from Walsh et al.[23]
[b]Data shown as mean (SD).

nights of restricted sleep, the participants were asked to perform various cognitive tasks, including the psychomotor vigilance task and Wisconsin card-sorting task (Table 1). Unlike participants who received placebo, participants who had received tiagabine demonstrated no impairment in the psychomotor vigilance task and better performance on the Wisconsin card-sorting task.[23]

SLEEP LATENCY

Difficulty falling asleep is one of the sleep complaints of individuals with insomnia and, as such, represents a key outcome variable when assessing the efficacy of hypnotic agents, regardless of the agent's mechanism of action.

Zolpidem reduces the latency to persistent sleep. Sleep latency was significantly shorter with zolpidem than with placebo for all doses except for the lowest dose (2.5 mg).[16] In a head-to-head study of zolpidem and zaleplon, patients with primary insomnia with a sleep latency ≥ 30 minutes and an average sleep time ≤ 6.5 hours received zaleplon 5 mg, zaleplon 10 mg, zaleplon 20 mg, zolpidem 10 mg, or placebo nightly for a month after a 7-night placebo run-in. Sleep latency was assessed via questionnaires, which were returned to the study site on a weekly basis. All doses of zaleplon and zolpidem reduced the median sleep latency at week 1; zaleplon 10 and 20 mg reduced it consistently for all 4 weeks of the study, whereas zaleplon 5 mg and zolpidem reduced it consistently through week 3.[25]

Patients with primary insomnia (N = 788) reported reduced sleep latency in a 6-month trial of eszopiclone 3 mg starting at week 1 and persisting for the entire 6 months of treatment.[26] Study participants provided information regarding sleep latency, sleep time, sleep quality, and other variables via an automated voice-response system, which they called weekly.[26] Eszopiclone also reduced sleep latency in the elderly.[27] Older patients with primary insomnia (ages 65 to 85) (N = 231) who slept > 6.5 hours a night and met a 30-minute sleep latency minimum were randomly assigned to receive placebo, eszopiclone 1 mg, or eszopiclone 2 mg for 2 weeks. Data were collected via twice-daily (upon waking and at bedtime) patient calls to an automated voice-response system. Eszopiclone 2 mg significantly reduced the average sleep latency compared with placebo (50 vs. 85.5 minutes, respectively; p = .0034), although the average sleep latency with the 1-mg dose was not significantly different from that achieved with placebo.

Gaboxadol has been shown to reduce sleep latency in patients with primary insomnia. Patients with primary insomnia who also met a sleep latency minimum and did not exceed a maximum total sleep time (N = 26) were ran-

domly assigned to receive placebo, gaboxadol 5 mg, or gaboxadol 15 mg on each of 3 study visits, such that all patients were exposed to all 3 treatment conditions in varying order. Gaboxadol 15 mg significantly shortened the latency to persistent sleep, relative to placebo (23.6 vs. 30 minutes, respectively; $p < .05$).[22] Gaboxadol has also been shown to shorten sleep latency in elderly subjects compared with placebo (18.1 vs. 28.5 minutes, respectively; $p < .05$).[20]

SLEEP QUALITY

Good sleep quality is associated with feelings of being refreshed, even when an inadequate amount of time is devoted to sleep. Improvement in sleep quality, along with sleep efficiency and duration, predicts an individual's feeling that his or her sleep has improved[28] and thus is a notable, if highly subjective, outcome variable.

In a head-to-head study of zaleplon and zolpidem for primary insomnia, zaleplon 10 and 20 mg, and zolpidem 10 mg, but not zaleplon 5 mg, were associated with better mean sleep quality, scored by the patient on a scale from 1 (excellent) to 7 (extremely poor), than placebo for the first week of treatment; however, in weeks 2, 3, and 4, only zolpidem 10 mg was associated with significantly better sleep quality than placebo.[25] Patients with primary insomnia receiving 6 months' treatment with eszopiclone experienced significantly greater median sleep quality than patients receiving placebo for all time points.[26]

Gaboxadol has also been shown to improve sleep quality in elderly patients, a population in which disrupted sleep and poor-quality sleep are common. Older volunteers (ages 63–78 years) without sleep disturbances or disorders received either placebo or gaboxadol for a 3-night study. Study participants rated their sleep quality as better (8.3 vs. 7.3 on a 10-point visual analog scale, where 0 = bad and 10 = good; $p < .05$) and their sleep as more intense (7.7 vs. 7.2 on a 10-point visual analog scale, where 0 = superficial and 10 = deep; $p < .05$) on nights when they received gaboxadol.[20]

CONCLUSIONS

The sleep-wake control system allows multiple intervention points for both wakefulness- and sleep-promoting agents. The high prevalence of sleep disorders in general, and insomnia specifically, in the general population points to a clear need for effective sleep-promoting agents, a need that has been filled largely by GABAergic agents. The most commonly prescribed GABAergic hypnotics are diffusely active. These agents effectively decrease sleep latency and improve sleep quality in patients with insomnia. Newer, more targeted agents, however, promote slow-wave sleep, which may provide cognitive and functional benefits.

Drug names: eszopiclone (Lunesta), flurazepam (Dalmane and others), phenobarbital (Luminal and others), ramelteon (Rozerem), tiagabine (Gabitril), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, gaboxadol, phenobarbital, and tiagabine are not approved by the U.S. Food and Drug Administration for the treatment of insomnia.

REFERENCES

1. National Sleep Foundation. 2005 Sleep in America Poll. Washington, DC: National Sleep Foundation; 2005
2. Roth T. Prevalence, associated risks, and treatment patterns of insomnia. J Clin Psychiatry 2005;66(suppl 9):10–13
3. Kuppermann M, Lubeck DP, Mazonson PD, et al. Sleep problems and their correlates in a working population. J Gen Intern Med 1995;10: 25–32
4. Varkevisser M, Kerkhof GA. Chronic insomnia and performance in a 24-h constant routine study. J Sleep Res 2005;14:49–59
5. Thase ME. Correlates and consequences of chronic insomnia. Gen Hosp Psychiatry 2005;27:100–112
6. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257–1263
7. National Institute of Neurological Disorders and Stroke. Brain Basics: Understanding Sleep. Bethesda, Md: National Institutes of Health; 2003
8. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat Rev Neurosci 2002;3: 679–693
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
10. Ting L, Malhotra A. Disorders of sleep: an overview. Prim Care 2005;32:305–318
11. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev 2006;10:49–62
12. Roehrs T, Bonahoom A, Pedrosi B, et al. Disturbed sleep predicts hypnotic self-administration. Sleep Med 2002;3:61–66
13. Wagner J, Wagner ML, Hening WA. Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. Ann Pharmacother 1998;32:680–691
14. Karacan I, Orr W, Roth T, et al. Dose-related effects of flurazepam on human sleep-walking patterns. Psychopharmacology (Berl) 1981;73: 332–339
15. Karacan I, Orr W, Roth T, et al. Dose-related effects of phenobarbitone on human sleep-waking patterns. Br J Clin Pharmacol 1981;12: 303–313
16. Merlotti L, Roehrs T, Koshorek G, et al. The dose effects of zolpidem on the sleep of healthy normals. J Clin Psychopharmacol 1989;9: 9–14
17. Rosenberg R, Caron J, Roth T, et al. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. Sleep Med 2005;6:15–22
18. Whitmore JN, Fischer JR Jr, Storm WF. Hypnotic efficacy of zaleplon for daytime sleep in rested individuals. Sleep 2004;27:895–898
19. Mathias S, Steiger A, Lancel M. The GABA(A) agonist gaboxadol improves the quality of post-nap sleep. Psychopharmacology (Berl) 2001;157:299–304
20. Mathias S, Zihl J, Steiger A, et al. Effect of repeated gaboxadol administration on night sleep and next-day performance in healthy elderly subjects. Neuropsychopharmacology 2005;30:833–841
21. Walsh JK, Deacon S, Dijk DJ, et al. Gaboxadol improves sleep onset and maintenance and enhances low-frequency components of NREM sleep EEG in a model of transient insomnia. Presented at the 159th annual meeting of the American Psychiatric Association; May 20–25, 2006; Toronto, Ontario, Canada
22. Deacon S, Staner L, Vorstrup S, et al. Acute administration of gaboxadol improves sleep initiation and maintenance in patients with primary insomnia. Presented at the SLEEP 2005 annual meeting of the Associated Professional Sleep Societies; June 18–23, 2005; Denver, Colo
23. Walsh JK, Randazzo AC, Stone K, et al. Tiagabine is associated with

sustained attention during sleep restriction: evidence for the value of slow-wave sleep enhancement? Sleep 2006;29:433–443
24. Walsh JK, Zammit G, Schweitzer PK, et al. Tiagabine enhances slow wave sleep and sleep maintenance in primary insomnia. Sleep Med 2006;7:155–161
25. Elie R, Ruther 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
26. 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
27. Scharf M, Erman M, Rosenberg R, et al. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. Sleep 2005;28:720–727
28. Vincent N, Penner S, Lewycky S. What predicts patients' perceptions of improvement in insomnia? J Sleep Res 2006;15:301–308

