

Introduction

Understanding Neuronal Pathways: Novel Targets for the Management of Insomnia

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Sleep disorders, particularly insomnia, are highly prevalent and remain underdiagnosed and undertreated within the United States and throughout the developed world. The 2005 Sleep in America poll, conducted by the National Sleep Foundation, revealed that more than 75% of adult Americans experience at least 1 symptom of a sleep disorder more than 1 night per week.¹ Fifty-four percent of the 1506 respondents reported experiencing at least 1 symptom of disturbed sleep, and 33% reported suffering from insomnia almost every night. The most common symptoms of insomnia were “waking up feeling unrefreshed” (38%) and “waking up a lot during the night” (32%). Other commonly reported symptoms included “difficulty falling asleep” (21%) and “waking up too early and not being able to get back to sleep” (21%).¹ The personal and societal costs of insomnia are enormous. Insomnia is associated with increased direct health care costs, as well as with indirect costs related to lost productivity and accidents. Individuals with insomnia report lower quality of life and impaired daily functioning and are more likely to develop depression.

Insomnia interacts with other aspects of mental and general health. Problems with sleep initiation or maintenance can be caused or aggravated by comorbid psychiatric disorders, medical illnesses, and the medications that treat them. In turn, research suggests that insomnia substantially increases the risk of new and recurrent bouts of depression and can promote poorer outcomes in psychiatric and medical illnesses.² Effective management of primary and secondary insomnia, including both medication and nonpharmacologic modalities, is therefore critical.

Potential therapeutic targets for the treatment of insomnia include γ -aminobutyric acid (GABA), the chief inhibitory neurotransmitter of the mammalian central nervous system (CNS), and melatonin, but most available pharmacotherapies modulate GABA receptor function. Barbiturates have been largely supplanted by benzodiazepine receptor agonists (BZRAs), which include both benzodiazepine and newer nonbenzodiazepine GABA_A receptor agonists. Most recently, selective extrasynaptic GABA_A agonists have been developed that may provide additional treatment options. Each of these drug classes targets the GABA_A receptors within the CNS, but they modulate different receptor subunits/inhibitory pathways and, therefore, differ in their effects on a variety of CNS functions.

Barbiturates decrease rapid eye movement (REM) sleep,³ and benzodiazepines suppress stage 3–4 sleep, known as slow-wave sleep.⁴ The function of slow-wave sleep is not clearly understood, but it is hypothesized to play an important role in determining sleep quality. Several of the newer nonbenzodiazepine receptor agonists do not lead to deficits in REM sleep or slow-wave sleep.^{5–8} Given the shortcomings of available therapies, researchers continue to search for compounds that modulate GABA_A receptors with increased efficacy, but with few or no adverse effects. Of experimental agents in development, gaboxadol, or THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol), has been shown to increase sleep duration through the activation of extrasynaptic GABA_A receptors, increasing slow-wave sleep without altering REM sleep.^{9,10}

The relationship between individual GABA_A receptor binding profile and treatment efficacy has been explored

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in recent studies. BZRAs are known to modulate synaptic GABA_A receptors expressed ubiquitously throughout the CNS.^{11–13} These agents initiate and maintain sleep via a general depression of the CNS. In contrast, the GABA_A agonist gaboxadol selectively targets the extrasynaptic receptors that have been shown to modulate tonic inhibitory currents.^{14,15} Preliminary research suggests that extrasynaptic GABA_A receptors desensitize more slowly and have a greater affinity for GABA compared with their synaptic counterparts; consequently, agents targeting extrasynaptic GABA_A receptors may offer more sustained sleep-promoting efficacy.

Through this unique and highly specific mechanism, gaboxadol activates GABA_A receptors in the ventrolateral preoptic nucleus (VLPO), believed to be a primary sleep-promoting region in the brain.¹⁶ Located in the hypothalamus, the VLPO comprises a key component in a theoretical “sleep-switch” that balances the arousal and sleep states of the CNS. During arousal, neuronal pathways from the wakefulness-promoting regions within the hypothalamus activate the cortex, and inhibitory connections decrease activity in the VLPO. Conversely, when the VLPO becomes active, it releases GABA and galanin to inhibit the arousal regions of the hypothalamus, thereby inducing sleep. Currently in phase III development, gaboxadol targets a different subset of GABA_A receptors from those targeted by BZRAs; hence, these receptors represent a novel therapeutic target for the management of insomnia.¹⁷

The potential role of cognitive-behavioral therapy (CBT) as an adjunct to pharmacotherapy is also being explored. A recent National Institutes of Health State-of-the-Science report stated that CBT may be “as effective as prescription medications are for short-term treatment of chronic insomnia.”¹⁸ Clinical studies have provided conflicting data on the efficacy of CBT interventions in conjunction with pharmacotherapy. However, these studies usually evaluated older benzodiazepines (e.g., temazepam, estazolam, flurazepam) administered at doses lower than those typically used in patients with insomnia.^{19–21} Nonetheless, CBT has shown clinical effectiveness in patients with insomnia, and its use as an adjunct to available and experimental pharmacologic agents may further improve the management of this currently underserved patient population.

This supplement includes 3 reviews describing the current state of and recent developments in the treatment of insomnia. Roth discusses the physiology of sleep in the context of hypnotic drug development. Harrison characterizes the GABA_A receptor subgroups and their relationship to sleep and describes ways in which current and future drugs targeting these receptors might impact the various components of the sleep cycle. Finally, Mendelson reviews the potential role of CBT and other nondrug thera-

pies both as monotherapy and as an adjunct to hypnotic medication.

Drug names: estazolam (ProSom and others), flurazepam (Dalmane and others), temazepam (Restoril and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, gaboxadol is 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. Thase ME. Correlates and consequences of chronic insomnia. *Gen Hosp Psychiatry* 2005;27:100–112
3. 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
4. Karacan I, Orr W, Roth T, et al. Dose-related effects of flurazepam on human sleep-waking patterns. *Psychopharmacology (Berl)* 1981;73:332–339
5. 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
6. 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
7. Whitmore JN, Fischer JR Jr, Storm WF. Hypnotic efficacy of zaleplon for daytime sleep in rested individuals. *Sleep* 2004;27:895–898
8. Glass J, Lancot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;331:1169
9. Mathias S, Steiger A, Lancel M. The GABA(A) agonist gaboxadol improves the quality of post-nap sleep. *Psychopharmacology (Berl)* 2001;157:299–304
10. 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
11. Nusser Z, Roberts JD, Baude A, et al. Immunocytochemical localization of the alpha 1 and beta 2/3 subunits of the GABA_A receptor in relation to specific GABAergic synapses in the dentate gyrus. *Eur J Neurosci* 1995;7:630–646
12. Sun C, Sieghart W, Kapur J. Distribution of alpha 1, alpha 4, gamma 2, and delta subunits of GABA_A receptors in hippocampal granule cells. *Brain Res* 2004;1029:207–216
13. Pirker S, Schwarzer C, Wieselthaler A, et al. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* 2000;101:815–850
14. Krogsgaard-Larsen P, Frolund B, Liljefors T, et al. GABA(A) agonists and partial agonists: THIP (Gaboxadol) as a non-opioid analgesic and a novel type of hypnotic. *Biochem Pharmacol* 2004;68:1573–1580
15. Wafford KA, Ebert B. Gaboxadol: a new awakening in sleep. *Curr Opin Pharmacol* 2006;6:30–36
16. Lu J, Sanchez C, Saper CB, et al. Gaboxadol activates endogenous sleep control mechanisms. Abstracts of the 33rd Annual Meeting of the Society for Neuroscience; Nov 8–12, 2003; New Orleans, La. Program No. 617.1
17. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;437:1257–1263
18. National Institutes of Health. NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. Bethesda, Md: National Institute of Health; 2005. Available at: <http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm>. Accessibility verified March 12, 2007
19. Rosen RC, Lewin DS, Goldberg L, et al. Psychophysiological insomnia: combined effects of pharmacotherapy and relaxation-based treatments. *Sleep Med* 2000;1:279–288
20. Morin CM, Colechi C, Stone J, et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA* 1999;281:991–999
21. Jacobs GD, Pace-Schott EF, Stickgold R, et al. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med* 2004;164:1888–1896