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.

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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

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 therapies 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.

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