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Treating insomnia: Current and investigational pharmacological approaches

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Abstract

Chronic insomnia affects a significant proportion of young adult and elderly populations. Treatment strategies should alleviate nighttime symptoms, the feeling of nonrestorative sleep, and impaired daytime function. Current pharmacological approaches focus primarily on GABA, the major inhibitory neurotransmitter in the central nervous system. Benzodiazepine receptor agonists (BzRA) have been a mainstay of pharmacotherapy; the classical benzodiazepines and non-benzodiazepines share a similar mode of action and allosterically enhance inhibitory chloride currents through the $GABA_A$ receptor, a ligand-gated protein comprising 5 subunits pseudosymmetrically arranged around a core anion channel. Variations in $GABA_A$ receptor subunit composition confer unique pharmacological, biophysical, and electrophysiological properties on each receptor subtype. Classical benzodiazepines bind non-selectively to $GABA_A$ receptors containing a $\gamma 2$ subunit, whereas non-benzodiazepine hypnotics bind with higher relative affinity to $\alpha 1$-containing receptors. The non-benzodiazepine compounds generally represent an improvement over benzodiazepines as a result of improved binding selectivity and pharmacokinetic profiles. However, the enduring potential for amnestic effects, next day residual sedation, and abuse and physical dependence, particularly at higher doses, underscores the need for new treatment strategies. Novel pharmacotherapies in development act on systems believed to be specifically involved in the regulation of the sleep–wake cycle. The recently approved melatonin receptor agonist, ramelteon, targets circadian mechanisms. Gaboxadol, an investigational treatment and a selective extrasynaptic $GABA_A$ receptor agonist (SEGA), targets $GABA_A$ receptors containing a δ subunit, which are located outside the synaptic junctions of thalamic and cortical neurons thought to play an important regulatory role in the onset, maintenance, and depth of the sleep process.

Keywords: $GABA_A$ receptors; Selective extrasynaptic GABA agonist (SEGA); Benzodiazepine receptor agonists (BzRA); Benzodiazepines; Non-benzodiazepines; Insomnia; Sleep initiation and maintenance disorders; Slow wave sleep (SWS); Slow wave activity (SWA); 5-$HT_{2A/C}$ antagonists; Melatonin receptor agonists

Contents

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1. Introduction

Approximately 1 in 4 adults experiences insomnia at some time; at least 10% of the general population consider the problem to be chronic (Mendelson et al., 2004; Sateia & Nowell, 2004). Insomnia patients have difficulty initiating or maintaining sleep, or experience sleep that is otherwise nonrestorative, resulting in daytime fatigue, impaired concentration, and reduced psychological well-being (Leger & Poursain, 2005; Leger et al., 2006). These individuals are also more likely to miss work and to experience reduced productivity and other functional impairments than those without sleep difficulties, to have more road accidents, and to utilize more medical services (Simon & VonKorff, 1997; Zammit et al., 1999; Leger et al., 2006). A recent small laboratory study has suggested that patients with chronic insomnia do exhibit impairments in psychomotor functioning as well as mood and other subjective disturbances (Varkevisser & Kerkhof, 2005). Insomnia has been shown to impair the quality of life to at least the same extent as that observed with other chronic conditions such as diabetes, arthritis, and heart disease (Katz & McHorney, 2002). The economic implications of this burden have been discussed in several recent articles (Simon & VonKorff, 1997; Brunello et al., 2000; Drake et al., 2003). The significant individual, social, and economic effects of insomnia underscore the need for effective treatments that are well tolerated.

Many patients self-medicate with non-prescription histamine-1 receptor antagonists such as diphenhydramine and doxylamine, which are marketed as sleep aids, despite little rigorous evidence of their efficacy and their acknowledged residual effects (Mendelson et al., 2004). Off-label prescribing of antidepressants such as trazodone or the tricyclic doxepin is also a common practice, probably because these agents are unscheduled. Some data suggest a degree of efficacy for trazodone in particular; however, this agent carries a risk of hypotension, dizziness, and daytime sedation, and doxepin is associated with cardiotoxic effects. Thus, either agent should be prescribed with caution, especially to elderly patients. Further consideration of H-1 antagonists or the off-label use of antidepressants for insomnia is beyond the scope of this review.

Among pharmacologic treatments currently approved for insomnia, the GABAergic benzodiazepine receptor agonists (BzRA) are preponderant. Considerable data and long clinical experience with the class have established the hypnotic efficacy of these agents. However, concerns exist about residual effects and the potential for abuse and dependence. A further question concerns their effects on the architecture of sleep (the patterning of sleep stages throughout the night, as revealed in the electroencephalogram [EEG]); while the BzRA improve sleep length and continuity, they do not normalize sleep architecture (Perlis et al., 1997). The clinical significance of these alterations is as yet unknown. New treatments are emerging, including the recently approved melatonin agonist ramelteon, which is unscheduled; the late-stage investigational compound gaboxadol, which influences GABAergic neurotransmission through a novel mechanism, with potentially important clinical ramifications; and several 5-HT_{2A} inhibitors.

Following a brief overview of some of the major causes of insomnia, we review the structure and neurobiology of sleep as prelude to an examination of the preclinical and clinical profiles of currently approved and emerging pharmacotherapies. Nonpharmacological treatments such as cognitive behavioral therapy (CBT) have demonstrated efficacy (Sateia & Nowell, 2004), but these fall outside our current focus.

2. Pathogenesis of insomnia

Similar presentations of insomnia may have different underlying causes. Complicating matters is the likelihood that multiple contributory factors may be present in an individual, as well as the fact that insomnia may be sustained by maladaptive coping behavior (Perlis et al., 1997). The hallmark of so-called psychophysiologic insomnia, a form of primary insomnia, is autonomic hyperarousal, apparent in increased metabolic rate and secretion of cortisol (Vgontzas et al., 2001). These individuals also report greater presleep arousal than do good sleepers (Morin et al., 2003), a fact confirmed by electroencephalographic data, which indicate heightened arousal at sleep onset and during sleep (Merica et al., 1998). Additionally, there is evidence to suggest that, paradoxically, patients with