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Viewpoint

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ACS Chemical Neuroscience Molecule Spotlight on Suvorexant

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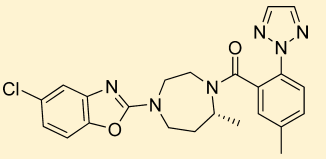
ABSTRACT: Suvorexant is a dual orexin antagonist currently in Phase III clinical trials for the modulation of sleep and is being developed by Merck. Recent Phase III results showed that patients taking the drug fell asleep faster and slept longer than those on placebo.



Suvorexant
Merck's Dual Orexin antagonist

KEYWORDS: *Sleep, insomnia, novel mechanism, orexin antagonist, bioavailability (F)*

Sleep, something all adults can use more of. However, for a large portion of adults, sleep is something that is very elusive. In fact, nearly one-third of all adults in the U.S. report weekly difficulties with sleep (reported as insomnia, a condition characterized by difficulty falling asleep, maintaining sleep, waking early, or experiencing nonrestorative sleep) and the overall numbers add up to a staggering toll on the workplace financially.[1] In a recent article, Kessler et al. estimated the total cost due to lack of sleep to be $63.2 billion in the U.S. alone, a number that amounts to nearly $2,300 dollars per worker.[2] Digging into the numbers further reveals that the average worker loses ∼11 days per year, nearly 50−70 million American employees report being impaired due to poor sleep, and an estimated 23% of workers are sleep deprived due to insomnia. Due to this, it is no wonder that the annual coffee market is nearly $40 billion and the amount people spend on sleep medications is approximately $200/year.[2]

The pharmaceutical industry has invested extensively in this lucrative market with the approvals of the very popular central nervous system agents that enhance signaling of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Although these agents were first discovered in the 1960s, later generations, known as nonbenzodiazepines, dominated the sleep market in the late 1990s and early 2000s. The most popular of this class of compounds, zolpidem (Ambien), reached peak sales in 2005 and 2006 with nearly $2 billion in sales per year.[3] Even though these newer generation agents addressed many of the issues with previous generations, they have generated their own concerns with reports of unexplained sleep walking and sleep driving, as well as other CNS-related adverse effects after long-term use. Ambien has been off-patent since 2007, with another similar compound eszopiclone (Lunesta) still being a prescribed sleep aid with 2010 sales nearly $950 million.[4] Despite the popularity of the GABA compounds as sleep aids, there are several issues that still raise many questions as to their use, namely, the fact that all of these compounds are classified as controlled substances and the label change that was required by the FDA (so-called, back-box warnings).[5] Due to these critical issues with GABA modulators, the search for novel mechanisms that can help with sleep issues is still a major research endeavor. The only compound with a novel mechanism of action to be approved by the FDA in over three decades was the melatonin receptor antagonist ramelteon (Rozerem), which was approved in 2005.[6] Even with this approval, there still remains significant improvement needed in sleep agents for general use.

Over the past several years, a novel mechanism for modulating sleep that has gained significant popularity is the orexin system due to its highly conserved nature and its ability to regulate arousal and wakefulness.[7] Neurons in the lateral hypothalamus produce the neuropeptides orexin A and orexin B, which then bind to the orexin receptors 1 and 2 (OX_1R and OX_2R).[8] Further understanding of the orexin system and significant medicinal chemistry has led to three clinical candidates, with the most recent compound being reported by the Merck Research Laboratories as MK-4305 or suvorexant.[9] Suvorexant is a potent antagonist of both OX_1R (0.55 nM, FLIPR) and OX_2R (0.35 nM, FLIPR) with excellent pharmacokinetic properties in both rat (F = 19%) and dog (F = 56%).[9a] The preclinical efficacy was shown in telemetry-implanted mice, and suvorexant was shown to significantly impact sleep behavior at 30 mg/kg with increases in both REM and delta sleep.[9a] In addition, the researchers measured the occupancy (*ex vivo*) in a transgenic line of mice that overexpress the human OX_2R in the brain. In this study, it was shown that at an IV dose of 1.3 mg/kg, suvorexant displayed 90% occupancy of the receptor (Occ90), which corresponds to 13 nM CSF levels. Based on the 30 mg/kg dose in the telemetry mice (21 nM, CSF), suvorexant achieved greater than 90% occupancy of the receptors.[9a]

Based on the favorable preclinical studies, suvorexant was advanced into phase I clinical trials in 2007, and just recently (June 2012), phase III data were first revealed at SLEEP 2012, the 26th Annual Meeting of the Associated Professional Sleep

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Societies.[10] The results presented were based on two phase III multicenter, randomized, double-blind, placebo-controlled trials enrolling >1000 patients per trial and evaluation of both a high (40 mg) and low (15/20 mg) dose in patients 18−64 years and 65 years and older. The end points were compared with placebo in both subjective (patient reporting) and objective (sleep lab based) measures of sleep onset and maintenance. In both trials, patients taking suvorexant fell asleep faster and stayed asleep longer on all primary subjective measures compared with placebo. On the objective measures, suvorexant reduced the time it took for patients to fall asleep and decreased time awake at night.[10] Suvorexant displayed a very favorable safety profile with the most common adverse events being reported (with the high dose) as sleepiness and headache.

Based on these very promising phase III studies, Merck remains on track to file a New Drug Application (NDA) for suvorexant in 2012, which could significantly impact the sleep-aid market going forward.[11]

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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