Suvorexant: A boon for Sleepless Nights

Anjan Khadka 1, Dick Brashier2, Amol Vijay Khanapure3, Pem Chuki2

1Department of Pharmacology, Nepalese Army Institute of Health Sciences, Nepal. 2Department of Pharmacology, Armed Forces Medical College, Pune-40, Maharashtra, India.

ABSTRACT

Insomnia is characterized by difficulty in falling asleep, difficulty maintaining sleep, or experiencing nonrestorative sleep. Insomnia is the most common medical complaint in general practice. Low efficacy and various side effects limit the use of existing treatment option. Suvorexant is an orexin receptor antagonist (ORA), first in a new class of drugs in development for the treatment of insomnia. It inhibits the wakefulness-promoting orexin neurons of the arousal system thereby promoting the natural transition from wakefulness. It also improves sleep onset and sleep maintenance and has a favorable tolerability and limited side-effect profile.

Keywords: insomnia; orexin; suvorexant; sleep.

Introduction

Orexins are neuropeptides synthesized from hypothalamus. There are two types of orexins viz. orexin A and orexin B. Both are endogenous ligand for G-protein coupled receptors.[1]

Insomnia persistently affects the quality and quantity of sleep. Currently approved treatments for insomnia primarily target γ-aminobutyric acid-A (GABA-A) receptor signalling and include benzodiazepines and GABA-A receptor modulators.[2]These drugs are used to address this sleep disorder, but have the potential for side effects such as tolerance and dependence, making them less attractive as maintenance therapy. [1,2]Forward and reverse genetic approaches in animals have implicated orexin signalling (also referred to as hypocretin signalling) in the control of vigilance and sleep/wake states. Screening for orexin receptor antagonists using in vitro and in vivo methods in animals has identified compounds that block one or other of the orexin receptors viz. single orexin receptor antagonists (SORAs) or dual orexin receptor antagonists (DORAs) respectively. SORAs have primarily been used as probes to further elucidate the roles of the individual orexin receptors, while a number of DORAs have progressed to clinical development as pharmaceutical candidates for insomnia.[2,3] The DORA, almorexant demonstrated significant improvements in a number of clinically relevant sleep parameters in animal models and in patients with insomnia but its development was halted.[4,6] Orexin receptor antagonists potentially represent a targeted, effective and well-tolerated new class of medications for insomnia.

Suvorexant is an orexin receptor antagonist. The orexin or hypocretins neuropeptide signalling system is a central promoter of wakefulness.[5,7] Inhibition of orexin receptors is thought to suppress wake drive.[4] FDA announced the approval of suvorexant on August 13, 2014, for the treatment of insomnia.[7]

Mechanism of action

Suvorexant is a potent dual orexin receptor antagonist that blocks both orexin receptor-1 and orexin receptor-2. It promotes sleep through inhibition of orexin A and B, neuropeptides that promote wakefulness.[2,4,5]

Correspondence:
Anjan Khadka
Nepalese Army Institute of Health Sciences, Kathmandu.
Email: anjankhadka14@yahoo.com
and compromised respiratory function. Precautions should be taken in conditions like abnormal thinking and behavioral changes, depression, hallucinations and sleep paralysis. There is risk of impaired alertness and motor coordination, including impaired driving.

**Adverse effects**

The most frequent adverse effects are somnolence (>5%), drowsiness and fatigue. Other occasional adverse effects are dizziness, headache, elevated aminotransferase levels, upper respiratory tract infection, etc.

**Dosing**

Recommended dose is 10 mg per oral once daily at bed time within 30 minutes of going to bed with at least 7 hours remaining before the planned time of awakening. Dose can be increased maximum upto 20 mg once daily.

**Drug interactions**

Potent CYP3A inhibitors such as fluconazole increase plasma concentrations of suvorexant. CYP3A inducers such as rifampin result in significantly reduced suvorexant plasma concentrations. Suvorexant is a mild inhibitor of CYP3A, but when administered with CYP3A substrates, including oral contraceptives and warfarin, it had minimal effects.

**CONCLUSION**

Suvorexant is an effective orexin receptor antagonist with a unique clinical profile and the first in a new class of drugs in development for the treatment of insomnia. Though benzodiazepines and non-benzodiazepines are effective for insomnia, their adverse-effect profiles and recommended limitations on long-term use called for other options. Patients who experience both sleep onset and sleep maintenance insomnia may be particularly challenging to treat. The recent approval of orexin antagonist has led to the new era in the treatment of insomnia.
References


