Asian Journal of Psychiatry 25 (2017) 79–90

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Review article

Zolpidem's use for insomnia

Jaime M. Monti, MD[a,*], David Warren Spence[b], Kenneth Buttoo[c], Seithikurippu R. Pandi-Perumal[d]

[a] Department of Pharmacology and Therapeutics, University of the Republic School of Medicine, Montevideo, Uruguay
[b] 652 Dufferin Street, Toronto, ON M6K 2B4, Canada
[c] Sleep Disorders Center, 601 Harwood Avenue South, Alax, ON L1S 2J5, Canada
[d] Somnogen Canada Inc, College Street, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form 11 September 2016
Accepted 9 October 2016

Keywords:
Hypnotic drugs
Insomnia disorder
Sleep
Non-rapid eye movement sleep
Rapid eye movement sleep
Zolpidem

ABSTRACT

Zolpidem is a short-acting non-benzodiazepine hypnotic drug that belongs to the imidazopyridine class. In addition to immediate-release (IR) and extended-release (ER) formulations, the new delivery forms including two sublingual tablets [standard dose (SD) and low dose (LD)], and an oral spray form have been recently developed which bypass the gastrointestinal tract. So far, Zolpidem has been studied in several clinical populations: cases poor sleepers, transient insomnia, elderly and non-elderly patients with chronic primary insomnia, and in comorbid insomnia.

Peak plasma concentration (Tmax) of zolpidem-IR occurs in 45 to 60 min, with the terminal elimination half-life ($t^1/_2$) equating to 2.4 h. The extended-release formulation results in a higher concentration over a period of more than 6 h. Peak plasma concentration is somewhat shorter for the sublingual forms and the oral spray, while their $t^1/_2$ is comparable to that of zolpidem-IR. Zolpidem-IR reduces sleep latency (SL) at recommended doses of 5 mg and 10 mg in elderly and non-elderly patients, respectively. Zolpidem-ER at doses of 6.25 mg and 12.5 mg, improves sleep maintenance in elderly and non-elderly patients, respectively, 4 h after its administration. Sublingual zolpidem-LD (5 mg) and zolpidem oral spray are indicated for middle-of-the-night (MOTN) wakefulness and difficulty returning to sleep, while sublingual zolpidem-SD (10 mg) is marketed for difficulty falling asleep.

With their array of therapeutic uses and their popularity among physicians and patients; this review describes the clinical pharmacology, indications and uses, identifying withdrawal symptoms, abuse and dependence potentials, and adverse drug reactions are discussed.

Contents

Abbreviations: CAP, cyclic alternating pattern; C_{max}, maximum plasma concentration; CNS, central nervous system; ER, extended-release; GABA, γ-aminobutyric acid; GAD, generalized anxiety disorder; IR, immediate-release; LPS, latency to persistent sleep; MDD, major depressive disorder; MOTN, middle-of-the-night; NREMS, non-rapid-eye-movement sleep; REMS, rapid-eye-movement sleep; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; $t_{1/2}$, terminal elimination half-life; T_{max}, peak plasma concentration; TST, total sleep time; WASO, wake time after sleep onset.

* Corresponding author at: Department of Pharmacology and Therapeutics, University of the Republic School of Medicine, Montevideo, Uruguay.
E-mail address: jmonti@mednet.org.uy (J.M. Monti).

http://dx.doi.org/10.1016/j.ajp.2016.10.006
1876-2018/

1. Introduction

The identification in the nineteen seventies of high affinity stereospecific receptors for benzodiazepines and the subsequent use of this class of drugs represented a significant breakthrough in the clinical treatment of insomnia. Their effectiveness and safety compared to the barbiturates, carbamates, and methaqualone focused considerable interest on the benzodiazepines and led to their use as the preeminent pharmacological agents for treating insomnia and allied sleep disorders (Harvey, 1980). In recent years however prescriptions for benzodiazepines have progressively declined due to dissatisfaction with their adverse side effect profile. These well documented effects have included their tendency to induce somnolence, dizziness, mental confusion, fatigue, rebound insomnia, dependence and abuse. These effects represented significant obstacles to patient acceptance and prevented the more widespread use of benzodiazepines for disturbed sleep. These concerns thus stimulated research interest in other agents which had the beneficial sleep-promoting properties of benzodiazepines but without their drawbacks. This interest led to the development of a structurally dissimilar group of nonbenzodiazepine derivatives, including the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem, and the pyrazolopyrimidine compound zaleplon, all of which are now currently indicated for the treatment of insomnia.

2. Chemistry

Zolpidem (N,N,6-trimethyl-2[4-methyl-phenyl]imidazo[1,2-a] pyridine-3-acetamide hemitartrate) is a hypnotic agent that belongs to the imidazopyridine class. It was synthesized by Synthelábo Recherche in the early 1980s, and following its release into the market, its therapeutic potential for the treatment of sleep disorders was quickly recognized.

2.1. Insomnia: diagnostic criteria

Insomnia is a complaint characterized by one or more of the following: difficulty falling asleep [sleep onset latency (SOL) = > 30 min], insufficient sleep [total sleep time (TST) = < 5.5–6 h], numerous nocturnal awakenings, increased wake time after sleep onset [WASO], early morning awakenings with inability to resume sleep, or non-restorative sleep. Common daytime complaints include somnolence, fatigue, irritability, and difficulty concentrating and performing everyday tasks. In addition, subjects with a diagnosis of insomnia are at risk for injury, drowsiness while driving, and illness (American Academy of Sleep Medicine, 2014).

The International Classification of Sleep Disorders (American Sleep Disorders Association, 1997) advocates the application of severity criteria in addition to a consideration of the patient's clinical status as guides to be used for the diagnosis of the disorder. The criteria for mild insomnia require that patients complain of not having a sufficient amount of sleep almost every night or of not feeling rested the following day. Despite having these symptoms there must be little or no impairment of social or occupational functioning. Moderate to severe insomnia refers to nightly complaints of having insufficient sleep or of not feeling rested the following day, accompanied by a moderate to severe impairment of daytime activities, including social and/or occupational functioning.

Insomnia has been classified into three major subtypes, including sleep-onset insomnia, sleep-maintenance insomnia, and insomnia characterized by early morning awakenings. These symptoms show considerable variation in individual patients however and the respective patterns are not always stable over the course of time (Hohagen et al., 1994). The instability of these symptoms therefore must be taken into consideration when determining the appropriate drug for the treatment of the disorder. Short acting hypnotic for instance would cease to be effective for many patients who received an initial diagnosis of sleep onset insomnia. An effective treatment program for insomnia therefore requires that the clinician take into consideration the dynamics of the sleep disorder over time and with attention to variations in its presentation in particular patients.

2.2. Mechanism of action of zolpidem

Due to its inhibitory actions γ-aminobutyric acid (GABA) is of particular interest for its associated sleep promoting properties. Additionally it has been found that hypnotic drugs which accomplish their sleep inducing actions by selectively affecting GABA receptors are the most therapeutically useful (Möhler, 2010).

A number of sub classes of GABA receptors, including $GABA_A$, $GABA_B$, and $GABA_C$, are receptors which have now been