Prescription Drugs Used in Insomnia

Sylvie Dujardin, MD[a], Angelique Pijpers, MD, PhD[a], Dirk Pevernagie, MD, PhD[a,b,*]

KEYWORDS

• Chronic insomnia • Prescription drugs • Pharmacotherapy • Sleep-effect

KEY POINTS

- Several prescription drugs are available that at least temporarily improve sleep duration and continuity, objectively and subjectively, with acceptable side effects.
- Prescription drugs used for insomnia promote sleep by a limited number of different mechanisms: enhancing GABAergic neurotransmission, antagonizing receptors for the wake-promoting monoamines, or binding the melatonin receptors. Orexin receptor antagonists comprise a new class of hypnotic drugs.
- The ideal sleeping pill still does not exist.
- When available, cognitive behavioral therapy for insomnia remains the first-line therapy for chronic insomnia.

INTRODUCTION

Various studies have shown the efficacy of cognitive behavioral therapy for insomnia (CBT-I) and were recently confirmed by meta-analysis.[1] The American Academy of Sleep Medicine (AASM) clinical practice guideline and the European guideline for the treatment of insomnia state that this nonpharmacologic therapeutic approach is the treatment of choice for chronic insomnia in adults, regardless of age.[2,3] By acting on different sleep mechanisms, CBT-I helps to tilt the delicate neurobiologic balance from wakefulness to sleep.

Prescription of pharmacologic treatment is to be considered when CBT-I is not available or not effective. In the acute phase of CBT-I, adding pharmacotherapy may have a slightly better effect compared with CBT-I alone, provided the medication is discontinued in the maintenance phase of CBT-I.[4] However, pharmacotherapy is not indicated for chronic use and efforts at discontinuation should be made when this is the case.[3] Moreover, discontinuation may improve rather than worsen the effects of CBT-I.[5]

Many studies have been conducted to evaluate the pharmacologic treatment of chronic insomnia. Unfortunately, large randomized controlled trials (RCTs) with representative patient populations are lacking. Studies are often weak from a methodologic point of view and, in addition, difficult to compare because of differences in patient samples, diagnostic and inclusion criteria, and outcome criteria. Finally, many studies are sponsored by the industry, which could lead to publication bias.

It is important to keep in mind that in the treatment of insomnia, whether pharmacologic or behavioral, a substantial placebo effect may confound clinical results. In a meta-analysis, the placebo effect was contended to account for almost two-thirds of the drug effect.[6] A recent meta-analysis comparing placebo with no treatment groups confirms the placebo effect in the subjective but not objective sleep measures.[7]

The authors have no disclosures to report.

[a] Sleep Medicine Center Kempenhaeghe, PO Box 61, Heeze 5590 AB, The Netherlands; [b] Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Corneel Heymanslaan 10, 9000 Ghent, Belgium

* Corresponding author. Sleep Medicine Center Kempenhaeghe, PO Box 61, Heeze 5590 AB, The Netherlands.
E-mail address: pevernagied@kempenhaeghe.nl

Sleep Med Clin 13 (2018) 169–182
https://doi.org/10.1016/j.jsmc.2018.03.001

This article provides an overview of pharmacologic and biologic features of different hypnotic drugs, with a reference to medical practice in adults with chronic insomnia without comorbidities. The focus is on prescription drugs and discussed are benzodiazepines (BZDs), non-BZD BZD receptor agonists (NBBzRAs), melatonin receptor agonists, orexin receptor antagonists, antidepressants, and antipsychotics. Over-the-counter preparations, including antihistamines, are outside the scope of this article. The main characteristics of the reviewed drugs are summarized in **Table 1**.

The reviewed compounds all have an impact on the neurobiologic processes of sleep and may even change its normal macrostructure and microstructure. Because hypnotic drugs act via different pathways within the central nervous system, they have dissimilar neuropharmacologic profiles. Remarkably, these differential properties have not been translated into evidence that would facilitate clinical decision making based on the pharmacologic signature of the drug.[8]

Practical advice for optimization of drug treatment is outside the scope of this article. For further study, we refer the reader to other references.[9]

BENZODIAZEPINES

Neuropharmacology

BZD receptor agonists constitute the most important class of drugs prescribed for insomnia and encompass BZDs and NBBzRAs. Both groups intensify γ-aminobutyric acid $(GABA)_A$-mediated neurotransmission and are therefore $GABA_A$ agonists.

GABA is the most important and abundant inhibitory neurotransmitter in the nervous system. Stimulating GABAergic action promotes sleep, but the exact locations in the brain are not yet fully disclosed.[10] At very high dose, $GABA_A$ agonists suppress c-Fos expression in the entire central nervous system, including the sleep-wake control centers.[11] At lower dose, $GABA_A$ agonists increase c-Fos expression in ventrolateral preoptic area (VLPO) neurons, albeit less than in natural sleep. The VLPO (and the median preoptic nucleus) contain sleep-active GABAergic neurons that send anatomic projections to the arousal systems, in which GABA release has been shown to increase during sleep.[12] Besides, systemic injection of $GABA_A$ receptor agonists consistently suppressed the expression of c-Fos in the tuberomammillary nucleus (TMN).[11] The VLPO and the TMN mutually inhibit each other.[12] Thus $GABA_A$ agonists might stimulate sleep through reinforcing the relief of the inhibition of the VLPO by the TMN.[11] Microinjections of triazolam into the perifornical hypothalamus containing hypocretin neurons significantly increased sleep.[13] BZDs might thus also act via inhibition of the hypocretin wake-promoting system.

Pharmacologic Properties

BZDs act as positive allosteric modulators of $GABA_A$ receptors: they increase the effect of GABA binding. $GABA_A$ receptors are located postsynaptically and consist of a pentameric complex forming a chloride channel. When the GABA is released in the synaptic cleft, the chloride channel opens. With BZD, the $GABA_A$ receptor increases the frequency of opening of its chloride-channel. By this mechanism, the cellular membrane of the post-synaptic neuron becomes hyperpolarized, thus inhibiting the activation of the neuron.[14]

The $GABA_A$ receptor carrying the α_1 subunit is believed to be the mediator of the sedative and amnesic effects of BZDs. The anxiolytic, myorelaxant, motor-impairing, and ethanol-potentiating effects are attributed to $GABA_A$ receptor, carrying other α subunits (α subunits 2, 3, 5).[15] Currently available BZDs are nonselective for $GABA_A$ receptors with different α subunits.[14]

Clinical Effects

BZDs have a positive effect on objective and subjective sleep parameters of people with insomnia. Recently, a meta-analysis was performed on two BZDs: triazolam and temazepam.[2] Two studies including a total of 72 patients addressed subjective sleep latencies (SL) and total sleep time (TST).[16,17] In the second study of 34 patients, objective SL and TST also were assessed.[17] Temazepam, 15 mg, decreased subjective SL by 20 minutes and objective SL by 37 minutes versus placebo. It increased subjective TST by 64 minutes and objective TST by 99 minutes versus placebo. The evidence for efficiency of triazolam is scarce. In a study of only subjective data with triazolam, 0.25 mg, improvements of subjective SL and TST (respectively −9 minutes and −25 minutes versus placebo) were not clinically relevant.[18]

Tolerance to hypnotic effect is a frequent manifestation in chronic use of BZDs. It has been shown that after 24 weeks of chronic BZD intake, the subjective sleep quality drops to a level below baseline. This was observed in BZDs with short and long half-life (lorazepam and nitrazepam, respectively).[19] Rebound insomnia is the most frequent symptom following acute withdrawal of BZDs, occurring in up to 71% of subjects.[20] Next to tolerance, dependence is of concern. The prevalence of misuse and dependency of BZDs and related Z-drugs has been estimated to be 5% in a German population. Approximately 20% of BZD users have a