New Developments in Insomnia Medications of Relevance to Mental Health Disorders

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KEYWORDS

• Personalization • Insomnia • Comorbid psychiatric disorders • Suvorexant • Doxepin • Prazosin • Eszopiclone

KEY POINTS

- There are a number of insomnia medications with high specificity of effects, many of which have recently become available.
- Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep.
- This approach promises an improved risk–benefit ratio over the traditional "one-size-fits-all" approach to insomnia therapy.
- This article reviews insomnia medications and discusses the implications for optimizing the treatment of insomnia occurring comorbid with psychiatric conditions.

INTRODUCTION

There are a number of different medications available for treating patients with insomnia. However, consistent with guidelines, these interventions are generally not administered with any degree of personalization.[1] The treatment of insomnia has long been carried out without subtyping insomnia patients and customizing the choice of treatment to match patient subtype.

The primary reason for this has been that, for many years, we have had only a limited set of interventions to administer and there has not been any evidence that these differ fundamentally in the nature of their therapeutic effects. Treatment was long dominated by a group of medications which bind to the benzodiazepine binding

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Abbreviations

α_1	α_1 adrenergic receptor
5-HT	Serotonin
5-HT-2	Serotonin 5-HT-2 receptor
FDA	Food and drug administration
GABA	Gamma-aminobutyric acid
GABA-A	Gamma-aminobutyric acid type A receptor
H1	Histamine H1 receptors
MT1	Melatonin type 1 receptor
MT2	Melatonin type 2 receptor
NE	Norepinephrine
OX1	Orexin type 1 receptor
OX2	Orexin type 2 receptor

site of the gamma-aminobutyric acid (GABA) type A (GABA-A) receptor complex.[2] Examples include triazolam, temazepam, flurazepam, zolpidem, zaleplon, and eszopiclone. These medications have been believed to differ only in their pharmacokinetic profiles that, along with medication dosage, determine the timing and duration of clinical effects. As a result, the personalization of therapy that has been possible has been limited to matching the time of night of effect of medications to the time of night of a given patient's sleep difficulty as specified in the US Food and Drug Administration (FDA) indications for these medications.[1–3] For example, zolpidem and zaleplon are indicated only for the treatment of problems falling asleep, whereas eszopiclone and the extended release formulation of zolpidem are indicated for the treatment of patients with sleep onset problems, sleep maintenance problems, or both.[2,3]

A greater degree of personalization is increasingly becoming possible in the clinical management of insomnia based on new research on insomnia therapies and the existence of medications with high specificity, many of which have become available recently.[3] These agents include drugs that act with high specificity at particular receptors and have a relatively focused impact on particular brain circuits. Such agents pave the way for a new paradigm for insomnia therapy where specific medications are selected to target the specific type of sleep difficulty experienced by each patient. This paradigm includes specific agents for patients with insomnia cooccurring with particular psychiatric disorders.

For example, evidence indicates that some insomnia medications have greater therapeutic effects in patients with insomnia occurring with major depression and generalized anxiety disorder than others.[3–8] This approach promises an improved risk–benefit ratio over the traditional "one-size-fits-all" model of insomnia therapy based on drugs without pharmacologic specificity and on drugs that have relatively global effects impacting many areas of the brain other than those needed to improve a patient's particular sleep problem. There are times when high effect specificity is not desirable, including instances where a medication is being used to treat more than 1 condition, such as insomnia and depression. Another instance where high specificity may not be optimal is when there are several processes driving insomnia, such as stress, pain, and depression.

The critical point is that we now have tools available with varying specificity of effects and different types of specific effects that provide us with unprecedented ability to target therapy to the particular needs of each patient. Taking advantage of this opportunity so as to optimize care requires that we understand the particular characteristics of each of our treatment options and the relative merits of administering these options to the various types of patients encountered in clinical practice. To this end,