HHS Public Access

Author manuscript

Psychiatr Clin North Am. Author manuscript; available in PMC 2018 May 28.

Published in final edited form as:

Psychiatr Clin North Am. 2015 December ; 38(4): 843–860. doi:10.1016/j.psc.2015.08.001.

NEW DEVELOPMENTS IN INSOMNIA MEDICATIONS OF RELEVANCE TO MENTAL HEALTH DISORDERS

Andrew D. Krystal, MD, MS

Director of Neruosciences Medicine, Duke Clinical Research Institute, Professor of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC 27705

Abstract

There are a number of insomnia medications with high specificity, many of which have recently become available. Such agents provide us with a window into the varying clinical effects of modulating specific brain systems for the first time. They establish a new guiding principal for conceptualizing insomnia medications: “mechanism matters” and open the door to a new paradigm for insomnia therapy in which specific drugs are selected to target the specific type of sleep difficulty for each patient. This paradigm includes administering specific treatments for patients with insomnia co-morbid with particular psychiatric disorders. This approach promises an improved risk/benefit ratio over the traditional therapeutic approaches. This article reviews the insomnia medications focusing on how they define the new paradigm of personalization and discusses the implications for optimizing the treatment of insomnia occurring co-morbid with psychiatric conditions.

Keywords

Personalization; Insomnia; co-morbid psychiatric disorders; suvorexant; doxepin; prazosin; eszopiclone

I. 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 very 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 site of the gamma-amino butyric acid (GABA) Type A receptor complex.[2] Examples include triazolam,

Address: Box 3309 DUMC, Durham, NC 27710, andrew.krystal@duke.edu.

temazepam, flurazepam, zolpidem, zaleplon, and eszopiclone. These medications have been believed to differ only in their pharmacokinetic profiles which, 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 U.S. Food and Drug Administration (FDA) indications for these medications.[1,2,3] For example, zolpidem and zaleplon are indicated only for the treatment of problems falling asleep, whereas eszopiclone, and the extended relase 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 recently become available.[3] These agents include drugs that act with high specificity at particular receptors which 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 co-occurring 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 which 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 one 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, this article reviews the insomnia medications in light of the new paradigm of personalization, with special emphasis on implications for optimizing the treatment of insomnia co-occurring with psychiatric conditions.

II. OVERVIEW OF INSOMNIA THERAPIES

The current primary treatment options for insomnia include non-medication therapies, most notably cognitive behavioral therapy for insomnia (CBTI), and a number of types of pharmacologic therapies. The scope of this article is limited to considering the medication therapies for insomnia. Pharmacologic therapies are comprised of the benzodiazepines, the

non-benzodiazepines, the selective melatonin receptor agonists, the selective histamine H-1 antagonists, the selective adrenergic α_1 antagonists, the selective hypocretin/orexin antagonists, antidepressants, antipsychotics, and "over the counter" non-selective H-1 antagonists. These agents vary in the specificity of their effects (see Table 1). Some agents have high pharmacologic specificity in terms of having effects at a single receptor. Of these agents, some have non-specific clinical effects because the receptor that they affect has a broad impact on brain function. Others have very specific clinical effects because binding to their target receptor has a relatively limited effect on the brain, mainly impacting specific sleep/wake modulating circuitry.[9] Insomnia medications are reviewed in the following sections, focusing on the degree of specificity of their effects and the implications for optimizing insomnia therapy.

III. INSOMNIA MEDICATIONS WITH RELATIVELY LOW SPECIFICITY OF EFFECTS

Medications with low specificity of effects include the benzodiazepines, the non-benzodiazepines, antidepressants, antipsychotics, and "over-the-counter" antihistamines. Their low specificity is due to either having clinically significant effects on multiple receptors or because the receptor that they bind to has a broad impact on brain function. These agents have long dominated the clinical treatment of insomnia and are the foundation upon which our current "one-size-fits-all" model of insomnia pharmacotherapy was built.

A. Benzodiazepines

- Distinguishing Characteristics – The benzodiazepines are a group of medications that share a common chemical structure.[10]
- Agents Used to Treat Insomnia – Agents U.S. FDA Approved for Insomnia: Triazolam, Flurazepam, Temazepam, Estazolam, Quazepam.[2] Agents U.S. FDA Approved for an indication other than insomnia: Clonazepam (approved for seizures, anxiety), Alprazolam (approved for anxiety), Lorazepam (approved for anxiety).[2]
- Mechanism of Action – The benzodiazepines are positive allosteric modulators of the GABA-A receptor complex. They bind to a site on the receptor complex, referred to as the "benzodiazepine binding site" and create a conformational change that enhances the inhibition that occurs when GABA binding activates the receptor.[11] The effects on sleep derive from enhancing the GABA-A mediated inhibition of wake promoting regions of the brain such as the lateral hypothalamus, the tubero-mammillary nucleus, and the locus coeruleus.
- Pharmacologic Specificity - The benzodiazepines have high pharmacologic specificity in dosages used to treat insomnia. At these dosages, all of the clinical effects of these agents are believed to be due to positive allosteric modulation of the GABA-A receptor complex at the benzodiazepine binding site. However, it should be noted that, among agents which bind to the benzodiazepine binding site of the GABA-A receptor complex, the benzodiazepines are relatively non-

specific. They cause clinically significant effects through binding to four different types of GABA-A receptors, each of which has a different distribution in the brain.[12,13]

- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - Benzodiazepines have quite broad inhibitory effects on brain function. This is because GABA is the predominant inhibitory neurotransmitter in the brain. As a result, enhancement of GABA-A mediated inhibition has the potential to have extremely broad effects. By exerting effects at four major GABA-A receptor types, the benzodiazepines produce widespread inhibition of brain activity.[9,12,13,14] The result of this widespread inhibition is that these medications have a number of clinical effects other than sleep enhancement. Such effects include anxiolytic effects, cognitive impairment, motor impairment, myorelaxation, anti-seizure effects, and rewarding effects associated with abuse potential.
- Clinical Implications for Personalization of Therapy – Based on the non-specific clinical effects of the benzodiazepines, they are well-suited for use in patients who have insomnia occurring in the setting of one or more conditions that can be improved by the non-sleep effects of these medications. Examples include patients with insomnia occurring with significant anxiety or pain, for which the anxiolytic and myorelaxant effects of these medications are highly desirable. Patients without such co-occurring conditions are best treated with another type of medication because of the non-sleep related effects of these agents, such as cognitive impairment, motor impairment, and abuse potential, which result in a risk/benefit ratio that is less favorable than that of other options for patients without co-occurring conditions such as severe anxiety. The one exception to this is that compared to other available options, the benzodiazepines and non-benzodiazepines (see below) administered in the dosages routinely used to treat insomnia have the most robust effects on sleep onset.[2] As a result, there may be some patients with severe sleep onset difficulty for whom a benzodiazepine may constitute the agent with the best risk/benefit ratio of available medications, even where there isn't an associated condition which is also being targeted for therapy.

B. Non-benzodiazepines

- Distinguishing Characteristics – The non-benzodiazepines are a heterogenous group of medications that do not have the chemical structure common to benzodiazepines but act via the same mechanism as the benzodiazepines.[10]
- Agents Used to Treat Insomnia – Agents U.S. FDA Approved for Insomnia: Zolpidem and Zaleplon (approved for the treatment of sleep onset difficulties only); Zolpidem Modified Release and Eszopiclone (approved for the treatment of sleep onset and maintenance difficulties).[2]
- Mechanism of Action – The non-benzodiazepines, like the benzodiazepines, are positive allosteric modulators of the GABA-A receptor complex; promoting sleep by enhancing GABA-A mediated inhibition of wake promoting regions of

the brain, such as the lateral hypothalamus, the tubero-mammillary nucleus, and the locus coeruleus.

- Pharmacologic Specificity - The non-benzodiazepines have high pharmacologic specificity in dosages used to treat insomnia. At these dosages, all of the clinical effects of these agents are believed to be due to positive allosteric modulation of the GABA-A receptor complex at the benzodiazepine binding site. However, they have greater pharmacologic specificity than the benzoadiazepines. While the benzodiazepines have clinically significant effects at 4 major types of GABA-A receptors, the non-benzodiazapines tend to preferentially bind to a subset of these GABA-A receptors.[12,13]

- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - The non-benzodiazepines, like the benzodiazepines have relatively broad inhibitory effects on brain function due to the wide distribution of GABA in the brain. However, the clinical effects of the non-benzodiazepines are believed to be relatively more focused than the benzodiazepines.[12,13] Zolpidem and zaleplon have effects predominantly at GABA-A receptors which enhance sleep but also lead to impairment of cognition and motor function.[12,13] Eszopiclone binding to GABA-A receptors has relatively greater anxiolytic, myorelxant, and perhaps antidepressant effects in addition to sleep enhancing effects. Indeed, when eszopiclone/fluoxetine co-therapy was compared with placebo/fluoxetine treatment of patients with depression and insomnia, eszopiclone was found not only to improve sleep but also to enhance the antidepressant response (eszopiclone led to improvement in non-sleep depression symptoms).[4,5] Eszopiclone similarly improved not only sleep but also symptoms of generalized anxiety disorder compared with placebo when administered with escitalopram.[6] However, when equivalent studies were carried out with zolpidem modified release, improvement in sleep compared with placebo was noted but not improvement in depression or symptoms of generalized anxiety disorder.[7,8]

- Clinical Implications for Personalization of Therapy – The differences among the non-benzodiazepines dictates different uses for these medications. Based on the available evidence, eszopiclone stands as the treatment of choice for combination with selective serotonin reuptake inhibitor therapy in the treatment of patients with insomnia co-occurring with major depression and generalized anxiety disorder.[4–6] Zolpidem and zaleplon have robust effects on sleep onset like the benzodiazepines. However, they are preferred over the benzodiazepines due to their relatively limited duration of effects and less broad clinical impact, which together represent an improved risk benefit profile for those with severe sleep onset difficulties.[2] In those with severe sleep onset problems who also have sleep maintenance difficulties, it is necessary to turn to eszopiclone and zolpidem modified release, which have both robust onset effects and therapeutic effects on sleep maintenance.[2] Note that these agents are preferred only where severe sleep onset problems occur along with maintenance difficulties. If it is not the case that onset problems are substantial, then there are other agents with more favorable risk/benefit ratios than the non-benzodiazepines (see below).

C. Antidepressants

- Distinguishing Characteristics – The antidepressants are a heterogenous group of agents of a number of chemical classes which have been approved by the U.S. FDA for the treatment of major depression. Despite their relatively widespread use for the treatment of insomnia, limited data exist regarding the treatment of insomnia with these agents.
- Agents Used to Treat Insomnia – There are no antidepressants approved by the U.S. FDA for the treatment of insomnia in the dosage range used to treat depression.[2] The antidepressants most frequently used "off-label" to treat insomnia include: trazodone, mirtazapine, amitriptyline, and doxepin.[2] These agents are generally used in dosages below their antidepressant dosages when used to treat insomnia. Doxepin, in dosages of 3–6 mg (antidepressant dosage range 75–150 mg), is approved by the U.S. FDA for insomnia treatment (see below).
- Mechanism of Action – The mechanism by which antidepressants are believed to have therapeutic effects on depression primarily involves inhibition of the serotonin (5-HT) and norepinephrine (NE) reuptake transporters. The mechanisms underlying their effects on sleep differ but derive from antagonism of one or more wake promoting systems mediated by blockade of 5-HT-2, α1 adrenergic, H-1 histaminergic, and muscarinic cholinergic receptors.[2]
- Pharmacologic Specificity - The antidepressants are non-selective agents pharmacologically with varying degrees of antagonism of 5-HT and NE transporters, and 5-HT-2, α1, adrenergic, H-1 histaminergic, andmMuscarinic cholinergic antagonism.[2]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - Because of the pharmacologic non-selectivity of these agents, they have relatively widespread effects on brain function, inhibiting a number of key neural systems. This results in effects other than sleep enhancement which vary among these agents and leads to a relatively unfavorable side-effect profile in many cases. Given the lack of trials of insomnia treatment with these agents, the side-effect profiles generally have to be inferred from trials of these patients carried out in patients with mood or anxiety disorders. Their side effects may include weight gain, orthostatic hypotension, dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, cardiotoxicity, sexual dysfunction, and potentially delirium.[2]
- Clinical Implications for Personalization of Therapy – Given the lack of data from controlled trials, it is not possible to reliably determine the risk/benefit ratio of these agents when used to treat insomnia. However, in theory, these agents would be expected to be particularly useful in cases where non-specific effects are advantageous. This would include patients with insomnia co-occurring with depression, anxiety, pain, stress. In this regard there have been three small double-blind controlled studies of the treatment of insomnia co-occurring mood disorders with trazodone 50–100 mg.[15–17] These studies provided some evidence

that trazodone improves sleep (primary benefit seen in sleep maintenance) when administered in this setting. However, benefit was offset by significant next-day morning impairment which was detected with objective testing. It is reasonable to consider the use of these agents in treatment-resistant insomnia patients in whom it might be advantageous to block multiple wake promoting systems.

D. Antipsychotics

- Distinguishing Characteristics – The antipsychotics, much like the antidepressants, are a heterogenous group of agents from a number of different chemical classes which have been approved by the U.S. FDA for the treatment of psychotic disorders. Like the antidepressants, they enjoy relatively widespread use for the treatment of insomnia despite the fact that minimal data exist regarding the treatment of insomnia with these agents.[2]
- Agents Used to Treat Insomnia – No antipsychotics are approved by the U.S. FDA for the treatment of insomnia.[2] The antipsychotics most frequently used "off-label" to treat insomnia include: quetiapine, olanzapine, lurasidone, and risperidone.[2] These agents are generally used in dosages below their antipsychotic dosages when used to treat insomnia.
- Mechanism of Action – The mechanism by which antipsychotic drugs are believed to have therapeutic effects on psychosis involves primarily blockade of the dopamine type 2 (D2) receptor. The mechanisms underlying their effects on sleep differ, but derive from antagonism of one or more wake promoting systems mediated by blockade of 5-HT-2, α1 adrenergic, H-1 histaminergic, dopaminergic, and muscarinic cholinergic receptors.[2]
- Pharmacologic Specificity - The antipsychotics are non-selective agents pharmacologically with varying degrees of antagonism of 5-HT-2, 5-HT-7, α1, adrenergic, H-1 histaminergic, dopaminergic (D1 and D2), and muscarinic cholinergic antagonism.[2]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - Because of the pharmacologic non-selectivity of these agents, they have relatively widespread effects on brain function, inhibiting a number of key neural systems. This results in effects other than sleep enhancement which vary among these agents and leads to a relatively unfavorable side-effect profile in many cases. Given the lack of trials of insomnia treatment with these agents, the side-effect profiles generally have to be inferred from trials of these patients carried out in patients with schizophrenia and bipolar disorder. The side effects may include weight gain, insulin resistance, orthostatic hypotension, dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, extrapyramidal side-effects such as tardive dyskinesia and parkinsonism, and sexual dysfunction.[2]
- Clinical Implications for Personalization of Therapy – As with antidepressants, given the lack of data from controlled trials, it is not possible to reliably determine the risk/benefit ratio of antipsychotic drugs when used to treat

insomnia. However, in theory, these agents would be expected to be particularly useful in cases where non-specific effects are advantageous. This would include patients with insomnia co-occurring with mania, schizophrenia, depression, anxiety, pain, or stress. It is also reasonable to consider these agents in treatment-resistant insomnia patients where it might be advantageous to block multiple wake promoting systems.

E. Non-Selective Antihistamines

- Distinguishing Characteristics – Medications referred to as "antihistamines" are generally those that were developed for the treatment of allergies.[3] Among these agents are a group that are available "over-the-counter" (OTC) and used to treat sleep problems. We refer to them as non-selective antihistamines in that they have clinically significant effects at receptors other than H-1 receptors in doses used for insomnia treatment. Like the antidepressants and antipsychotics, these agents are used by many people suffering from disturbed sleep despite the fact that minimal data exist on their risk/benefit profile in the treatment of insomnia patients.[2,9]
- Agents Used to Treat Insomnia – The agents available OTC with significant histamine H-1 receptor antagonism that are most commonly used to treat insomnia are diphenhydramine, doxylamine, and chlorpheniramine.[2,3]
- Mechanism of Action – The mechanisms underlying the sleep enhancing effects of these agents is believed to be antagonism of H-1 histamine receptors and muscarinic cholinergic receptors.[2,9] This antagonism blocks the wake promoting effects of histamine neurons in the tuberomammillary nucleus and mitigates the wake promotion mediated by acetylcholine.[2,9]
- Pharmacologic Specificity – These agents, in the dosages used to treat sleep disturbance, are relatively non-selective among those which block H-1 receptors (see below) because of their clinically significant effects at both H-1 and muscarinic cholinergic receptors.[2,9]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - The cholinergic antagonism of these agents results in effects other than sleep enhancement, which leads to a relatively unfavorable side-effect profile compared with the selective H-1 antagonists (see below) in many cases. The associated side effects may include dry mouth, blurred vision, constipation, urinary retention, cognitive impairment and delirium.[2,3,9]
- Clinical Implications for Personalization of Therapy – The limited data on insomnia treatment with these agents limits estimating their risk/benefit profile. No data exist for chlorpheniramine. Doxylamine has only been studied in a double-blind, placebo-controlled trial in patients experiencing sleep disturbance post-surgery which found some benefit in self-reported sleep with this agent.[18] A few trials have been carried out with diphenhydramine, which preliminarily indicate that this agent has more benefit for sleep maintenance than onset, though in one study, sleep enhancing effects were lost over several days of dosing.[19–24]

As more selective H-1 antagonists have robust effects on sleep maintenance, a better side-effect profile, and have been definitively found not to lose benefit in up to 3 months of nightly use, they should be preferred for use over these non-selective H-1 antagonists. The only exception to this is the treatment of insomnia occurring in patients with rhinitis, where the anticholinergic effects of these agents would be of benefit.[9,25,26]

IV. INSOMNIA MEDICATIONS WITH HIGHLY SPECIFIC EFFECTS

There are a number of medications available for treating patients with insomnia that have highly specific pharmacologic effects which lead to relatively focused effects on brain function. These agents provide us, for the first time, with a window into the varying clinical effects of modulating specific brain systems. They establish a new guiding principal for conceptualizing insomnia medications: “mechanism matters” and open the door to a new paradigm for insomnia therapy, where medications are chosen to address the specific type of problem experienced by subgroups of insomnia patients. In this section, we discuss these medications, reviewing the support for this new paradigm and outlining how each drug fits into this paradigm in terms of clinical indications for their optimal use.

A. Selective H-1 Histamine Receptor Antagonists

- Distinguishing Characteristics - This group of agents is distinguished from the non-specific histamine H-1 antagonists by having greater pharmacologic specificity.[2,9] The non-specific antihistamines reviewed above have relatively greater effects at muscarinic cholinergic receptors than the agents considered to be highly selective.
- Agents Used to Treat Insomnia – Doxepin, in dosages of 3 to 6 mg, is the only highly selective H-1 antagonist that is available for use in the treatment of insomnia patients.[2,9] Doxepin is referred to as a “tricyclic antidepressant”, and in dosages from 75–300 mg this agent has broad pharmacologic effects and is FDA approved for the treatment of depression.[2,9] However, in dosages of 3–6 mg doxepin becomes a highly selective and potent H-1 antagonist and is FDA approved for the treatment of insomnia.
- Mechanism of Action – Selective H-1 antagonists enhance sleep by preventing the arousing effect of histamine mediated by binding to H-1 receptors.[9]
- Pharmacologic Specificity – Although many agents are referred to as “antihistamines”, doxepin, in the 3 to 6 mg range, is actually a more potent and selective H-1 antagonist than any agent available in the U.S. that is referred to as an “antihistamine”.[9] Doxepin’s most potent effect is H-1 antagonism and its affinity for this receptor is more than 7 times greater than its affinity for any other receptor.[9] The consequence of this relatively greater H-1 affinity is that there should be a dosage where doxepin has clinically relevant effects at H-1 and at no other receptors.[9] This appears to be the case for the 3–6 mg range, whereas in dosages from 75–300 mg, doxepin has clinically important effects at multiple receptors including the 5-HT and NE transporters, which are believed to

represent the mechanisms responsible for its robust antidepressant effects.[9] Thus, doxepin, in the 3–6 mg range, is an intervention with high pharmacologic specificity for antagonism of histamine H-1 receptors. The trials carried out with low dose doxepin administration provide our first glimpse into the clinical effects associated with highly specific H-1 antagonism.

- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) – As a consequence of the pharmacologic specificity of doxepin 3–6 mg for histamine H-1 receptors and the relatively limited impact of the histamine system, this agent has relatively circumscribed effects on brain function.[9] Because histamine H-1 receptor activation plays a limited role in functions other than enhancing arousal, the clinical effects of doxepin in the 3–6 mg range are also limited primarily to preventing arousal, as evidenced by the relative absence of side-effects observed in clinical trials.[9,25–28] Further, given that histamine is only one of a set of wake promoting systems that function in parallel and can maintain the arousal level even if histamine H-1 receptors are blocked (norepinephrine, hypocretin/orexin, acetylcholine, 5-HT, etc), the clinical effects of doxepin 3–6 mg are limited to situations where histamine release is significant and activity in the other wake promoting systems is relatively minimal.[9] This occurs primarily in the middle and end of the night. At other times, blocking histamine is of relatively minimal consequence as arousal is maintained by the other parallel wake promoting systems. As a result, doxepin 3–6 mg has a highly circumscribed effect that is limited to enhancing sleep during the middle and end of the night. The clinical manifestation of having such a focal impact is an improved risk/benefit ratio over other options for treating sleep maintenance problems.[9,25–28]

- Clinical Implications for Personalization of Therapy – Based on the relatively favorable risk/benefit ratio of doxepin 3–6 mg for treating patients with sleep maintenance insomnia, this agent should be considered for patients experiencing difficulty staying asleep in the relative absence of problems falling asleep. Of particular note, this agent, along with the hypocretin/orexin antagonists are the only drugs that can improve sleep in the last third of the night without substantially increasing the risk of morning impairment.[9] In fact, doxepin 3–6 mg is unique in having its largest therapeutic effect size in the last hour of the night.[25,26] As such, it is the treatment of choice for those whose sleep difficulties are predominantly problems with early morning awakening, a group that includes many patients with psychiatric disorders (Table 2). The robust therapeutic effect such individuals have in response to treatment with such focused H-1 antagonism suggests that they represent a subgroup of insomnia patients who have histamine overactivity underlying their insomnia. This is consistent with preclinical data on the physiology of the histamine system, which indicate that the primary effect of this system is to increase arousal at the end of the night.[9,29] This subgroup of patients who experiences sleep disturbance predominantly in the last 3rd of the night, includes many older adults and defines the target phenotype for this medication. By identifying this subgroup and treating them with the specific

intervention which best targets their type of sleep difficulty, i.e., doxepin 3–6 mg, it is possible to improve the risk/benefit ratio as compared to providing insomnia therapy which is not personalized in this way.

B. Selective Hypocretin/Orexin Antagonists

- Distinguishing Characteristics – This group of agents is distinguished by having as their predominant pharmacologic effect antagonism of receptors of the peptide hypocretin/orexin (hereafter referred to as orexin).
- Agents Used to Treat Insomnia – There is currently only one orexin antagonist available for the treatment of insomnia. This agent, suvorexant, blocks both types of orexin receptors (OX1 and OX2) and is approved by the FDA for treatment of problems falling asleep and staying asleep in dosages of 10–20 mg.[30–32]
- Mechanism of Action – Orexins are peptides released by the lateral hypothalamus that play an important role in maintaining wakefulness. (See Chapter 2). Support for this role derives in part from evidence that loss of orexin neurons is associated with narcolepsy in humans and a number of different animals.[33] Selective orexin antagonists enhance sleep by preventing the arousing effects of orexin peptides which are mediated by their binding to OX1 and OX2 receptors.[33]
- Pharmacologic Specificity – There are a number of orexin antagonists with high pharmacologic specificity, including suvorexant, which is potent and selective in terms of having orexin receptor antagonism as its predominant effect.[32]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) – Orexin receptor antagonists have highly focused effects on the brain. Remarkably, there are only 10–20,000 neurons in the entire brain that release orexins.[33,34] The orexin antagonists block only the receptors targeted by these neurons. However, the orexin receptors modulate the activity of a number of key brain areas that are responsible for their arousing effects but also would be expected to affect motivation, reward function, feeding behavior, locomotion, and sympathetic nervous system tone.[35] This occurs because of the presence of orexin receptors on neurons in the cortex, basal forebrain, tuberomammillary nucleus, periaqueductal gray, dorsal raphe, locus coeruleus, nucleus accumbens, substantia nigra, nucleus of the solitary tract, and ventromedial medulla.[35] So, while the orexin receptors have highly limited effects on brain function, in addition to promoting arousal, these agents would be expected to modulate several other functions that may be of clinical relevance. However, these modulatory effects do not manifest in adverse effects clinically. The side-effect profile observed in clinical trials with suvorexant suggests a quite favorable risk/benefit ratio, with limited adverse effects, consistent with a medication that is highly specific, having effects predominantly on arousal systems.[31,32] Of particular interest with respect to the adverse effects of these agents, there is no evidence that suvorexant causes narcolepsy-like symptoms, such as cataplexy,

hallucinations, and paralysis, that might have been expected based on the fact that loss of orexin neurons is associated with narcolepsy.[31–33]

- Clinical Implications for Personalization of Therapy – The clinical effects of orexin receptor antagonists have been evaluated primarily in patients with primary insomnia.[31,32] Although one study included patients with medical and psychiatric conditions co-occurring with insomnia, the sizes of the groups of subjects with these conditions was insufficient to allow subgroup analyses.[32] As a result, relatively little is known about the effects of orexin antagonists on the various presentations of insomnia patients encountered in clinical practice. However, we can infer that insomnia subgroups likely to improve with treatment with orexin receptor antagonists on the basis of information regarding the anatomy and physiology of the orexin system. As discussed above, consideration of the outputs of the orexin neurons indicates a primary effect of promoting arousal but also modulation of motivation, reward function, feeding behavior, locomotion, and sympathetic nervous system tone.[35] Consideration of the inputs to orexin neurons can provide insight about what triggers orexin neurons to increase the arousal level and modulate motivation, reward, and other functions. A key input to the orexin neurons comes from the circadian clock, the suprachiasmatic nucleus of the hypothalamus.[35] (See Chapter 3). The input from the clock is responsible for what is believed to be among the most important functions of orexin neurons, which is to maintain arousal during the biological day so as to allow long, consolidated periods of wakefulness.[35] Orexin-mediated arousal increases over the course of the day to counteract the increasing homeostatic sleep drive which would otherwise lead to periodic sleep episodes, as is seen in patients with narcolepsy who lack orexin neurons.[33–35] On this basis, orexin antagonists would seem to be particularly well-suited for individuals attempting to sleep at an adverse circadian time (e.g. shift workers, jet lag, etc), where wakefulness is being maintained at least to a degree by clock-driven orexin-mediated arousal.[34] Individuals who seem to get a “second wind” in the late evening and cannot shut down and sleep would also be prime candidates for a selective orexin receptor antagonist.[34] Other key inputs to orexin neurons include the lateral septum, amygdala, periaqueductal gray, and parabrachial nucleus.[35] These inputs to orexin neurons are believed to mediate stress/anxiety associated anxiety increases in arousal.[35] On this basis it would be reasonable to consider the use of orexin antagonists in those patients experiencing difficulty sleeping in the setting of stress and/or anxiety.[34] Inputs from the nucleus accumbens and the ventral tegmental area are believed to trigger arousal in the context of loss of rewarding stimuli via orexin neurons.[35] As such, it would be reasonable to consider using orexin receptor antagonists in individuals with disturbed sleep in the context of recently discontinuing substances of abuse or who are driven by low reward states to pursue goal-directed behavior and have difficulty sleeping in that context.[34] Given our limited experience with orexin receptor antagonists, future research studies will be needed to test the proposed hypotheses that orexin receptor antagonists are particularly well-suited for use in these insomnia subgroups. However, this very

specific intervention illustrates the potential for achieving an improved risk/benefit ratio by using a medication that targets insomnia occurring in specific contexts with a therapy that has specific effects on the key neural system underlying the symptoms.

C. Selective α1 Adrenergic Antagonists

- Distinguishing Characteristics – This group of agents is distinguished by having as their predominant pharmacologic effect antagonism of α_1 adrenergic receptors.
- Agents Used to Treat Insomnia – The only selective α_1 adrenergic receptors that has been used to any significant degree in the treatment of insomnia is prazosin. This agent is approved by the FDA for treatment of hypertension but is used "off-label" for the treatment of insomnia in dosages from 1–12 mg.[30,36–40]
- Mechanism of Action – Norepinephrine plays an important role in mediating arousal, particularly in the context of stress, anxiety, and novelty.[41] Selective α_1 adrenergic antagonists enhance sleep by preventing the arousal that occurs when norepinephrine binds to α_1 adrenergic receptors.
- Pharmacologic Specificity – Prazosin has high pharmacologic specificity for α_1 adrenergic receptors.[41]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) - Prazosin also has clinical effects which are highly specific. The effects are limited to modifying sleep and blood pressure. In terms of effects on sleep, there have been no trials evaluating the treatment of primary insomnia patients with prazosin. However, four placebo-controlled trials have provided data indicating that prazosin has significant effects on nightmares and sleep maintenance in patients with post-traumatic stress disorder (PTSD).[36–40] (See Chapter 5). The studies also suggest that the only non-sleep adverse effects of significance with prazosin administration are orthostatic hypotension and dizziness.[36–40]
- Clinical Implications for Personalization of Therapy – The available data on the risks and benefits of using prazosin as a treatment for patients with sleep disturbance suggest that prazosin should be the treatment of choice for treating nightmares and problems with sleep maintenance in patients with PTSD.[36–40] Using this highly specific intervention in PTSD patients promises an improved risk/benefit ratio over less selective options. Whether prazosin has therapeutic effects on insomnia occurring in other settings remains unknown, as no studies of its use for treating insomnia in other settings have been carried out. However, potentially relevant to the clinical use of prazosin is evidence that many patients with insomnia have elevated serum levels of norepinephrine.[43,44] Although peripheral elevation of norepinephrine may occur independent of elevation in central nervous system norepinephrine, it seems of interest to investigate whether individuals with elevated serum norepinephrine might represent an increased

norepinephrine insomnia subtype and might respond preferentially to treatment with a selective adrenergic antagonist like prazosin.

D. Selective Melatonin Receptor Agonists

- Distinguishing Characteristics - This group of medications is distinguished by having as their predominant pharmacologic effect agonism of melatonin receptors.
- Agents Used to Treat Insomnia – The hormone melatonin is available "over the counter" and ramelteon, a substantially more potent agonist at melatonin MT1 and M2 receptors is approved by the U.S. FDA for treatment of sleep onset difficulties.[2]
- Mechanism of Action – These agents promote sleep onset by binding to neuronal membrane-bound MT1 type melatonin receptors.
- Pharmacologic Specificity – Melatonin has effects at all three types of melatonin receptors.[45] Ramelteon has high specificity for MT1 and MT2 receptors.[45]
- Specificity of Effects on Brain Functions (Effects on Systems Other Than Sleep/Wake Systems) – Both melatonin and ramelteon also have very specific effects on brain function that is primarily limited to modulation of sleep, as evidenced by the results of clinical trials with these agents. Both agents have been found to have therapeutic effects only on sleep onset difficulties.[2,46,47] Adverse effects have been relatively limited and both are without abuse potential. Studies of melatonin are somewhat difficult to interpret because they have involved a variety of dosages, preparations, and timing of dosing.[46,47] These studies indicate that melatonin has a greater effect on patients with delayed sleep phase syndrome than on patients with insomnia, though meta-analyses suggest that melatonin has some therapeutic effect on sleep onset in insomnia patients.[46,47] Available evidence suggests that ramelteon is safe for use in patients with sleep apnea and chronic obstructive pulmonary disease (COPD).[48,49]
- Clinical Implications for Personalization of Therapy – Given the relatively favorable side-effect profile of these agents and the fact that they have clinical effects only on sleep onset, they should be considered for treating individuals with sleep onset difficulty in the absence of sleep maintenance problems or when sleep onset problems are the predominant type of sleep difficulty. It should be noted that patients who have been previously treated with benzodiazepines and non-benzodiazepines may be less satisfied with the effects of these agents. Melatonin is the treatment of choice for patients with sleep onset problems in the setting of delayed sleep phase syndrome.[46,47] Melatonin has also been found to have therapeutic effects on sleep difficulties in patients with autism and other neurodevelopmental disorders and should be considered for use in these populations.[50–51]

V. CONCLUSIONS

Recent developments in research on insomnia treatments and the emergence of treatments with high pharmacologic specificity allow an unprecedented degree of personalization of insomnia therapy. By tailoring the mechanism and characteristics of the chosen insomnia therapy to the specific nature of each patient's insomnia, the clinician can achieve an improved risk/benefit ratio over providing treatment according to the traditional model of insomnia therapy, where little to no tailoring of therapy to the specifics of patients occurs. In order to facilitate having practitioners provide this type of improved care, this article has reviewed the available insomnia medications, pointing out where data support targeting treatment to particular subtypes of insomnia patients, with a focus on patients with psychiatric disorders. However, it must be understood that this is a work in progress. We have only limited evidence to guide how to best match specific treatment options to specific patient subgroups. Nevertheless, once "pie-in-the-sky", this approach already allows improving the risk/benefit ratio for many patients with insomnia. The emergence of new data and new agents will bring an expanding capacity to personalize insomnia therapy and better allow us to improve the lives of the many patients suffering from insomnia.

Acknowledgments

Disclosure Statement:

Grants/research support: NIH (HHS-N271-2012-000006-I, R01 MH095780, R01 MH091053, R01HL096492, R01 MH078961, R01 MH076856), Teva, Sunovion, Neosynch, Brainsway, Janssen, Novartis, Eisai.

Consultant: Attentiv, Teva, Eisai, Jazz, Janssen, Merck, Neurocrine, Novartis, Otsuka, Pfizer, Lundbeck, Roche, Sunovion, Paladin, Pernix, Transcept

LIST OF ABBREVIATIONS

α1	α1 adrenergic receptor
CBTI	cognitive behavioral therapy for insomnia
COPD	chronic obstructive lung disease
D-1	dopamine D-1 receptor
D-2	dopamine D-2 receptor
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GABA-A	gamma-aminobutyric acid type A receptor
H-1	histamine H-1 receptors
5-HT	serotonin
5-HT-2	serotonin 5-HT-2 receptor
5-HT-7	serotonin 5-HT-7 receptor

MT1	melatonin type 1 receptor
MT2	melatonin type 2 receptor
NE	norepinephrine
OTC	over the counter
OX1	orexin type 1 receptor
OX2	orexin type 2 receptor
PTSD	post-traumatic stress disorder

References

1. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008 Oct 15; 4(5):487–504. [PubMed: 18853708]
2. Krystal AD. A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: the empirical basis for U.S. clinical practice. Sleep Med Rev. 2009; 13(4): 265–74. [PubMed: 19153052]
3. Minkel J, Krystal AD. Optimizing the Pharmacologic Treatment of Insomnia: Current Status and Future Horizons. Sleep Med Clin. 2013 Sep 1; 8(3):333–350. [PubMed: 24015116]
4. Fava M, McCall WV, Krystal A, Wessel T, Rubens R, Caron J, Amato D, Roth T. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry. 2006 Jun 1; 59(11):1052–60. [PubMed: 16581036]
5. Krystal A, Fava M, Rubens R, Wessel T, Caron J, Wilson P, Roth T, McCall WV. Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. J Clin Sleep Med. 2007; 3(1):48–55. [PubMed: 17557453]
6. Pollack M, Kinrys G, Krystal A, McCall WV, Roth T, Schaefer K, Rubens R, Roach J, Huang H, Krishnan R. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Arch Gen Psychiatry. 2008; 65(5):551–62. [PubMed: 18458207]
7. Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, Roth T. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry. 2011; 72(7):914–28. [PubMed: 21208597]
8. Fava M, Asnis GM, Shrivastava R, Lydiard B, Bastani B, Sheehan D, Roth T. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. J Clin Psychopharmacol. 2009 Jun; 29(3):222–30. [PubMed: 19440075]
9. Krystal AD, Richelson E, Roth T. Review of the histamine system and the clinical effects of H1 antagonists: basis for a new model for understanding the effects of insomnia medications. Sleep Med Rev. 2013 Aug; 17(4):263–72. [PubMed: 23357028]
10. Minkel J, Krystal AD. Optimizing the Pharmacologic Treatment of Insomnia: Current Status and Future Horizons. Sleep Med Clin. 2013 Sep 1; 8(3):333–350. [PubMed: 24015116]
11. Sieghart W, Sperk G. Subunit composition, distribution and function of GABA(A) receptor subtypes. Curr Top Med Chem. 2002; 2:795–816. [PubMed: 12171572]
12. Sanna E, Busonero F, Talani G, Carta M, Massa F, Peis M, Maciocco E, Biggio G. Comparison of the effects of zaleplon, zolpidem, and triazolam at various GABA(A) receptor subtypes. Eur J Pharmacol. 2002; 451(2):103–110. [PubMed: 12231378]
13. Jia F, Goldstein PA, Harrison NL. The modulation of synaptic GABA(A) receptors in the thalamus by eszopiclone and zolpidem. J Pharmacol Exp Ther. 2009; 328(3):1000–1006. [PubMed: 19033556]

14. Lancel M. Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep. 1999; 22:33–42. [PubMed: 9989364]
15. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. Am J Psychiatry. 1994; 151(7):1069–72. [PubMed: 8010365]
16. Saletu-Zyhlarz GM, et al. Insomnia related to dysthymia: polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. Neuropsychobiology. 2001; 44:139–149. (2001). [PubMed: 11586054]
17. Saletu-Zyhlarz GM, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Progress in Neuro-Psychopharmacol and Biological Psychiatry. 2002; 26:249–260.
18. Smith G, Smith PH. Effects of doxylamine and acetaminophen on postoperative sleep. Clin Pharmacol Ther. 1985; 5(549–557)
19. Kudo Y, Kurihara M. Clinical evaluation of diphenhydramine hydrochloride for the treatment of insomnia in psychiatric patients: a double-blind study. J Clin Pharmacol. 1990; 30(11):1041–1048. [PubMed: 2243152]
20. Rickels K, Morris RJ, Newman H, Rosenfeld H, Schiller H, Weinstock R. Diphenhydramine in insomniac family practice patients: a double- blind study. J Clin Pharmacol. 1983; 23(5–6):234–242. [PubMed: 6348106]
21. Morin C, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep. 2005; 28(11):1465–1471. [PubMed: 16335333]
22. Meuleman J, Nelson RC, Clark RL. Evaluation of temazepam and diphenhydramine as hypnotics in a nursing-home population. Drug Intell and Clin Pharm. 1987; 21(9):716–720.
23. Glass JRSB, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. J Clin Psychopharm. 2008; 28(2):182–188.
24. Richardson G, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. J Clin Psychopharm. 2002; 22(5):511–515.
25. Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T. Efficacy and safety of Doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep. 2010; 33:1553–1561. [PubMed: 21102997]
26. Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, Roth T. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep. 2011; 34:1433–1442. [PubMed: 21966075]
27. Roth T, Rogowski R, Hull S, Schwartz H, Koshorek G, Corser B, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep. 2007; 30(11):1555–1561. [PubMed: 18041488]
28. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry. 2008; 69(10):1557. [PubMed: 19192438]
29. Parmentier R, Ohtsu H, Djebbara-Hannas Z, Valatx JL, Watanabe T, Lin JS. Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep-wake control. J Neurosci. 2002; 22:7695–711. [PubMed: 12196593]
30. Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D, Spiegelhalder K. Insomnia disorder. Nature Reviews. In Press.
31. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, Krystal AD, Walsh JK, Benca RM, Rosenberg R, Sangal RB, Budd K, Hutzelmann J, Leibensperger H, Froman S, Lines C, Roth T, Michelson D. Efficacy and safety of the Orexin receptor antagonist suvorexant in patients with insomnia: Results form two 3-month randomized, double-blind, placebo-controlled, clinical trials. Biological psychiatry. 2014 [Epub ahead of print].
32. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3

randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2014; 13:461–471. [PubMed: 24680372]

33. Sakurai T. Nature Reviews Neuroscience. 2014; 15:719–731. [PubMed: 25301357]
34. Krystal AD, Benca R, Kilduff T. J Clin Psychiatry. 2013; 74(suppl 1):3–20.
35. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2011; 51:243–66. [PubMed: 21034217]
36. Krystal AD, Davidson JR. The use of prazosin for the treatment of trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biological psychiatry. 2007; 61:925–927. [PubMed: 17397667]
37. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O'Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Mayer CL, Freed MC, Engel C, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013; 170(9):1003–10. [PubMed: 23846759]
38. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008; 63(6):629–32. [PubMed: 17868655]
39. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007 Apr 15; 61(8):928–34. [PubMed: 17069768]
40. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Tröster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003 Feb; 160(2):371–3. [PubMed: 12562588]
41. Goddard AW, Ball SG, Martinez J, Robinson MJ, Yang CR, Russell JM, Shekhar A. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depress Anxiety. 2010; 27(4):339–50. [PubMed: 19960531]
42. Davey MJ. The pharmacology of prazosin, an alpha 1-adrenoceptor antagonist and the basis for its use in the treatment of essential hypertension. Clin Exp Hypertens A. 1982; 4(1–2):47–59. [PubMed: 6122521]
43. Irwin M, Clark C, Kennedy B, Christian Gillin J, Ziegler M. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. Brain Behav Immun. 2003 Oct; 17(5):365–72. [PubMed: 12946658]
44. Vgontzas AN, Tsigos C, Bixler EO, Stratakis CA, Zachman K, Kales A, Vela-Bueno A, Chrousos GP. Chronic insomnia and activity of the stress system: a preliminary study. J Psychosom Res. 1998 Jul; 45(1):21–31. [PubMed: 9720852]
45. Miyamoto M. Pharmacology of Ramelteon, a Selective MT1/MT2 Receptor Agonist: A Novel Therapeutic Drug for Sleep Disorders. CNS Neurosci Ther. 2009; 15(1):32–51. [PubMed: 19228178]
46. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013; 8:e63773. [PubMed: 23691095]
47. Buscemi N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. Journal of General Internal Medicine. 2005; 20:1151–1158. [PubMed: 16423108]
48. Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung. 2007; 11:159–164. [PubMed: 17294232]
49. Kryger M, Roth T, Wang-Weigand S, Zhang J. The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. Sleep & breathing = Schlaf & Atmung. 2009; 13:79–84. [PubMed: 18584227]
50. Wirojanan J, Jacquemont S, Diaz R, Bacalman S, Anders TF, Hagerman RJ, Goodlin-Jones BL. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. J Clin Sleep Med. 2009; 5(2):145–50. [PubMed: 19968048]

51. Niederhofer H, Staffen W, Mair A, Pittschieler K. Brief report: melatonin facilitates sleep in individuals with mental retardation and insomnia. J Autism Dev Disord. 2003; 33(4):469–72. [PubMed: 12959427]

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 difficulty for each patient.
- This approach promises an improved risk/benefit ratio over the traditional "one-size fits all" approach to insomnia therapy.

This article reviews insomnia medications, focusing on how they define the new paradigm of personalization and discusses the implications for optimizing the treatment of insomnia occurring co-morbid with psychiatric conditions.

Table 1

Specificity of Insomnia Therapies

Treatment	Pharmacologic Specificity	Specificity of Effect on Brain Function	Target
Suvorexant	Highly Specific	Highly Specific	Antagonism of Orexin receptors
Doxepin 3–6 mg	Highly Specific	Highly Specific	Antagonism of H1 Histamine receptors
Prazosin	Highly Specific	Highly Specific	Antagonism of α_1 Adrenergic receptors
Ramelteon	Highly Specific	Highly Specific	Agonism of Melatonin M1/M2 receptors
Benzodiazepines	Highly Specific	Non-Specific	Binding to Benzo binding site on GABA-A Receptor Complex leads to broad CNS inhibition
Non-Benzodiazepines	Highly Specific	Non-Specific	Binding to Benzo binding site on GABA-A Receptor Complex leads to broad CNS inhibition
Antidepressants	Non-Specific	Non-Specific	Antagonism of 5HT and NE Transporters, 5HT2, α_1, Adrenergic, H1 Histaminergic, and Muscarinic Cholinergic antagonism
Antipsychotics	Non-Specific	Non-Specific	Dopamine D2, Dopamine D1, 5HT2, α_1, Adrenergic, H1 Histaminergic, and Muscarinic Cholinergic antagonism
OTC “Antihistamines”	Non-Specific	Non-Specific	Antagonism of H1 Histamine receptors and Cholinergic Receptors

Table 2

Personalizing Insomnia Therapies for Patients with Psychiatric Disorders

Condition Associated with Insomnia	**Most-Specific Agents Suited for Use**	**Non-Specific Agents Best-Suited for Use**
Generalized Anxiety Disorder	Suvorexant (theoretical basis)	Eszopiclone
Post-Traumatic Stress Disorder	Prazosin	
Major Depression		Eszopiclone
Substance Dependence/Discontinuation	Suvorexant (theoretical basis)	
Psychosis		Antipsychotic
Any Condition Associated Only with Early Morning Awakening or Early Morning Awaking and Sleep Maintenance Difficulty	Doxepin 3–6 mg	
Any Condition Associated Only with Problems Falling Asleep	Ramelteon/Melatonin	Zolpidem/Zaleplon
Any Condition Associated with Problems Falling Asleep and Staying Asleep	Suvorexant	Eszopiclone, Zolpidem Extended Release
Delayed Sleep Phase Syndrome	Melatonin	
Autism and Other Neurodevelopmental Disorders	Melatonin	