Pharmacotherapy of Insomnia

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ABSTRACT: Insomnia remains a common clinical concern that is associated with negative daytime consequences for patients and represents a significant public health problem for our society. Although a variety of therapies may be employed to treat insomnia, the use of medications has been a dominant approach. Regulatory agencies have now classified insomnia medications into 4 distinct pharmacodynamic classes. Medications with indications approved for insomnia treatment include benzodiazepine receptor agonists, a melatonin receptor agonist, a selective histamine receptor antagonist, and a dual orexin/hypocretin receptor antagonist. Both pharmacodynamic and pharmacokinetic advances with hypnotic medications in recent years have expanded the pharmacopoeia to allow personalized treatment approaches for different patient populations and individual sleep disturbance patterns.

KEYWORDS: benzodiazepine, drugs, hypnotics, insomnia, medication, sleep

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Insomnia: Contemporary Perspectives

The conceptualization of insomnia as a clinical disorder has evolved considerably in recent decades. This is reflected in the numerous nosology revisions which have occurred in this time and which are currently represented in the International Classification of Sleep Disorders (Third Edition; ICSD-3) and the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition; DSM-5).1,2 These contemporary diagnostic approaches employ broad definitions of insomnia disorders that avoid the shortcomings found in previous versions, such as the use of multiple subtypes, specific developmental disorder categories, and attempts to differentiate primary, secondary, or comorbid insomnia. The ICSD-3 includes 2 insomnia disorders (chronic and short-term) plus an “other” category for provisional use before a final diagnosis is established.1 Chronic and short-term insomnia disorders have similar criteria with the exception of the duration of symptoms (ie, longer or shorter than 3 months). Essential features of insomnia include difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance to going to bed on an appropriate schedule, or difficulty sleeping without parent or caregiver intervention. Required sleep difficulty associations include the following: fatigue or malaise; impairment in attention, concentration, or memory; social, family, vocational, or academic performance impairment; mood disturbance or irritability; daytime sleepiness; behavioral problems such as hyperactivity, impulsivity, and aggression; decreased motivation, energy, and initiative; proneness for errors and accidents; or dissatisfaction or concerns about sleep. The number of sleep difficulty associations varies with each patient and the course of the insomnia disorder. The sleep and wake complaints must not be attributable to inadequate circumstances or opportunity for sleep, nor should they be better explained by another sleep disorder.

Difficulty with sleep onset and sleep maintenance is the most common sleep-related complaint encountered in primary care and many medical specialty practices. General population prevalence estimates vary depending on specific survey questions. Naturally, broad questions about sleep complaints result in relatively high prevalence rates, whereas more narrow questions representing diagnostic criteria find much lower rates. Studies typically estimate that approximately one-third of adults experience at least one insomnia symptom. Nighttime sleep difficulty along with daytime impairment is reported by about 10% to 15% of the population. The insomnia disorder criteria are satisfied in 6% to 10% of adults. Women have increased risk for insomnia compared with men with a ratio of 1.44. Older individuals also have a greater likelihood of sleep difficulty. Finally, people with comorbid psychiatric and medical conditions are at greater risk for having insomnia symptoms.2

The plan for treating chronic insomnia patients should evolve from a comprehensive evaluation that considers the history of the sleep-related symptoms; the presence of additional sleep, medical, and psychiatric disorders; past treatment effects; concurrent medications; treatment availability; and patient preference.1 The treatment of insomnia may include

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combinations of healthy sleep habit recommendations, psychological, and behavioral strategies (eg, cognitive behavioral therapy); timed exposure to bright light or darkness; and the use of assorted pharmacologic agents. The American Academy of Sleep Medicine has published guidelines regarding the pharmacologic treatment of insomnia in adults.\(^3\) Key recommendations include the incorporation of behavioral and psychotherapeutic strategies along with the use of medications. Choices regarding medication selection should be based on the patient’s sleep-related symptoms during the nighttime and daytime, any comorbid conditions, sex, reproductive status, age, work or school schedules, and lifestyle routines. Of course, the potential for drug-drug interactions must be reviewed. Patients should be monitored regularly for the safety and efficacy of recommended medications. Generally, lower doses should be employed with elderly patients and others with debilitating medical conditions.\(^3\)

### Insomnia Pharmacotherapy

The current generation of medications approved for the treatment of insomnia includes a wide diversity of compounds differing in their pharmacodynamic and pharmacokinetic characteristics. Overall, these represent a major advance in safety compared with historic pharmacologic classes (eg, barbiturates) employed for insomnia. The domain of substances that people take with the intention of improving their sleep represents a top-down approach. That is, the discussion focuses on pharmacologic features of those compounds that have been approved for the treatment of insomnia or otherwise are commonly employed for this purpose. The goal is to highlight the wide diversity of insomnia remedies and to review data that may aid in clinical decision making. Often treatment selections are based on advertising, word of mouth, and tradition, rather than pharmacodynamic and pharmacokinetic properties. The medications with regulatory approval for insomnia treatment all have been comprehensively evaluated for their efficacy and safety characteristics in populations of healthy individuals and subjects with insomnia. In contrast, very limited efficacy and safety evidence is available for the other medications and substances when used to treat insomnia.

The domain of this discussion is compounds available in the United States. An international catalog of all available insomnia medications would be beyond the scope of this article. Fortunately, most of the products licensed for insomnia treatment elsewhere also are marketed in the United States. The primary exceptions are selected benzodiazepine receptor agonist (BZRA) hypnics for which review in this article remains relevant.

### Medications Approved for the Treatment of Insomnia

The medications approved for treating insomnia represent 4 fundamental pharmacodynamic categories with key actions related to receptors for \(\gamma\)-aminobutyric acid (GABA), melatonin, histamine, or orexin/hypocretin. All are based on well-established neurotransmitter effects on sleep and waking.\(^6\) These medications all have been evaluated for efficacy and safety in placebo-controlled clinical trials with populations of insomnia subjects. Some medications improve sleep onset or sleep maintenance, whereas others improve both variables, typically consistent with their pharmacokinetic parameters.

The common side effects, contraindications, pregnancy category, and predictable drug-drug interactions are highlighted in the prescribing information. Most of the approved hypnotics in the United States are classified as Schedule IV controlled substances due to some degree of abuse potential, although 2 (dopamine and ramelteon) are considered unscheduled because of their absence of risk for abuse. These features are detailed in Tables 1 to 3. Broad warnings for hypnotic medication include the potential for rare allergic reactions and for complex sleep-related behaviors.\(^6\)
Benzodiazepine Receptor Agonists

Hypnotic medications classed as BZRA became available beginning in the 1970s, and at the time they represented a safer alternative to the commonly prescribed barbiturates. The earliest BZRA hypnotics were defined by their characteristic benzodiazepine structure (benzene and diazepine rings); however, the more recent additions to this class have alternate "non-benzodiazepine" structures. The indications are for insomnia characterized by difficulty with sleep onset, difficulty with sleep onset and sleep maintenance, or middle-of-the-night awakenings with difficulty returning to sleep. The more common side effects associated with BZRA hypnotics include somnolence, dizziness, headache, fatigue, ataxia, anterograde amnesia, and confused behaviors. Rebound insomnia may occur with abrupt discontinuation.

The BZRA hypnotics all are manufactured in immediate-release tablet or capsule formulations, with the exception of zolpidem which is additionally available in an extended-release bedtime use tablet, oral dissolvable doses for bedtime or middle-of-the-night use, and an oral liquid spray formulation.

**Pharmacodynamics**

All BZRA hypnotics are positive allosteric modulators of GABA responses at the GABA$_A$ receptor complex. GABA is the most widespread inhibitory neurotransmitter in the central nervous system (CNS) and also has targeted action in hypothalamic regions involved in the regulation of sleep and wakefulness. The GABA$_A$ receptor complex is a pentameric transmembrane structure with a central chloride ion channel. When GABA attaches to the GABA recognition site, negative chloride ions are able to enter the cell, a process that hyperpolarizes the cell membrane and decreases the likelihood of an action potential. When a benzodiazepine agonist

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**Table 1. Medications Approved by the U.S. Food and Drug Administration for the Treatment of Insomnia.**

| GENERIC NAME | BRAND NAME | AVAILABLE DOSES (MG) | ELIMINATION HALF-LIFE (HR) |
|--------------|------------|----------------------|---------------------------|
| **BENZODIAZEPINE RECEPTOR AGONISTS** | | | |
| **Benzodiazepine Immediate Release** | | | |
| Estazolam | ProSom | 1, 2 | 10 - 24 |
| Flurazepam | Dalmane | 15, 30 | 2.3/48 – 160 active metabolite |
| Quazepam | Doral | 7.5, 15 | 39/73 active metabolite |
| Temazepam | Restoril | 7.5, 15, 22.5, 30 | 3.5 – 18.4 |
| Triazolam | Halcion | 0.125, 0.25 | 1.5 – 5.5 |
| **Nonbenzodiazepine Immediate Release** | | | |
| Zolpidem | Ambien | | |
| | Lunesta | 1, 2, 3 | 6/ 9 in elderly |
| | Sonata | 5, 10 | 1 |
| | Zolpidem | 5, 10 | 2.8 in males |
| **Nonbenzodiazepine Extended Release** | | | |
| | Zolpidem ER | Ambien CR | 6.25, 12.5 | 1.6 – 4.5 |
| **Nonbenzodiazepine Alternate Delivery** | | | |
| | Zolpidem oral spray | Zolpimist | 5, 10 | 2.7 – 3.0 |
| | Zolpidem sublingual | Edluar | 5, 10 | -2.5 |
| | Zolpidem sublingual | Intermezzo | 1.75, 3.5 | -2.5 |
| **SELECTIVE MELATONIN RECEPTOR AGONIST** | | | |
| Ramelteon | Rozerem | 8 | 1 – 2.6 |
| **SELECTIVE HISTAMINE RECEPTOR ANTAGONIST** | | | |
| Doxepin (low dose) | Silenor | 3, 6 | 15.3 |
| **DUAL OREXIN RECEPTOR ANTAGONIST** | | | |
| Suvorexant | Belsomra | 5, 10, 15, 20 | 12 |
Table 2. Approved indications for US insomnia medications.

| MEDICATION         | UNSPECIFIED INSOMNIA | SLEEP ONSET | SLEEP MAINTENANCE | EARLY AWAKENING |
|--------------------|-----------------------|-------------|-------------------|-----------------|
| Estazolam          | ✓                     | ✓           | ✓                 | ✓               |
| Flurazepam         | ✓                     | ✓           | ✓                 | ✓               |
| Quazepam           | ✓                     | ✓           | ✓                 | ✓               |
| Temazepam          | ✓                     |             |                   |                 |
| Triazolam          | ✓                     |             |                   |                 |
| Eszopiclone        | ✓                     | ✓           |                   |                 |
| Zaleplon           | ✓                     |             |                   |                 |
| Zolpidem           | ✓                     |             |                   |                 |
| Zolpidem ER        | ✓                     | ✓           |                   |                 |
| Zolpidem spray     | ✓                     |             |                   |                 |
| Zolpidem sublingual| ✓                     |             |                   |                 |
| Zolpidem sublingual—MOTN |             |             |                   | ✓               |
| Ramelteon          | ✓                     |             |                   |                 |
| Low-dose doxepin   | ✓                     |             |                   |                 |
| Suvorexant         | ✓                     |             |                   |                 |

Abbreviation: MOTN, middle of the night.

Table 3. Drug Enforcement Administration (DEA) class, pregnancy category (PC), and most common side effects for US insomnia medications.

| MEDICATION         | DEA CLASS | PC | MOST COMMON SIDE EFFECTS                                                                 |
|--------------------|-----------|----|------------------------------------------------------------------------------------------|
| Estazolam          | IV        | X  | Somnolence, hypokinesia, dizziness, abnormal coordination                                  |
| Flurazepam         | IV        | X  | Dizziness, drowsiness, lightheadedness, loss of coordination, staggering, falling          |
| Quazepam           | IV        | X  | Drowsiness, headache                                                                      |
| Temazepam          | IV        | X  | Drowsiness, dizziness, lightheadedness, difficulty with coordination                       |
| Triazolam          | IV        | X  | Drowsiness, headache, dizziness, "pins & needles," coordination difficulty, lightheadedness|
| Eszopiclone        | IV        | C  | Unpleasant taste, headache, somnolence, rash, respiratory and viral infections, dizziness, dry mouth, anxiety, hallucinations |
| Zaleplon           | IV        | C  | Drowsiness, lightheadedness, dizziness, "pins & needles," difficulty with coordination     |
| Zolpidem           | IV        | C  | Drowsiness, dizziness, diarrhea, drugged feeling                                          |
| Zolpidem ER        | IV        | C  | Headache, next-day somnolence, dizziness                                                 |
| Zolpidem spray     | IV        | C  | Drowsiness, dizziness, diarrhea, drugged feeling                                          |
| Zolpidem sublingual| IV        | C  | Drowsiness, dizziness, diarrhea, drugged feeling                                          |
| Zolpidem sublingual—MOTN |     | C  | Headache, nausea, fatigue                                                                |
| Ramelteon          | —         | C  | Somnolence, dizziness, fatigue, nausea, exacerbated insomnia                              |
| Low-dose doxepin   | —         | C  | Somnolence/sedation, nausea, upper respiratory tract infection                             |
| Suvorexant         | IV        | C  | Somnolence                                                                               |
interacts with a separate benzodiazepine recognition site on
the receptor complex, the result is an enhanced influx of chlo-
ride ions with a greater inhibitory effect when GABA is
present.⁹

Pharmacokinetics
The BZRA hypnotics all are relatively rapidly absorbed, so
may be beneficial for sleep onset. The hepatic cytochrome
P450 (CYP)3A4 pathway is the primary route of metabolism
for these medications, although additional CYP isoenzymes
or glucuronide conjugation may have significant roles, as with
temazepam.¹⁰ The elimination half-lives vary considerably
and approximately correlate with the duration of action and
risk for next-day residual sedation and impairment. Benzodiazepine BZRA medications range from approxi-
mately 3.5 hours for triazolam to more than 24 hours for flu-
razepam and quazepam when active metabolites are included. The nonbenzodiazepine BZRA medications range from
1 hour for zaleplon to approximately 6 to 9 hours for eszopi-
clone, with zolpidem in between at about 2.5 hours for the
basic compound. The finding of a gender effect on zolpidem
metabolism characterized by higher area under the curve and
peak plasma concentration values in women than men led to
the recommendation to reduce by 50% the dosage of some
formulations of the hypnotic agent.¹¹

Melatonin Receptor Agonist
Melatonin is a hormone produced in the pineal gland under
control of the circadian system in the hypothalamic suprachi-
amas tic nucleus (SCN).¹² Normally the melatonin level is low
throughout the daytime, gradually rises in the evening as bed-
time approaches, plateaus during the typical sleep period at
nighttime, and then declines by the typical wake time around
dawn. The circadian system promotes an arousal signal in the
late afternoon and evening which opposes the homeostatic
sleepiness accumulating since sleep last occurred, thus allowing
alertness during the day and evening. With the later-evening
melatonin rise, the circadian arousal level declines, leaving the
homeostatic sleep drive unopposed. In this manner, the melatoni-
in rise facilitates sleep onset and additionally reinforces the
timing of the circadian system.⁴

In the United States, ramelteon is the only melatonin recep-
tor agonist indicated for the treatment of insomnia.¹³ This
agent has a specific indication for difficulty with sleep onset. It
has no abuse potential. In the United States, melatonin itself is
an unregulated dietary supplement, although in the European
Union, an extended-release melatonin formulation is available
only by prescription.¹⁴ Tasimelteon also is a melatonin receptor
agonist, although it is indicated for the treatment of non–24-
hour circadian rhythm sleep–wake disorder.¹⁵ Agomelatine, marketed as an antidepressant and not currently available in
the United States, has multiple receptor effects that include
melatonin receptor agonist activity.¹⁶

Pharmacodynamics
Ramelteon is a selective agonist for the MT1 and MT2 melatoni-
ner receptors that are highly represented in the SCN.¹⁷
Accordingly, ramelteon may enhance sleep onset by decreasing
the evening circadian arousal and may also help stabilize the
timing of the sleep–wake cycle.

Pharmacokinetics
The time to maximum concentration (Cmax) for ramelteon is
approximately 0.75 hour in the fasted state. Metabolism is pri-
marily through CYP1A2, and to a limited extent through
CYP2C and CYP3A4. Adjustments may be necessary for
inducers and inhibitors for these pathways. A specific contrain-
dication is stated for coadministration of ramelteon with flu-
voxamine, a potent CYP1A2 inhibitor. The ramelteon
elimination half-life is 1 to 2.6 hours and is about 2 to 5 hours
for M-II, a less potent active metabolite.¹⁸

Histamine Receptor Antagonist
Low-dose doxepin is the histamine H1 receptor antagonist
approved for the treatment of insomnia with a specific indica-
tion for difficulty with sleep maintenance.¹⁹ While prescribing
guidelines for doxepin as an antidepressant goes as high as
300 mg daily and the largest pill strength is 150 mg, the approved
insomnia doses are merely 3 and 6 mg. Doxepin should not be
coadministered with monoamine oxidase inhibitors.

Pharmacodynamics
Histamine is a potent wake-promoting neurotransmitter pro-
duced in the brain in the tuberomammillary nuclei of the hypo-
thalamus. Antagonists at the H1 receptor have sedating
properties. Doxepin is very highly selective for the H1 receptor
and at very low doses has minimal additional pharmacodynamic
activity. During the usual nighttime sleep period, wake-promot-
ing neurotransmitters typically are quiescent; however, hista-
mine remains active to a limited extent so may be targeted for
antihistaminic action to promote a sedating effect at these low
doses, particularly during the latter part of the nighttime.²⁰

Pharmacokinetics
The time to Cmax for low-dose doxepin is 3.5 hours. CYP2C19
and CYP2D6 are the primary metabolic pathways. The elimi-
nation half-life is 15.3 hours.¹⁹

Orexin/Hypocretin Receptor Antagonist
The orexin/hypocretin system, discovered by 2 independent
research groups in 1998, includes 2 similar neuropeptides
(orexin A and orexin B) and 2 receptors (OX1R and OX2R)
with overlapping distributions.²¹,²² Orexin/hypocretin–produc-
ing neurons in the perifornical lateral hypothalamic region have
projections to the cerebrum and to numerous nuclei producing
wake–promoting neurotransmitters with a net effect of enhancing and stabilizing the waking state. It is notable that narcolepsy is associated with decreased orexin/hypocretin activity. The single currently approved orexin/hypocretin receptor antagonist is suvorexant, although other compounds are being investigated. The indication is for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance. The presence of narcolepsy is a contraindication.

Pharmacodynamics
Suvorexant promotes sleep by decreasing orexin/hypocretin-associated CNS arousal. It functions as a reversible dual (OX1R and OX2R) receptor antagonist. The mechanism of action targets a region of the hypothalamus critical for the regulation of sleep and waking and therefore may avoid more global CNS effects. This approach may offer additional daytime benefits for insomnia patients characterized as having symptoms of hyperarousal.

Pharmacokinetics
Suvorexant is manufactured as an immediate–release tablet. The median time to $C_{\text{max}}$ under fasting conditions is 2 hours, although there is considerable variability among individuals, and there may be a delay following a high–fat meal. Metabolism is primarily through the CYP3A pathway with limited contribution from CYP2C19. Dosage adjustments may be necessary for CYP3A inducers and inhibitors. The elimination half-life is approximately 12 hours.

Alternate Medications Prescribed for Sleep
As noted above, numerous neurotransmitters have been identified as having wake– or sleep–promoting properties. For example, acetylcholine, norepinephrine, serotonin, dopamine, glutamate, and orexin/hypocretin tend to be wake promoting, whereas GABA and galanin are sleep promoting. Adenosine appears to be associated with the homeostatic sleep drive. In humans, melatonin facilitates sleep onset during certain circadian periods. Therefore, compounds functioning as agonists or antagonists have the potential to influence sleep and waking, possibly with desired or undesired consequences. It should be noted that medications may have multiple effects and sometimes incorporate both wake– and sleep–promoting actions simultaneously. Most medications prescribed “off label” for insomnia have not been evaluated for either efficacy or safety and have not been studied in subjects with insomnia. Among the nonsomnia–indicated medications sometimes prescribed primarily for sleep enhancement are antidepressants (eg, trazodone, amitriptyline, and mirtazapine), anxiolytics (eg, alprazolam and clonazepam) antipsychotics (eg, quetiapine), and antihypertensives (eg, clonidine). The ideal situation is when a patient with insomnia also has a comorbid condition for which the medication is indicated, as might be the case with mirtazapine for a depressed individual or quetiapine for someone treated for schizophrenia. Unfortunately, little evidence is available to guide the use of these medications in the treatment of insomnia. Excessive sedation is a common side effect among these medications, as many have relatively long elimination half–lives, but each of the drugs has specific potential adverse effects that must be considered when prescribed for insomnia.

OTC Sleep Aids
By definition, OTC products are available without a prescription but are subject to regulatory agency approval for their doses, manufacture, indications, and marketing. These medications are antihistamines, primarily diphenhydramine and doxylamine.

Although the sleep–promoting pharmacodynamic effect of an antihistamine is predictable, additional receptor effects at recommended doses may lead to adverse effects. Antagonist activity at the acetylcholine muscarinic receptor may be associated with confusion, delirium, dry mouth, constipation, and urinary retention. Elderly individuals and people concomitantly taking other medications with anticholinergic properties are the most vulnerable to these effects. With initial use, the OTC antihistamine sleep aids may offer benefits to sleep onset and sleep maintenance. Tolerance for the sleep–promoting effects of these products is possible, and for this reason, some individuals may increase the dose beyond the recommended amounts. The elimination half–lives of these products are moderately long and may contribute to next–morning grogginess following bedtime use.

Dietary Supplements Marketed for Sleep
These compounds are essentially unregulated, though are limited in the extent to which they can be marketed with specific health claims. Products within this category may be marketed as sleep aids. Often they are considered to be in the realm of complementary and alternative or homeopathic medicine. In the United States, there are 2 major categories: (1) melatonin and (2) everything else. There is minimal evidence supporting the use of melatonin at bedtime for the treatment of insomnia. However, there is considerable evidence for the efficacy of melatonin in the treatment of selected circadian rhythm sleep–wake disorders, for which insomnia often is a key symptom. It is difficult to generalize about the remarkably diverse assortment of other sleep aid products that contain one or more ingredients derived from plants or minerals and sometimes melatonin as well. Among the common ingredients are valerian, kava–kava, hops, lavender, skullcap, chamomile, and magnesium. The evaluation of these products is complicated by the multitude of molecules in many of the plant extracts. There is no strong evidence supporting the efficacy of these sleep aids, although typically they are regarded as safe, with the exception of kava–kava, for which there have been warnings regarding hepatic failure.
Conclusions
A diverse array of substances is used in the attempt to treat insomnia. Regulatory agencies have approved medications in 4 distinct pharmacodynamic classes with indications for insomnia treatment, in some cases specifically for sleep onset, sleep maintenance, middle-of-the-night awakenings, or early morning awakenings. The assortment of hypnotic medications with different pharmacodynamic and pharmacokinetic properties allows a personalized approach to insomnia pharmacotherapy. Each option is associated with particular risks and benefits. Alternate treatment strategies additionally may include the “off-label” use of other sedating prescription-required medications. People also may turn to OTC antihistamine or unregulated dietary sleep aids, although there is limited support for the use of these products in treating insomnia. Clearly there is a need for further preclinical research on the regulation of sleep and wakefulness, as well as the pathophysiology of insomnia, that will guide the clinical development of new compounds for the safe and effective treatment of this very common disorder.

Author Contributions
All authors reviewed and approved the final manuscript.

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