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Optimizing the Pharmacologic Treatment of Insomnia: Current Status and Future Horizons

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Abstract

A number of medications are available for treating patients with insomnia. These medications include agents approved as insomnia therapies by the U.S. Food and Drug Administration (FDA), agents approved by the FDA for another condition that are used "off-label" to treat insomnia, and agents available "over-the-counter" that are taken by individuals with insomnia. These agents differ in their properties, their safety and efficacy when used for different insomnia patient subtypes, and the available data on their efficacy and safety in these subtypes. As a result, optimizing the medication treatment of insomnia for a given patient requires that the clinician select an agent for use which has characteristics that make it most likely to effectively and safely address the type of sleep difficulty experienced by that individual. This article is intended to assist clinicians and researchers in carrying out this optimization. It begins by reviewing the basic characteristics of the medications used to treat insomnia. This is followed by a review of the fundamental ways that individuals with insomnia may differ and affect the choice of medication therapy. This review includes discussions that illustrate how to best choose a medication based on the characteristics of the available medications, the key differences among insomnia patients, and the available research literature. Lastly, we discuss future directions for the optimizing pharmacologic management of insomnia. It is hoped that the treatment tailoring methods discussed herein serve as a means of improving the clinical management of insomnia and, thus, improve the lives of the many patients who suffer from this common and impairing condition.

Keywords

Insomnia; Pharmacotherapy

I. Introduction

A number of different types of medications are currently available for the treatment of insomnia. These agents include: 1) a group that are approved by the U.S. Food and Drug Administration (FDA) for this purpose; 2) agents which are approved by the FDA for the treatment of another condition but are used "off-label" for the treatment of insomnia; and 3) agents that are available "over-the-counter" (OTC) for insomnia treatment.

The use of these medications is often carried out as a "one-size-fits-all" endeavor in which clinicians identify a medication that they prefer and administer it to all individuals who complain of disturbed sleep. However, this approach does a disservice to insomnia sufferers.

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The nature of the sleep problem experienced by those with insomnia varies. The medications available for treating insomnia also vary in their characteristics and, as a result, in their suitability for patients with the different presentations of insomnia that are encountered in practice.

One of the ways in which insomnia patients differ is the time of night when their sleep problems occur (problems with onset, maintenance, and/or early morning sleep difficulty). Another such factor distinguishing patients is is the temporal pattern of their sleep problems across nights (nightly, intermittent and frequent, intermittent and occasional). A final factor that must be addressed in order to optimize pharmacotherapy of insomnia is the presence of co-morbidities such as mood disorders, anxiety disorders, pain, and substance use/ dependence.

Optimizing the medication management of insomnia for a given patient requires that the clinician select an agent which has characteristics that make it most likely to effectively and safely address the sleep difficulty experienced by that individual. Carrying out this process requires awareness of: 1) the basic characteristics of all of the insomnia medications; 2) the fundamental ways that insomnia may differ among individuals that can affect the optimal choice of treatment; and 3) the available data that provide guidance as to how to match insomnia medication characteristics to the nature of an individual's sleep complaint.

This article provides the information required to optimize medication management of insomnia. It begins by reviewing the basic characteristics of the medications used to treat insomnia. This is followed by a review of fundamental patient characteristics that affect the choice of medication therapy. This review illustrates how to best choose a medication based on the characteristics of the available medications, the key differences among insomnia patients, and the available research literature. Lastly, we consider the types of studies needed to further optimize pharmacologic approaches for insomnia management.

2. Type of Pharmacologic Treatment for Insomnia Available

2.1. Prescription agents approved by U.S. FDA for treatment of insomnia

2.1.1 Benzodiazepines

Pharmacology: The benzodiazepines are a class of chemically-related medications known for their sedative-hypnotic properties. Included among these agents are triazolam, temazepam, flurazepam, alprazolam, clonazepam, and lorazepam (among many others). These medications are sedating due to their effects on GABA, the primary inhibitory neurotransmitter throughout the brain. Benzodiazepines bind to the GABA-A receptor and promote its inhibitory effects by causing conformational changes in the proteins that form channels through which chloride ions flow across neuronal membranes.[1] The change facilitates the inward flow of negative ions, which results in hyperpolarization, thus biasing the neuron away from depolarization, and ultimately reducing neuronal firing. The activity in GABAergic projections to wake-promoting regions of the brain are thus increased, decreasing arousal and facilitating sleep. GABA-A receptors are. however, also found outside of brain areas involved in sleep/wake function. Benzodiazepines therefore have additional effects beyond sleep enhancement, including anxiolytic effects, reward, memory impairment, motor impairment, anticonvulsant effects and myorelaxation. Adverse effects may therefore include sedation, cognitive impairment (anterograde short-term memory loss), motor impairment and the potential for abuse. Anxiolytic and myorelaxant effects however may be beneficial in the treatment of insomnia because anxiety and/or pain are frequent comorbidities.[2]

The most commonly prescribed benzodiazepines in the treatment of insomnia are triazolam, flurazepam, temazepam, estazolam, quazepam, clonazepam, lorazepam, and alprazolam.[3] Of these, only triazolam, flurazepam, and temazepam are FDA approved in the U.S.A. for the treatment of insomnia. Although, benzodiazepines differ in their effects on GABA-A receptors in different brain regions to a degree, the primary factors that distinguish the benzodiazepines are route of metabolism and elimination half-life. Longer half-life and higher dosage tend to produce longer lasting clinical effects. Shorter half-life and lower dosage tends to produce fewer next-day effects. Of the benzodiazapines commonly prescribed for insomnia, triazolam has the shortest half-life and is least likely to produce next-day effects. Some benzodiazepines have half-lives that exceed 24 hours, including flurazepam, quazepam and clonazepam. These medications are relatively likely to lead to next-day effects, such as daytime sedation.

Evidence base: A number of controlled trials have established the efficacy of benzodiazapines for the treatment of insomnia. Triazolam, temazepam, flurazepam, quazepam, and estazolam have been found to have beneficial effects on sleep onset and maintenance for insomnia patients aged 18–65.[3] In older adults (aged 65 and greater) triazolam and flurazepam have been found to benefit sleep onset and maintenance. Temazepam has been found to be helpful for sleep maintenance only. Although there have been fewer trials in patients with insomnia and co-occuring medical or psychiatric conditions, the available evidence suggests that they can provide sleep-improving benefits in these populations as well.

Three placebo-controlled studies were carried out evaluating the addition of clonazepam to fluoxetine in those with major depression[4–6]. In all three studies clonazepam improved sleep whereas two of the studies showed greater improvement in depression symptoms with combined therapy than with fluoxetine alone. However, there results also suggest that improvement in depression symptoms with clonazepam may not be sustained with longer duration of therapy.

There has also been one placebo-controlled study where patients with rheumatoid arthritis and disturbed sleep were treated with a benzodiazepine. In this study patients reported a benefit of triazolam relative to placebo for both sleep and morning stiffness.[7]

2.1.2. Non-Benzodiazapines

Pharmacology: The non-benzodiazepines include some of the most commonly prescribed sleep-promoting medications, including zolpidem, zaleplon, and eszopiclone.[3] These agents are chemically unrelated to benzodiazapines (thus the term “non-benzodiazepines”), but have similar effects by acting through related pharmacological mechanisms. Although they bind to the same site on the GABA-A receptor complex as do the benzodiazepines, they bind more specifically to subtypes of GABA-A receptors.[8] In contrast to benzoadiazepines, which tend to have broad effects at the receptors containing the α_1, α_2, α_3, and α_5 subunit-containing GABA receptors, the non-benzodiazapines tend to selectively bind to a subset of these subunit-containing GABA-A receptors.[8,9] On this basis, Zolpidem and zaleplon, which bind relatively preferentially to α_1 containing GABA receptors, would be expected to have effects limited to anticonvulsant, amnestic, and motor impairing effects as well as sleep enhancement.[10] Eszopiclone, on the other hand, would be expected to have anxiolytic and myorelaxant effects in addition to sleep enhancement, due to its relatively greater effects at α_2 and α_3 subunits-containing GABA A receptors.

The non-benzodiazepine agents also differ in terms of elimination half-lives. All of these agents have shorter half lives than most benzodiazepines (with the exception of triazolam) and may, therefore, have fewer next-day effects. However, the limited data on head to head

comparisons of these two classes of medications cannot confirm that prediction. Zaleplon and zolpidem each have a relatively short half-life and therefore can be expected to be most effective in facilitating sleep onset.[3] Indeed both of these agents are FDA approved only for treating sleep onset problems. Longer acting agents such as eszopiclone and a controlled-release version of zolpidem are useful for maintaining sleep as well as facilitating sleep onset and are FDA approved for treating both onset and maintenance difficulties.[3]

Evidence base: A substantial literature supports the efficacy of the non-benzodiazepines in the treatment of insomnia. Zolpidem and zaleplon have been shown to be effective in the treatment of sleep onset problems in younger and older adults with primary insomnia.[3] Zolipdem CR has demonstrated efficacy for improving sleep onset and maintenance in adults 18–65.[3] Eszopiclone has been shown to be effective for treating sleep onset and maintenance difficulties in older adults (age 65+) as well.[3]

In contrast to benzodiazepines, the non-benzodiazepines have been evaluated for longer-term efficacy and safety. Eszopiclone has been evaluated through 6 months in a two placebo-controlled trials[11,12] and up to 12 months in an open-label extension.[13] Zaleplon has been shown to be safe in 6–12 month open label studies of older adults.[14] Zolpidem CR has not been evaluated in a placebo-controlled study of nightly treatment of more than 3 weeks in duration, however it has been found to have sustained efficacy over six-months in a placebo-controlled study wherein patients received doses 3–7 nights per week.[15]

The non-benzodiazepines have also been evaluated in patients with comorbid psychiatric disorders. A controlled trial of patients with insomnia and major depression compared fluoxetine-plus-eszopiclone to fluoxetine-plus-placebo. Patients with the active insomnia medication demonstrated better sleep and greater and faster, reductions in depression symptoms.[16] A similar study of patients with insomnia and generalized anxiety disorder (GAD) found that eszopiclone-plus-escitalopram improved both sleep and anxiety outcomes over eszopiclone-plus-escitalopram.[17] Interestingly, essentially identical trials were carried out with zolpidem CR and, unlike eszopiclone, sleep was improved but no effects on depression or GAD outcomes were found.[18,19] Both eszopiclone and zolpidem were found to improve sleep in menopausal insomnia.[20,21] Two placebo-controlled studies have also been carried out with eszopiclone establishing that it has therapeutic effects on sleep and pain in those with chronic pain syndromes. One was carried out in patients with rheumatoid arthritis and eszopiclone was also evaluated in a placebo-controlled trial as an add-on therapy to open-label naproxen in 54 patients with chronic low back pain and found to significantly improve sleep and pain outcomes.[22] A placebo-controlled trial of eszopiclone was also carried out in patients with rheumatoid arthritis and indicated that this agent significantly improved sleep, ratings of daytime functions, and some pain outcomes compared with placebo.[23] Lastly, a placebo-controlled cross-over study carried out in 24 patients with insomnia occurring comorbid to post-traumatic stress disorder (PTSD) indicated that patients receiving eszopiclone 3 mg had significantly greater improvements in both sleep disturbance and PTSD symptoms than did those receiving placebo.[24]

Overall, the strong evidence base for the non-benzodiazepines makes them an attractive option in the treatment of insomnia. The side effect profile of non-benzodiazepines has been found to be similar to the benzodiazepines and includes sedation, dizziness and psychomotor impairment. Non-benzodiazepines appear to have lower abuse potential at recommended dosages, but may still have a significant risk at higher doses.[25] Zaleplon and zolpidem both have relatively lower risks of unwanted daytime sedation while still providing effective treatment for sleep onset difficulties. The longer acting agents eszopiclone and zolpidem CR are effective for the treatment of sleep maintenance problems as well as sleep initiation.

These are the only agents other than benzodiazepines that are currently FDA approved for the treatment of both sleep onset and sleep maintenance problems.

2.1.3. Melatonin Receptor Agonists

Pharmacology: Melatonin is an endogenous hormone produced by the pineal gland that is intimately involved in circadian rhythms. Two melatonin agonists are currently available in the U.S.: melatonin (available as an over-the-counter supplement), and ramelteon(FDA approved for the treatment of insomnia). Unlike benzodiazepines and non-benzodiazepines, the sleep enhancing effects of melatonin agonists have not been found to vary with dose.

Ramelteon is melatonin receptor agonist (MT1 and MT2) that was introduced in 2005. It has a strong affinity for the MT1 receptor which is believed to regulate drowsiness by dampening wake promoting signals from the SCN.[26] The half-life of melatonin is very short, between 1 and 3 hours, making it useful for sleep onset insomnia, but not for sleep maintenance insomnia.[26] There is no evidence that ramelteon carries any risk of tolerance or abuse and, therefore, it is one of only two FDA–approved medications for insomnia that has not been designated by the U.S. Drug Enforcement Administration (DEA) as having a significant potential for abuse (the other being doxepin).[25]

Evidence base: Exogenous melatonin is available as a supplement that is not regulated by the FDA and is therefore available in a wide range of doses. Controlled studies have not found it to have substantive therapeutic effects in insomnia patients.[26] However, it does show some promise in some populations including children with neurodevelopmental disorders.[27–41] Unfortunately, a limitation in interpreting the results of studies carried out with melatonin is that the dose of melatonin in the studies has ranged from 0.1 to 75 mg and timing has varied from 30 minutes to 3 hours before bedtime, making the application of their findings to clinical practice quite challenging.[42,43] Studies that have attempted to establish a dose-response curve have been unsuccessful, finding no relationship between serum blood levels of melatonin agonists and therapeutic effects.[43] The efficacy of ramelteon for treating insomnia has been demonstrated in several randomized, placebo-controlled trials. Most studies have evaluated a dose of 8 mg administered 30 minutes prior to lights out.[3] Studies have been done in olderxs adults (age 65+) as well as in those between the ages of 18 and 65. The effects have been limited to improvements in sleep onset latency with larger effects shown by polysomnography than by subjective measures of sleep. The most commonly reported side effects were headache, somnolence and sore throat, but these were not significantly elevated relative to placebo.

Ramelteon and melatonin have favorable profiles of adverse effects and no significant potential for abuse (although they have not been studied in populations at high risk for substance abuse). The most common adverse-effects of melatonin are headache, sedation and slowed reaction times.[34,44–46] There is some evidence that it may temporarily affect fertility in both men and women,[47–50] and is, therefore, not the treatment of choice for individuals trying to conceive. Ramelteon has also been associated with somnolence, dizziness, nausea and fatigue, but no effects on fertility have been reported. It has also been found to be safe for use in patients with mild to moderate sleep apnea[51] and moderate to severe obstructive pulmonary disease.[52] Placebo-controlled trials have also demonstrated that ramelteon is safe and effective over a long period (up to 6 months) with nightly use.[53]

2.1.4 H1 antagonists (Antihistamines)

Pharmacology: The term ”antihistamine” is typically used for agents that were developed for the treatment of allergies, but many other agents are significant antagonists of H1 histamine receptors and could therefore also be referred to as antihistamines. For the sake of

clarity, we will use the term “antihistamine” only to refer to agents that were intended to treat allergies, but also have been used to treat insomnia. H1 antagonists are believed to exert therapeutic effects on sleep by blocking the wake promoting effects of histamine.[54] Among the antihistamines, diphenhydramine and doxylamine are the most commonly used. Both are available “over-the-counter” both alone and in combination with non-prescription analgesics (e.g., Tylenol PM). Both medications have similar properties and the usual dose for each is 25–50 mg. Both have significant muscarinic cholinergic antagonist effects that are believed to contribute to their effects on sleep and be the primary source of side effects.

Evidence base: There have been no placebo-controlled trials in insomnia patients to evaluate the safety or efficacy of doxylamine, but a few exist for diphenhydramine.[55–59] Unlike benzodiazepines and non-benzodiazepines, diphenhydramine appears to have stronger effects on sleep maintenance than sleep onset in the few available studies. Doxylamine has only been evaluated for the treatment of insomnia in one large double-blind trial of postoperative patients. Results indicated a significant benefit on subjective measures of sleep.[60] One study of diphenhydramine suggests that benefits from daytime dosing are lost over consecutive days of administration and similar studies are needed to determine if tolerance occurs to nighttime dosing as well.[61]

The only selective H1 antagonist that has been studied for the treatment of insomnia is Doxepin, a tricyclic antidepressant which has FDA approval for the treatment of depression in dosages from 75–150 mg and for the treatment of insomnia in dosages from 3–6 mg.[54] Notably, doxepin is a more potent and selective H1 antagonist than any agent we refer to as an antihistamine currently available in the U.S. As with diphenhydramine, low-dose doxepin has stronger effects on sleep maintenance than it has on sleep onset. The therapeutic effect on sleep maintenance has been demonstrated for both younger and older adults and it is FDA approved for treating sleep maintenance but not sleep onset problems.[3,54] Of particular note, doxepin is the only agent available which has been demonstrated to have therapeutic effects in the last third of the night, including the final hour of an eight hour sleep period, without significant morning adverse effects.[54,62,63]

The most common adverse-effects associated with antihistamines are anticholinergic effects such as dry mouth, blurred vision, constipation, urinary retention, and delirium, and should therefore be avoided in patients at risk for complications due to anticholinergic effects, such as those with dementia, urinary retention and narrow-angle glaucoma. Other adverse effects include sedation, dizziness and weight gain. Less frequent side-effects of diphenhydramine include agitation and insomnia. Case reports have suggested that doxylamine may be associated with coma and rhabdomyolysis.[64] It is important to note that doxepin is without any anticholinergic side-effects in the approved 3–6 mg dosage range due to its H1 selectivity and it appears to be without risk for weight gain or other adverse effects commonly associated with the antihistamines, nearly all of which are due to receptor effects other than H1 antagonism.[54] The abuse potential of antihistamines is relatively negligible, making them appropriate for abuse-prone insomnia patients. The benefits for allergies make antihistamines particularly well-suited to insomnia occurring with allergies or nasal congestion.

2.2. Prescription agents used off-label for treatment of insomnia

2.2.1. Antidepressants—Antidepressants are often used in the treatment of insomnia, but relatively little data exist on their efficacy and safety when used for this purpose.[3,65] Trazodone in particular is prescribed for the treatment of insomnia much more frequently that one would expect given the evidence base.[3] Notably, trazodone has been one of the most frequently prescribed agents for the treatment of insomnia for many years and yet, it

has only been evaluated in a single large-scale placebo-controlled trial in patients with insomnia and in that study it failed to have significant sustained therapeutic effects compared to placebo.[66]

Because of the paucity of placebo-controlled trials with these agents, their use cannot be recommended except in those individuals who fail or for some reason are precluded from the usual treatments. Antidepressants are typically prescribed at lower doses for the treatment of insomnia than for the treatment of major depression. These agents enhance sleep through antagonism of wake promoting systems including serotonin, norepinephrine, acetylcholine and histamine, though the relative degree of these effects differs among the antidepressants. We will review the pharmacology and limited evidence base for those agents including doxepin (dosages above 6 mg), amitriptyline, and trimipramine (tricyclic antidepressants) as well as, trazodone and mirtazapine.

Tricyclic Antidepressants: These agents promote sleep by antagonism of norepinephrine, histamine, and acetylcholine, all of which are involved in maintaining wakefulness and arousal. Most of data on the sleep effects of these agents come from trials of patients with major depression.[67] Only two tricyclic antidepressants have been investigated in the treatment of primary insomnia. Trimipramine dosed at 50–200 mg has been found to improve sleep quality and sleep efficiency, but not sleep onset latency.[68,69] Doxepin has been evaluated in three studies in a range of 25–50 mg. Findings from these studies support its efficacy for improving sleep quality, sleep onset and sleep maintenance.[68,70–72] Tricyclic antidepressants have a number of side effects including sedation, weight gain, orthostatic hypotension and anticholinergic side-effects (dry mouth, blurred vision, constipation, urinary retention, exacerbation of narrow-angle glaucoma, and risk of delirium).[73,74] More severe side-effects include impairment of cardiac electrical conduction, resulting in heart block and/or seizures, but these side effects are not common. These are all dose-dependent side-effects derived from anti-histaminergic, anti-cholinergic, anti-serotinergic, and anti-adrenergic effects. The abuse potential for tricyclic antidepressants is negligible so these agents may be useful in the treatment of insomnia among patients at high-risk for substance abuse. In addition, they may be useful in treating insomnia in the context of comorbid conditions such as anxiety disorders or chronic pain.[75] Due to a lack of data, it is unclear how effective these agents are in treating both depression and insomnia in a single patient. The safety and efficacy of combining these agents with non-sedating antidepressants is also unknown, so better established combined treatments are generally preferred. Caution should be exercised when administering these agents to patients with significant heart disease and/or sensitivity to anticholinergic effects of these medications. Finally, these agents must be prescribed with great caution in those at risk for suicide as they can be lethal in overdose.

Trazodone: Trazodone is FDA approved for the treatment of major depression in dosages from 200–600 mg, but is also frequently used “off-label” to treat insomnia at lower doses (25–150 mg). Despite a relative lack of controlled trials demonstrating efficacy for insomnia, trazodone has been among the most frequently administered treatments for insomnia over the last 20 years.[65] It's sleep enhancing effects are believed to derive from its antagonism of serotonin (5HT2 receptors), norepinephrine (α_1 receptors), and histamine (H1) receptors. Trazodone is metabolized into a wake-promoting molecule (methyl-chlorophenylpiperazine or mCPP) to a highly variable degree due to a genetic polymorphism that is not rare in the population.[76,77] This may undermine the therapeutic effects of trazodone for some patients and lead them to have distressing levels of anxiety. It is helpful to inform patients about this possibility prior to prescribing the medication. Genetic polymorphisms that affect the metabolism of trazodone into an active, sedating, metabolite and the elimination of that metabolite also exist. As a result, some individuals experience prohibitive daytime sedation with this agent.

Given its frequency of use, it is perhaps surprising that there has been only one placebo-controlled study of trazodone for insomnia.[66] This was a two week study wherein trazodone was dosed at 50 mg. The group receiving active medication reported better sleep than placebo treated subjects for the first week, but there were no differences between groups in the second week of treatment. Two smaller placebo-controlled studies, one in abstinent alcoholics and another in patients with major depression,[78,79] reported sleep-promoting effects of trazodone, but did not evaluate in the treatment of insomnia per se.

The most common adverse effects associated with trazodone are sedation, dizziness, headache, dry mouth, blurred vision and orthostatic hypotension.[3,66] Although rare, trazodone has been associated with priapism, a prolonged erection associated with pain, that can lead to irreversible impotence.[80] Trazodone does not appear to have significant abuse potential and may be appropriate for use in abuse-prone insomnia patients. The small placebo-controlled trial in abstinent alcoholics did not show any problems with abuse of the medication.[78] Because trazodone has antidepressant properties, it is possible that there would be a benefit for mood in individuals with comorbid anxiety and depression, but given the difference in dosage used for each disorder, this cannot be assumed and has not been systematically evaluated. Preliminary evidence suggests that it can be safely used to treat insomnia in conjunction with fluoxetine and buproprion but its use with other antidepressants has not been evaluated.[79]

Mirtazapine: Mirtazapine is believed to have sleep promoting effects related to its antagonism of serotoninergic (5HT2 and 5HT3), adrenergic (α_1), and histaminergic (H1) receptors.[81] In addition, it is believed to antagonize adrenergic α_2 receptors, which are presynaptic and inhibit the release of norepinephrine.[82] As a result of this property, the sleep enhancing effects of mirtazapine are thought to decrease as the dose increases. While the range for antidepressant dosing is 7.5–45 mg, dosages below 30 mg are generally used to promote sleep.

There have been no placebo-controlled trials of mirtazapine for the treatment of insomnia. The evidence that mirtazapine may benefit sleep comes from a double-blind evaluation of mirtazapine vs. fluoxetine in patients with major depression, an open-label study of healthy volunteers without sleep complaints, preoperative patients at risk for insomnia due to surgery, and a pilot study of depressed patients.[83–85]

Based on trials treating major depression, the most common side effects associated with mirtazapine are sedation, increased appetite, weight gain, dry mouth, and constipation.[82] As with other antidepressants, mirtazapine is appropriate for use with substance abuse prone patients due to its low potential for abuse. Because of the overlap in dosages used to treat insomnia and depression, mirtazapine can be considered for single-agent therapy for those with insomnia and co-morbid depression. Future studies will be needed to evaluate this agent's effectiveness relative to combining a non-sedating antidepressant with an established insomnia therapy.

2.2.2 Antipsychotics

Pharmacology: Similar to the antidepressants used to enhance sleep, some antipsychotics are used “off-label” to treat insomnia. The antipsychotics most commonly used to treat insomnia are quetiapine (dosed at 25–250 mg) and olanzapine (dosed at 2.5–20 mg).[65,86] The doses used for insomnia are somewhat lower than would be used to treat thought or mood disorders. These agents enhance sleep through antagonism of dopamine, histamine (H1 receptors), serotonin (5HT2 receptors), acetylcholine (muscarinic receptors) and norepinephrine (α1 receptors).[3] Olanzapine has a tmax of 4–6 hours, making it better suited for the treatment of sleep maintenance problems than for sleep onset problems. Quetiapine

on the other hand has a tmax of 1–2 hours and a half-life of 7 hours[3] making it well suited for both sleep onset problems and sleep maintenance problems.

Evidence base: No placebo-controlled trials have been completed with these agents for the treatment of insomnia specifically, therefore the risk-benefit profile is difficult to assess. Evidence for a sleep enhancing effect of quetiapine (25–75 mg) was reported from open-label studies with primary insomnia patients and with healthy volunteers[87] while olanzapine has been noted to enhance sleep in an open-label study of healthy volunteers only.[86] Evidence for effects on sleep is greater for patients with comorbid thought disorders or mood disorders.[86,88,89]

The most common side-effects associated with antipsychotic agents in the treatment of insomnia are sedation, dizziness, anticholinergic side-effects (dry mouth, blurred vision, constipation, urinary retention), and increased appetite,[86] with some agents having better side effect profiles than others. Other potential side-effects associated with dopamine antagonism can result as well, including parkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.[87] These extrapyramidal side-effects are less common with atypical antispychotics than with typical antipsychotics. Olanzapine has been found to increase risk of insulin resistance, impaired cognition and mortality in dementia patients. All of these agents should be used with caution in older adults due to increased risk of cardiac-related mortality.[90]

Antipsychotic agents are not generally used in patients with insomnia who do not have a co-occurring psychotic or mood disorder, but may be particularly useful in this population. In addition to the effects mentioned above, many of these agents have mood stabilizing properties useful in the treatment of mania. Quetiapine is also FDA approved for the treatment of depression. Antipsychotic agents can also be considered for use in abuse-prone patients with insomnia due to their low abuse potential.

2.2.3 Anticonvulsants

Pharmacology: Anticonvulsants such as gabapentin, pregabalin and tiagabine, are sometimes used in the treatment of insomnia. Gabapentin and pregabalin bind to the alpha-2-delta subunit of N-type voltage-gated calcium channels, which decreases the activity of wake promoting glutamate and norepinephrine systems. Tiagabine enhances sleep by inhibiting the reuptake of GABA.[91,92] Gabapentin has a relatively long tmax of 3 – 3.5 hours, making it relatively unlikely to facilitate sleep onset.

Evidence base: Gabapentin and pregabalin have been demonstrated to have sleep enhancing effects in a variety of populations including healthy volunteers, patients with restless legs syndrome, chronic pain patients and patients with partial seizures.[93–96] A smaller study demonstrated a benefit of gabapentin on time to relapse in patients with alcohol dependence but found no benefit over placebo on sleep parameters.[97] In placebo-controlled trials with primary insomnia patients, tiagabine has been found to increase slow-wave sleep, but has not been shown to improve sleep onset or sleep maintenance consistently.[98–101]

The most common side effects associated with gabapentin are ataxia and diplopia, while pregabalin is associated with dry mouth, cognitive impairment, peripheral edema and increased appetite. Tiagabine is most commonly associated with nausea. Of these medications, only pregabalin is associated with abuse potential and should be used with caution in patients who are prone to substance abuse.[102] Prelminary evidence suggests gabapentin to be effective for the treatment of insomnia in patients with alcohol use disorders. For insomnia that is comorbid with pain, gabapentin and pregabalin may be particularly useful. Pregabalin should be considered in the treatment of insomnia in

fibromyalgia patients because available evidence suggests it is effective for both conditions. Preliminary evidence also suggests that gabapentin may be indicated for patients with restless legs syndrome and periodic movements of sleep.

2.2.4 Antihypertensives

Pharmacology: Prazosin is an antihypertensive medication with relatively recently discovered benefits for sleep, primarily in those who experience frequent nightmares and sleep disturbance associated with post-traumatic stress disorder (PTSD).[103] It is an α_1 adrenoreceptor antagonist, but it is not yet possible to propose a pharmacololgic mechanism that explains the basis of the therapeutic effect on nightmares in PTSD.[104] Studies to date have generally prescribed 2–6 mg for most patients with an upper limit of 15–20 mg. The recommended starting dose is 1 mg to prevent hypotension, then the dose is slowly titrated upward until a therapeutic effect is achieved.[105] In addition, it is important to warn patients that orthostatic hypotension is most likely to occur the morning after dose increases.

Evidence base: Placebo-controlled trials have reported benefits of prazosin in the treatment of sleep disturbance and trauma-related nightmares in military veterans and civilians with PTSD.[105–108] Evidence to date has consistently shown prazosin to reduce nightmares and improve sleep overall and results have been similar for samples of military veterans and civilians. Improvements in self-reported symptoms associated with prazosin include nightmare frequency, insomnia severity, and PTSD symptom severity; home-PSG-measured symptom improvement has also been found for total sleep time, REM sleep time, and REM duration.[105–108] One study found comparable rates of improvement in prazosin and a behavioral sleep intervention, both of which outperformed placebo.[108]

Prazosin has been found to be well tolerated in all trials to date. Although studies to date have not been powered to detect adverse-effects in prazosin relative to placebo, the following symptoms have been reported in the trials listed above: transient dizziness, nasal congestion, initial insomnia, dry mouth, sweating, depression and lower extremity edema.[103–108] It is likely that some of these symptoms are not related to medication as they were also reported by patients in the placebo condition, but further study is needed to more adequately characterize adverse events associated with this agent. Prazosin is the only sleep-enhancing agent shown to reduce sleep impairment due to nightmares and is therefore particularly useful in sleep disturbances associated with PTSD.

3. Factors to Be Considered for Optimizing Medication Management of Insomnia

3.1. Time of Night of Sleep Problem

As reviewed in the previous section, the medications used to treat insomnia differ as to the time of night during which they have been established to have therapeutic effects. Some have been found only to improve problems with sleep onset, some have reliable therapeutic effects on sleep maintenance without onset effects, and some have reliable effects on both onset and sleep maintenance. Among those with sleep maintenance effects some agents have these effects to the end of the night while others do not. The time of night during which sleep problems occur differs among insomnia sufferers. Treatment optimization therefore depends on selecting a medication that has therapeutic effects at the time of night during which an individual's sleep problem occurs. In the following discussion we review how to match the choice of medication to the patient's specific type of sleep problem.

3.1.1 Patient's With Only Sleep Onset Difficulties—For those who have difficulties falling asleep without difficulties staying asleep, the optimal strategy is to choose a

medication which has been demonstrated to have therapeutic effects on sleep onset with the least associated adverse effects. This includes those agents which have been demonstrated to have therapeutic effects on sleep onset without having effects on sleep maintenance. These medications include:

Ramelteon

Zaleplon

Zolpidem

Any of these might be appropriate for treating a patient with sleep onset difficulties. However, optimizing the choice among these agents requires considering the patient's past history with medications (have they failed to improve with one or more of these agents in the past? Did they have problems with side-effects with one or more of these agents in the past?) and the other patient-specific factors that affect medication choice including the temporal pattern of sleep problems and the presence of comorbidities (see below). Although not a factor related to optimizing the matching of medication to the patient's sleep problem, cost may affect what medication can practically be obtained or which is tried first. If any of the above factors precludes the use of all 3 of the medications best-suited for treating those with sleep onset problems listed above, the following agents which have been demonstrated to have therapeutic effects on both sleep onset and sleep maintenance could be considered for second line use with the understanding that they are likely to have a greater risk of adverse effects.

Eszopiclone

Temazepam

Zolpidem CR

3.1.2 Patient's With Only Sleep Maintenance Difficulties—For those who have difficulties staying asleep without difficulties falling asleep, the optimal strategy is to choose a medication which has been demonstrated to have therapeutic effects on sleep maintenance with the least associated adverse effects. This includes the agents which have been demonstrated to have therapeutic effects on sleep maintenance without having effects on sleep onset. These medications include:

Doxepin 3–6 mg

Sublingual Zolpidem (Intermezzo) dosed during a middle of the night awakening

Zaleplon dosed during a middle of the night awakening

For those individuals who have difficulties in the last 2 hours of the night, the only option is doxepin 3,6 mg as described above.[62,63,70,72,109]

If factors such as prior experience with the medications, temporal pattern of the sleep problem, co-morbidities or cost factors precludes the use of all 3 of the medications listed above, the following agents which have therapeutic effects on both sleep onset and sleep maintenance could be considered for second line use with the understanding that they are likely to have a greater risk of adverse effects.

Eszopiclone

Zolpidem CR

Temazepam

A final consideration is that doxepin is the only agent demonstrated to have therapeutic effects in the last 2 hours of the night without substantively increasing the risks of daytime impairment.[109] As a result, for those with this type of sleep difficulty, there is no good second-line therapy.

3.1.3 Patient's With Both Sleep Onset and Sleep Maintenance Difficulties—A subset of the agents used in the treatment of insomnia have been demonstrated to have therapeutic effects in patients with both sleep onset and sleep maintenance problems. These are: .

Eszopiclone

Temazepam

Zolpidem CR

In those with difficulties in the last 2 hours of the night, the only option is to use doxepin to address this end of the night problem and combine it with an agent with therapeutic effects only for sleep onset problems such as:

Ramelteon

Zaleplon

Zolpidem

The need to administer two medications in this circumstance due to the absence of a single medication that improves sleep at the end of the night and also improves sleep onset suggests an unmet need in the field of insomnia.

3.2 Temporal Pattern of Sleep Problem

Another factor that is necessary to consider in the optimization of the medication management of insomnia is the patient's temporal pattern of sleep difficulties over nights. Some individuals have their problems nightly, whereas others have their problems intermittently. Among those with intermittent insomnia, their problem can occur anywhere from rarely to nearly every night. The temporal pattern has important implications for determining the optimal strategy for medication management.

3.2.1. Patients with Nightly Problems Falling Asleep—For patients with nightly difficulties falling asleep, nightly administration of an agent targeting sleep onset is generally indicated (See 3.1.1). However, a challenge that arises is that nightly use of an effective sleep medication may make it difficult to determine if the insomnia ceases at some point such that the medication is no longer needed. This situation can make both patients and prescribers uncomfortable because it raises the possibility that once treatment with a sleep medication begins, it continues indefinitely.

Further contributing to this problem is the concern that rebound insomnia occurring with discontinuation after a period of nightly use may falsely reinforce a sense of an ongoing need for nightly medication. Notably, a substantial number of relatively recent studies have indicated that significant rebound insomnia did not occur with nightly treatment for: 6 months with eszopiclone; up to 1 year with zaleplon (open-label study); 1 year with zolpidem; 6 months with ramelteon, and 3 months with doxepin.[11,12,14,53,110] However, rebound insomnia does at times occur as was observed on the first night after discontinuing treatment after 3 weeks of nightly therapy with zolpidem CR.[111] Although rebound insomnia can occur, our experience suggests it is more commonly the case that reluctance to discontinue nightly use of medications for insomnia reflects either the return of sleep

problems after elimination of an effective therapy or anxiety about not sleeping well without medication. Without systematic data collection, such experiences can create the perception among clinicians that rebound insomnia is nearly universal. This can lead practitioners to avoid treating patients with nightly insomnia with medications or to require that their patients use the medications non-nightly.

In our experience, the most effective means for addressing this challenge is to have an a priori strategy for stopping medications in those with nightly sleep problems. The most effective strategy has been to agree, prior to starting medications, that after a fixed period of time, typically 3 months, a trial medication taper will be instituted. This taper is nearly always effective in allowing patients to discontinue medications if they are warned to expect a transitory worsening of sleep following medication discontinueation and and if the taper is carried out slowly enough. Once the patient has discontinued use of the medication, an assessment can be made about whether the patient was better off using the medication or not using the medication. If the former is the case, the medication is re-started with a plan to institute another trial taper in 3 months. If the latter turns out to be true, the medication is discontinued. This type of exit strategy tends to make both patients and prescribers less anxious about the nightly use of medications for insomnia in those with nightly sleep problems and ensures that medication use will persist for roughly the period that it is needed.

All three of the medications which have been reported to have therapeutic effects on sleep onset without effects on sleep maintenance, ramelteon, zaleplon, and zolpidem, have all been demonstrated to be safe and effective for at least 6 months of nightly treatment and could all be used in individuals with nightly difficulties falling asleep. When the use of these medications is precluded, eszopiclone, which has also been demonstrated to have a good efficacy/safety profile in 6 months of nightly use, could also be considered.

3.2.2 Patients with Nightly Problems Staying Asleep—There are two options for treating patients with problems staying asleep. One is to administer a medication at bedtime in an attempt to prevent the awakening from occurring. The other is to have the patient take a medication if they wake up in the middle of the night in order to speed the return to sleep. When the problem with middle of the night awakenings occurs on a nightly basis, however, the best strategy is to take medication nightly at bedtime to prevent the awakening from occurring, rather than having to suffer from awakening nightly and then having to wait for the medication to take effect. If nightly sleep maintenance problems occur in the absence of problems falling asleep, doxepin, which has been demonstrated to be efficacious and safe in 3 months of nightly use could be used. If both problems falling asleep and staying asleep are present, then the best choice from the point of view of long-term safety and efficacy is eszopiclone. As with nightly onset problems, when prescribing these medications nightly it is necessary to have a plan for stopping the medication such as instituting periodic trial medication tapers.

3.2.3 Patients with Intermittent Problems Falling Asleep—When trouble falling asleep occurs intermittently, the optimal treatment strategy depends on whether the affected individual is able to tell prior to going to bed whether they are likely to have a bad night. In those able to predict difficulties falling asleep, medication therapy can be administered on nights when problems are anticipated. Where prediction isn't possible, one option is to have patients try to sleep and then take a medication if they fail to do so. However, for patients prone to developing a worsening of insomnia if they if they have nights wherein they try to sleep and fail, then this strategy is best avoided and implementation of cognitive behavioral insomnia therapy should be considered.

3.2.4. Patients with Intermittent Problems Staying Asleep—For those with difficulty staying asleep occurring nightly or nearly nightly, nightly treatment at bedtime in an attempt to prevent the awakening is generally the best strategy. However, for those with relatively infrequent difficulties waking up in the middle of the night, optimal treatment would involve providing an intervention to take in the middle of the night only on those nights when the awakening occurs. If it were possible to predict the nights where the middle of the night awakenings were most likely to occur, then a strategy of using a medication prior to bedtime to prevent those awakenings would be optimal. However, these awakenings are generally not predictable at bedtime. As a result, the strategy of taking a medication in the middle of the night has the substantial advantage over nightly bedtime dosing in that it only requires medication use on nights when the sleep problem occurs, thereby reducing the number of nights medication is used. This strategy decreases the cost and associated risks of the medication used.

Data demonstrating that this strategy can be employed effectively and safely have been reported for sublingual zolpidem (Intermezzo) and zaleplon when these are taken up to 4 hours before getting out of bed in the morning.[112,113] As a result, these agents could be considered for those patients who experience intermittent unpredictable middle of the night awakenings. There are no studies demonstrating the safe and effective use of a medication for a middle of the night awakening that occurs less than 4 hours before getting out of bed. As a result, this sort of practice cannot be recommended.

3.3 Co-Morbidities

One additional consideration needed in order to optimize the medication management of insomnia is the presence of co-morbidities such as mood disorders, anxiety disorders, pain, and substance use/dependence. This consideration is highly important since patients with co-morbid medical and psychiatric conditions constitute the majority of patients with insomnia.[2] The available agents vary in their therapeutic effects and risks in patients with co-morbidities. As a result, failure to consider the presence of such co-morbidities can result in suboptimal or adverse treatment outcomes. The following discussion provides guidance for optimizing treatment for those co-morbid conditions for which the most data are available and which are most commonly associated with insomnia. These include major depression, generalized anxiety disorder, post-traumatic stress disorder, chronic pain, and alcoholism.

3.3.1. Insomnia Co-Morbid with Major Depression—The long-standing view of insomnia occurring in those with major depression has been that insomnia is a secondary symptom of the depression that does not merit specific treatment. It was assumed that effective antidepressant therapy would eliminate insomnia just as it improves other symptoms of depression. However the available data clearly indicate that this view is incorrect and speak to the need to provide insomnia-targeted treatment along with administering antidepressant therapy.[114] Options for treating insomnia in those with co-morbid major depression include administering a non-sedating antidepressant along with a medication targeting insomnia or administering a single agent that has antidepressant and sleep enhancing properties.

As described above, five studies have been carried out in which patients with insomnia co-morbid with major depression were treated with an antidepressant medication along with an agent used in the treatment of insomnia or placebo. These studies provide some support for the utility of adding clonazepam to selective serotonin reuptake inhibitor therapy in patients with depression and insomnia. Sleep was improved in 3 of the studies conducted and in two it was associated with greater improvement in depression symptoms.[4–6].

In all three studies carried out with clonazepam, this agent improved sleep and in two it was associated with greater improvement in depression symptoms, though it appears that with longer duration of treatment the improvement in depression symptoms with clonazepam may not be sustained. A study of patients with insomnia and rheumatoid arthritis reported a benefit of triazolam relative to placebo for both sleep and morning.[7]

As described above, a study in which patients with insomnia and co-morbid depression were randomized to receive eszopiclone or placebo along with fluoxetine indicated that eszopiclone improved not only sleep but also was associated with more rapid and greater improvement in depression symptoms (sleep items were removed from the depression rating scale).[16] Notably, essentially the identical trial was carried out with Ambien CR and this agent was found to improve sleep but not depression symptoms compared with placebo.[18]

In terms of single agent therapy, a few placebo-controlled studies have assessed the therapeutic sleep effects of antidepressants (a small study of tricyclic antiderpessants and one study of mirtazapine) in therapeutic antidepressant dosages in patients with co-morbid insomnia and depression.[67,83] These studies provide some support for the use of single-agent therapy for such patients but it must be kept in mind that this is based on a relative paucity of data, and the relative utility of single-agent therapy vs combining a hypnotic agent and a non-sedating antidepressant remains unknown.

Overall, the available data most strongly suggest the use of eszopiclone along with a non-sedating antidepressant for initial therapy of those with insomnia co-morbid with major depression. Although it should be noted that data exist only for combining eszopiclone with fluoxetine, and it remains unknown whether similar effects would be seen with other antidepressants. Clonazepam could be considered for use in these patients but the relatively higher risk of daytime sedation and possibility of loss of antidepressant benefit over time suggests that it should be reserved for second tier use. Zolpidem CR could also be considered, though eszopiclone would be preferred due to the relatively greater benefit on depression symptoms. Lastly, employing single-agent therapy with mirtazapine is also a supported option. While a small amount of data supports the use of single-agent therapy with tricyclic antidepressants, the risk/benefit for these agents is far inferior to the other options. Data are needed to evaluate the utility of single-agent therapy with mirtazapine vs. the combination of eszopiclone and a non-sedating antidepressant.

Another consideration relevant to those with depression and co-morbid insomnia is the choice of treatment when an individual is treated with an antidepressant and improves but has sustained insomnia which has not been treated. Studies have been carried out trazodone and zolpidem for this circumstance.[79,115] Trazodone was found to improve sleep in a placebo-controlled trial with 15 patients treated with several different antidepressants. Zolpidem was observed to improve sleep more than a placebo in a larger study (N=110) of patients who had achieved depression remission with paroxetine, fluoxetine, or sertraline. On the basis of these studies, zolpidem and perhaps trazodone could be considered for patients with insomnia who have remitted to non-sedating antidepressant therapy.

3.3.2. Insomnia Co-Morbid with Generalized Anxiety Disorder—As with major depression, it has long been assumed that it was not necessary to administer insomnia-specific treatment in those with generalized anxiety disorder (GAD). However, relatively recent guidelines recommend administering insomnia targeted therapy along with anxiolytic therapy in those with GAD.[114] As described above, only two placebo-controlled trials have been carried out which assessed the therapeutic effects of adding insomnia therapy (eszopiclone 3 mg) vs placebo to anxiolytic therapy (escitalopram).[17] As with the similar study in those with major depression, eszopiclone led to greater improvement not only in

sleep but also in anxiety, whereas an essentially identical study carried out with zolpidem CR found improvements in sleep but not anxiety with this agent.[19] Clearly more data on the treatment of insomnia occurring co-morbid with GAD are needed. However, based on available data, eszopiclone would be the treatment of choice when adding a sleep targeted therapy to treatment with a selective serotonin reuptake inhibitor. Zolpidem CR could also be considered for improving sleep but should be considered as a second choice based on the lesser improvement in anxiety symptoms.

3.3.3 Insomnia Co-Morbid with Post-Traumatic Stress Disorder—Few studies have been carried out on the pharmacologic treatment of sleep problems occurring in the setting of post-traumatic stress disorder (PTSD). As reviewed in section 2, the only agents that have been evaluated in placebo-controlled trials are eszopiclone and prazosin. Eszopiclone improved both sleep disturbance and PTSD symptoms in a cross-over study conducted with 24 patients.[24] Four placebo-controlled studies have been carried out with prazosin in PTSD patients with sleep disturbance, and they all show significant improvement in sleep disturbance and nightmares.[105–108] Given the larger evidence base supporting the therapeutic effects of prazosin, that fact that it is the only agent that has been found to reduce nightmares in addition to disturbed sleep, and the fact that it is well tolerated, this agent should be considered for first-line use in patients with PTSD-related sleep disturbance. Eszopiclone should also be considered for use in in these patients based on the small cross-over study carried out.

3.3.4. Insomnia Co-Morbid with Chronic Pain—The available evidence suggests that individuals with insomnia occurring co-morbid with chronic pain are best treated by administering both pain-targeted and insomnia-targeted therapies.[114] As outlined in section 2 above, three placebo-controlled trials with insomnia pharmacotherapy evaluating this paradigm have been carried out. Triazolam was found to improve sleep and morning stiffness in those with rheumatoid arthritis[7] and eszopiclone led to improvement in sleep and some pain ratings in this same population.[23] There is also evidence that eszopiclone has therapeutic effects when added to naproxen treatment in patients with chronic low back pain.[22] These studies provide a modest evidence base for carrying out treatment decisions in patients with insomnia and chronic pain conditions. However, they indicate that eszopiclone has potential as a sleep-targeted therapy in this setting and triazolam could also be considered. Studies with other insomnia medications are needed to establish whether the therapeutic effects seen in pain patients are specific to eszopiclone and triazolam or would be seen with other medications.

3.3.5. Insomnia Co-Morbid with Alcoholism—The pharmacologic treatment of sleep problems occurring in patients with alcoholism have been the subject of little research. As reviewed above, only one small placebo-controlled trial with trazodone has been found to have therapeutic effects on sleep in patients with alcoholism (recently abstinent).[78] In general, benzodiazepines and non-benzodiazepines are avoided in this population because of abuse risk. Trazodone which appears to have minimal abuse potential should be considered in this population but more studies are needed with agents without significant abuse potential to help guide the management of insomnia in patients with alcoholism.

4. Future Directions

As should be evident from the review above, there is a need for more studies aimed at identifying how to optimally manage patients with insomnia, particularly among patients with co-morbid conditions. Additional studies are also needed to define how to best manage patients with nightly sleep onset problems. Although agents with established therapeutic effects on sleep onset and sleep maintenance are available for use in clinical practice, a need

remains for the development of new agents that have therapeutic effects at the end of the night without increasing the risks of daytime sedation and that have this effect along with a therapeutic effect on sleep onset. Two agents in development are worthy of note in this regard. One is the S-isomer of the antidepressant mirtazapine discussed above. This agent has a comparable pharmacologic profile as the racemate with predominant, highly potent, and selective H1 antagonist effects. Based on its pharmacology, this agent administered in relatively low dosages as have been evaluated would be expected to have similar properties to the selective H1 antagonist doxepin. Preliminary data from 4 placebo controlled studies have been presented with S-mirtazapine and they suggest that this is essentially the case, though effects on sleep onset may be more evident. These studies suggest that S-mirtazapine has consistent therapeutic effects on sleep maintenance, and tends to have therapeutic effects on sleep onset, though these effects are not as large or consistent and are dose-dependent., In addition there appears to be a dose-dependent risk of daytime sedation.[116–119]

Another agent with potential to make a significant contribution to the armamentarium of insomnia medications is the dual hypocretin/orexin receptor antagonist suvorexant, which has potential to improve both sleep onset, and sleep maintenance, including at the end of the night without prohibitive daytime adverse effects. Hypocretin/orexin is a relatively recently discovered set of peptidergic neurons arising in the lateral hypothalamus that play an important role in maintaining wakefulness.[120] As a result, blocking these hypocretin/orexin receptors has the potential to have sleep enhancing effects. Preliminary data from several trials suggest that this agent has therapeutic effects on sleep onset and maintenance (including in the last third of the night) and has sustained therapeutic effects with long-term nightly use without significant withdrawal or rebound insomnia upon discontinuation and overall appears to have a favorable adverse effects profile.[121–124]

These agents have the potential to add to the options that are available for providing individualized insomnia pharmacotherapy that best meets the needs of insomnia patients. The clinical availability of agents such as these and the completion of more studies to help define how to best tailor the choice of treatment for each patient promise to continue the steady evolution of the field towards greater capacity to select insomnia medications which optimize outcomes and thereby improve the treatment of the many who suffer from insomnia.

References

1. Sieghart W, Sperk G. Subunit composition, distribution and function of GABA(A) receptor subtypes. Curr Top Med Chem. 2002; 2:795–816. [PubMed: 12171572]
2. Ford D, Kamerow D. Epidemiologic study of sleep disturbances in psychiatric disorders. JAMA. 1989; 262:1479–1484. [PubMed: 2769898]
3. Krystal AD. A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: the empirical basis for US clinical practice. Sleep Med Rev. 2009; 13(4): 265. [PubMed: 19153052]
4. Londborg P, Smith WT, Glaudin V, Painter JR. Short-term cotherapy with clonazepam and fluoxetine: anxiety, sleep disturbance and core symptoms of depression. J Affect Disord. 2000; 61:73–79. [PubMed: 11099743]
5. Smith W, Londborg PD, Glaudin V, et al. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. Am J Psychiatry. 1998; 155(10):1339–1345. [PubMed: 9766764]
6. Smith W, Londborg P, Glaudin V, Painter J. Is extended clonazepam cotherapy of fluoxetine effective for outpatients with major depression? J Affect Disord. 2002; 70(3):251–259. [PubMed: 12128237]

7. Walsh J, Muehlbach MJ, Lauter SA, Hilliker NA, Schweitzer PK. Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. J Rheumatol. 1996; 23(2):245–252. [PubMed: 8882027]
8. 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]
9. 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]
10. Crestani F, Assandri R, Tauber M, et al. Contribution of the alpha1-GABA(A) receptor subtype to the pharmacological actions of benzodiazepine site inverse agonists. Neuropharmacology. 2002; 43:679–684. [PubMed: 12367613]
11. Walsh J, Krystal AD, Amato DA. Nightly treatment of primary insomnia with eszopiclone for six months: Effect on sleep, quality of life and work limitations. Sleep. 2007; 30(8):959–968. [PubMed: 17702264]
12. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over six months of nightly treatment: Results of a randomized, double-blind, placebo controlled study in adults with chronic insomnia. Sleep. 2003; 26:793–799. [PubMed: 14655910]
13. Roth T, Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. Sleep Med. 2005; 6(6): 487. [PubMed: 16230048]
14. Ancoli-Israel S, Richardson GS, Mangano RM, Jenkins L, Hall P, Jones WS. Long-term use of sedative hypnotics in older patients with insomnia. Sleep Med. 2005; 6(2):107–113. [PubMed: 15716214]
15. Krystal AD, Erman M, Zammit GK, et al. Long-Term Efficacy and Safety of Zolpidem Extended-Release 12.5 mg, Administered 3 to 7 Nights Per Week for 24 weeks, in Patients With Chronic Primary Insomnia: A 6-Month, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study. Sleep. 2008; 31(1):79–90. [PubMed: 18220081]
16. Fava M, McCall WV, Krystal A, Rubens R, Caron J, Wessel T, Amato T, Roth T. Eszopiclone Co-administered With Fluoxetine in Patents with Insomnia Co-existing with Major Depressive Disorder. Biol Psychiatry. 2006; 59:1052–1060. [PubMed: 16581036]
17. Pollack M, Kinrys G, Krystal A, Mccall WV, Roth T, Schaefer K, Rubens R, Roach J, Huang H, Krishnan R. Eszopiclone Co-Administered With Escitalopram in Patients with Insomnia and Comorbid Generalized Anxiety Disorder. Arch Gen Psychiatry. 2008; 65(5):551–562. [PubMed: 18458207]
18. Fava M, Asnis GM, Shrivastava RK, et al. 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):914–928. [PubMed: 21208597]
19. Fava M, Asnis GM, Shrivastava R, et al. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. J Clin Psychopharmacol. 2009; 29(3):222–230. [PubMed: 19440075]
20. Soares C, Rubens R, Caron J, Amato D, Roach J, Hayduk R, Joffe H. Eszopiclone treatment during menopausal transition: Sleep effects, impact on menopausal symptoms, and mood. Sleep. 2006; 29:A239.
21. Dorsey C, Lee KA, Scharf MB. Effect of zolpidem on sleep in women with perimenopausal and postmenopausal insomnia: a 4-week, randomized, multicenter, double-blind, placebo-controlled study. Clin Ther. 2004; 26(10):1578–1586. [PubMed: 15598474]
22. Goforth H, Preud'homme X, Krystal A. A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain. Sleep. in press.
23. Roth T, Price JM, Amato DA, Rubens RP, Roach JM, Schnitzer TJ. The effect of eszopiclone in patients with insomnia and coexisting rheumatoid arthritis: a pilot study. Prim Care Companion J Clin Psychiatry. 2009; 11(6):292. [PubMed: 20098520]

24. Pollack MH, Hoge EA, Worthington JJ, et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011; 72(7):892–897. [PubMed: 21367352]
25. Griffiths R, Johnson M. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psych. 2005; 66(suppl 9):31–41.
26. Richey S, Krystal A. Pharmacological advances in the treatment of insomnia. Curr Pharm Des. 2011; 17(15):1471–1475. [PubMed: 21476952]
27. Hughes R, Sack RL, Lewy AJ. The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: assessment in a clinical trial of melatonin replacement. Sleep. 1998; 21(52–68)
28. Singer C, Tractenberg RE, Kaye J, Schafer K, Gamst A, Grundman M, Thomas R, Thal LJ. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. Sleep. 2003; 26(7):893–901. [PubMed: 14655926]
29. Smits M, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. 2001; 16(2):86–92. [PubMed: 11292231]
30. Zhdanova I, Wurtman RJ, Morabito C, Piotrovska VR, Lynch HJ. Effects of low oral doses of melatonin, given 2–4 hours before habitual bedtime, on sleep in normal young humans. Sleep. 1996; 19(5):423–431. [PubMed: 8843534]
31. Zhdanova I, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. J Pediatr Endocrinol. 1999; 12(1):57–67.
32. Zhdanova I, Wurtman R, Regan M, Taylor J, Shi J, Leclair O. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab. 2001; 86:4727–4730. [PubMed: 11600532]
33. Waldhauser F, Saletu B, Trinchard-Lugan I. Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology. 1990; 1990(100):2. 222–226.
34. Dalton E, Rotondi D, Levitan RD, Kennedy SH, Brown GM. Use of slow-release melatonin in treatment-resistant depression. J Psychiatr Neurosci. 2000; 25(1):48–52.
35. Andrade C, Srihari B, Reddy K, Chandramma L. Melatonin in medically ill patients with insomnia: a double-blind, placebo-controlled study. J Clin Psych. 2001; 62(1):41–45.
36. Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. Int J Geriatr Psychiatry. 2002; 17(12):1120–1127. [PubMed: 12461760]
37. Suresh Kumar P, Andrade C, Bhakta SG, Singh NM. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. J Clin Psych. 2007; 68(2):237–241.
38. Van der Heijden K, Smit s MG, Van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry. 2007; 46(2):233–241. [PubMed: 17242627]
39. Wasdell M, Jan JE, Bomben MM, Freeman RD, Rietveld WJ, Tai J, Hamilton D, Weiss MD. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. J Pineal Res. 2008; 44(1):57–64. [PubMed: 18078449]
40. Braam W, Didden R, Smits M, Curfs L. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. J Intellect Disabil Res. 2008; 52(3):256–264. [PubMed: 18261024]
41. Haimov I, Lavie P, Laudon M, Herer P, Vigder C, Zisapel N. Melatonin replacement therapy of elderly insomniacs. Sleep. 1995; 18(7):598–603. [PubMed: 8552931]
42. Mendelson WB. Efficacy of melatonin as a hypnotic agent. J Biol Rhythms. 1997; 12(6):651–656. [PubMed: 9406041]
43. Sack R, Hughes RJ, Edgar DM, Lewy AJ. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? Sleep. 1997; 20(10):908–915. [PubMed: 9415954]
44. Graw P, Werth E, Krauchi K, Gutzwiller F, Cajochen C, Wirz- Justice A. Early morning melatonin administration impairs psychomotor vigilance. Behav Brain Res. 2001; 121:167–172. [PubMed: 11275293]

45. Dollins A, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature and performance. Proc Natl Acad Sci. 1994; 91:1824–1828. [PubMed: 8127888]
46. Krystal A. The Possibility of Preventing Functional Imapairment Due to Sleep Loss by Pharmacologically Enhancing Sleep. Sleep. 2005; 28(16–7)
47. Lerchl A. Melatonin administration alters semen quality in normal men. J Androl. 2004; 25(2): 185–186. [PubMed: 14760004]
48. Ianas O, Manda D, Câmpean D, Ionescu M, Soare G. Effects of melatonin and its relation to the hypothalamic-hypophyseal-gonadal axis. Adv Exp Med Biol. 1999; 460:321–328. [PubMed: 10810528]
49. Partonen T. Melatonin-dependent infertility. Med Hypotheses. 1999; 52(3):269–270. [PubMed: 10362288]
50. Pang S, Li L, Ayre E, et al. Neuroendocrinology of melatonin in reproduction: recent developments. J Chem Neuroanat. 1998; 14(3–4):157–166. [PubMed: 9704894]
51. Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. Sleep Breath. 2007; 11(3):159–164. [PubMed: 17294232]
52. 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 Breath. 2009
53. Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep. 2009; 32(3):351. [PubMed: 19294955]
54. 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
55. Kudo Y, Kurihara MC. linical 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]
56. 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]
57. 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]
58. 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.
59. 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.
60. Smith G, Smith PH. Effects of doxylamine and acetaminophen on postoperative sleep. Clin Pharmacol Ther. 1985; 5(549–557)
61. 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.
62. 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]
63. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 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]
64. Koppel C, Tenczer J, Ibe K. Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. Hum Toxicol. 1987; 6(5):355–359. [PubMed: 3679242]
65. Walsh JK. Drugs used to treat insomnia in 2002: regulatory-based rather than evidence-based medicine. Sleep. 2004; 27(8):14441–14442.

66. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol. 1998; 13:191–198.

67. Dunleavy D, Brezinova V, Oswald I, MacLean AW, Tinker M. Changes during weeks in effects of tricyclic drugs on the human sleep brain. Br J Psychiatry. 1972; 120:663–672. [PubMed: 4339630]

68. Riemann D, Voderholzer U, Cohrs S, Rodenbeck A, Hajak G, Rüther E, Wiegand MH, Laakmann G, Baghai T, Fischer W, Hoffmann M, Hohagen F, Mayer G, Berger M. Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. Pharmacopsychiatry. 2002; 35(5):165–174. [PubMed: 12237787]

69. Hohagen F, Montero RF, Weiss E. Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics? Eur Arch Psychiatry Clin Neurosci. 1994; 244(2):65–72. [PubMed: 7948056]

70. Rodenbeck A, Cohrs S, Jordan W, Huether G, Ruther E, Hajak G. The sleep-improving effects of doxepin are paralleled by a normalized plasma cortisol secretion in primary insomnia. Psychopharmacology (Berl). 2003; 170:423–428. [PubMed: 13680082]

71. Hajak G, Rodenbeck A, Adler L, Huether G, Bandelow B, Herrendorf G, Staedt J, Rüther E. Nocturnal melatonin secretion and sleep after doxepin administration in chronic primary insomnia. Pharmacopsychiatry. 1996; 29(5):187–192. [PubMed: 8895944]

72. Hajak G, Rodenbeck A, Voderholzer U, Riemann D, Cohrs S, Hohagen F, Berger M, Rüther E. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psych. 2001; 62(6):453–463.

73. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther. 1984; 230(1):94–102. [PubMed: 6086881]

74. Ziegler V, Biggs JT, Ardekani AB, Rosen SH. Contribution to the pharmacokinetics f amitriptyline. J Clin Pharmacol. 1978; 18(10):462–467. [PubMed: 711927]

75. Murphy D, Siever LJ, Insel TR. Therapeutic responses to tricyclic antidepressants and related drugs in non-affective disorder patient populations. Prog in Neuropsychopharm and Biol Psychiatry. 1985; 9(1):3–13.

76. Caccia S, Ballabio M, Fanelli R, Guiso G, Zanini MG. Determination of plasma and brain concentrations of trazodone and its metabolite, 1-m-chlorophenylpiperazine, by gas-liquid chromatography. J Chromatogr. 1981; 5(210):311–318. [PubMed: 7263792]

77. Greenblatt DJ, Friedman H, Burstein ES, Scavone JM, Blyden GT, Ochs HR, Miller LG, Harmatz JS. Trazodone kinetics: Effects of age, gender and obesity. Clin Pharmacol Ther. 1987; 42:193–200. [PubMed: 3608351]

78. Le Bon O, Murphy JR, Staner L, Hoffmann G, Kormoss N, Kentos M, Dupont P, Lion K, Pelc I, Verbanck P. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. J Clin Psychopharm. 2003; 23(4):377–383.

79. Nierenberg A, Adler L, Peselow E, Zornberg G, M. R. Trazodone for antidepressant-associated insomnia. Am J Psychiatry. 1994; 151:1069–1072. [PubMed: 8010365]

80. Warner M, Peabody CA, Whiteford HA, Hollister LE. Trazodone and priapism. J Clin Psychiatry. 1987; 48(6):244–245. [PubMed: 3584080]

81. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psych. 1996; 57(suppl 4):19–25.

82. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. J Affect Disord. 1998; 51(3):267–285. [PubMed: 10333982]

83. Winokur A, Sateia MJ, Hayes JB, Bayles-Dazet W, MacDonald MM, Gary KA. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry. 2000; 48(1):75–78. [PubMed: 10913511]

84. Winokur, A DNr; McNally, DP.; Gary, EM.; Cormier, JL.; Gary, KA. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. J Clin Psych. 2003; 64(10):1224–1229.

85. Sørensen M JJ, Viby-Mogensen J, Bettum V, Dunbar GC, Steffensen K. A double-blind group comparative study using the new anti-depressant Org 3770, placebo and diazepam in patients with

expected insomnia and anxiety before elective gynaecological surgery. Acta Psychiatr Scand. 1985; 71(4):331–346. [PubMed: 4039877]

86. Krystal A, Goforth HW, Roth T. Effects of antipsychotic medications on sleep in schizophrenia. Int Clin Psychopharmacol. 2008; 23(3):150–160. [PubMed: 18408529]
87. Wiegand MHLF, Brückner T, Pohl C, Veselý Z, Jahn T. Quetiapine in primary insomnia: a pilot study. Psychopharmacology (Berl). 2008; 196(2):337–338. [PubMed: 17922110]
88. Moreno R, Hanna MM, Tavares SM, Wang YP. A double-blind comparison of the effect of the antipsychotics haloperidol and olanzapine on sleep in mania. Braz J Med Biol Res. 2007; 40(3): 357–366. [PubMed: 17334533]
89. Todder D, Caliskan S, Baune BT. Night locomotor activity and quality of sleep in quetiapine-treated patients with depression. J Clin Psychopharmacol. 2006; 26(6):638–642. [PubMed: 17110822]
90. Kirshner H. Controversies in behavioral neurology: the use of atypical antipsychotic drugs to treat neurobehavioral symptoms in dementia. Curr Neurol Neurosci Rep. 2008; 8(6):471–474. [PubMed: 18957183]
91. Rose M, Kam CA. Gabapentin: pharmacology and it's use in pain management. Anaesthesia. 2002; 57:451–462. [PubMed: 11966555]
92. Gajraj N. Pregabalin: its pharmacology and use in pain management. Anesth Analg. 2007; 105(6): 1805–1815. [PubMed: 18042886]
93. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol. 2007; 20(5):456–472. [PubMed: 17873599]
94. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep. 2005; 28(2):187–193. [PubMed: 16171242]
95. de Haas S, Otte A, de Weerd W, van Erp G, Cohen A, van Gerven G. Exploratory polysomnographic evaluation of pregabalin on sleep disturbance in patients with epilepsy. J Clin Sleep Med. 2007; 3(5):473–478. [PubMed: 17803010]
96. Garcia-Borreguero D, Larrosa O, de la, Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002; 59(10):1573–1579. [PubMed: 12451200]
97. Brower K, Myra, Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res. 2008; 32(8):1429–1438. [PubMed: 18540923]
98. Walsh J, Zammit G, Schweitzer PK, Ondrasik J, Roth T. Tiagabine enhances slow wave sleep and sleep maintenance in primary insomnia. Sleep Med. 2006; 7(2):155–161. [PubMed: 16260179]
99. Roth T, Wright KP Jr, Walsh J. Effect of tiagabine on sleep in elderly subjects with primary insomnia: a randomized, double-blind, placebo-controlled study. Sleep. 2006; 29(3):335–341. [PubMed: 16553019]
100. Walsh J, Perlis M, Rosenthal M, Krystal A, Jiang J, Roth T. Tiagabine increases slow-wave sleep in a dose-dependent fashion without affecting traditional efficacy measures in adults with primary insomnia. J Clin Sleep Med. 2006; 2(1):35–41. [PubMed: 17557435]
101. Walsh J, Randazzo AC, Frankowski S, Shannon K, Schweitzer PK, Roth T. Dose-response effects of tiagabine on the sleep of older adults. Sleep. 2005; 28(6):673–676. [PubMed: 16477953]
102. Guay D. Pregabalin in neuropathic pain: a more “pharmaceutically elegant” gabapentin? Am J Geriatr Pharmacother. 2005; 3(4):274–287. [PubMed: 16503325]
103. Taylor F, Raskind MA. The [alpha] 1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. Journal Clin Psychopharmacol. 2002; 22(1):82–85.
104. Krystal AD, Davidson J. The use of prazosin for the treatment of trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007; 61(8): 925. [PubMed: 17397667]

105. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma PTSD: a placebo-controlled study. Biol Psychiatry. 2008; 63(6): 629. [PubMed: 17868655]
106. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003; 160(2):371–373. [PubMed: 12562588]
107. Raskind MA, Peskind ER, Hoff DJ, et al. 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; 61(8):928–934. [PubMed: 17069768]
108. Germain A, Richardson R, Moul DE, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US military veterans. J Psychosom Res. 2012; 72(2):89–96. [PubMed: 22281448]
109. Krystal AD, Lankford A, Durrence HH, et al. 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(10):1433. [PubMed: 21966075]
110. Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. J Psychopharmacol. 2012; 26(8):1088–1095. [PubMed: 22004689]
111. Roth T, Soubrane C, Titeux L, Walsh JK, on behalf otZSG. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. Sleep Med. 2006; 7(5): 397–406. [PubMed: 16815744]
112. Roth T, Krystal A, Steinberg FJ, Singh NN, Moline M. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. Sleep. 2013; 36(2): 189–196. [PubMed: 23372266]
113. Zammit G, Corser B, Doghramji K, et al. Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening. J Clin Sleep Med. 2006; 2(4):417–423. [PubMed: 17557470]
114. NIH State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults statement. Sleep. 2005; 28(9):1049–1057. [PubMed: 16268373]
115. Asnis GM, Chakraburtty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. Journal of Clinical Psychiatry. 1999; 60:668–676. [PubMed: 10549683]
116. Krystal A, Roth T, Pong A, Stet L, Ivgy-May N. Efficacy and Safety of Esmirtazapine in Elderly Patients with Primary Insomnia in a 2-Week Sleep Laboratory Trial. Sleep. 2012; 35:A222–A222.
117. Ivgy-May N, Roth T, Amari N, Pathiraja K, Walsh J. Efficacy and Safety of Esmirtazapine in Non-Elderly Adult Patients with Primary Insomnia. A 2-Week Outpatient Trial. Sleep. 2012; 35:A222–A223.
118. Ivgy-May N, Amari N, Pathirajaj K, Rowe E, Roth T. Efficacy and Safety of Esrmitazapine in a Six-Week Sleep Laboratory Study in Patients with Primary Insomnia. Sleep. 2012; 35:A223.
119. Ruwe F, Ivgy-May N, Ijzerman-Boon P, Roth T, Zammit G. A Phase II Randomized, 4-way Crossover, Double-Blind, Placebo-Controlled, Multi-Center, Dose-Finding Trial with Esmirtazapine in patients with primary insomnia. Sleep. 2012; 35:A224–225.
120. Mignot E. The perfect hypnotic? Science (New York, NY). 2013; 340(6128):36–38.
121. Sun H, Kennedy W, Wilbraham D, et al. Phase II Randomized, 4-way Crossover, Double-Blind, Placebo-Controlled, Multi-Center, Dose-Finding Trial with Esmirtazapine in patients with primary insomnia. Sleep. 2013; 36:259–267. [PubMed: 23372274]
122. Herring WJ, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology. Dec 4; 2012 79(23):2265–2274. [PubMed: 23197752]
123. Connor, K.; Budd, K.; Snavely, D., et al. Efficacy and safety of suvorexant, an orexin receptor antagonist, in patients with primary insomnia: a 3-month phase 3 trial (trial# 1). Paper presented at: Journal of Sleep Research; 2012.

124. Herring W, Snyder E, Paradis E, et al. Long Term safety and efficacy of suvorexant in patients with primary insomnia. Sleep. 2012; 35:A217.

Key Points

- A number of different types of medications are available for treating patients with insomnia
- Medications available for treating insomnia patients differ in their properties
- Insomnia patients differ as to the risk/benefit ratio associated with the use of the available insomnia medications.
- Optimizing the medication treatment of insomnia for a given patient requires that the clinician select an agent for use which has characteristics that make it most likely to effectively and safely address the type of sleep difficulty experienced by that individual.