

Current and Emerging Pharmacotherapies in the Management of Insomnia in Adults

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Abstract: This review primarily focuses on the pharmacotherapy for insomnia, including current and emerging pharmacotherapy for insomnia. Currently, there are 10 FDA-approved drugs for the treatment of insomnia. The mainstay treatments are benzodiazepine receptor agonists, which are now available in controlled release formulation to support sleep maintenance. Melatonin receptor agonists are usually used for sleep initiation insomnia. Doxepin an antidepressant is approved for treatment of insomnia. Anticonvulsants and antipsychotics are used ‘off-label’ to treat insomnia, despite limited data to support its use. 5-HT_{2A} serotonin receptor inverse agonists and orexin receptor antagonists are in Phase II and III clinical trials for insomnia with different mechanisms of action.

When treating insomnia patients, it is important to individualize treatment by considering various comorbid conditions. Further research is needed to evaluate the efficacy and safety of newly emerging medications, as well as medications that are frequently used without established clinical evidence.

Keywords: insomnia, pharmacotherapy, treatment

Clinical Medicine Reviews in Therapeutics 2013;5 11–23

doi: [10.4137/CMRT.S10265](https://doi.org/10.4137/CMRT.S10265)

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Background

Insomnia is one of the most common sleep disorders, with population-based studies indicating prevalence in the U.S. to be between 6%–10%.^{1,2} Up to 30% of Americans report experiencing at least one insomnia symptom.³ Insomnia is characterized by a combination of nocturnal symptoms, including difficulties initiating sleep, maintaining sleep and early morning awakenings, and daytime symptoms that impair occupational, social, or other areas of functioning. Insomnia can exist alone or in conjunction with comorbid medical and/or psychiatric conditions.

Insomnia is recognized as an independent disorder in all diagnostic classification systems. The International Classification of Sleep Disorders, 2nd edition (ICSD) and the Diagnostic and Statistical Manual for Mental Disorders 4th edition (DSM-IV) include diagnostic criteria of insomnia as having both nocturnal symptoms (ie, difficulty initiating or maintaining sleep, early morning awakenings, or nonrestorative sleep) and daytime symptoms characterized by impairment of daytime functioning (ie, difficulties with memory or concentration that are related to sleep difficulty) accompanied by marked distress due to sleep disturbance.

There are pharmacological and non-pharmacological treatment options available for insomnia. This review primarily focuses on the pharmacotherapy for insomnia, including current and emerging pharmacotherapy for insomnia. Non-pharmacological options include cognitive-behavioral therapy for insomnia (CBTI), which is an effective treatment of insomnia, alone and in combination with pharmacotherapy. CBTI is a short-term treatment that, on average, includes 4–8 sessions and adopts a multicomponent approach, which typically includes sleep restriction, stimulus control, cognitive therapy, sleep hygiene and relaxation training, and can help patients learn how to fall asleep quicker and improve sleep quality. While a full review of non-pharmacological treatments is beyond the scope of this article, see Siebern et al for a review.⁴

Pharmacological Treatment for Insomnia

Pharmacotherapy has been the treatment of choice for insomnia for more than 100 years, beginning with barbiturates in the early 1900s. Treatment is recommended

when insomnia has a significant impact on a patient's sleep quality, health, daytime functioning or comorbid conditions.⁵ Pharmacological treatment for insomnia has its basis in neurotransmitter systems affecting sleep and wake promoting systems. Wake-promoting neurotransmitters include Norepinephrine (NE), Serotonin (5-HT), Acetylcholine (ACh), Histamine (HA) and Hypocretin/Orexin (HOX). Sleep-promoting inhibitory neurotransmitters consist of Adenosine (AD), Gamma-aminobutyric acid (GABA), Galanin, and Melatonin (MT). A mutually inhibitory relationship exists between the sleep-promoting systems and the wake-promoting systems.⁶ The treatment agents used to treat insomnia antagonize wake-promoting systems or enhance sleep-promoting systems. Pharmacological agents commonly used to treat insomnia include benzodiazepine-receptor agonists (BzRAs; benzodiazepines and nonbenzodiazepines), melatonin receptor agonists, antidepressants, antipsychotics, anticonvulsants, antihistamines, 5-HT_{2A} serotonin inverse agonists, and orexin receptor antagonists. The Food and Drug Administration (FDA) currently approve 10 medications for the treatment of insomnia (See Table 1).

Benzodiazepine receptor agonists

Benzodiazepine receptor agonists (BzRAs) are the allosteric modulators of gamma-aminobutyric acid type receptor (GABA) benzodiazepine receptor (BzR).⁷ When BzRAs bind to benzodiazepine receptors (BzR), these compounds enhance inhibitory action of gamma-aminobutyric acid (GABA) by opening the chloride channel, which then hyperpolarizes the neuron and leads to the inhibition of neuronal action potential firing.⁷ GABA is the primary inhibitory neurotransmitter in the brain and exerts its action by binding at two distinct types of GABA receptors (A and B).⁸ The GABA_A receptors have a 5-protein transmembrane channel constructing a pentameric structure. The α , β , and γ subunits occur in different combinations within particular locations of the brain, resulting in substantial diverse effects of GABA on brain function.⁹ The sleep-enhancing effects of both benzodiazepines and non-benzodiazepine result from their binding to the GABA_A complex at a site on the α subunits.⁹ These agents differ in their affinity for different alpha subunits (α 1– α 6); of these, α 1, α 2, and α 3 are most abundant in the brain.^{10–12} Binding to



Table 1. Characteristics of FDA-approved insomnia pharmacological agents.

Generic name	Trade name	Type	Elimination half-life (hours)	T _{max} (hours)	Major metabolic pathway	Available tablets (mg)	Recommended dose for adults (mg)	Habit forming
Zaleplon	Sonata	Pyrazolopyrimidine	0.9–1.1	1.1	Aldehyde oxidase, CYP3A4	5, 15	10	Yes
Zolpidem tartrate	Ambien Ambien CR Eduar Intermezzo Zolpimist	Imidazopyrimidine	2.0–5.5	1.7–2.5	CYP3A4, CYP1A2, CYP2C9	5, 10 6.25, 12.5	10	Schedule IV drug
Eszopiclone	Lunesta	Cyclopyrrolone	6–7	1.3–1.6	CYP3A1, CYP2E1	1, 2	2–3	Schedule IV drug
Triazolam	Halcion	Benzodiazepine	2–5.5	1–3	CYP3A4, glucuronide conjugation	0.125, 0.25	0.25	Schedule IV drug
Temazepam	Restoril	Benzodiazepine	8–20	1–3	Glucuronide conjugation	7, 5, 15, 30	30	Schedule IV drug
Estazolam	ProSom	Benzodiazepine	10–24	1.5–2.0	CYP3A4	1, 2	2	Schedule IV drug
Flurazepam	Dalmane	Benzodiazepine	40–250	0.5–1.5	CYP2C19, CYP3A4	15, 30	30	Schedule IV drug
Quazepam	Doral	Benzodiazepine	–20–120	2	CYP3A4, CYP2C19	7.5, 15	7.5–15	Schedule IV drug
Ramelteon	Rozerem	Melatonin receptor agonist	0.8–2	0.7–0.95	CYP1A2, CYP2C, CYP3A4	8	8	No
Doxepin	Silenor	Tricyclic antidepressant	0–50	1.5–4	CYP3A4, CYP2C19, CYP2D6, CYP2C9, CYP1A2	3, 6	3–6	No

Notes: *Schedule IV drug: According to the Controlled Substances Act, the medication has a low potential for abuse compared to Schedule III substances, but abuse may lead to limited physical dependence or psychological dependence; This risk may be greater with higher dosages of the medication.



the $\alpha 1$ subunit appears to have the potential for anti-convulsant, amnesic and ataxic effects, in addition to sleep-enhancing effects. Binding to the $\alpha 2$ or $\alpha 3$ subunits may have anxiolytic and myorelaxant effects, while binding to the $\alpha 5$ subunits may lead to myorelaxation, or cognitive impairment.^{10–14} The benzodiazepine non-selectively binds to $\alpha 1$ – $\alpha 5$ subunits.⁷ Non-benzodiazepine BzRAs have a more selective profile, binding preferentially to $\alpha 1$ subunits for sedating effects.¹¹

The mechanism for the predominant treatment of insomnia is enhancing the inhibitory effects of GABA to promote sleep. These include benzodiazepine and non-benzodiazepine BzRAs. There are currently 5 benzodiazepines that are FDA-approved for the treatment of insomnia. These are estazolam (ProSom), flurazepam (Dalmane), quazepam (Doral), temazepam (Restoril), and triazolam (Halcion). There are individual differences in the pharmacokinetic and pharmacodynamic actions of BzRAs; thus, the clinical efficacy and safety profile may vary among individuals. Despite the variation in rapidity of onset and duration of hypnotic action, benzodiazepines have been shown to be efficacious for the treatment of insomnia. Meta-analyses of benzodiazepines have been reported to improve sleep and wake complaints, daytime functioning or distress, and PSG measures of reduction in the sleep latency (SL), number of arousals, and wake after sleep onset (WASO), as well as increase total sleep time (TST).^{15,16} Although meta-analyses are helpful in describing general effects of these medications because they combine studies of various agents at multiple doses, they are less helpful in guiding specific treatment decisions.

Non-benzodiazepine BzRAs that are currently FDA-approved include zolpidem tartrate, zaleplon, and eszopiclone for the short-term treatment of insomnia. These drugs demonstrate hypnotic efficacy similar to that of benzodiazepines along with better safety profiles. Non-benzodiazepine BzRAs generally cause less disruption of normal sleep architecture than benzodiazepines.¹⁷ Psychomotor and memory impairment may be less problematic, especially when compared to longer-acting benzodiazepines.

Zolpidem tartrate preferably binds to $\alpha 1$ subunits of GABA_A receptor, and the selective binding produces sedation without interfering with other benzodiazepine properties. Zolpidem tartrate is currently

sold in four different forms based on indication and delivery method; zolpidem tartrate immediate release (Ambien[®]), zolpidem tartrate controlled release (Ambien CR[®]), zolpidem tartrate oral solution (Zolpimist[®]), and zolpidem tartrate sublingual tablet (Intermezzo[®], Edluar[®]).

Zolpidem tartrate was approved by the FDA (U.S. Food and Drug Administration) for the short-term treatment of insomnia. Its bioavailability after oral administration is 70%, it has a half-life of 1.5–2.4 hours and its effects can last up to 8 hours.¹⁸ It is excreted as inactive metabolites mainly by the kidney (56%) and enterally (37%). The excretion is reduced in the elderly, and in patients with hepatic and renal impairment. The effectiveness of zolpidem, compare to placebo, has been shown to improve SL, sleep duration, and efficacy, with persistent improvements throughout 35 days¹⁹ and up to 12 months of follow up.²⁰ Headaches are the most commonly reported adverse effect, which appears to be dose-dependent. A small percentage of patients experience CNS-related effects such as drowsiness, incoordination, dizziness, hallucinations and ataxia. Sleep-related events such as preparing and eating food, compulsive house cleaning, sleep driving, house painting, and sleepwalking have been reported.^{21–23} These reports indicate that patients typically do not have a memory of the sleep-related event, and in most cases, the behavior resolved when zolpidem was discontinued. Sudden withdrawal from zolpidem may precipitate an epileptic seizure. Most of the case reports indicated that zolpidem withdrawal seizures occur after withdrawal of supratherapeutic doses ranging from 130 mg to 600 mg per day.^{24–27}

The controlled release formulation of zolpidem tartrate is sold under the trade name Ambien-CR[®], which is a 2-layer tablet that provides a biphasic release zolpidem: an immediate release phase followed by a prolonged release phase. This allows immediate release of 60% of the dose, with the remainder being released at a slower rate.²⁸ Zolpidem controlled release (12.5 mg) produces plasma concentrations that are higher in the middle of the typical sleep cycle than with 10 mg zolpidem immediate release. This, in turn, produces a benzodiazepine agonist effects in the 3–6 hour postdosage.¹⁸ There is one double-blind placebo controlled study of zolpidem controlled release in chronic primary insomnia for 6 months. This study revealed that zolpidem controlled release for-



mulation provided sustained improvements in sleep onset and maintenance compared to placebo. Thus, it is FDA approved for sleep onset and/or sleep maintenance insomnia.²⁹ Zolpimist[®] is an oral solution of zolpidem tartrate, currently marketed as Ambien[®], as an oral spray.³⁰ It is approved by the U.S. FDA with indication for the short-term treatment of insomnia characterized by difficulty with sleep initiation. Zolpimist is considered bioequivalent to the immediate release tablet formulation, without having to ingest with water.³¹ Zolpimist has slightly more rapid and peak serum concentration, which leads to faster onset of action. Each spray delivers 5 mg of zolpidem tartrate in 100 mL. Clinically recommended doses are 10 mg for adults and 5 mg for the elderly once daily, immediately before bedtime.³¹ Intermezzo[®] is a low-dose sublingual tablet of zolpidem tartrate, and is FDA approved for sleep maintenance insomnia, especially for middle-of-the-night awakening.³⁰ This formulation contains a lower dose of the drug (1.75 mg and 3.5 mg tablet), and is recommended only if there is at least 4 more hours before the patient's planned awakening. Recommended dose is 1.75 mg for women, and 3.5 mg for men, once per night if needed. Edluar[®] is a sublingual tablet of zolpidem tartrate. It has been reported to initiate sleep significantly earlier as compared to an equivalent dose of oral zolpidem,³² and also has more convenient administration. It is FDA-approved for short-term treatment of insomnia characterized by difficulties with sleep initiation. It is supplied as a 5 mg or 10 mg sublingual tablet. The recommended doses are 5 mg for elderly and 10 mg for adults, once daily immediately before getting into bed.

Zaleplon (Sonata[®]) was approved by the FDA for the short-term treatment of insomnia. Like zolpidem, it acts as a selective agonist on the GABA_A receptor, but with low affinity.³³ It has a short half-life of about 0.9–1.1 hours and effects usually last for up to 4 hours. Considering the short half-life of Zaleplon, it was primarily indicated for the short-treatment of insomnia. Clinical trials suggest that Zaleplon is also useful for patients who have frequent nocturnal awakenings (sleep maintenance insomnia) because it can be taken for middle-of-the-night insomnia, as long as it is taken 4 hours or more before expected wake up time, without residual sedating effects.³⁴ A double-blind, placebo controlled, crossover dosing study revealed

that zolpidem (10 mg) and zaleplon (10 mg) effectively shortened SL and increased TST compared to placebo. Residual sedation was not detected as little as 4 hours after zaleplon 10 mg, whereas residual sedation was detected with zolpidem.³⁵ Rebound insomnia after discontinuing nightly treatment with zaleplon has been investigated in a double-blind design study for up to 5 weeks, and rebound insomnia has not been found in these trials.^{36,37} Similarly, no withdrawal syndrome was identified following discontinuation of nightly zaleplon use.³⁶

Eszopiclone (Lunesta[®]), another non-benzodiazepine BzRA, has high relative affinity for α_2 , and α_3 subunits.³⁸ It is metabolized by cytochrome P450-3A (CYP3A). Eszopiclone is rapidly absorbed and has a half-life of 6–7 hours, longer than the other nonbenzodiazepine BzRAs.³⁹ Eszopiclone consistently improves sleep maintenance relative to placebo, based on measures of shortened wake time after sleep onset, and prolonged TST.^{40–42} However, eszopiclone may also produce residual sedation and impairment of driving performance in the initial waking hours. It should therefore be prescribed to patients who expect to spend 8 hours or more in bed after ingestion. Eszopiclone has also been associated with dysgeusia (bitter taste), although this is not considered an adverse effect.

FDA-approved benzodiazepines are generally recommended for short-term use, as long-term use may result in adverse events, such as residual next day sedation, impaired motor and cognitive function, frequent falls for elderly, amnesia and rebound daytime anxiety.^{43,44} Residual sedating effects occur more commonly with long acting benzodiazepines. Tolerance is defined as a reduction of a drug's effect with repeated administration of a stable dose, or the need to increase the dose to maintain effects for repeated use. Several randomized double-blind studies assessed the effects of continuous sedative hypnotic use: zolpidem for 5 weeks,¹⁹ zaleplon for 4³³ and 5 weeks,³⁷ and eszopiclone for 6¹⁸ and 12 months.^{41,45} In long-term use of benzodiazepines (2 years), no notable dose escalation were seen. Subgroups with a higher risk of dose escalation included antidepressant recipients and patients who filled duplicate prescriptions at different pharmacies.⁴⁶

Rebound insomnia is a common discontinuation effect of BZRA hypnotics, which is defined as a worsening of sleep relative to the patient's status



before starting treatment. It typically lasts for 1–2 nights immediately after hypnotic discontinuation, and is more likely to occur after abrupt discontinuation of the shorter-acting agents.⁴⁷ Rebound insomnia is different from recrudescence, which is a return of symptoms to pretreatment level, and withdrawal syndrome, which is the appearance of new symptoms.

Abuse liability has been a concern as chronic use of BZRA may lead to their abuse following behavioral and/or physical dependence. Patients who use chronic hypnotics rarely self-escalate the dose and use it for nontherapeutic (ex. daytime) purposes. There is one study with a follow-up period of 12 months of nightly zolpidem use, which reported no evidence of dose escalation.²⁰ In contrast, the placebo group increased their placebo dose. This suggests that hypnotic self-administration can be explained by therapy-seeking behavior, and does not reflect behavioral dependence. While abuse potential of BZRA (zolpidem, and eszopiclone) seem to be very low, individuals with a history of substance abuse or dependence, or psychiatric comorbidities are at risk.⁴⁸

Melatonin receptor ligands

Melatonin is a hormone secreted by the pineal gland in the brain, synthesized from serotonin. It is involved in circadian system regulation and has sleep-enhancing effects. There are 3 different melatonin (MT) receptors (MT1, MT2, and MT3). Agonists of MT1 are thought to induce sleepiness, whereas MT2 receptors are responsible for regulation of circadian rhythms. These receptors are primarily located in the suprachiasmatic nucleus (SCN) and binding to MT1 receptors could attenuate SCN stimulatory output (alerting signal), subsequently promoting a hypnotic effect.^{49,50}

Melatonin is an over-the-counter (OTC) medication, sold as a food supplement. It has a time to maximum concentration (T_{max}) of 0.5 hours and an elimination half-life of roughly 1 hour.⁵¹ A dose-response relationship does not appear to exist for melatonin, and the means to determine optimal dosing are lacking.¹⁷ There is controversy regarding the sleep-promoting effects of melatonin because of widely varying inclusion and exclusion criteria, melatonin dosages, and timing of administration.⁵² In one study, no significant differences in SL or TST were seen in 10 primary insomnia patients compared

to placebo, when given 0.3 mg or 1 mg of melatonin, or placebo 1 hour before bedtime in a double-blind cross-over design.⁵³ Similarly, a study on 10 patients with persistent insomnia who were randomized to 1 or 5 mg of melatonin revealed a lack of improvement in sleep SL or TST, and no effect on mood or alertness, but reported a subjective sense of improved sleep quality.⁵⁴ A much higher dose of melatonin (75 mg) improved SL, and daytime alertness compared to placebo in a double-blind study of 13 insomnia patients.⁵⁵ A recent meta-analysis showed a reduction in SL by 4 minutes, increased sleep efficiency (SE) by 2.2% and increased TST by 12.8 minutes.⁵⁶ Melatonin doses as high as 75 mg have been used in clinical trials without significant toxicity.⁵⁵

Ramelteon is a melatonin receptor agonist, which is FDA-approved for the treatment of sleep initiation insomnia. It has a half-life of 0.8–2 hours, and T_{max} of 0.7–0.95 hours.⁵⁷ It binds to MT1 and MT2 melatonin receptors within the SCN, and is metabolized by CYP1A2, with CYP2C and CYP3A4.⁵⁸ Ramelteon, like melatonin, has no clear dose-response relationship; however, a therapeutic dosage of 8 mg and timing of dosing 30 minutes before bedtime has been recommended.⁵⁷ Ramelteon (16 mg or 64 mg), when given to normal adults of transient insomnia, improved SL by 10–15 min, and increased TST; however, wake after sleep onset (WASO), time spent in each sleep stage and number of awakenings were not significantly different from placebo.⁵⁹ Similar studies revealed improvement in SL for primary insomnia patients with different doses of Ramelteon in adults (4 and 32 mg) and in elderly (4 and 8 mg), but no subjective improvements in sleep quality or TST.^{44,60} Effects persisted even if treatment was extended to 5 weeks for both adults and elderly primary insomnia patients.^{61,62} Adverse effects occur in more than 2% of patients, and the most commonly reported symptoms are headache, somnolence, and sore throat.⁶⁰ Elevation of prolactin has been reported with Ramelteon compared with placebo in women.⁶³ There were no reports of rebound insomnia after medication discontinuation, and no significant effects of abuse potential or motor and cognitive impairment at up to 20 times the recommended therapeutic dose.^{59,64} Smoking is an inducer of the CYP1A2 isozyme, decreasing ramelteon efficacy, and dose reduction is recommended when attempting smoking cessation.⁶⁵



Agomelatine (AGO-178) is a chemical compound that is structurally related to melatonin. It is a MT1 and MT2 receptor agonist as well as a 5-HT_{2c} antagonist. It was initially investigated as a chronobiotic; however, with the discovery of 5-HT_{2c} serotonergic receptor it is more focused on anxiolytic and antidepressant effects. The approval indication in the European Union (EU) is depression. There are currently no randomized studies with primary insomnia patients, and most clinical studies are done in patients with major depressive disorder. Study results have shown it to positively influence disturbed circadian rhythms in depressed patients by significantly improving all phases of disturbed sleep and the overall quality of sleep, with a favorable impact on daytime alertness.⁶⁶

Tasimelteon (VEC-162) is a melatonin receptor agonist (MT1 and MT2). Tasimelteon was effective in reducing SL (in phase II and III clinical trials) and in resetting the circadian melatonin rhythm (in phase II trials), which indicated its potential suitability as treatment for jet lag, shift work and circadian rhythm sleep disorders.⁶⁷ The drug is well tolerated without next-day functioning impairment. Further studies concerning efficacy and safety are still pending.

Antidepressants

Antidepressants are widely used for the treatment of insomnia, and its effects on sleep are based on the findings from clinical studies in patients with mental psychiatric problems. Their mechanisms for insomnia treatment include blocking wake-promoting neurotransmitters (acetylcholine, histamine, norepinephrine, serotonin, and dopamine) for sleep enhancing effects.^{6,57} Among them, the main sedating effects are caused by the anticholinergic and antihistamine effects.¹⁷ The most commonly prescribed antidepressants are tricyclic antidepressants (doxepine, amitriptyline, trimipramine), tetracyclic antidepressant (mirtazapine) and trazodone. Except for doxepin, most of the antidepressants for insomnia are off-label use. However, antidepressants are commonly used as hypnotics in conjunction with single medication for insomnia and psychiatric disorders, or to avoid benzodiazepine side effects and dependence. Serotonin reuptake inhibitors (SSRI), and serotonin and norepinephrine reuptake inhibitors (SNRI) block serotonin reuptake, as well as noradrenaline reuptake. This may

frequently be associated with insomnia, via rapid eye movement (REM) suppression and sleep disruption.⁶⁸

Doxepin is a tricyclic antidepressant, and FDA-approved for sleep maintenance insomnia. Typical antidepressant doses are 25–150 mg, and hypnotic doses are 3–6 mg. In the high dose range, doxepin has antihistamine, anticholinergic, anti-serotonergic and antiadrenergic effects, but in hypnotic doses (<10 mg) it has a relatively pure anti-histamine effect.⁶⁹ In a large clinical trial, adults and elderly patients with primary insomnia were prescribed 1 mg or 3 mg of doxepin, or placebo for 12 weeks of nightly use. Doxepin improved the sleep parameters including WASO, TST, and overall SE, and treatment effects were maintained until the end of the study.⁷⁰ It is remarkable to note that participants did not report significant next-day residual effects. In a similar study, adults with chronic primary insomnia were followed for 35 days with 3 mg and 6 mg of doxepin, which resulted in improvement in sleep maintenance, and early morning awakenings without next-day residual effects.⁷¹ In a double-blind, placebo-controlled trial in elderly patients with primary insomnia, 6 mg of doxepin produced significant improvements in sleep maintenance, sleep duration, and sleep quality, compared to placebo, and treatment effects were maintained throughout the 4 weeks of trial.⁷² Rebound insomnia or withdrawal effects upon discontinuation were not seen in these trials.

Amitriptyline is a tricyclic antidepressant, with a long half-life of 10–100 hours and a T_{max} of 2–5 hours.⁵⁷ A long T_{max} needs to be considered when choosing the dosing hour needed in order to achieve optimal time to fall asleep.^{17,57} There is no data on the effects of amitriptyline in patients with primary insomnia. Open label trials without control groups indicated some improvements in sleep quality in comorbid insomnia (anxiety and depression).⁷³ One study compared sleep effects of amitriptyline and escitalopram to placebo in healthy subjects. Amitriptyline reduced WASO and REM, and increased sleep continuity compared to placebo. However, increased periodic limb movements (PLM), and PLM arousal index, as well as increase daytime sleepiness were observed the next day.⁷⁴ The side effects are orthostatic hypotension, weight gain, dry mouth, constipation, urinary retention, and cardiac dysrhythmias.

Trazodone is a triazolopyridine antidepressant that antagonizes 5-HT₁, 5-HT₂ and also has a weak



serotonin reuptake inhibition effect. The half-life is 7–15 hours, and T_{\max} is 1–2 hours.⁵⁷ It was the most commonly used medication for insomnia until 2002.⁷⁵ Despite its popular use, there are limited studies focused on efficacy and safety of trazodone. In primary insomnia patients, trazodone increases slow wave sleep (SWS).⁷⁶ In one study, insomnia patients who were prescribed 50 mg of trazodone were compared to placebo controls, and those taking trazodone displayed fewer night time awakenings, fewer minutes of stage 1 sleep and provided self-reports citing difficulty sleeping. However, trazodone was also associated significant impairment in short-term memory, verbal learning, equilibrium, and arm muscle endurance across time points.⁷⁷ Trazodone has lead to demonstrated improvement of both depression and insomnia.^{78,79} The common side effects are residual morning sedation, orthostatic hypotension, and priapism.

Mirtazapine is a tetracyclic piperazinoazepine with inhibition of 5-HT₂, 5-HT₃ and α -adrenergic receptors. It has half-life of 20–40 hours and a T_{\max} of 0.25–2 hours.⁵⁷ There were no randomized clinical trials of mirtazapine in primary insomnia. In healthy adults, mirtazapine has been shown to reduce SL and increase SWS and SE.^{80,81} Oral doses of 5 mg, 15 mg, and 30 mg of mirtazapine, placebo, and 10 mg diazepam were given the night before surgery, and self-reported assessment of sleep quality improved in mirtazapine without significant side effects.⁸² Additionally, sleep quality improved in a dose-dependent manner. Mirtazapine in depressed patients without clinically diagnosed insomnia showed improvement in SL and TST, but these studies were not controlled by a placebo group.^{83,84} There were improvements in SL, TST, SE, and WASO by PSG measures when comparing 2 weeks of mirtazapine to fluoxetine.⁸⁵ Additionally, depression assessment based on the 21-item Hamilton Rating Scale for Depression (HAM-D) demonstrated improvement in depression symptoms, largely associated with the degree of subjective sleep complaints by means of the 3 sleep items.⁸⁵ Interestingly, studies have shown that mirtazapine improved sleep quality in perimenopausal women with hot flashes.⁸⁶ Mirtazapine in combination with melatonin for women with peri-menopausal insomnia improved sleep quality.⁸⁷ Mirtazapine causes significant weight gain,

which may be attributed to mirtazapine's high antihistaminic (H1) receptor affinity.^{88,89} The mirtazapine may also cause dry mouth and constipation.

Antipsychotics

Antipsychotics are used to treat insomnia, which is best indicated for patients with psychotic disorders.⁵ The antipsychotics antagonize dopamine, histamine, serotonin, cholinergic and adrenergic receptors, and thus induce sleep.⁵⁷ The most commonly used antipsychotics are quetiapine and olanzapine.⁷⁵ Quetiapine has a half-life of 7 hours, and T_{\max} of 1 hour. In healthy subjects, quetiapine significantly improved sleep initiation and continuity compared to a placebo control when measured by polysomnography (PSG).⁹⁰ A study in primary insomnia demonstrated quetiapine improved PSG variables of TST and SE, and subjective sleep measures indexed using the PSQI (Pittsburgh Sleep Quality Index).⁹¹ A typical dose of quetiapine for insomnia is less than the recommended dose for psychotic disorders, but even with low doses of quetiapine, body weight increase has been reported as a side effect.⁹²

Olanzapine has a half-life of 30 hours and a T_{\max} of 5 hours, which makes it relatively unlikely to be effective for sleep onset difficulty when taken near bed time; however, it likely has a prolonged sleep enhancing effect.^{17,57} There is a scarcity of information regarding efficacy in insomnia and proper dosage. Additionally, the safety profile of increased risk of metabolic syndrome largely limits its use with insomnia patients. Olanzapine is primarily studied in schizophrenia, with a reported increased risk of metabolic syndrome. The overall rate of metabolic syndrome in patients who are treated with olanzapine is 41.6% with a hazard ratio of 1.62, and the incidence is 27.4% with a hazard ratio of 1.88.⁹³ Olanzapine cause significant weight gain of >7% of body weight changes in 23.6%–61.5% of patients.

Anticonvulsants

Anticonvulsants are also prescribed off-label for insomnia. It is recommended and beneficial for patients who suffer from both insomnia and an underlying epileptic disorder. Gabapentin and pregabalin are a structural analogue of GABA, but are thought to exert their primary central nervous system effects by binding to the alpha-2-delta subunit of the N-type



voltage gated calcium channels, thereby diminishing the release of wake-promoting neurotransmitters such as glutamate and norepinephrine.⁹⁴ Tiagabine is a GABA reuptake inhibitor and a sleep-promoting inhibitory neurotransmitter. They are FDA-approved for partial seizures but not for insomnia, and there are limited studies on effective doses for insomnia.

Gabapentin in normal adults have been shown to increase SWS.⁹⁵ There is one study on the treatment effects of gabapentin in primary insomnia. A total of 18 primary insomnia patients were treated with gabapentin for 4 weeks, and showed increase in SWS, along with improvement in SE and spontaneous arousals.⁹⁶ Gabapentin is also effective in insomnia during alcohol abstinence, and treating sleep disturbance in pain related disorders, epilepsy, and restless legs syndrome.^{97–100} The most common side effects of gabapentin are sedation, dizziness, and ataxia.

Pregabalin increases SWS in normal adults.¹⁰¹ Currently, there are no studies on the effects of pregabalin in primary insomnia. However, pregabalin has been reported to improve sleep disturbance in fibromyalgia, anxiety and pain-related syndrome.^{102–104} The most common side effects of pregabalin are sedation, dizziness, dry mouth, cognitive impairment and increased appetite.

Tiagabine is a GABA reuptake inhibitor. In primary insomnia patients, tiagabine 4, 8, 12, and 16 mg lead to a significant increase in SWS in a dose-dependent manner as compared to a placebo. However, no significant changes were seen in SL and TST, and improvement in WASO was only observed in the 16 mg dose.¹⁰⁵ One other study with primary insomnia patients reported no improvements in SL, TST, or WASO in the tiagabine treatment group compared to placebo, but increases in SWS were seen.¹⁰⁶ These studies reported drowsiness and nausea as the most common side effects of tiagabine. Although tiagabine is FDA-approved for treating partial seizure, there have been reports regarding an increased risk of de novo seizures, which limited its use to treat seizures.^{107,108}

Antihistamine

Antihistamines are primarily indicated for the treatment of allergies. However, there are agents with potent anti-histamine efficacy including antidepressants of doxepin and mirtazapine, as well as antipsychotics including olanzapine and quetiapine.⁵⁷

Diphenhydramine and Doxylamine are the two most commonly used antihistamines for insomnia that cross the brain blood barrier.

Diphenhydramine is an over-the-counter insomnia medication. It has a half-life of 5–11 hours, and a T_{max} of 2–2.5 hours.¹⁷ There is 1 recent randomized placebo control study in primary insomnia patients. In mild insomnia patients, there were increases in SE and TST reported in sleep diaries compared to placebo, but no objective significance measured by PSG.¹⁰⁹ Similar sleep maintenance effects were seen in groups of psychiatric patients, as well as in outpatients in a primary care practice.^{110,111} The most common side effects are sedation, dizziness, psychomotor impairment, cognitive impairment, dry mouth, blurred vision, constipation, urinary retention, and weight gain. Doxylamine is also available as over-the-counter medication. It has a half-life of 10–12 hours, and a T_{max} of 1.5–2.5 hours.¹⁷ No studies examining the treatment in insomnia with doxylamine have been reported.

5-HT_{2A} serotonin receptor inverse agonists

5-HT_{2A} serotonin receptor inverse agonists are developed as neuroleptics, which are also under clinical trials for treatment of insomnia. Inverse agonists bind to the same receptors as agonists but induce the opposite response to that agonist. For this to happen, the receptor must have an intrinsic basal activity level, and binding of inverse agonist blocks such activity. Serotonin is a wake-promoting neurotransmitter. Some atypical selective serotonin reuptake inhibitors have been shown to increase SWS, particularly those that bind to the serotonin 5-HT_{2A} receptor.¹¹² A decrease in SWS leads to a lighter level of sleep, which may increase arousal, wakefulness, and sleep fragmentation. Currently, 5-HT_{2A} serotonin receptor inverse agonists are under investigation for sleep maintenance therapy, but none have been approved for treatment of insomnia.

Pimavanserin (ACP-103) is currently undergoing Phase III trials for psychosis and Phase II trials for insomnia.¹¹³ In 45 healthy volunteers, Pimavanserin significantly increased SWS in a dose-dependent manner and decreased number of awakenings compared to placebo. Other PSG variables including TST, SL, and number of stage shifts did not change significantly.¹¹⁴



Nelostanserin (APD-125) is a 5-HT_{2A} receptor inverse agonist. In 173 adults with primary insomnia, 10 and 40 mg of Nelostanserin were compared to placebo controls for 7-day treatment periods.¹¹⁵ PSG measurement of WASO decreased in comparison to placebo in the 10 mg dose (day 1/2 and 6/7), and the 40 mg dose (day 1/2), but not significantly by day 6/7 at the 40 mg dose. No serious adverse events were reported, and there was no significant next-day psychomotor impairment. These results were not replicated in a double-blinded, randomized placebo controlled trial in 675 patients with primary insomnia. There were no improvements in primary (subjective number of awakenings after sleep onset) or secondary end points (WASO, TST, and SL), which lead to its discontinuation for development.¹¹⁶

Eplivanserin (SR-46349) had completed 3 Phase III trials indicating reduced WASO and number of nocturnal awakenings compared to placebo, without residual effects or withdrawal symptoms after waking.¹¹⁶ However, the pharmaceutical company withdrew its application for approval.

Orexin receptor antagonists

Orexin (= Hypocretin) is a wake-promoting neurotransmitter produced in the lateral hypothalamus. They promote wakefulness through orexin receptors (OX₁, and OX₂). A deficiency in orexin is known as narcolepsy, characterized by symptoms of excessive daytime sleepiness, cataplexy, hypnagogic hallucination, sleep paralysis and disrupted nocturnal sleep. Compared to benzodiazepine receptor agonists, orexin receptor antagonists lead to less confusion, amnesia, and unsteady gait and have been proposed to have lower abuse liability.¹¹⁷ Orexin receptor antagonists are currently under clinical investigation for the treatment of insomnia; however, none have been approved by FDA.

Suvorexant (MK-4305) is a nonselective (dual) OX₁/OX₂ receptor antagonist. A Phase I study in 103 volunteer subjects revealed improvement in SL, TST, and WASO measured by PSG, without next-morning residual cognitive effects. A Phase II study reported improvement in SE, and Phase III clinical trials reported improvement in SL and TST in the first month of a 12-month study comparing treatment to placebo. During the following 2 months after 12 months of suvorexant treatment, there was worsening SL and TST after switching from suvorexant to placebo.

There were no withdrawal or rebound insomnia after discontinuation. Merck recently announced that they have been accepted for standard review by the U.S. Food and Drug Administration, in November, 2012, and are now waiting for approval.

Amorexant (ACT-078573) was withdrawn from clinical studies due to its side effect profile. However, studies have shown it to decrease wakefulness in a dose-dependent manner in healthy human subjects, without evidence of cataplexy.¹¹⁸ In primary insomnia, increases in SE, reductions in SL and reductions in WASO were reported.^{44,116}

Conclusion

In a search for different options for the pharmacotherapy of insomnia, we are now faced with an ample number of drug options that are under development. These agents have mechanisms of action that are different from benzodiazepine receptor agonists, which allows for a different pharmacological approach. Further research evaluating the efficacy and safety of newly emerging medications are needed, along with research evaluating currently used medications without FDA approval, in order to support their widespread use. Therapeutic approaches should also consider non-pharmacological treatments of insomnia, such as cognitive-behavioral therapy for insomnia, as an adjunctive therapeutic option, and should consider different co-morbid conditions to tailor treatment for insomnia patients.

Author Contributions

Analyzed the data: PS, SS. Wrote the first draft of the manuscript: PS. Contributed to the writing of the manuscript: PS, SS. Agree with manuscript results and conclusions: PS, SS. Jointly developed the structure and arguments for the paper: PS, SS. Made critical revisions and approved final version: PS, SS. All authors reviewed and approved of the final manuscript.

Funding

This study was supported by a grant from the National Research Foundation of Korea Grant funded by the Korean Government. [NRF-2012-S1A5BA01].

Competing Interests

Author(s) disclose no potential conflicts of interest.



Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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