

Pharmacotherapeutic options for treatment of insomnia**Jarnail Singh*, Janardhan Singh**

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ABSTRACT

Insomnia is a functionally debilitating condition characterized by repeated difficulty with sleep initiation, maintenance, or quality of sleep despite adequate opportunity. If left untreated, it can lead to increased risk of depression, poor memory, reduced concentration, poor work performance, and poor general health. Although gamma-aminobutyric acid (GABA) ergic system remains the primary target for current insomnia treatments, still over-the-counter (OTC) drugs with a different mechanism of action are in use for insomnia. OTC drugs target only one of the parallel arousing systems and may improve mild insomnia for a short period. They are not likely to improve symptoms over long-term and thus are not the ideal agents. Studies evaluating the efficacy and outcomes of sedative hypnotic drugs beyond 1 year are limited. Currently, there are no Food and Drug Administration approved pharmacotherapies for insomnia in the pediatric population. Increased understanding of complex neuronal networks involved in sleep and wake has led to the development of new drugs for insomnia that target a diverse range of receptors. Potential agents under investigations are targeting mechanisms and pathways including histamine (H₁) receptor, melatonin, and orexin receptors. This review describes the pharmacotherapy of insomnia and the drugs under development for the treatment of insomnia.

Keywords: Insomnia, Benzodiazepines, Gamma-aminobutyric acid, Melatonin, Orexin

INTRODUCTION

Insomnia is the most common sleep disorder affecting millions of people with an estimated prevalence of 10-50% in the general population.¹ The International Classification of Sleep Disorders-2nd edition defines insomnia as a condition characterized by repeated difficulty with sleep initiation, maintenance, or quality despite adequate sleep opportunity.² Insomnia can contribute to increased risk of depression, poor memory, reduced concentration, poor work performance, and poor general health.³ Some changes in sleep patterns are normal with advancement of age including an increased amount of light sleep (Stages 1 and 2 of the sleep cycle), a decreased amount of deep sleep (Stages 3 and 4 of the sleep cycle), and less time spent in the rapid eye movement (REM) stage of sleep with decreased overall sleep quality and sleep efficiency (total sleep time [TST]/total bedtime). TST changes with age, i.e., sleep time requirement is over 18 hrs for neonates, 11 hrs for young children, 9 hrs for adolescents, and about 7.5 hrs for adults.⁴

NEUROBIOLOGY OF INSOMNIA

The sleep-wake state occurs by a dynamic interaction between arousing and sleep-inducing physiologic systems. The neurotransmitter systems including noradrenaline, serotonin, acetylcholine, dopamine, glutamate, histamine, and orexin 1 and 2 promote wakefulness, whereas gamma-aminobutyric acid (GABA), glycine, galanin, melatonin, and adenosine promote sleepiness.⁵

Drug treatment options for insomnia

Treatment of insomnia involves behavioral changes like minimizing habits that interfere with sleep, e.g., drinking coffee or engaging in stressful activities in the evening; and pharmacotherapy with sedating antidepressants, sedating antihistamines, anticholinergics, benzodiazepines (BZDs), or non-BZD hypnotics (Z-drugs). The BZDs and the newer sedative hypnotics zolpidem, zaleplon, and zopiclone (Z-drugs) work through GABA receptors. Ramelteon, a hypnotic approved by the United States Food and Drug

Administration (US-FDA) in July 2005 (Table 1), is a selective agonist at melatonin receptors (MT₁ and MT₂). Z-drugs have been sought for multiple reasons, including a reduction of the risk of tolerance, dependence, and abuse associated with BZDs. From pharmacokinetics point of view drugs with a shorter half-life might help a person fall asleep faster but are less effective for increasing TST per night. In general use of insomnia, drugs is recommended for a short-term, i.e., 1 month; but some individuals may require longer-term treatment.

Over-the-counter (OTC) insomnia treatments

Most of the OTC sleep-promoting agents contain antihistamines that block H₁ receptors, thus decrease arousal. Antihistamines may improve mild insomnia for a short period, but they are not ideal because they are not effective to improve the symptoms over a long period. Side effects are mainly due to the diffuse and systemic anticholinergic properties, e.g., dry mouth, dizziness, daytime sedation, and memory problems. These medications are not recommended for pregnant women or breast-feeding mothers. Elderly people are particularly sensitive to the anticholinergic side effects, thus not suitable for this age group. Melatonin is another commonly used OTC sleep aid for insomnia. It is a sleep-promoting hormone made by the pineal gland that regulates the circadian rhythm by its action on melatonin receptors in the suprachiasmatic nucleus.⁶ It has been shown to decrease sleep onset latency and improve subjective sleepiness upon awakening although it did not improve scores of sleepiness, fatigue, and alertness throughout the day in more formal studies.⁷ Although melatonin is a natural supplement, but it can cause side effects like alterations in cardiac rhythmicity, blood pressure, gastrointestinal motility, and glucose metabolism.

BZDs

BZDs are prescribed to relieve anxiety, including well-known medicines such as estazolam, flurazepam, temazepam, quazepam, and triazolam. Anxiolytic BZDs that are not approved for the treatment of insomnia (alprazolam, clonazepam, lorazepam, diazepam) are prescribed off-label for this purpose. BZDs may cause tolerance, anterograde amnesia, sleepwalking behaviors, delirium, cognitive impairment, fall and fracture risk, and respiratory drive suppression. Very short-acting BZDs such as midazolam and triazolam are known to cause amnesia.

Triazolam, structurally related to BZDs and acts on GABA receptors in different regions of the brain. It is indicated for short-term treatment of insomnia and should not be used for more than 3 consecutive weeks. In clinical studies, triazolam decreased sleep latency, increased duration of sleep, and decreased number of night awakenings in patients with insomnia. The most common side effects are drowsiness, nausea, vomiting, headache, dizziness, and difficulty in coordination, thus the elderly people should

receive lower doses as a caution. Cases of auditory and visual hallucinations after administration of triazolam have also been reported.⁸

Second generation hypnotics (Z-drug hypnotics)

Zolpidem is an imidazopyridine, first selective agonist of GABA_A receptor α_1 subunit, has a plasma half-life of 2.5 hrs and has no active metabolites. Its main indication is for rapid induction, with no effect on sleep consolidation. It is eliminated by kidneys, and dose is to be reduced in patients with chronic renal failure.⁹

Zopiclone is a cyclopyrrolone, has a longer t_{1/2} (5 hrs), less selective, acting on GABA_A receptors subunit α_1 and α_2 . It has great potential for residual sleepiness in the morning.¹⁰ Zaleplon is a pyrazolopyrimidine, has the ultrashort half-life (1 hr), and binding similar to zolpidem (GABA_A receptors) and its main indication is for rapid induction of sleep, with little effect on its maintenance and can be used in the middle of the night, in cases of early awakening.⁹

Zolpidem and zaleplon slightly alter the structure of sleep, are well-tolerated and are associated with little occurrence of tolerance and dependence with prolonged use. Both reduce the latency to sleep onset (LSO), and zolpidem can cause additional increase in TST. A modified release (MR) version of zolpidem maintains sustained plasma levels during the night, improving maintenance of sleep. A recent multicenter study has demonstrated safety and efficacy in the use of zolpidem MR 3-7 times/week for 6 months in the treatment of chronic insomnia (Table 1).¹¹

Z-drugs are known to cause tolerance, abuse potential and cross tolerance to alcohol and sedatives linked to GABA_A receptors. Auditory hallucinations, visual hallucinations, and delusions have been reported at therapeutic doses of Z-drugs. Numerous cases of sleep-driving have been reported while taking Z-drugs, as well as cases of sleepwalking, sleep eating, sleep conversations, sleep sex, and sleep shopping. When dose of Z-drugs is more than recommended, or these agents are mixed with alcohol or opiates, risk of these side-effects increases dramatically.¹²

Third generation hypnotics

Eszopiclone

Eszopiclone, an isomer of zopiclone, has been approved by the US-FDA for the treatment of insomnia. It was the first released for use in chronic insomnia and is indicated for both difficulty in initiating and maintaining sleep. It has been shown that the eszopiclone can exhibit different binding properties on GABA_A receptor, compared to zolpidem it is also less selective for the GABA_A receptor α_1 -subunit.¹¹ Also in a double-blind, randomized, placebo-controlled trial it improved daytime functioning at a dose of 3 mg without evidence of tolerance, dependence, or abuse.¹³

Indiplon

Indiplon is a new pyrazolopyrimidine with selectivity for GABA_A receptor α_1 -subunit, and high affinity and selectivity at some selectivity for α_1 -subunit is associated with sedation. Indiplon promotes reduction of sleep latency, number of awakenings after sleep onset (NAASO); and no daytime residual effects due to its short half-life. Indiplon immediate release appears safe and efficacious in the treatment of insomnia in both adult and elderly populations as demonstrated by improvements in latency to persistent sleep, LSO, TST, wake after sleep onset (WASO), NAASO, and sleep quality. Post-bedtime dosing or middle of the night dosing is a possibility with indiplon.¹⁴

Melatonergic agents

Ramelteon

Ramelteon is a selective agonist of melatonin receptors (MT₁ and MT₂) with high affinity. The agonism of melatonin at MT₁ and MT₂ is thought to dampen the activity of the reticular activating system and its monoamines (5-hydroxytryptamine [5-HT], DA, NE), thereby promoting sleep.¹⁵ It is indicated for the treatment of sleep onset insomnia. Mayer et al. observed safety, good tolerability, and a low incidence of adverse effects with the use of ramelteon for a period of 6 months to a year. The same study identified no potential for induction of rebound insomnia, withdrawal symptoms, potential for abuse and/or dependence, cognitive or motor impairment, suggesting a therapeutic option in patients with a history of substance abuse.¹⁶

Melatonin prolonged-release

Melatonin is a hormone secreted by the pineal gland, during the night, and functions as an endogenous regulator of the sleep-wake cycle. Exogenous melatonin and melatonergic drug effects are mediated via MT₁ and MT₂ receptors, especially in the suprachiasmatic nucleus. The ultrashort half-life of elimination (0.5-0.8 hrs) of melatonin is the biggest obstacle to its use in the treatment of chronic primary insomnia, which has favored the emergence of extended-release formulation.¹⁷ Melatonin has an established role in the treatment of circadian rhythm disorders, and it has a good safety and tolerability profile, with few side effects.¹⁸ It has been approved in Europe for treatment of primary insomnia in the elderly for 13 weeks.

GABA_A agonists

Tiagabine

Tiagabine, a selective GABA reuptake inhibitor, increases synaptic GABA availability via selective inhibition of

the GABA transporter-1. Walsh et al. demonstrated that tiagabine, in dose 4-16 mg increased slow wave sleep percentage in dose-dependent manner, the trend toward an increase in TST and decrease in WASO. Most common adverse events reported with 12 and 16 mg tiagabine were dizziness and nausea.¹⁹

Anti-depressants

Doxepin

Doxepin, a tricyclic antidepressant, is a potent histamine (H₁) antagonist. Brain histamine is believed to be one of the key elements in maintaining wakefulness, and the activation of the H₁ receptor is thought to play an important role in mediating arousal. Blockade of the H₁ receptor by doxepin likely plays a role in reducing wakefulness.²⁰ The exact mechanism by which it exerts sleep maintenance effect is not known, but is thought to be antagonism of histamine H₁ receptors. Doxepin has been studied mainly in older patients with primary insomnia, difficulty falling asleep, frequent waking or sleep duration <6.5 hrs. In sleep studies comparing 3 mg and 6 mg doses for 2 nights, there was an increase in total sleep duration by 25-38 mins compared with placebo.²¹ There was no significant decrease in sleep latency and also no much benefit in younger adults. Higher dose formulations of doxepin have a black boxed warning for suicide risk, but no reports of suicide with low dose doxepin.²²

Trazodone

Although the use of trazodone to treat insomnia is off-label, it is clinically effective, has a relatively short half-life and does not cause dependence (Table 2).

Hypnotic effects of trazodone are due to its antagonistic action on histamine (H₁), α_1 and 5-HT_{1A} receptors. Trazodone has been shown to be effective in treating primary insomnia and in insomnia associated with depression, anxiety, post-traumatic stress disorder, and dementia, during the last decade.²³

Mirtazapine

It is an atypical antidepressant, has an antagonistic effect on α_1 -adrenergic receptors, a postsynaptic antagonist of 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ receptors. Its potent antihistaminic (H₁) action explains the strong sedative effect (Table 2).²⁴

Amitriptyline

Amitriptyline shows significant sedative effects due to its anticholinergic, antihistaminic (H₁) and anti- α_1 profile, and also due to the blockage of 5-HT_{2A} and 5-HT_{2C} receptors. The sedative effects are immediate, preceding the antidepressant effects, and decrease after a few weeks of treatment (Table 2).

Mianserin

This is an atypical antidepressant with a sedative effect due to anti-histaminic (H_1) and 5-HT_{2A/2C} receptor antagonistic effects. There are no long-term studies proving the efficacy and safety of mianserin for treating insomnia.

Agomelatine

It is a new antidepressant with a distinct pharmacological profile, is an agonist of melatonin receptors (MT_1 and MT_2) and antagonist of 5-HT_{2C} receptors.²⁵ The effect of agomelatine has improved synchronization of circadian rhythms, which could contribute to an improved mood in patients with depression. Agomelatine reduces LSO, number of awakenings, can increase slow-wave sleep and the efficiency of sleep. It has been shown to be effective in depression at doses of 25-50 mg with safety, good tolerability, and low potential side effects like sexual dysfunction.²⁶

Others medications for insomnia

Quetiapine

It is an antipsychotic drug and promotes sleep initiation by antagonism of histamine (H_1), noradrenergic (α_1 and α_2), 5-HT and DA. Its 5-HT_{2A} receptor antagonism promotes normalization of sleep architecture improving REM and NREM sleep ratio on occurrence of sleep. Quetiapine is widely used off-label as a treatment for insomnia. Because of potential adverse effects of quetiapine, in the treatment of insomnia, it is recommended only in patients with specific co-morbid psychiatric disorders.²⁷

Antihistamines

These drugs include OTC sleep medications (diphenhydramine, doxylamine and hydroxyzine) and prescription drug doxepin. Blockade of H_1 receptors in the cortex and ventrolateral preoptic nucleus in the hypothalamus turns the sleep-wake switch off. The absence of the stimulating effect of histamine in these areas ultimately promotes sedation and sleep. Antihistamines may be associated with anticholinergic side effects, i.e., blurred vision, constipation, memory problems, and dry mouth. They tend to have longer half-lives and can produce morning sedation and dizziness. As compared to BZDs antihistamines have significantly lower or no risk for addiction, abuse, ataxia, and respiratory suppression.¹⁵

Barbituates

Barbiturates have many potential drawbacks such as addiction, drug interactions, lethality in overdose, and cognitive impairment. Barbiturates are not commonly prescribed, but for short-term treatment of insomnia on rare occasions. Safer

treatments are clearly available and should be considered before the use of barbiturates. Amobarbital, butobarbital, pentobarbital, secobarbital, and phenobarbital may be considered for their hypnotic effects. Of these, phenobarbital has a long duration of action as compared to the others.²⁸

Molecules under development

1. Tasimelteon: an agonist at MT_1 and MT_2 receptors, has been approved by US-FDA for transient insomnia
2. Piromelatine (Neu-P11), a novel compound under development for sleep and cognition, is an agonist of melatonin receptors and 5-HT_{1A} and 5-HT_{1D} receptors. It has demonstrated efficacy and safety in insomnia patients in Phase-II clinical trials
3. Eplivanserin, an antagonist at 5-HT_{2A} receptors; and has almost no affinity for dopamine, histamine, or adrenergic receptors.²⁹ The French Drug Maker Sanofi-Aventis has withdrawn both US and EU marketing authorization applications for insomnia drug eplivasserin in 2010.²⁹
4. Orexin antagonists: Neuropeptides orexin-A and orexin-B (hypocretins) are endogenous ligands that bind to orexin receptors (OX_1 and OX_2) that are found in the lateral hypothalamus. The orexin system plays an important role in the regulation of sleep and wakefulness, especially in the maintenance of sustained wakefulness. Orexin neurons discharge during active waking and cease firing during sleep. Thus, orexin receptor antagonists could suppress arousal and wakefulness and induce sleep reducing wakefulness in patients with insomnia.³⁰ Suvorexan, an antagonist of orexin receptors (OX_1 and OX_2), is in Phase III clinical trials and could enter the market for prescription in 2015. Another orexin receptor antagonist, almorexant was under investigation, but further work on it has been stopped.³¹
5. GABA receptor modulators - Brotizolam is BZD analog (approved in EU). EVT 201 is in phase-II clinical trials for use in primary insomnia. SKP 1041 (a delayed release formulation of zaleplon, is also under Phase-II clinical investigations for sleep maintenance insomnia.²⁹
6. Casopitant, a neurokinin receptor inhibitor, is under Phase-II clinical trials for insomnia.²⁹
7. LY2624803, a 5-HT_{2A} and H_1 receptor antagonist is under Phase-II clinical studies for chronic insomnia and transient insomnia.²⁹
8. Esmirtazapine (Org 50081), is the inverse agonist at H_1 and 5-HT_{2C} receptors and antagonist at α_2 receptors. It is under Phase-III clinical trials for elderly subjects having chronic primary insomnia.²⁹
9. Gaboxadol is still in the testing phase and has approval for use in insomnia. Unlike non-BZD hypnotics, which are GABA agonists or modulators; gaboxadol is a GABA-A receptor agonist. It directly activates GABA-A receptors, thus forming a new class of hypnotics. Studies in the elderly have showed improved subjective sleep quality.³²

Table 1: FDA approved drugs for insomnia.²⁹

| Active ingredient | Dose (mg, at bedtime) | Mechanism of action | Half-life (hrs) |
|-------------------|-----------------------|---|-----------------|
| Estazolam | 1-2 | GABA _A modulator | 10-24 |
| Flurazepam | 15-30 | GABA _A modulator | 2 |
| Triazolam | 0.25-0.5 | GABA _A modulator | 1.5-5 |
| Temazepam | 7.5-30 | GABA _A modulator | 8 |
| Quazepam | 7.5-30 | GABA _A modulator | 39 |
| Quazepam | 10 | GABA _A $\alpha 1\beta\gamma 2$ modulator | 1 |
| Zolpidem | 10 | GABA _A $\alpha 1-3\beta\gamma 2$ modulator | 2.5 |
| Zolpidem-CR | 12.5 | | 2.8 |
| Zopiclone | 5-7.5 | GABA _A $\alpha 1\beta\gamma 2$ modulator | 5 |
| Eszopiclone | 2-3 | | 6-9 |
| Ramelteon | 8 | Melatonin (MT ₁ and MT ₂) receptor agonist | 1-3 |
| Doxepin | 3-6 | Histamine (H ₁) receptor antagonist | 15 |

FDA: Food and Drug Administration, GABA: Gamma-aminobutyric acid

Table 2: Non-FDA-approved sleep medications (off-label use).²⁹

| Agent | Mechanism of action | Dose (mg, at bedtime) | Half life (hrs) |
|-----------------|--|-----------------------|-----------------|
| Trazodone | TCA | 100-150 | 7 |
| Amitriptyline | TCA | 75 | 15 |
| Nortriptyline | TCA | 25 | 15-39 |
| Diphenhydramine | H ₁ and H ₂ receptor antagonist | 50-100 | 6-8 |
| Doxylamine | H ₁ receptor antagonist | 6.25-25 | 6-12 |
| Hydroxyzine | H ₁ receptor antagonist | 25-50 | 7-25 |
| Mirtazapine | H ₁ receptor antagonist | 15 | 26-37 |
| Nefazodone | SNRI, 5-HT ₂ antagonist | 100 | 2-4 |
| Quetiapine | D ₂ and 5-HT ₂ receptor antagonist | 100-300 | 6 |
| Olanzapine | D ₂ and 5-HT ₂ receptor antagonist | 2.5-5 | 21-54 |
| Melatonin | Hormone | 1-10 | 0.5-1 |
| Valerian | Plant extract | 400-900 | Not established |

TCA: Tricyclic antidepressants, 5-HT: 5-hydroxytryptamine, D₂: Dopamine, SNRI: Serotonin-norepinephrine reuptake inhibitor

CONCLUSIONS

Since insomnia is a chronic disorder requiring long-term treatment, and sleep medicine remains an area of active research. The number of OTC and prescription drugs for insomnia has increased. Currently, the GABAergic system is the main target for drug treatment of insomnia, but agents targeting other mechanisms, i.e., melatonin, orexin, and histamine also have become available for clinical use or are in clinical trial pipeline. More studies are required on to evaluate the long-term use of sleep prescription medications. Insomnia is commonly associated with several medical, psychiatric, and other primary sleep conditions. Sedative antidepressants are commonly used among patients with insomnia for prolonged use, and in subtherapeutic doses for depression with optimal improvement in mood and anxiety. Therefore, treatment approach for insomnia should be individualized, based on the co-morbid conditions and efficacy and side effect profile of the drug.

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