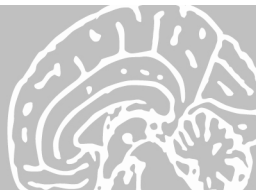
Update in sleep disorders
Pharmacotherapies in the management of adults



송파멜라
인제대학교 의과대학 일산백병원 신경과

Pamela Song, MD
Department of Neurology, Inje University Ilsan-Paik Hospital

Insomnia is one of the most common sleep disorders, and is commonly comorbid with various medical and psychiatric conditions. This review primarily focuses on the updates in pharmacotherapy for insomnia, including current and emerging pharmacotherapy. Prolonged release melatonin, Circadin® has been released in Korea. Following approval of rameltean for insomnia, new melatonin receptor agonists tasimelteon, Hetlioz® has been approved by FDA for the treatment of non-24-hour sleep–wake disorder in totally blind people. Additionally, orexin receptor antagonis, suvorexant, Belsomra® has been approved by FDA for insomnia.

Key Words: Sleep, Insomnia, Pharmacotherpay

Background

Insomnia is one of the most common sleep disorders, it is characterized by a combination of nocturnal symptoms, including difficulties initiating sleep, maintaining sleep and early morning awakenings, and daytime dysfunction. Insomnia disorder can exist alone or in conjunction with comorbid medical and/or psychiatric conditions. There are pharmacological and non-pharmacological treatment options available for insomnia. This review primarily focuses on the updates in pharmacotherapy for insomnia, including current and emerging pharmacotherapy for insomnia.

Pharmacological Treatment for Insomnia

Pharmacotherapy has been the treatment of choice for insomnia 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.[1] 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). In contrary, 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.[2] The treatment agents used to treat insomnia antagonize the wake promoting system or enhance sleep promoting systems.

BENZODIAZEPINE RECEPTOR AGONISTS

Benzodiazepine receptor agonists (BzRAs) are the allosteric modulators of gamma-aminobutyric acid type receptor (GABA) benzodiazepine receptor (BzR).[3] When BzRAs binds to benzodiazepine receptors (BzR), these compounds enhance inhibitory action of gamma-aminobutyric acid (GABA) by opening the chloride channel, which then hyperpolarize the neuron and lead to the inhibition of neuronal action potential firing.[3] GABA is the

Pamela Song, MD
Department of Neurology, Inje University Ilsan-Paik Hospital, 2240 Daehwa-dong, IlsanSeo-gu, Goyang, Korea
Tel:+82-31-910-7013
E-mail: songpama@gmail.com

primary inhibitory neurotransmitter in the brain and exerts its action by binding at two distinct type of GABA receptors (A and B).[4] The $GABA_A$ receptors have a five-protein transmembrane channel constructing a pentameric structure. The α, β, and γ subunits occur in different combination forms with particular location in the brain resulting in substantial diverse effects of GABA on brain function.[5] 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.[5] These agents differ in their affinity for different alpha subunits (α 1- α6); of these α1, α2, and α3 are most abundant in the brain.[6-8] Binding to the α1 subunit appears to have the potential for anticonvulsant, amnestic and ataxic effects in addition to sleep enhancing effects. Binding to the α2 or α3 subunits may have anxiolytic and myorelaxant effects and α5 subunits may lead to myorelaxation, or cognitive impairment.[6-10] The benzodiazepine non-selectively binds to α1-α5subunits.[3] Non-benzodiazepine BzRAs have a more selective profile, binding preferentially to α1 subunits for sedating effects (Table 1).[7]

The mechanism for the predominant treatment of insomnia is enhancing the inhibitory effects of GABA to promote sleep. There are numerous benzodiazepine and non-benzodiazepine BzRAs for the treatment of insomnia: estazolam, flurazepam, quazepam, temazepam, and triazolam (Halcion). Meta-analyses of benzodiazepines have reported to improve sleep and wake complaints, daytime functioning or distress, and PSG measures of reduction in the sleep latency (SL), number of arousals, wake after sleep onset (WASO), and increase total sleep time (TST).[11,12] 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 There are three non-benzodiazepine BzRAs currently in use zolpidem tartrate, zaleplon, and eszopiclone for the short-term treatment of in-

Table 1. Characteristics benzodiazepine receptor agonists insomnia pharmacological agents

Generic Name	Trade Name	Type	Elimination half-life (hours)	Tmax (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 Edluar Intermezzo Zolpimist	Imidazopyrimidine	2.0-5.5	1.7-2.5	CYP3A4, CYP1A2, CYP2C9	5, 10 6.25, 12.5	10	Schedule IV drug
Eszopliclone	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

*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.

somnia, and zoldpiem tartrate is approved for use in Korea. 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.[13] Psychomotor and memory impairment may be less problematic, especially when compared to longer-acting benzodiazepines.

Zolpidem tartrate preferably binds to α1 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 (스틸녹스®, 졸피람정®, 졸피신정®, 졸피드정®, 졸피움정®, 졸피뎀정®), zolpidem tartrate controlled release (스틸녹스 CR®), zolpidem tartrate oral solution (Zolpimist®), and zolpidem tartrate sublingual tablet (Intermezzo®).

Zolpidem tartrate is for the short-term treatment of insomnia. Its bioavailability after oral administration is 70%, and has a half-life of 1.5-2.4 hours and its effects can last up to 8 hours.[14] It is excreted as inactive metabolites mainly by the kidney (56%) and enterally (37%). The reduction in excretion in the elderly, and in patients with hepatic and renal impairment should be considered. The effectiveness of zolpidem, compare to placebo, has shown to improve SL, sleep duration, and efficacy, with persistent improvements throughout 35 days[15] and up to 12 months of follow up.[16] 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 and house painting, and sleepwalking have been reported.[17-19] These reports indicate that patients typically do not have 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 130mg to 600 mg per day.[20-23]

The controlled release formulation is a two 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[24] 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.[14] 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 formulation provided sustained improvements in sleep onset and maintenance compare to placebo.[25] Zolpimist® is an oral solution of zolpidem tartratem as an oral spray.[26] Zolpimist® is considered bioequivalent to the immediate release tablet formulation, without having to ingest without water.[27] 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 mcL.[27] Intermezzo® is a low dose sublingual tablet of zolpidem tartrate[26] 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 four 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 equivalent dose of oral zolpidem,[28] and also has more convenient administration. It is supplied as a 5 mg or 10mg sublingual tablet. The recommended doses are 5 mg for elderly, and 10 mg for adults, once daily immediately before getting into bed.

Zaleplon (Sonata®) like zolpidem, it acts as a selective agonist on the $GABA_A$ receptor, but with low affinity.[29] It has a short half-life of about 0.9-1.1 hour 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.[30] A double-blind, placebo controlled, crossover dosing study revealed zolpidem (10 mg) and zaleplon (10 mg) effectively shortened SL and increased TST compare to placebo. Residual sedation was not detected as little as 4 hours after zaleplon 10 mg, whereas residual sedation was detected with zolpidem.[31] 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.[32,33] Similarly, no withdrawal syndrome was identified following discontinuation of nightly zaleplon use.[32]

Eszopiclone (Lunesta®), another non-benzodiazepine BzRA, has high relative affinity for α2, and α3 subunites.[34] 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.[35] Eszopiclone consistently improves sleep maintenance relative to placebo, based on measures of shortened wake time after sleep onset, and prolonged TST.[36-38] 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 it is not considered an adverse effect.

The 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.[39,40] Residual sedating effects occur more commonly with long acting benzodiazepines.

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 three 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.[41,42]

Melatonin has been recently approved for prescribed medication for insomnia, in Korea. However, it is an over-the counter (OTC) medication, sold as a food supplement in USA. It has a time to maximum concentration (T_{max}) of 0.5 hours and an elimination half-life of roughly 1 hour.[43] A dose-response relationship does not appear to exist for melatonin, and the means to determine optimal dosing are lacking.[13] There is controversy regarding the sleep promoting effects of melatonin because of widely varying inclusion and exclusion criteria, melatonin dosages, and timing of administration.[44] In one study, no significant differences in SL or TST were seen in ten primary insomnia patients compare to placebo, when given 0.3 mg or 1mg of melatonin, or placebo 1 hour before bedtime in a double-blind cross over design.[45] Similarly, study on 10 patients with persistent insomnia were randomized to 1 or 5 mg of melatonin revealed lack of improvement in sleep SL or TST, nor any effect on mood or alertness, but reported a subjective sense of improved sleep quality.[46] Much higher dose of melatonin (75 mg) improved SL, and daytime alertness compare to placebo in a double-blind study of 13 insomnia patients.[47] Recent meta-analysis showed a reduction in SL by 4 minutes, increased sleep efficiency (SE) by 2.2% and increased TST by 12.8 min.[48] Melatonin dose as high as 75mg, have been used in clinical trials without significant toxicity.[47]

Circadin®, which has been approved in Korea, is a prolonged release melatonin, it contains 2 mg melatonin. It

has been approved by Europena Medicine Agency for patients aged 55 or over, as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep. It releases melatonin gradually in the gut over extended time of 8-10 hours, thereby mimicking physiological patterns of melatonin secretion. Peak plasma concentrations are reached 3 h after dosing with a plateau time of 3.5 h, before gradually declining to reach baseline levels within 10 h.[49] Circadin compare to placebo, improves sleep latency, and daytime wakefulness by subjective; sleep diary and quationnarie, and objective; overnight polysomnography, and Critical Flicker Fusion threshold, measurements.[49-52]

Ramelteon is a melatonin receptor agonist, which is 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.[53] It binds to MT1 and MT2 melatonin receptors within the SCN, and metabolized by CYP1A2, with CYP2C and CYP3A4.[54] Ramelteon, like melatonin, has no clear dose-response relationship; however, a therapeutic dosage of 8mg and timing of dosing 30 minutes before bedtime has been recommended.[53] 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 compare to placebo.[55] 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.[40,56] Effects persisted even if treatment was extended to 5 weeks for both adults and elderly primary insomnia patients.[57,58] Adverse effects occur in more than 2% of patients, and the most commonly reported symptoms are headache, somnolence, and sore throat.[56] Elevation of prolactin has been reported with Ramelteon compared with placebo in women.[59] 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.[55,60] Smoking is an inducer of the CYP1A2 isozyme, decreasing ramelteon efficacy, and dose reduction is recommended when attempting smoking cessation.[61]

Tasimelteon (VEC-162), Hetlioz®, is a melatonin receptor agonist (MT1 and MT2). Tasimelteon was approved by the FDA (May- 2013) solely for the treatment of non-24-hour sleep-wake disorder. It was effective in reducing SL, and in resetting the circadian melatonin rhythm, which indicated its potential suitability as treatment for jet lag, shift work and circadian rhythm sleep disorders.[62] The drug is well tolerated without next day functioning impairment.

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-HT2c antagonist. It was initially investigated as a chronobiotic, however with the discovery of 5-HT2c serotoninergic receptor it is more focused on the anxiolytic and antidepressant effects. The approval indication in 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 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.[63]

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 are blocking wake promoting neurotransmitters (acetylcholine, histamine, norepinephrine, serotonin, and dopamine) for sleep enhancing effects.[2,53] Among them, the main sedating effects are caused by the anticholinergic and antihistamine effects.[13] The most commonly prescribed antidepressants are tricyclic or tetracyclic antidepressants, doxepin, amitriptyline, trimipramine, trazodone and mirtazapine.

ANTIPSYCHOTICS

Antipsychotics are used to treat insomnia, which is best indicated for patients with psychotic disorders.[1] The antipsychotics antagonize dopamine, histamine, serotonin, cholinergic and adrenergic receptors, and thus induces sleep.[53] The most commonly used antipsychotics are quetiapine and olanzapine.[64]

ANTICONVULSANTS

Anticonvulsants are also being prescribed off label for insomnia. It is best recommended and beneficial for patients who suffer from both insomnia and an underlying epileptic disorder. Gabapentin and pregabalin are a structural analogue of GABA, which binds to the alpha-2-delta subunit of N-type voltage gated calcium channels, thereby diminishing the release of wake promoting neurotransmitter: glutamate and norepinephrine.[65]

ANTIHISTAMINE

Antihistamines are primary indicated for treatment of allergies. However there are agents with potent anti-histamine efficacy including antidepressants of doxepin and mirtazapine, and antipsychotics including olanzapine and quetiapine.[53] Diphenhydramine and Doxylamine is two most commonly used antihistamine for insomnia which crosses the brain blood barrier.

5-HT2A SEROTONIN RECEPTOR INVERSE AGONISTS

5-HT2A serotonin receptor inverse agonists are developed as neuroleptics, which are also under clinical trials for treatment of insomnia. Inverse agonist binds to the same receptor as an agonist but induces 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-HT2A receptor.[66] A decrease in SWS increases lighter level of sleep, which may increase arousal, wakefulness, and sleep fragmentation. Currently, 5-HT2A serotonin receptor inverse agonists are under investigation for sleep maintenance therapy, but none have been approved for treatment of insomnia.

Pimavanserin (ACP-103), Nuplazid® is currently finished the Phase III trials for parkinson's disease psychosis, and reveled improvement in psychosis along with nighttime sleep and daytime wakefulness. Based on this report the FDA granted Breakthrough Therapy, and it is currently in preparation for New Drug application (NDA) for submission to the FDA.[67] It is a selective serotonin inverse agnois preferentially targeting 5-HT2A receptors with no significant affinity or acidity at dopamine receptor. Phase II trials for insomnia.[68] In 45 healthy volunteers, Pimavanserin significantly increased SWS in dose dependent manner, decreased number of awakenings compare to placebo. Other PSG variables including TST, SL, and number of stage shifts did not change significantly.[69]

Nelostanserin (APD-125) is a 5-HT2A 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.[70] PSG measurement of WASO decreased in compare to placebo in 10mg dose (day 1/2 and 6/7), and 40mg dose (day1/2), but not significant by day 6/7 at the 40mg dose. No serious adverse events were reported, along with 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 the discontinuation for development.[71]

Eplivanserin (SR-46349) had completed three Phase III trials indicating reduced WASO and number of nocturnal awakening compare to placebo, without residual effects after waking or withdrawal symptoms.[71] 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 of orexin is known as narcolepsy, characterized with symptoms of excessive daytime sleepiness, cataplexy, hypnogogic hallucination, sleep paralysis and disrupted nocturnal sleep. Compared to benzodiazepine receptor agonists, orexin receptor antagonists have less confusion, amnesia, and unsteady gait and have been proposed to have lower abuse liability.[72]

Suvorexant (MK-4305), Belsomra® is a nonselective (dual) OX1/OX2 receptor antagonist. It was approved by FDA on August 13, 2014 for insomnia. It have been shown to improve SL, TST, SE and WASO measured by PSG, without next morning residual cognitive effects. There were no withdrawal or rebound insomnia after discontinuation.

Amorexant (ACT-078573) was also under development as oretexin receptor antagnosi, however, iw was abandoned after Phase III clinical study due to side effect profiles. However, studies have shown to decrease wakefulness in a dose dependent manner in healthy human subjects, without evidence of cataplexy.[73] In primary insomnia, increases in SE, reductions in SL and reductions in WASO were reported.[40,71]

Conclusion

In a search for different options in pharmacotherapy of insomnia, we are now faced with ample number of drug options under development. These agents have mechanisms of action that are different from benzodiazepine receptor agonists, which allows a different pharmacological approach. Further research evaluating the efficacy and safety of newly emerging medications are needed. Therapeutic approaches should also consider non-pharmacological treatments of insomnia, such as cognitive-behavioral therapy for insomnia, as an adjunctive therapeutic option and consider different co-morbid conditions to tailor treatment for insomnia patients.

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