Pharmacotherapy of Insomnia and Current Updates

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Abstract

Insomnia is highly prevalent and is associated with a range of psychological, psychiatric, and medical conditions. Insomnia affects health by influencing cognitive, emotional and social functioning. Circadian and sleep homeostatic processes play an important role in insomnia development and its maintenance. Several efficacious treatments, both pharmacologic and non-pharmacologic, exist for the management of insomnia. Among non-pharmacologic treatments including stimulus control therapy, sleep restriction, relaxation, sleep hygiene and cognitive therapy have been shown to be efficacious. Pharmacological treatment acts as adjuvant to cognitive behavioural treatment. Despite availability of various classes drugs for insomnia treatment, none can be considered as an ideal agent. Novel therapies are still being explored and tested to arrive at a hypnotic that has acceptable side effects and tolerability profile while still being efficacious.

Introduction: Definition, Epidemiology and Symptoms

The International Classification of Sleep Disorders defines “insomnia as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep.”¹ It is a sleep disorder that occurs acutely and may become chronic if not treated in time. It occurs in approximately 10% - 48% of general population and is more prevalent among women and elderly. It affects the social and professional life of individual and results in the high burden for the family and the society. Its presence is associated with a variety of medical and psychiatric conditions and has been found associated closely with anxiety and depression.

Insomnia is of three types—transient, acute and chronic. Transient insomnia normally last for few days to a week. It can be triggered by excess environmental noise, medications and extreme temperatures. One example of transient insomnia is jet lag, in which traveling through time zones causes a temporary disruption of the body’s circadian rhythm. Acute insomnia is most common and often cause by situations such as stress at work, family pressures or a traumatic event. Acute insomnia may last for weeks. On the other hand, chronic insomnia lasts for months or longer. They are mostly secondary to the symptom or side effect of some other problem.

Chronic insomnia does not resolve spontaneously, although the presenting form of insomnia can vary over a period. Chronic insomnia tends to be unremitting, disabling and may pose a risk for additional medical and psychiatric disorder. Fortunately, there are number of safe and effective treatments for insomnia available today.

Assessment and Diagnosis

A thorough assessment of sleep, medical and psychiatric history is required to confirm the diagnosis of insomnia. The patient should report at least one of the following sleep-related complaints like difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically Nonrestorative or poor in quality. It is important to differentiate between primary insomnia from secondary insomnia due to some underlying co-morbid conditions. These conditions may require prior intervention and treated in conjunction with the primary disorder. These include untreated or unstable medical, psychiatric or substance abuse conditions (e.g., gastroesophageal reflux disease, cardiopulmonary disorders, seizure disorders, some neuroendocrine disorders, sleep apnoea, bipolar disorder, severe mental illness, active substance dependence).

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Therapy of Insomnia

Variety of remedies including prescription medications, herbal supplements, and sleep aids are available for management of insomnia. In addition, a number of non-pharmacologic approaches, including cognitive and behavioral therapy also exists.

Non-pharmacological Therapy

Behavioral and cognitive therapy should always be a part of any first line pharmacotherapy.

Cognitive therapy

It is observed that patients with insomnia have negative thoughts and beliefs about their condition and its consequences. These therapies are mainly focused on paradoxical intention, cognitive restructuring and safety behaviors. The approaches may differ in procedure but all of this will help patients to challenge the veracity and usefulness of these beliefs. It is the basis of cognitive therapy and is thought to decrease the anxiety and arousal associated with insomnia.

Stimulus control therapy

Patient suffering from chronic primary insomnia, stimulus control therapy should be considered as the first line behavioral treatment. It consists of instructions which limit the amount of time spend by patient to stay awake in bed or the bedroom. These typical instructions include keeping a fixed wake time 7 days per week, irrespective of how much sleep you get during the night; to avoid any behavior in the bed or bedroom other than sleep or sexual activity; sleep only in the bedroom; leave the bedroom when awake for approximately 10 to 15 min; and return to bed only when sleepy. Thus such instructions help to re-establish the circadian sleep-wake cycle to the desired phase.

Sleep hygiene

It is a sleep tip given to the patient to maintain good sleep habits such as keeping an environment and routine conducive to sleep, maintaining a regular bed and wake time, avoiding tobacco, alcohol, large meals and vigorous exercise for several hours prior to bed. It is always helpful when it is given with other non-pharmacological or pharmacological interventions to treat insomnia.

Sleep restriction

Sleep restriction therapy (SRT) helps the patients to maintain the amount of time spend in bed to an amount equal to their average total sleep time. The therapy can be established by maintaining daily sleep diaries for one to two week regarding total sleep time, maintain fixed wake time and adjustments made on the weekly basis until treatment completion.

Phototherapy

It has sleep-promoting effects for patients who have difficulty in maintaining the circadian rhythms. Exposure to morning bright light is indicated if the patient is suffering from delay phase component of insomnia (i.e., the patient prefers to go to bed late and wake up late). On the other hand, evening exposure to bright light is indicated if the patient’s insomnia has a phase advance component (i.e., the patient prefers to go to bed early and wakes up early).

Pharmacotherapy

Historically, barbiturates and then benzodiazepines were the most commonly used sedative-hypnotics. While both classes have demonstrated efficacy for insomnia but barbiturates have greater levels of tolerance, abuse potential, lethal dose threshold and alterations to sleep pattern. For these reasons, barbiturates are now rarely being used as hypnotics. Though similar attributions were made for the benzodiazepines, albeit with far less evidence.

Many neurotransmitters are involved in the sleep-wake cycle. Sleep-promoting neurotransmitters are adenosine, melatonin, galanin and gamma aminobutyric acid (GABA). On the other hand, wakefulness-promoting neurotransmitters are norepinephrine, orexin, acetylcholine, dopamine and histamine. Medications most commonly used for insomnia produce their effects by acting through GABA, melatonin and histamine. Current pharmacological treatment of insomnia consists of mainly three groups namely benzodiazepines; novel benzodiazepine receptor agonists (Z compounds) and melatonin receptor agonist.

Benzodiazepines (BZDs)

BZDs decrease the onset to sleep and increase the total sleep duration. Benzodiazepines namely flurazepam, quazepam, estazolam, temazepam, triazolam, etc. act by binding to GABA receptor at a site other than GABA (γ-aminobutyric acid) binding site and increase the amount of chloride current through the GABA-chloride ion channel complex. These drugs are approved by U.S. Food and Drug Administration (U.S. FDA) to improve sleep maintenance by decreasing the awakening in night. BZDs are not suitable especially for the patient with chronic insomnia as they are associated with dependence and tolerance on long term use and used mainly for treating short term insomnia. They are also associated with excessive sedation, motor incoordination, cognitive impairment and anterograde amnesia as common adverse effects. Irrespective of use of BZDs, there is always increase in residual daytime sleepiness and risk of accidental fall and hip fracture.

Novel Benzodiazepine Receptor Agonists (Z Compounds)

Z compounds bind to the α1 subunit of GABA receptor. It produces sedative and hypnotic effect and provides better efficacy and safety than other previous drugs. There are three drugs in this
group namely zolpidem, zaleplon and eszopiclone. Zolpidem is a short acting drug approved for short-term treatment of insomnia. It helps to reduce the time for sleep onset and/or sleep maintenance and has been approved to use for 7-10 days for management of insomnia with difficulty of sleep onset. If taken for an extended period, it has the potential to induce dependence. Zaleplon has a shorter half life and is approved for the patient who has difficulty in falling asleep. Both the drugs have similar degrees of efficacy and have an advantage of no rebound insomnia on abrupt discontinuation. Eszopiclone, an active S(+) enantiomer of zopiclone is effective in both sleep onset and maintenance for the transient and chronic insomnia.

Melatonin Receptor Agonist

Melatonin is a hormone secreted by the pineal gland and plays a major role in maintaining circadian rhythm. Melatonin secretion occurs mostly in night hours and it promotes sleep by reducing the effect of wake promoting signals in the suprachiasmatic nucleus of the hypothalamus. Its acts by binding to two receptors namely, MT1 receptors which promotes the onset of sleep; and by binding to MT2 receptors, that shifts the timing of the circadian system. Ramelteon is an agonist for both MT1 and MT2 melatonin receptors. It is primarily used for the sleep onset insomnia and somnolence, dizziness, fatigue, etc. are few adverse effects of the drug. Advantage of melatonin receptor agonist is that there is no sign of withdrawal symptoms or rebound insomnia on discontinuation after long term use.

Tasimelteon is a newer selective agonist for the melatonin receptors MT1 and MT2. It is similar to other members of the melatonin receptor agonist class namely ramelteon and agomelatine. Tasimelteon is approved by the U.S. FDA in January 2014 for the treatment of non-24-hour sleep-wake disorder. The patient may experience improved sleep timing and reversion to baseline sleep performance within a month of discontinuation. It exhibits a greater affinity for the MT2 as compared to the MT1 receptor and thus has a greater effect on shifting the timing of circadian system. The most important undesirable effect is that it may impair the ability to perform activities that require complete mental alertness, not suitable in some patients who require mental work for daily needs. It is given in the dose of 20 mg at bedtime. The peak concentration of tasimelteon occurs at approximately 0.5 to 3 hours. CYP1A2 and CYP3A4 are the isozymes involved in the metabolism of tasimelteon.

Doxepin

It is a tricyclic antidepressant with antagonist effect on histamine H1/H2 receptors. It has shown efficacy with low doses of 3 to 6 mg/night for treating insomnia. It does not cause clinically significant side effects. Drowsiness and tiredness may occur if there is an overdose of the drug.

Off-label Drugs

These are the drugs that are not approved by regulatory authorities for the treatment of insomnia but are being used as an alternative established therapy. Antihistaminics having sedative property like diphenhydramine, doxylamine; antidepressants with property of sedation like trazodone, mirtazapine, amitriptyline and trimipramine. Long term efficacy of these drugs is unknown and adverse effects like sedation, motor incoordination and tolerance associated with these drugs may not be considered desirable.

Orexin Receptor Antagonists

Orexin-A and -B, also known as hypocretin-1 and hypocretin -2 are neuropeptides found to have profound effect on arousal and sleep by acting through OX-1 and OX -2 receptors. Orexin receptor antagonists are a novel class of drugs developed for the treatment of insomnia. These neuropeptide that play a key role in promoting wakefulness, appetite, metabolism, reward, stress, autonomic function and regulating the sleep-wake cycle. Suvorexant is the first oral dual orexin receptor antagonist developed by Merck and was approved by the U.S. FDA in August 2014. Food does not interfere with its absorption and is mainly metabolized by the CYP3A4 system. The recommended dose is 10 mg once at night and it can be increased to a maximum of 20 mg. Suvorexant is safe and well tolerated in patients. The most common adverse effect reported has been somnolence on the next day which might be not acceptable in working patients. The higher doses above 20 mg significantly cause motor impairment and driving impairment. It has potential sedative additive effect when used with antidepressants and other sedative drugs. Suvorexant has not yet been compared to other drugs approved for insomnia, so its relative advantages in terms of efficacy or adverse effect profile, will emerge more clearly in future, after head to head comparative trials with the already available drugs. Suicidal ideation seen with higher doses in the clinical trials and mood related adverse effects needs monitoring. Orexin - 2 receptor antagonisms plays a more important role in regulating sleep/wakefulness as compared to OX-1 receptor. Thus pharmacology of a more selective antagonism of either OX-1 receptor or OX-2 receptor needs to be properly elucidated.
Recent Advances in Pharmacotherapy of Insomnia

Pharmacologic therapy that are safe, efficacious and do not possess unwanted side effects are need of the hour. The search is still on for agents that should have properties close to an ideal hypnotic.

5-HT\textsubscript{2A} Receptor Inverse Agonist

A agents targeting the 5-HT\textsubscript{2A} serotonin receptor subtype (e.g. volinanserin, eplivanserin, pruvanserin) were being developed. These compounds have been developed with minimal affinity to dopamine, histamine and adrenergic receptors, compared to existing sedating antidepressants. These agents had been associated with improvement in sleep maintenance and increases in slow wave sleep. Despite positive phase III efficacy data, eplivanserin development was discontinued for reasons unknown. Subsequently the development of volinanserin, and pruvanserin were also suspended.

Lorediplon

Lorediplon is a non-benzodiazepine compound of the pyrazolopyrimidine family that is being pursued as a treatment for insomnia but has not yet completed development. It is a novel, longer acting non-BZD drug that modulates the GABA\textsubscript{A} receptor. It has demonstrated potent hypnotic profile and extended systemic half-life; properties that could confer potential clinical benefits in terms of sleep maintenance and sleep architecture. A recent phase I pharmacodynamic study with lorediplon (in a phase advanced model of insomnia) demonstrated that this orally available compound has a best-in-class efficacy profile in terms of sleep maintenance and sleep quality when compared to market leader zolpidem. It is safe and well tolerated, with no residual effects observed up to fourteen hours after dosing. It has no next-day residual effects and other side effects linked to other treatments available in this class. Currently, the drug is in Phase IIa of clinical development.

Serotonin Receptor Modulators

There are reports which suggest that serotonin (5-HT) have role in promoting sleep. LY2624803 (H\textsubscript{1} receptor antagonist and 5HT\textsubscript{2A} receptor antagonist) is under development that can modulate the serotonin receptor and improve insomnia. LY2624803 has completed phase II clinical trial for chronic insomnia. The minor side effects were seen in trials with patients of transient insomnia are headache, dizziness, back pain, diarrhoea and dermatitis. The frequency and profile of the adverse effects seen in the study was less than zolpidem. This drug was associated with less awakenings during sleep, decrease in total time awake and better sleep efficiency than zolpidem.

Newer Orexin Receptor Antagonists

Filorexant (MK-6096) is an orexin antagonist which is or was under development by Merck for the treatment of insomnia. It is a dual antagonist of the OX-1 and OX-2 receptors. It causes dose-dependent decrease in locomotor activity and significantly increased sleep. It represents a novel and selective therapy. It has completed phase II clinical trials. Unfortunately, further development was not pursued due to the cost involved or it might have caused significant unwanted side effects.

Lemborexant (Phase II), MIN-202 (Phase I), SB-649868 (Phase I) and ACT-462206 are the newer orexin receptor antagonists which are in various phases of clinical development. These drugs were found to significantly reduce latency to persistent sleep, wake after sleep onset (WASO), sleep efficiency (SE) and increased total sleep time (TST) as compared to Z-compounds and placebo. As of now, these drugs are considered to have a favourable safety profile as compared to the prototype of this class, suvorexant.

Newer Melatonin Receptor Agonist

Piromelatine (Neu-P11) is an agonist at melatonin MT1 and MT2 and serotonin 5-HT\textsubscript{1A}/5-HT\textsubscript{1D} receptors. It improves circadian rhythms in primary insomnia. It has demonstrated efficacy and safety in a Phase II clinical trial in patients with primary insomnia. Piromelatine has a good potential for the treatment of primary insomnia characterized by sleep maintenance disturbances. Additionally, it was found to preserve REM sleep and induce deeper sleep with less arousal. It is generally safe and well tolerated as found in the study, with no detrimental effects on next-day psychomotor performance as compared to placebo.

Esmirtazapine

Esmirtazapine, a high-affinity antagonist at 5-HT\textsubscript{2A} and H\textsubscript{1} receptors, was assessed for its hypnotic efficacy. Six weeks of treatment with esmirtazapine was associated with consistent improvements in sleep onset, maintenance, and duration as assessed by polysomnography and patient reported parameters. It was generally well tolerated, and residual daytime effects were minimal and no rebound insomnia was observed. Drowsiness, dizziness, strange dreams, weight gain are some of the minor side effects may not be acceptable to some. In
another double blind trial of two weeks in non-elderly adult patients of primary insomnia, treatment with esmirtazapine consistently and significantly improved patient-reported sleep parameters, and was well tolerated as compared to placebo.

**Newer Formulation of Old Drugs**

Zolpidem sublingual tablet is approved by U.S. FDA for use in patients who have difficulty resuming sleep after MOTN (middle-of-the-night) awakenings. Another new formulation is the modified release formulation of SKP-1041 (Zaleplon). It also improves MOTN awakenings when given at the dose of 15 mg.

**Conclusion**

“One size fits all” does not hold true in case of insomnia therapy as well. All medications are not suitable for all patients. Additional choices in medications are needed for different patients. Though availability of drugs from different pharmacological class have made it possible to treat insomnia to a certain extent but still it is far from perfect. Pharmacotherapy is always a part of cognitive and behavioural therapy for insomnia. Current therapies have shown a great leap in treating insomnia but still there are concerns about their side effects and thus reducing their overall utility. The available therapies have sedation, motor incoordination, cognitive impairment, abuse potential, etc. as important side effects. Overcoming such problems are highly desirable and may hopefully addressed by future therapies that are being explored. We should expect that newer drugs that have selective interaction with their receptor and lesser potential to cause undesirable effects for example daytime sedation, tolerance, abuse liability, etc. may be considered a welcome approach. There is immense opportunity for drug companies in the pharmacotherapy of insomnia as it is going to become an important health related issue of the modern society.

**References**