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Review Article

Management of insomnia: current trends

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ABSTRACT

Insomnia is one of the most commonly occurring sleep disorders worldwide.[1] With increased prevalence of insomnia the demand of the people seeking pharmacological treatment for this disease is continuously increasing. Numerous options are currently available for its treatment and with our increased understanding of the neurophysiological factors involved in the insomnia continuous research is being conducted to seek newer pharmacological treatments. Recent advancement in treatment of insomnia is the introduction of non-benzodiazepine hypnotic medications such as zaleplon, zolpidem, and eszopiclone. Ramelteon, a melatonin agonist, is also helpful for sleep initiation difficulties. Tri-cyclic antidepressants have long been used for insomnia but use has been limited by unwanted anticholinergic side-effects. A hypocretin/orexin antagonist MK-4035 is presently in clinical trials. Serotonin antagonists and inverse agonists are being investigated for their usefulness in insomnia; newer research examining other mechanisms of action suggest that agents which modulate the histaminergic, serotonergic, melontonergic, and hypocretin/orexin and perhaps gamma-aminobutyric acid B systems could play a promising role in management of insomnia.

Keywords: Insomina, Sleep disorders

INTRODUCTION

Insomnia is considered to be most common sleeping disorder worldwide.[1] Although there have been lots of advances in terms of its diagnosis and management, but still it is unrecognized and untreated in most of the cases.[2]

According to a study conducted recently, approximately 25% of adult population have sleeping disorders and out of these around 6-10% have insomnia.[3] Individuals suffering from insomnia experiences difficulty in falling or staying asleep, lack of restorative sleep, and daytime symptoms such as fatigue, trouble concentrating and mood disturbances.[4]

Patients suffering from insomnia usually have altered quality of life, impaired daytime functioning with an increased risk of work and motor vehicle related accidents. Insomnia is commonly associated with chronic medical condition, mental disorders like depression and anxiety and metabolic illness or vice versa.[5]

These individuals are more prone to anxiety and depression and are at higher risk of developing congestive heart failure and diabetes. Insomnia not only affects an individual but at large it has substantial economic and societal burden in the form of poor productivity, absence from work, and high healthcare costs.[1,6]

Insomnia can occur as a primary sleep-awake disturbance or as a comorbid with other conditions such as psychiatric disturbance or medical disease. The most common comorbid condition is psychiatric disorders including depression, anxiety, panic, adjustment disorders and personality disorders.[7] Other conditions with which insomnia can occur comorbidly are hyperthyroidism, arthritis, cancer, heart failure, asthma, sleep apnea, diabetes, gastroesophageal reflux disease, overactive thyroid, stroke, Parkinson disease, Alzheimer disease, chronic pain, and restless legs syndrome.[7]

Insomnia may also occur secondary to the use of medications such as antihypertensives, antidepressants, stimulants (such as methylphenidate), corticosteroids, decongestants, acetaminophen/caffeine pain relievers, and weight loss products. Insomnia may also result from some extrinsic factors such as jet lag and shift work.[7]

MANAGEMENT OF INSOMNIA

Identification of cause of insomnia should be the first step in management of insomnia. If it occurs as a secondary condition to a psychiatric medical illness, treatment of these roots causes may help in reducing insomnia.[8]

If insomnia is a primary disorder then the patient should be subjected to full sleep study with polysomnographic evaluation. Several non-pharmacological interventions such as cognitive behavioral therapies (CBTs) can also be employed to manage insomnia. These include progressive muscle relaxation therapy, guided imagery, light therapy, chronotherapy, to progressive delay of bedtime.[9] In addition to CBT the patient should also be educated about healthy sleep practices and sleep hygiene measures that promotes sleep.[10,11]

If insomnia is managed in the early stages there is a possibility of ruling out the occurrence of more complex sleep related syndromes. If insomnia is left untreated then its recurrent episodes can lead to chronic and intractable insomnia. If this condition continues for a long duration then such an individual can develop a pattern of psychophysiological (conditioned) insomnia where the sleep difficulties become psychologically and physiologically entrained and thus will become more difficult to resolve.[12]

DRUGS USED FOR TREATMENT OF INSOMNIA

Currently several pharmacologic agents are available to manage insomnia. Some commonly used categories of drugs used for treatment of insomnia are benzodiazepine receptor agonists (including non-benzodiazepines and benzodiazepines), melatonin receptor agonists, and off-label uses of antipsychotics, sedating antidepressants, and antihistamines (such as diphenhydramine).[13]

Benzodiazepine receptor agonist hypnotics

It includes both benzodiazepines (BDZ) and non-benzodiazepines receptor agonist hypnotic derivatives. Benzodiazepine receptor agonists are the oldest and primary pharmacological agents used for the management of insomnia.[14] Non-benzodiazepines receptor agonist hypnotics were the later invention, they are also known as "Z" drugs. Drugs of both these groups have same fundamental mechanism of action. Although, the newer non-benzodiazepine receptor agonist hypnotics differ as they have selective pharmacodynamic properties that add to their safety and tolerability.[15]

The major difference between the benzodiazepines and Z drugs is in their structure, unlike benzodiazepine drugs the Z drugs lack the benzene ring, but they still bind at the BDZ receptor. Non-benzodiazepine receptor agonists bind more specifically to the alpha-1 subunit of the gamma-aminobutyric acid-A ($GABA_A$) receptor, which is associated with sedation and thus also produces lesser side effects due to this specificity. They are drugs of choice for treatment of sleep-onset insomnia.

They also have shorter elimination half-life that reduces the possibility of hangover symptoms in the morning. There are research-based evidences that these agents demonstrate equivalent to superior efficacy in the promotion of sleep with a generally superior safety profile.[16-20]

These agents, however, are associated with a risk of dependence (psychological or physical). Thus they are approved for short-term use (i.e., 7-10 consecutive days) only.[4,21]

Non-benzodiazepine receptor agonist includes zaleplon, zolpidem, eszopiclone; short-acting benzodiazepine receptor agonists (triazolam) and intermediate-acting benzodiazepine receptor agonists (estazolam, temazepam).

Eszopiclone and sustained-release zolpidem are effective in both sleep-onset and sleep-maintenance insomnia, with a reduced abuse potential and long-term efficacy of up to 6 months as compared with nonselective benzodiazepine receptor agonists.[22]

Short-acting (e.g., triazolam) and intermediate-acting (e.g., estazolam and temazepam) benzodiazepine receptor agonists are useful for sleep-onset insomnia.

Benzodiazepines are not recommended in the elderly because of the risk of falls; if used, they should be prescribed at the lowest effective dose for the shortest duration of time. The older sedative-hypnotics that have a prolonged half-life increase the risk for next-day sedation and daytime psychomotor impairment and pose an increased risk for abuse and dependence. Other complications of benzodiazepine use are tolerance, withdrawal, abuse, and rebound insomnia.[23]

Zaleplon

Zaleplon has a rapid onset of action and an ultra-short duration of action, thus it a good choice for treatment of sleep-onset insomnia.

Eszopiclone

Eszopiclone is a non-benzodiazepine hypnotic pyrrolopyrazine derivative. Its mechanism of action is unknown, but it is believed to interact with GABA receptors at binding domains close to or allosterically coupled to benzodiazepine receptors.

It is indicated for insomnia to decrease sleep latency and improve sleep-maintenance. It has a short half-life (6 hrs). Higher doses (i.e., 2 mg for elderly adults and 3 mg for nonelderly adults) are more effective for sleep-maintenance, whereas lower doses (i.e., 1 mg for elderly adults and 2 mg for nonelderly adults) are suitable for difficulty in falling asleep.

Triazolam

Triazolam depresses all levels of the CNS (e.g. limbic and reticular formation), possibly by increasing activity of GABA. It is indicated for short-term insomnia. Triazolam was the first short-acting benzodiazepine for promoting sleep but it is not a drug of choice due to reports of amnesia with its use.

Estazolam

Estazolam is an intermediate-acting benzodiazepine with a slow onset of action and a long duration. Estazolam is preferably used for sleep-maintenance insomnia.

Temazepam

Temazepam is a short- to intermediate-acting benzodiazepine with longer latency to onset and half-life. Temazepam is more helpful in sleep-maintenance insomnia than in sleep-onset insomnia.

Selective melatonin receptor agonist

- Ramelteon was introduced in 2005. It is a selective agonist of melatonin MT1 and MT2 receptors. It was considered as a major advancement in the treatment of insomnia as it was the first compound with entirely new mechanism of action. MT1 and MT2 receptors are highly concentrated in the hypothalamic suprachiasmatic nucleus (SCN).[24] It plays important role in timekeeping of the circadian system. The timing of the sleep-wake cycle is influenced by the SCN, which is entrained by the photoperiod.[25]
- Ramelteon enhances sleep-onset by decreasing the evening circadian arousal.
- Ramelteon has been shown to improve sleep during the early portion of the sleep period. It also may reinforce the timing of the circadian system to increase the probability of sleepiness occurring regularly at bedtime.[26]
- Ramelteon produces it maximum therapeutic effect over a period of several nights or weeks. It is available as 8 mg tablet. It is recommended to prescribe it 30 min before bedtime. It is not recommended for use in patients with moderate to severe hepatic impairment or (in those taking fluvoxamine).[27] It is also associated with a low incidence of somnolence, fatigue and dizziness.[28]

5-HT2A receptor antagonists and related compounds

It has been clinically proven that drugs that have postsynaptic 5-HT receptor antagonism activity are associated with sedation and some of these increases the amount of slow wave sleep. Drugs like mirtazapine and trazadone produce this effect and can serve in treatment to insomnia but so far these drugs are not approved for use in insomnia. Since these drugs have effect on multiple receptor and thus large bracket of side effects is associated with them so their use for this condition is limited.[29]

Recently lots of emphasis is being given to development of 5-HT_{2A} receptor antagonists for the treatment of insomnia. About nine compounds of this category are currently under study and some of them are under phase 3 evaluation.

Orexin antagonists

The excitatory neuropeptides termed "orexins" or "hypocretins" are the neurons originating in the lateral hypothalamus. They have widespread projections to several brain regions. Various studies revealed that there is deficiency of orexins in the sleep disorder. Narcolepsy that highlighted the stimulatory role of these compounds in helping to stabilize wakefulness. It has been hypothesized that if low orexin activity is associated with excessive sleepiness, then decreasing orexin functioning might promote sleep, at least for some patients who have insomnia.[30]

On the basis of this research at least two compounds that have pharmacodynamic characteristics of orexin antagonists have been investigated as possible insomnia treatments. Phase 3 studies are currently evaluating the orexin antagonist almorexant. Preliminary studies have shown that almorexant is well tolerated and provides benefits in sleep-onset, sleep-maintenance, and sleep-efficiency.[31]

$\alpha_{2\delta}$ calcium channel modulators

These drugs bind to voltage-sensitive calcium channels and inhibit the release of several different neurotransmitters.

Pregabalin is a $\alpha_{2\delta}$ calcium channel modulators; it is used for treating various pain syndromes and partial onset seizures but also has been evaluated for the treatment of insomnia. A new compound, PD-200390, is being studied as a possible insomnia medication.

The compounds of this group are especially interesting because they may increase the amount of slow wave sleep.

NEWER ADVANCES IN TREATMENT OF INSOMNIA

Due to increased need, vigorous research is being conducted by the pharmaceutical companies to find newer treatments for insomnia. Several newer and unique compounds are under investigation to determine their potential as pharmacotherapeutic therapy for insomnia. Some of the pharmacological categories that are being investigated include neurokinin$_1$ receptor antagonist, a 5-HT_{1A} agonist (MN-305) and a 5-HT_6 antagonist, corticotropin-releasing hormone antagonists, cytokines, glutamatergic antagonists, adenosine enhancers, and H_3 agonists.[32]

With increasing knowledge of regulation of sleep-wake cycle, researchers are developing newer compounds to treat insomnia that work on pathways that are separate from GABA system.[15] Agomelatine is a newer selective melatonin receptor agonist that interacts with M1/M2 receptors and functions as a 5-HT_{2C} antagonist.[33] It is indicated for depression. It is found to increase sleep-efficacy, reduced time awake after sleep onset, greater slow-wave sleep and improved sleep quality and continuity.[34]

Ultra low-dose doxepin formulations and benzodiazepine agonists with alternative delivery strategies for middle-to-mid-night sleep are the recent advances in the treatment of insomnia.[35]

SUMMARY AND CONCLUSION

Insomnia has now become a common clinical condition characterized by difficulty in initiating or maintaining sleep, along with symptoms such as irritability or fatigue during wakefulness. Insomnia can lead to impaired routine functioning, development of other medical and mental disorders and increased health-care costs.

There has been abundant research and significant advances in the pharmacological management of insomnia. Numerous newer medications are now available in market and many more are under trails. The goal of such innovations should be to develop drugs with enhance efficacy and safety along with promotion of nighttime sleep and daytime functioning. Improvement of quality of life for insomnia sufferers must be the baseline for any new invention for insomnia.

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