

Insomnia: Current Treatment and Recent Advances***Dhiren M. Pranami¹, Jyoti Kaushal¹, Garima Bhutani²**

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ABSTRACT

Insomnia is defined as difficulty with the initiation, maintenance, duration or quality of sleep which affects daytime functioning. About one third of world population suffer from insomnia. It can be classified by various ways i.e. primary or secondary; transient, short term or chronic insomnia; or difficulty in onset or difficulties in maintaining sleep. The derangement of various neurotransmitters e.g. histamine, orexins, noradrenaline, acetylcholine and serotonin leads to insomnia. Predisposing conditions leading to insomnia are familial or genetic tendency, illness, stress and maladaptive sleep habits. Insomnia leads to chronic fatigue, inattention, irritability, emotional outbursts, absence from work, diminished productivity, risk of accidents and other health related problems. The treatment options for insomnia include cognitive behavioural therapy, pharmacological therapy and combined approach. Cognitive behavioural therapy includes stimulus control therapy, sleep restriction therapy, relaxation therapy, sleep hygiene and cognitive therapy. The pharmacological options currently widely in use are benzodiazepines and Z-drugs. Alternative drug delivery methods and innovative treatments hold promise for increasing access to care and accelerating improvement. The newer targets for treatment of insomnia are orexin receptors, melatonin receptors and serotonin receptors. A combined approach of pharmacological treatment, cognitive behavioural treatment and newer formulations for improving drug delivery is required to combat the problem of insomnia.

Keywords: Cognitive behavioural therapy in insomnia, insomnia, new drugs for insomnia, orexin receptor antagonists, recent advances in insomnia

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INTRODUCTION**Definition of Insomnia**

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].

Epidemiology

In the general population, about one third people have one or more symptoms of insomnia and about 10% fulfil the criteria for a clinical diagnosis of insomnia [2].

Insomnia is more prevalent among women, older adults, and in individuals with less education. Insomnia symptoms are found to be associated with a range of conditions, especially mental conditions, pain

conditions with uncertain aetiology and, to a lesser extent, chronic pain conditions [3]. There is close relationship between insomnia, depression, and anxiety [4].

Classification of insomnia

Insomnia can be classified according to variety of ways. According to International Classification insomnia is divided into two broad categories; primary insomnia or comorbid (secondary). In primary insomnia disturbance cannot be explained by any underlying medical, psychiatric, or environmental problem. Comorbid insomnia can be associated with medical conditions (e.g., chronic pain, thyroid dysfunction, oesophageal reflux), psychiatric disorders (anxiety, depression, bipolar disorder), neurologic disorders (Parkinson disease,

Alzheimer disease), primary sleep disorders (sleep apnoea, restless legs syndrome), and drugs [5]. Another method of classifying insomnia is by their duration: transient, defined as insomnia for less than 2 weeks; short term lasting for 2-4 weeks; and chronic, lasting for more than 4 weeks [6]. According to symptoms insomnia can be of three types: difficulty in onset of sleep; difficulty in maintaining sleep and non-restorative sleep.

PHYSIOLOGY OF SLEEP

Sleep cycle

Sleep is divided into two distinct states known as rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The American Academy of Sleep Medicine (AASM) further divides NREM into three stages: N1, N2, and N3. Stage N3, characterized by the presence of high voltage slow waves (delta waves), is also termed slow wave sleep (SWS) and provides an indication of the intensity or depth of sleep [7]. REM sleep is characterised by irregular rapid movement of eye, low voltage EEG and low muscle tone. About 5% of sleep time is spent in stage I, 45% to 50% in stage II, and 25% to 30% in stages III and IV, while REM sleep accounts for 20% of total sleep time [5]. Sleep consist of approximately five to six cycles of 90 minutes, each cycle consisting of alternative NREM and REM stages of sleep [8].

Neurochemistry of sleep

Wake promoting neurons release histamine or orexins, which directly stimulate the arousal centres as well as the cerebral cortex itself. Noradrenaline, acetylcholine and serotonin are also involved in the regulation of wakefulness [9].

PATHOGENESIS OF INSOMNIA

Causes of insomnia

Spielmen proposed most widely accepted 3P model which describes **p**redisposing conditions, **p**recipitating circumstances, and **p**erpetuating factors for development & maintenance of chronic insomnia [10]. Predisposing conditions may be having role in development of insomnia like hyper-arousal and familial or genetic tendency. Compare to normal sleepers, Insomnia patients are found to be more aroused and less sleepy in bedroom before sleep [11].

Precipitating factors such as illness, family, work and school and other stressors may adversely influence a person's sleep [12]. Maladaptive sleep habits (e.g., extended time in bed, irregular sleep-wake schedules, irregular napping, sleep-incompatible activities in bed), dysfunctional cognitions (e.g., worry, unrealistic expectations, misattributions) are the perpetuating factors for insomnia [10].

TREATMENT OPTIONS

Insomnia is associated with various daytime impairments such as chronic fatigue, inattention, irritability, diminished productivity, emotional problems and absenteeism. Insomnia can also increase the health related problems, use of alcohol, risk of accidents, and work impairment [13]. Current treatment options for treatment of insomnia can be divided into two parts: pharmacological therapy and cognitive behavioural therapy.

A. COGNITIVE BEHAVIOURAL THERAPY (CBT)

Cognitive behavioural therapy is very important in case of insomnia. Cognitive behaviourally based self-help book is very beneficial to the patients of insomnia (reduces insomnia severity, and improve sleep and day-time functioning in adults with insomnia and co-morbid problems). The beneficial effects can be enhanced by adding brief, structured weekly therapist support over the telephone [14]. Cognitive behavioural therapy offers clinically effective option for treatment of the insomnia. In some studies it is found that CBT improves insomnia by decreasing sleep latency and wake time after sleep onset and increasing total sleep time and sleep efficacy [15, 16]. Benefits due to CBT and combination of CBT plus pharmacotherapy last longer than pharmacotherapy alone [17].

Stimulus Control therapy (SCT)

It was the first non-pharmacological treatment to develop for the treatment of insomnia which later becomes gold standard for other non-pharmacological therapy. In many patients of insomnia, bed and bed room are associated with behaviour which is incompatible with sleep such as watching TV, eating, lying awake, and worrying. Aim of SCT is to dissociate

such type of behaviour by giving simple instructions such as, going into bed only when you are sleepy, not using the bed for any other activity other than sleep and sex and not staying awake in bed for more than 10 minutes, leaving the bedroom and coming back when feel sleepy. Waking up in the morning same time everyday irrespective of hours of sleep and not sleeping during daytime [10].

Sleep-Restriction Therapy (SRT)

SRT is very useful for patients who spend too much time in bed attempting to sleep {low sleep efficiency (SE: ratio of total sleep time to time spent in sleep)}. Rational behind partial sleep deprivation is that it increase homeostatic sleep drive and consolidates sleep. In SRT, initially mean total sleep time (TST) is determined by maintain sleep diary for 2 weeks before therapy. A wake time is fixed and according to mean TST required, a bed time is adjusted. For example if wake up time is fixed to 6:00 AM and total sleep time for patient is 7 hours, patient need to go to sleep at 11:00 PM. During each week bed time is reduced 15 minutes. Duration of SRT is 6 weeks [10]. Patient is not prescribed less than 5 hour of sleep time. If SE <85%, 15 minutes are reduced from time in bed. If SE > 90%, additional 15 minutes given to patient to sleep; & no change made if SE between 85-90% [10]. According to Taylor DJ et al, 8 week SRT and hypnotic withdrawal reported better sleep quality and dose reduction as compared to sleep hygiene education alone and also improvement in follow-up sessions [18].

Relaxation therapy

Relaxation therapy, useful in insomnia with hyper-arousal, includes progressive muscle relaxation, deep breathing, guided imagery, meditation, yoga, and hypnosis [10]. As a monotherapy, relaxation therapy is not found to be effective but as a part of combination therapy, it is useful [19, 20].

Sleep Hygiene and education (SHE)

Sleep hygiene controls all behavioural and environmental factors that precede sleep and may interfere with sleep [21]. In SHE patient is educated about sleep and its functions along with sets of rules that are to be followed like- avoiding coffee, alcohol and nicotine before bedtime, hide clock to

avoid repeated watching of time, avoiding heavy meal near bedtime or skipping meals in the evening, minimize noise, light and excessive temperature during sleep, take a warm (not hot) bath before bedtime, use appropriate size of pillow and bedding according to comfort [22, 23].

Cognitive Therapy

Various unrealistic cognitive beliefs play a role in development and maintenance of insomnia. Cognitive therapy targets these dysfunctional beliefs by challenging the validity of those beliefs through therapeutic process [24]. In a trial by Harvey et al. treating patients with cognitive therapy alone significantly improved symptoms of insomnia and day time impairment and was maintained through 12 month follow-up [25].

B. PHARMACOLOGICAL TREATMENT

Current pharmacological treatment of insomnia consists of mainly three groups: Benzodiazepines; Novel Benzodiazepine Receptor Agonists (Z compounds); Melatonin receptor agonist.

Benzodiazepines (BZDs)

FDA approved benzodiazepines for insomnia includes flurazepam, quazepam, estazolam, temazepam, and triazolam. BZDs increase total sleep duration by increasing time spent in stage II of NREM sleep, despite decrease in time spends in stage I, III & IV, & REM sleep. BZDs agonists act by binding to GABA_A receptor at a site other than GABA (γ -aminobutyric acid) binding site and increase the amount of chloride current generated by GABA_A activation [26]. BZDs decrease sleep latency and in some cases improve sleep maintenance by decreasing the awakening in night but are not useful in non-restorative sleep. BDZs are used to treat short term insomnia as their chronic use is associated with dependence and tolerance. In elderly, benefit of use of BZDs does not outweigh risk [27-29]. Common adverse events associated with BZDs include excessive sedation, motor incoordination, cognitive impairment and anterograde amnesia [29]. According to Wagner et al, use of long and short acting BZDs is associated with an increased incidence of hip fracture with peak at 2weeks of use [30]. Long acting as well as short acting BZDs increase residual day

time sleepiness and are associated with increase the risk of accidental fall and hip fracture [31].

Novel Benzodiazepine Receptor Agonists (Z compounds)

These compounds provide better alternative in terms of safety with comparable efficacy. Z compounds bind to the $\alpha 1$ subunit of GABA_A receptor and produce sedative and hypnotic effect without any anxiolytic or anticonvulsant or muscle relaxant property [32].

Zolpidem is a short acting drug, FDA approved for short term treatment of insomnia with difficulty in sleep onset. Zolpidem extended-release tablet is approved by FDA for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Commonly observed adverse events of zolpidem are drugged feeling, lethargy and drowsiness [33, 34]. According to Krystal et al, the most common adverse effects associated with zolpidem extended-release as compared to placebo are headache, anxiety, somnolence, dizziness, fatigue, disturbance in attention, irritability, nausea, and sinusitis [35]. Zaleplon and zolpidem are effective in relieving sleep-onset insomnia and have been approved by the FDA for use for up to 7-10 days at a time [26]. Both the drugs have sustained hypnotic efficacy without occurrence of rebound insomnia on abrupt discontinuation [36]. Zaleplon and zolpidem have similar degrees of efficacy. Zolpidem has a $t_{1/2}$ of approximately 2 hours, which is sufficient to cover most of a typical 8-hour sleep period, and is presently approved for bedtime use only [26].

Zaleplon has a shorter $t_{1/2}$ ~1 hour and is approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime. Because of its short $t_{1/2}$, zaleplon has not been shown to be different from placebo in measures of duration of sleep and number of awakenings [26].

Eszopiclone is the active S(+) enantiomer of zopiclone. In various studies, it is found to be effective in both sleep onset and sleep maintenance type of insomnia. Food and Drug Administration (FDA) approved eszopiclone for the transient and chronic insomnia [26].

Melatonin receptor agonist

Melatonin is a hormone secreted by pineal gland and has very important role in the maintenance of circadian rhythm regulation. Secretion of melatonin in body corresponds to the night hours [37]. Melatonin promotes sleep by reducing the effect of wake promoting signals in suprachiasmatic nucleus of hypothalamus [38]. Binding of melatonin to MT₁ receptors promotes the onset of sleep while melatonin binding to MT₂ receptors shifts the timing of the circadian system [39].

Prolong release melatonin (PRM)

A prolonged- release melatonin (PRM) is licensed in Europe and other countries for the treatment of primary insomnia in patients aged 55 years and over for a duration of up to 3 months [40]. In some studies, Prolong release melatonin shows improvement in efficacy parameters of insomnia such as sleep latency, morning alertness, quality of life [41, 42]. It is the only drug that is approved for the treatment of insomnia with poor quality of sleep. According to Lemoine et al, discontinuation of PRM even after 12 months of use was not associated with adverse events, withdrawal symptoms, or suppression of endogenous melatonin production [40].

Ramelteon

Ramelteon is a new FDA approved drug for onset type of insomnia and it acts as an agonist at MT₁ and MT₂ melatonin receptors located in the suprachiasmatic nuclei of the brain [43]. Adverse effects of ramelteon at the dose of 8mg/day include somnolence, dizziness and fatigue [44]. Long term use of ramelteon is not associated with dependence and tolerance with no withdrawal symptoms or rebound insomnia on discontinuation [45]. It was found that there was significant impairment of driving performance, cognition, memory and psychomotor performance when ramelteon 8 mg was given at bedtime but it did not produce balance impairment [46].

Off-label drugs to treat insomnia

Some of the commonly used off label medications include sedative antihistaminics like diphenhydramine, doxilamine; sedative antidepressants like trazodone, amitriptyline, doxepin, trimipramine, mirtazapine, agomelatine[9].

Very few short term studies are available for over the counter medications and efficacy and safety of these medications for long term use is not known [47]. Doxepin, a tricyclic anti-depressant was approved by US FDA in 2010 for the treatment of insomnia with difficulty in sleep maintenance [9].

Alternative treatments

Some of the herbal drugs used as an alternative medicine for insomnia include kava-kava and valerian [5]. Efficacy and safety of these medications for treatment of insomnia is not known.

RECENT ADVANCES

Orexin receptor antagonists

Orexin-A & -B are neuropeptides, also known as hypocretin-1 & -2 (as produced in lateral hypothalamus) are found to be having profound effect on arousal and sleep by acting through OX-1 & -2 receptors. In various studies, it was found that loss of orexin producing neurons led to development of narcolepsy in humans and rodents. Consequently interest in development of orexin receptor antagonist raised as a novel therapy for treatment of insomnia [48, 49]. Suvorexant (MK-4305), OX-1 & -2 antagonist, is a new molecule under development for treatment of insomnia and has completed phase III trial [9].

Melatonin receptor agonist

Tasimelteon is a newer melatonin receptor agonist currently in phase III of clinical trial for the treatment of insomnia. Tasimelteon got an orphan drug status in the USA for treatment of non-24 hour sleep-wake disorder in blind people without light perception on 19th January 2010 [50]. NEU-P11 is a novel melatonin agonist under development for the treatment of insomnia. In various animal studies, it was found that it also inhibits weight gain and improves insulin sensitivity in high fat/high sucrose fed rats [51].

Serotonin receptor modulators

It is now established that serotonin (5-HT) functions have role in promoting wakefulness and inhibition of REM sleep [52]. Various drugs are under development that modulates the serotonin receptor. Modulation of serotonin receptor remains worthwhile exploring.

CONCLUSION

Prevalence of insomnia is high and is associated with a range of psychological, psychiatric, and medical conditions. Insomnia affects health by influencing cognitive, emotional, and social functioning. Insomnia develops under stressful conditions that lead to arousal, maladaptive sleep habits, and dysfunctional cognitions. Circadian and sleep homeostatic processes play an important role in insomnia development, maintenance, and treatment. Psychological and behavioural treatments for insomnia are efficacious for primary and comorbid insomnia. The common elements of CBT are stimulus control therapy, sleep restriction therapy, relaxation therapy, sleep hygiene and cognitive therapy. Adding pharmacological treatment to cognitive behavioural treatment can help in improving the condition. Alternative delivery methods and innovative treatments hold promise for increasing access to care and accelerating improvement.

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