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Review Article

Managing insomnia efficiently

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ABSTRACT

Insomnia remains a common clinical concern that is associated with negative daytime consequences for patients and represents a significant public health problem. The reported prevalence of insomnia is 9% in the general population and about 30% suffer from occasional insomnia. The medications approved for treating insomnia represent 4 fundamental pharmacodynamic categories with key actions related to receptors for γ-aminobutyric acid (GABA), melatonin, histamine, or orexin/hypocretin. Addiction and insomnia frequently co-exist, as lack of sleep creates multiple physical and emotional issues that some individuals will attempt to self-medicate with drugs or alcohol.

1. Introduction

1.1. Defining Insomnia

Primary insomnia can be understood as a difficulty in initiating or maintaining sleep, early waking or nonrestorative, poor quality sleep which occurs despite adequate opportunity and appropriate circumstances for sleep, resulting in impairment in daytime functioning (including impairment in concentration or attention, social or vocational dysfunction, mood disturbance, daytime sleepiness, headaches or gastrointestinal symptoms and worry or concern about sleep) which can not be attributed to an underlying physical or mental health problem.[1]

1.2. Types

Transient insomnia is difficulty in sleeping that lasts for a few days or up to one week. It can be caused by anxiety over short term life events leading to acute situational stress, such as a job interview, relationship troubles or conditions such as the viral infection.

Acute Insomnia: A brief episode of difficulty sleeping. Generally lasting less than three months. Acute insomnia is usually caused by a life event, such as a stressful change in a person's job, receiving bad news, or travel. Often acute insomnia resolves without any treatment.

Onset insomnia. Difficulty falling asleep at the beginning of the night.

Maintenance insomnia. difficulty staying asleep, or waking too early and struggling to get back to sleep.

Chronic insomnia is characterized by difficulty initiating or maintaining sleep despite adequate opportunity for sleep, with associated distress or impairment of daytime functioning lasting three months or longer for at least three nights each week.

Comorbid Insomnia: Insomnia often occurs with other sleep disorders, medical conditions, or psychological disorders. Cortisol is the stress hormone in humans, but it is also the awakening hormone.

It is estimated that among patients diagnosed with insomnia, 25% to 30% suffer from primary insomnia. Secondary insomnia, in contrast, has been defined historically as insomnia resulting from other medical and psychiatric illnesses, medication use, or other primary sleep

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disorders.[2]

1.3. Prevalence of Insomnia

Insomnia symptoms occur in 33-50% population and insomnia symptoms with distress occur in 10-15%. In women, insomnia is more prevalent with both the onset of menses and menopause. Lower levels of progesterone can, like estrogen, correlate with insomnia in menopausal women.

1.4. Causes of Insomnia ***[Table 1]***

1.5. Types of Sleep

A sleep episode begins with a short period of NREM stage 1 progressing through stage 2, followed by stages 3 and 4 and finally to REM. However, individuals do not remain in REM sleep the remainder of the night but, rather, cycle between stages of NREM and REM throughout the night. NREM sleep constitutes about 75 to 80 percent of total time spent in sleep, and REM sleep constitutes the remaining 20 to 25 percent.Table 2[3]

1.5.1. Neurotransmitters in sleep

1. There is a great deal of evidence that *acetylcholine* is associated with REM sleep. For example, release of ACh in the cortex is highest during waking and REM sleep, and lowest during delta sleep.
2. The other two neurotransmitters that have been implicated as playing an important role in sleep are norepinephrine *(NE) and serotonin (5-HT)*. The cell bodies that are most important in sleep with these two neurotransmitters are located in the locus coeruleus and the raphe nuclei for NE and 5-HT respectively. NE plays a role in vigilance or attention, encouraging the organism to notice unusual and important stimuli. 5-HT levels, on the other hand, vary in the exact opposite manner.
3. Hypothalamic neurons and adjacent groups of basal forebrain neurons produce the neurotransmitter gamma-aminobutyric acid (GABA). Projections of these GABA neurons inhibit the firing of cells involved in wakefulness.[4]

Overactivation of the arousal system, the emotion regulating system and parts of the cognitive system is accompanied by reduced activation of the prefrontal cortex (PFC) and the caudate head. Prefrontal hypoactivation is assumed to be associated with daytime fatigue and reduced recruitment of the caudate head is assumed to be related to arousal regulation.

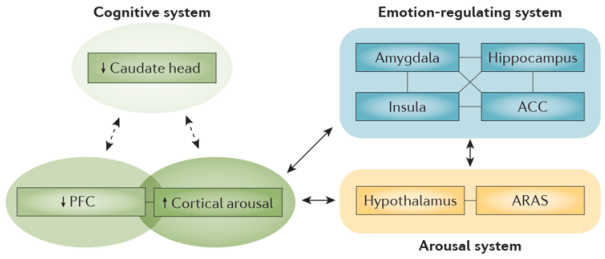

Fig. 1: Pathways that are potentially involved in the psychopathology of insomnia.

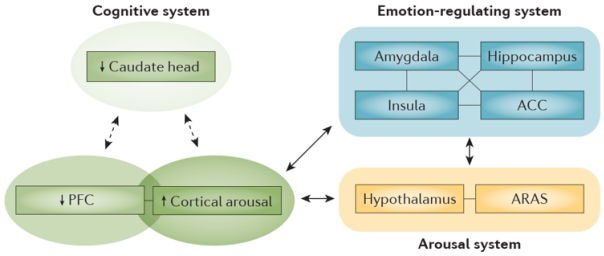

Fig. 2: Complications of Insomnia:[5]

1.6. Managing Insomnia

1.7. Artificial Light

Because light is the most potent natural system , or time cue, for the circadian timing system, phototherapy can be used as part of a treatment regimen to adjust the timing of the sleep/wake cycle and address a corresponding complaint of insomnia and/or sleepiness, Artificial bright light has been shown to improve sleep maintenance insomnia in older adults.

Exercise can increase sleep quality and slow-wave sleep, and reduce sleep latency in some individuals, including older adults.

Elevation of core body temperature by external body heating during the early evening also increases slow-wave sleep in both young and older individuals, and improves sleep continuity in older women with insomnia.

The goal of sleep restriction is to decrease time in bed in order to maximize the sleep efficiency of time spent in bed. After sleep efficiency reaches desired levels (typically 90%), time allowed in bed can be increased by increments of 15 minutes until desired total sleep time at night is reached.

A number of relaxation therapies have been used for insomnia, including progressive muscle relaxation and biofeedback to diminish physiologic arousal, and imagery techniques, autogenic training, and meditation to reduce cognitive arousal. Relaxation treatments may be most useful for sleep onset insomnia.[6]

Table 1:

Situational	Medical	Psychiatric	Pharmacological
Work related stress	Endocrinal: Diabetes, hyperthyroidism	Manic depressive psychosis	Steroids
Financial crises	CVS: Angina, CCF, hypertension	Obsessive Compulsive disorder	B-Adrenergic blockers
Personal Problems	Respiratory : Asthma, COPD, Sleep apnoea	Generalised Anxiety	Diuretics
	GI : GERD, Peptic ulcer disease	Substance abuse	Selective serotonin reuptake inhibitors
	CNS: Parkinsons disease , epilepsy		
	Pregnancy		

Table 2:

NREM	REM
In adults it constitutes about 75-80% of total sleep time	Follows after every NREM cycle
Has four stages which cyclically occur 4-5 times at night	Characterised by an increased heart rate, postural muscle atonia and increased activity on the EEG
NREM are sign of quiet wakefulness occur at stage 1 and disappear in the deeper sleep stages	Most dreams happen during REM sleep
Stages 3 and 4 are referred to as deep sleep , because arousal threshold is high (perceived as high-quality sleep)	

Table 3: Nonpharmacologic Treatments

Sleep Hygiene	Increase exercise to 3-4 times weekly
	Limit intake of alcohol, caffeine and nicotine
	Create comfortable sleep environment
	Avoid drinking large quantities of fluids in the evening to prevent night time trips to the bathroom
	Eat small meal at bedtime
	Utilise relaxation and anxiety management techniques before bedtime

1.8. Pharmacotherapy

Classification of anti insomnia drugs[7] Table 3

1.9. Drug Profile

Zolpidem is a $GABA_A$ receptor agonist of the imidazopyridine class. It works by increasing GABA effects in the central nervous system by binding to $GABA_A$ receptors at the same location as benzodiazepines. zolpidem was at least as effective as zopiclone but showed significantly less rebound on withdrawal; overall it was better tolerated. Adverse effects of zolpidem include nightmares, agitation, headache, gastrointestinal upset, dizziness, and daytime drowsiness. zolpidem is a sedative/hypnotic that shares some characteristics of a family of sedatives called benzodiazepines but Zolpidem has selectivity in that it has little of the muscle relaxant and anti-seizure effects and more of the sedative effect so it is used primarily as a medication for sleep. zolpidem was at least as effective as zopiclone, showed significantly less rebound on discontinuation and was better tolerated.

Zopiclone is a hypnotic agent belonging to a class of hypnosedative drugs, the cyclopyrrolones, with a chemical structure unrelated to benzodiazepines. It is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep. Treatment should be as short as possible. The duration of treatment, including a tapering off period, should not exceed 4 weeks. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status. Long-term continuous use is not recommended. The mechanism of action of the cyclopyrrolone hypnotic drug zopiclone involves allosteric modulation of the $GABA_A$ receptor. Extended use of this drug may lead to an increased tolerance which makes an individual even more susceptible to addiction.

Eszopiclone acts by binding to the $GABA_A$ receptor. In contrast to the benzodiazepine (BZD) hypnotics, eszopiclone has more selectivity for certain subunits of the $GABA_A$ receptor. Oral eszopiclone is rapidly absorbed and extensively distributed to body tissues including the brain. Tolerance did not occur during active drug administration for a 12-month period. Thus eszopiclone can be efficacious not only during short- and intermediate-term administration but also in patients requiring prolonged

Table 4:

Drug	Dosage Form	Recommended Dosage	Indications/ Specific Comments
Benzodiazepine Receptor Agonistic Modulators(Schedule IV Controlled Substances)			
Non-benzodiazepines			
Cyclopyrrolones Eszopiclone	1,2,3 mg tablets	2-3 mg hs 1 mg hs in elderly or debilitated; max 2 mg 1 mg hs is severe hepatic impairment; max 2mg	• Primarily used for sleep-onset and maintenance insomnia; • Intermediate-acting; • No short-term usage restriction
Imidazopyridines zolpidem Zolpidem (controlled release)	5, 10mg 6.25, 12.5 mg tablets	10 mg hs; max 10 mg 5 mg hs in elderly, debilitated, or hepatic impairment 12.5 mg hs 6.25 mg hs in elderly, debilitated, or hepatic impairment	• Primarily used for sleep-onset insomnia • Short-to intermediate-acting • Primarily used for sleep-onset and maintenance insomnia; • Controlled release; swallow whole, not
Pyrazolopyrimidines Zaleplon	5, 10 mg capsules	10 mg hs; max 20 mg 5 mg hs in elderly, debilitated, mild to moderate hepatic impairment, or concomitant cimetidine	• Primarily used for sleep onset insomnia • Maintenance insomnia as long as 4 hours is available for further sleep • Short-acting
Benzodiazepines			
Estazolam	1,2 mg tablets	1-2 mg hs 0.5 mg hs in elderly or debilitated	• Short-to intermediate-acting
Temazepam	7.5, 15, 30 mg capsules	15-30 mg hs 7.5 mg hs in elderly or debilitated	• Short-to intermediate-acting
Triazolam	0.125, 0.25 mg tablets	0.25 mg hs; max 0.5 mg 0.125 mg s in elderly or debilitated; max 0.25	• Short-acting
Flurazepam	15, 30 mg capsules	15-30 mg hs 15 mg hs in elderly or debilitated	• Long-acting • Risk of residual daytime drowsiness
Melatonin Receptor Agonists(Non-Scheduled)			
Ramelteon	8 mg tablet	8 mg hs	• Primarily used for sleep-onset insomnia • Short-acting • No short-term usage restriction

regular drug usage.

The mechanism of action of these drugs involves inhibition of histamine H1 receptors. Histaminic neurons in the posterior hypothalamus promote wakefulness through interactions with ascending cholinergic nuclei and through projections through the thalamus. Inhibition of H1 receptors leads to decreased alertness and subjective sedation. Because of their sedating properties, the first-generation antihistamines diphenhydramine and doxylamine are available over the counter as sleep aids. Moreover, antihistamines are associated with potent anticholinergic effects, such as dry mouth, constipation, and confusion.

Ramelteon is a tricyclic synthetic analog of melatonin that acts specifically on MT1 and MT2 melatonin receptors. Ramelteon's halflife is longer than that of melatonin, being metabolized in the body to four main metabolites, M-I, M-II, M-III, and M-IV. M-II has an affinity to MT1 and MT2 of about one-tenth of the parent compound, but its concentration in the circulation exceeds that of ramelteon by more than an order of magnitude. Ramelteon is effective in decreasing latency to persistent sleep and increasing total sleep time. The most frequent adverse events leading to discontinuation in subjects receiving Ramelteon were somnolence, dizziness, nausea, fatigue, headache, and insomnia; all of which occurred in 1% of the patients or less.

Agomelatine is antidepressant, an agonist of melatonergic MT_1/MT_2 receptors as well as an antagonist of serotonergic 5-HT_{2C} receptors. The unique mode of action of agomelatine may improve the management of major depression by counteracting the pathogenesis of depression at cellular level and reduce insomnia. Agomelatine produces both subjective and objective improvements in sleep, with increased slow-wave sleep and improved sleep quality and continuity, with no effect on REM sleep. The recommended dose is 25 mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.

1.10. Benzodiazepines

Triazolam, flurazepam, quazepam and estazolam are effective in sleep onset and sleep maintenance problems whereas temazepam is effective in only sleep-onset problems in adults, 18–65 years old; in adults 65 years and older, triazolam and flurazepam are helpful for sleep onset and maintenance problems, whereas temazepam has been shown to be helpful for only sleep maintenance problems Although the benzodiazepines may reduce sleep fragmentation, their long-term use may also cause health problems, such as complete obstructive sleep apnea in heavy snorers or short repetitive central sleep apnea in patients with recent myocardial infarction. Some epidemiological studies have suggested that the use of hypnotic medications were associated with increased mortality. Benzodiazepines can be effective in the short-term treatment of severe insomnia, i.e., for one to two weeks, but there is no evidence supporting the longterm use of benzodiazepines for the treatment of insomnia.

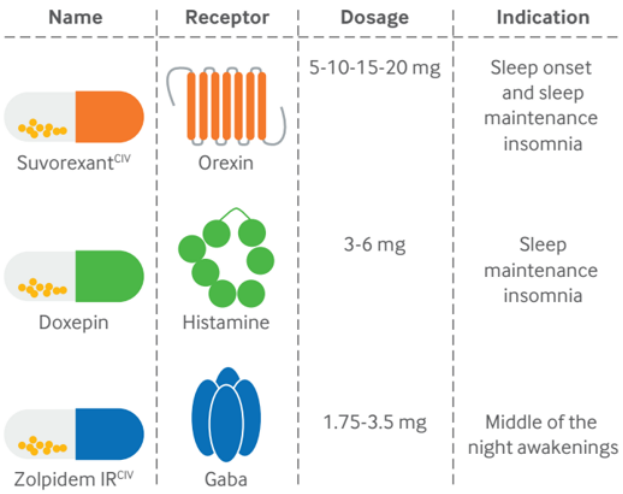

Fig. 3:

1.11. Suvorexant

Is the first marketed drug in a new category of insomnia medications known as orexin receptor antagonists. Orexins are neurotransmitters that regulate wakefulness and sleep. Suvorexant was approved in August 2014 for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance. The recommended starting dosage for suvorexant in insomnia patients is 10 mg administered once per night within 30 minutes of going to bed. The dose may be increased to a maximum of 20 mg as tolerated. The drug should be administered no later than seven hours before the planned time of awakening.[8,9]

1.12. Herbal Drugs

Clinical studies to evaluate the effectiveness and safety of herbs are scarce. More information is required before these herbs can be recommended as a first line of treatment against insomnia. Table 4

Table 5:

Herbal Drugs	Evidence based clinical trials	Evidence Level for Insomnia
Valeriana spp (Valerian)	Yes	Low
Passiflora spp (Passion flower)	Yes	Low
Humulus lupulus (Hops)	Yes	More research needed
Piper methysticum (Kava)	Yes	More research needed
Zizyphus jujube (Sour date)	No	More research needed
Lavendula spp (Lavender)	No	More research needed
Matricaria recutita (Chamomile)	No	More research needed
Albizia julibrissin (Mimosa)	No	Low

Valerian (Valeriana officinalis) extract comes from a flowering plant native to Europe and Asia. Valerian has a mechanism of action similar to benzodiazepines; however, instead of binding to the gamma subunit like a benzodiazepine, it appears to bind to the beta subunit on the GABA-A receptor instead. Regardless, the side effect profile of valerian seems to be tolerable with headaches, dizziness, and GI disturbances being the most common complaints, though not significant. Common doses of 300 to 400 mg of standardized extract (containing at least 0.5% essential oil) at bedtime may be seen for the treatment of insomnia.[10,11]

2. Conclusion

Combating insomnia may require lifestyle adjustments such as changing sleep habits, changing medications or stopping unnecessary drugs, reducing intake of caffeine, sugar, or tobacco and avoiding eating heavy meals late at night. The proposed drugs for insomnia come from various therapeutic groups. The GABAergic benzodiazepines (BZDs) and Z-drugs (zolpidem, zopiclone, and zaleplon) are FDA-approved for insomnia disorders with a strong evidence base, they have many side effects, including cognitive impairment, tolerance, rebound insomnia upon discontinuation, car accidents/falls, abuse, and dependence liability. Benzodiazepines are given in single doses, very short (1 to 7 days) or short (2 to 4 weeks) courses only. The use of melatonin by healthy adults shows promise to prevent phase shifts from jet lag and improvements in

insomnia, but to a limited extent. For the initiation of sleep and sleep efficacy, the data cannot yet confirm a positive benefit. Doxepin is a sedating tricyclic antidepressant (TCA) with a high affinity for histamine (H_1) receptors. It is approved for the treatment of insomnia characterized by difficulty with sleep maintenance but has limited use. Most of drugs for insomnia are addicting, life style interventions should be preferred. Insomnia drugs have to be used with restraint.

3. Source of Funding

None.

4. Conflict of Interest

None.

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