Insomnia: Therapy and Role of neurotransmitters

Litty Joseph[1], Saneha.O.R* and Chinchu Ravi[2]

[1]Professor, Department of Pharmaceutical Sciences, Centre for Professional and Advanced Studies, Cheruvandoor, Ettumanoor, Kottayam 686631.

Email: liityjimmyalappatt@gmail.com

[2]Assistant professor, East point college of pharmacy, Jnana Pranha, Virgo Nagar post, Bengaluru, Karnataka 560049

Email: chinchuravi2013@gmail.com

* For Correspondence

Ms. Saneha.O.R

Department of Pharmaceutical Sciences

(Previously by Mahatma Gandhi University)

CPAS, Ettumanoor, Kottayam, Kerala.686631

Mob:7025195125

Email: sanehaor123@gmail.com

Abstract

Insomnia is one of the most common sleep disorders which affects 30-40 percent of the adult population. The present article provides a combined review on prevalence, categories of insomnia, pathophysiology, role of neurotransmitter on sleep and different types of therapies for insomnia. From this review it was estimated that hormones like melatonin, cortisol, and others produced by the hypothalamic-pituitary-adrenal axis regulate the sleep-wake cycle. Disturbance of this cycle leads to insomnia. Furthermore, Neurotransmitter like GABA-L-glutamic acid, Acetylcholine, Norepinephrine, Dopamine, Serotonin, Steroids, Orexin, and Adenosine plays a major role in sleep regulation. Any alteration or disturbance in the neurotransmitter level affects sleep. It was concluded that Mechanism of action of almost all natural and synthetic derived drugs in regulation of neurotransmitters.

Keywords*: insomnia, sleep-wake cycle, melatonin, cortisol, hypothalamic-pituitary-adrenal axis, neurotransmitters.*

Introduction

Insomnia disorder is described as a subjective experience of difficulties start, duration, consolidation, or quality of sleep that occurs despite ample sleep opportunity and leads to some type of daily impairment. It is regarded as a serious public health problem [1]. Insomnia is defined by the International Classification of Sleep Disorders as "difficulty starting and/or maintaining sleep. Many variants on this description have been proposed or utilized in research, and there is no definitive definition of insomnia. "Insomnia is an experience of insufficient or poor-quality sleep defined by one or more of the following: difficulty falling asleep, difficulty maintaining sleep, getting up too early in the morning, non-refreshing sleep," according to the National Institutes of Health in 2005[2].

Prevalence

Insomnia is a prevalent neuropsychiatric problem that affects 30 to 45 percent of the adult population. Primary insomnia (insomnia without an underlying cause) affects 1-10% of the general population, with rates as high as 25% in the elderly [3] . We are also more vulnerable to accidents when we don't get enough sleep or have poor quality sleep. Insomniacs are seven times more likely than good sleepers to be involved in an accident that results in death or serious injury. Insomnia harms all aspects of a person's life. Insomnia can harm work performance, resulting in a change in personality and a decrease in job quality. If the disease is not treated, it may result in a reduction in career opportunities and perhaps job loss [4].

Categories of insomnia: -

Insomnia was categorized into three categories by the National Institute of Mental Health Consensus Development Conference in 1984:

• **Transient insomnia** is defined as insomnia that lasts for three days or less and is induced by a transient environmental or situational stressor. It might react to being reminded of sleep hygiene requirements.

• **Short-term insomnia** lasts three days to three weeks and is frequently brought on by a personal stressor like illness, sadness, or a job problem.

• **Long-term insomnia** is defined as insomnia that lasts longer than three weeks and for which no specific stressor can be identified [5].

Only when insomnia causes severe distress or anxiety, or when it causes daytime impairment, is it deemed a disorder. The 2nd Edition of the International Classification of Sleep Disorders lists the following categories of insomnia:

- **Acute insomnia**

  Acute insomnia, often known as short-term insomnia, is a type of adjustment insomnia. It is frequently brought on by a stressful situation and lasts only a few days or weeks. According to epidemiologic research, the one-year prevalence of adjustment insomnia in adults is likely to be between 15-20%. Adjustment insomnia can affect anyone at any age, however, establishing a link between specific stress and sleep disturbance in newborns

can be challenging. Women are more likely than males to experience adjustment insomnia, and older persons are more likely than younger individuals and children.

- **Childhood behavioral insomnia:**

Children are affected by two types of insomnia. When a youngster identifies falling asleep with an activity (being held or rocked), an object (a bottle), or a setting (parents' bed), he or she is unable to fall asleep if the association is broken. When a youngster delays and refuses to go to sleep due to a lack of firmly enforced bedtime limits, this is known as the limit-setting type. This disease affects between 10 and 30 percent of children.

- **Idiopathic insomnia**

Idiopathic insomnia is a type of insomnia that starts in childhood and lasts a lifetime and cannot be explained by any other factors. According to available data, this illness affects approximately.7% of adolescents and 1.0 percent of very young adults.

- **Inadequate sleep hygiene:**

This type of insomnia is caused by inadequate sleeping habits that keep you awake or cause your sleep routine to be disrupted. Adolescents and young adults with this illness account for 1-2 percent of the population. This disorder was found in 5-10% of sleep clinic patients.

- **Insomnia due to drug or substance, medical condition, or mental disorder**

Insomnia symptoms are frequently caused by one of three causes: a drug or substance, a physical ailment, or a mental disease. More than any other medical problem, insomnia is linked to a psychological problem, such as depression. According to surveys, around 3% of the population suffers from insomnia as a result of a medical or psychological illness. The prevalence of this type of insomnia is slightly lower among adolescents and young adults. This kind of insomnia affects about 2% of the overall population. This disorder affects around 3.5 percent of all sleep-center patients.

- **Paradoxical insomnia**

Paradoxical insomnia occurs when a person complains of severe insomnia due to the absence of objective evidence of a lack of sleep. The overall population's prevalence is unknown. This syndrome is often encountered in less than 5% of patients with insomnia in clinical populations. Young and middle-aged adults are likely to be the most affected.

- **Psychophysiological insomnia**

Psychophysiological insomnia: This type of insomnia is characterized by a high level of anxiety and stress about sleep and sleeplessness. This disorder affects 1-2 percent of the general population and 12-15 percent of all sleep center patients. It affects more women than men. It is uncommon in young children, but it is more prevalent in teenagers and adults of all ages [6] .

Pathophysiology

The sleep-wake cycle is regulated by hormones like melatonin, cortisol, and others produced by the hypothalamic-pituitary-adrenal (HPA) axis, whose malfunction can interrupt sleep and whose secretory activity follows a specific 24-hour pattern [7]. Excessive activation of the HPA-axis, or abnormalities in the HPA axis, are linked to sleep disturbances and stress. The release of Corticotropin-Releasing Hormone (CRH) is increased when the HPA-axis is activated, which raises cortisol levels. As a result, elevated cortisol levels have always been linked to stress and sleep problems [8].

Neurotransmitter and Sleep

Spinal reflexes and sleep regulation are controlled by neurotransmitters. The neurotransmitters that are involved in sleep are listed below.

a) GABA (Gamma Aminobutyric acid)

GABA is an amino acid derivative that functions as an inhibitory neurotransmitter, blocking or slowing the transmission of certain nerve signals. Nervous signals in the retina and the central nervous system are controlled by it. Drugs can temporarily raise GABA levels, reducing anxiety and providing anti-convulsant effects.
GABA's main effect is to suppress neuronal activity by interacting with a particular receptor protein that raises the chloride ion conductance of the postsynaptic membrane. Outside of the brain, GABA is not present in substantial concentrations. GABA is a neurotransmitter found only in mammals central nervous systems. GABA agonists are included in several sedatives and hypnotics. The overall balance between neuronal excitation and inhibition, which is necessary for optimal brain function, must be maintained. Either severe imbalance can result in death [9].

b) L- Glutamic acid
L- Glutamic acid, generally known as glutamate, is an amino acid that serves as the body's most prevalent neurotransmitter. Glutamate is released by 80% of the brain's neurons. The most important role of glutamate as a neurotransmitter is in cognitive tasks such as memory and learning. Scientists have implicated glutamic acid in epileptic seizures because glutamate can also serve as a precursor for the creation of GABA. The pontine reticular formation (PnO) contains endogenous glutamate and GABA, which help to regulate sleep duration [10].

c) Acetylcholine
Scientists were the first to discover the neurotransmitter, Ach. Ach has very much important in the sleep process. The Pons and the Basal Forebrain are two locations of the brain where Ach has cell bodies. It is implicated in the REM sleep schedule. As measured by an EEG, the activity of ACh neurons is associated with cortical arousal (increase in wave frequency) and desynchrony. When acetylcholine levels in some parts of the brain are low, Alzheimer's disease develops. Both REM and the control of the body's temperature during sleep are facilitated by the preoptic area and anterior hypothalamus (often referred to as POAH). It's also possible to reverse the causative direction by altering the POAH, which can result in insomnia or tiredness, and if the POAH is artificially warmed, the brain is induced to go into a deep sleep. During NREM sleep, the temperature of both the brain and the body drops. The temperature drops as the NREM-sleep event lasts longer. REM sleep, on the other hand, causes an increase in brain temperature. POAH neuron firing increases during sleep and in reaction to an increase in body temperature, indicating that: a) lesions of the basal forebrain cause insomnia, whereas stimulation causes drowsiness and sleepiness; b) warming the POAH induces delta sleep, and c) POAH nerve firing increases during sleep and in response to an increase in body temperature [11].

d) Norepinephrine
Because it elevates heart rate and blood pressure, this neurotransmitter is mainly important in the "fight or flight" response and other stressful conditions. Increased norepinephrine levels have been linked to symptoms in several mood disorders, according to studies. The cortical portion of the brain becomes more active when these neurons in the locus coeruleus at the bottom of the brain are activated. As a result, norepinephrine is assumed to play a role in causing people to wake up. Under a variety of conditions, the NE-deficient mice had a much-reduced latency to sleep, as evaluated both behaviorally and with electroencephalography. These findings show that NE promotes wakefulness between the onset of sleep and the occurrence of a slightly stressful event or a low dose of amphetamine. The Norepinephrine-deficient animals did not display any deficiencies in wakefulness or an increase in rapid eye movement sleep, as predicted by existing models of Norepinephrine's role in these two states' regulation [12].

Under mild stress and SD, norepinephrine enhances wakefulness during transitions between sleep and wake, but not under normal circumstances [13].

e) Dopamine
Another inhibitory neurotransmitter involved in motivation and voluntary action. Dopamine, also known as the "salience chemical," is involved in pleasure and subjective experiences of happiness. Dopamine is increased by alcohol, cigarettes, and some recreational substances. Dopamine levels in the frontal lobes of the brain are associated with schizophrenia. These findings are significant because they show how dopamine, which is generally elevated during times of excitement, can directly suppress the creation and release of melatonin, a chemical that causes tiredness and prepares the body for sleep [14].

f) Serotonin
Memory, emotions, moods, appetite, and thermoregulation are all functions that serotonin plays in the body. It helps in the regulation of sleep-wake cycles. Depression, anger, OCD, sleep disorders, irritable bowel syndrome, and a variety of other mental and physical problems have all been connected to serotonin deficiency. Serotonergic control

of the sleep/wake cycle occurs through a variety of postsynaptic receptors that mediate various or even opposing responses [15].

g) Steroids

Steroids are also involved in the regulation of sleep. Cortisol promotes REM sleep, and estrogen supplements appear to improve sleep in postmenopausal women, although this could be due to an indirect process. The sleep EEG and nocturnal hormone secretion are both regulated by growth hormone-releasing hormone (GHRH). GHRH causes an increase in slow-wave sleep (SWS) and growth hormone (GH) secretion, as well as a reduction in cortisol release, in healthy volunteers. GHRH inhibition has been linked to sleep-endocrine abnormalities in depression(16), and the corticotropin-releasing hormone is also involved in sleep regulation [17].

h) Orexin

The orexin (Hypocretin) system is a key regulator of sleep/wake cycles, eating behavior, and reward processes. In humans, dogs, and rats, orexin deficiency causes narcolepsy, indicating that the orexin system is critical for maintaining awake. Orexin depletion also results in problems in energy homeostasis and reward systems. To maintain a prolonged, consolidated awake state, orexin activates wake active monoaminergic and cholinergic neurons in the hypothalamus and brainstem regions [18].

i) Adenosine

Adenosine is assumed to be generated inside cells or on their surfaces, largely through the breakdown of adenine nucleotides, and is neither stored nor released like a classic neurotransmitter. It is created as a byproduct of energy metabolism and has a role in sleep homeostasis by inhibiting wake-promoting neurons. Damage or alterations to these neurons, which are located in the basal forebrain, seems to have a role in the progression of Alzheimer's disease. During extended wakefulness, the extracellular concentration of adenosine rises in the cortex and basal forebrain, then drops during sleep recovery. As a result, adenosine is found to act as a sleep homeostat and a connection between the humoral and neuronal systems of sleep-wake regulation. The adenosine A (1) receptor (A (1) R) and the adenosine A (2) receptor (A (2) R) are both involved in sleep initiation. PGD's somatogenic effects are mostly mediated through the A(2A)R [2,19].

INSOMNIA THERAPY

Cognitive Behavioral Therapy for Insomnia (CBT-I):

CBT-I is a multimodal treatment that includes instruction about good sleep habits and managing sleep expectations, as well as stimulus control, time limitations in bed, and relaxation training. It can be done with the help of experienced therapists or with the use of self-guided online tools like SHUTi and Sleepio. Because of its favorable risk/benefit profile, it is presently the gold standard of treatment for insomnia in adults. CBT-I for older persons had moderate quality evidence of improvement in the Insomnia Severity Index (ISI), PSQI, and waking after sleep onset (WASO), according to the American College of Physicians clinical practice guideline. It has been proven to provide consistent, long-term benefits in 70% to 80% of patients, and may even minimize the use of sedatives. A number of RCTs in the elderly have found that CBT-I is more effective and has longer-lasting therapeutic effects than pharmaceutical therapies in both subjective and objective sleep metrics. Meta-analysis has revealed a wide range of impact sizes, ranging from minor effects for sleep maintenance insomnia to moderate and significant effects on a variety of sleep outcomes.

Brief Behavioral Treatment for Insomnia (BBT-I)

BBT-I (brief behavior treatment for insomnia) is a shorter version of CBT-I.9 It consists of four behavioral strategies that increase sleep consolidation by enhancing sleep "drive," reinforcing sleep regularity, lowering arousal, and increasing bed-and-sleep associations. In an RCT of 62 older individuals with chronic insomnia, BBT-I was found to be helpful in reducing sleep variability as measured by a sleep diary and actigraphy. Four weeks following trial beginning, the proportion of participants without insomnia (55 percent versus 13 percent) was considerably higher for those getting BBT-I than for those receiving printed educational material, according to a 2011 RCT of 79 older individuals. Self-reported sleep, sleep diary results, and actigraphy results were all considerably better in the BBT-I group.

Sleep Restriction Therapy

Sleep Restriction Therapy (SRT) is a type of CBT-I that can also be used as a stand - alone treatment for insomnia. Four trials fulfilled appropriate methodological strength to investigate the efficacy of treatment for chronic pain in a

2014 review of SRT with an average age of 63.0 years. The results showed that self-reported sleep diary measures of sleep onset latency (SL), wake time after sleep onset (WASO), and sleep efficiency had moderate-to-large weighted effect sizes (SE). Another research of 34 geriatric individuals found that SRT reduced sleep onset latency while having no effect on total sleep time (TST). When compared to sleep hygiene recommendations alone, a 2015 study found that a simplified sleep restriction (SSR) intervention administered over two quick visits was helpful in reducing primary insomnia over six months.

Stimulus Control Therapy

Another part of CBT-I is stimulus control therapy, which teaches people to link their bedroom with sleep and re-establish a regular sleep-wake cycle. While few studies particularly look at this element of CBT-I in older persons, one found that gains were maintained over a 6-week follow-up period. It is considered an effective therapeutic therapy in the treatment of persistent insomnia in the general population by the American Association of Sleep Medicine (AASM).

Relaxation Training

The goal of relaxation training is to minimize somatic tension and intrusive thoughts that keep you awake at night. Based on four RCTs, two of which focus on the elderly, the AASM guidelines encourage relaxation training. The first demonstrated considerable SL improvements that did not last at the follow-up. In the second research, the HART group exhibited considerable improvements in three of the seven metrics, but not as much as the CBT group.

Mindfulness:

Because mindfulness training does not require experienced therapists, it may be a cost-effective strategy for individuals with sleep difficulties who may not fulfil the criteria for an insomnia diagnosis. A standardized mindful awareness practices (MAPs) intervention was found to be superior to a sleep hygiene education (SHE) intervention in enhancing sleep quality in a 2015 RCT. In the short term, formalized mindfulness-based therapies may help older persons with sleep issues, with a benefit that appears to carry over into lowering sleep-related daytime impairment.

Light Therapy

A 2003 open study of 11 institutionalized, demented elderly individuals indicated that bright light exposure improved sleep significantly. The amount of time spent waking during nocturnal sleep was reduced by approximately two hours, and SE increased from 73% to 86%. For multivariable examination of sleep outcomes, a 2016 meta-analysis on light therapy found a significant average effect.

Music Therapy

The Pittsburgh Sleep Quality Index indicated no significant differences between groups in a 2010 RCT on the influence of music on depression and SQ in the elderly. In a 1995 pilot trial using music therapy for sleep disturbances in the elderly, twenty-four (96%) of the participants reported improved sleep, with many others reporting that their sleep issues were at least considerably decreased.

White Noise

When compared to typical environmental noise, broadband sound dramatically reduced the delay to stable sleep in an experimental model of transitory insomnia in young healthy individuals. Furthermore, this intervention improved both subjective and objective SQ in patients who had difficulty starting sleep. This, however, has not been studied in patients with clinically diagnosed insomnia. Furthermore, sleep architecture and SQ perception typically alter with age, and the participants in this study were young people [20].

Natural Therapies for Sleep Disorders

Valerian (*Valeriana officinalis*)

In both the United States and Europe, *Valerian* is the most often used herbal sleep aid. Valerenic acid, along with other more polar chemicals, has a role in the activity of V. Officinalis, and the mechanism is thought to be linked to

elevated levels of GABA in the brain or interact with GABA-ergic neurotransmission, resulting in a sedative effect [21,22,23].

Passionflower (*Passiflora incarnata*)

Passiflora incarnata L., a medicinal plant native to tropical America, has also been reported to have hypnotic properties. Experiments on male adult Wistar rats indicate that Passiflora incarnata includes components that promote the presence of the SWS while inhibiting REM sleep. As a result, it's used to treat insomnia patients who have been having trouble falling asleep[24].

Kava (*Piper methysticum*)

The herbal substance kava act on both GABA and BZD binding sites, resulting in antispasmodic, anticonvulsive, central muscular-relaxant and sedative, effects. Kava is derived from a shrub (Piper methysticum) growing in the Pacific islands. Anxiety, stress, and restlessness—all significant causes of persistent insomnia—are treated with over-the-counter kava-containing medicines[25,26].

Chamomile *(Chamomilla recutita /Chamaemelum nobile*)

To treat insomnia and promote sleep, chamomile products such as tea and essential oil aromatherapy have traditionally been used. Chamomile has known for being a mild sedative and sleep aid. Apigenin, a flavonoid that binds to benzodiazepine receptors in the brain, could be responsible for the sedative effects. Anticonvulsant and CNS depressive effects have been discovered in preclinical models. Although ten cardiac patients were reported to fall into a deep slumber lasting 90 minutes after consuming chamomile tea, clinical trials are absent. Other chemicals found in chamomile extracts will bind BDZ and GABA receptors in the brain which may be responsible for the sedative action; however, many of these chemicals are still unknown [27].

Peppermint *(Mentha piperita L.)*
According to a study on the effects of inhalation aromatherapy with peppermint essential oils on the sleep quality of cardiac patients, it may be useful in enhancing sleep quality. Aromatherapy with peppermint essential oil was found to be useful in enhancing sleep quality[28].

Hops (*Humulus lupulus)*

A study comparing the efficacy and safety of a valerian-hops combination and diphenhydramine for the treatment of minor insomnia found that the valerian-hops combination and diphenhydramine had a small hypnotic effect when compared to placebo. Improved sleep with a valerian-hops combination has been linked to a higher quality of life. During this trial, both medications appeared to be safe and did not cause rebound insomnia when they were stopped [29].

Lemon balm:
The effects of a botanical supplement comprising valerian/lemon balm on sleep patterns in menopausal women aged 50-60 years. The research shows that Valerian/lemon balm can help women who are going through menopause and are having trouble sleeping or have indications of a sleep problem. There were also no known side effects [30].

St. John's Wort:
St. John's Wort (*Hypericum perforatum*) is an antioxidative herbal medicine that is commonly used in Europe to treat psychiatric problems such as anxiety and depression. It inhibits serotonin, dopamine, GABA, and norepinephrine re-uptake while boosting serotonin and norepinephrine release. The protective effect of St. John's Wort extract on anxiety-like behavior and oxidative damage after 72 hours of sleep deprivation suggests that it can be used to treat sleep deprivation and the resulting behavioral and biochemical changes [31].

Ashwagandha (*Withania somnifera*)
Ashwagandha is an important plant in Ayurveda, India's traditional medicine system. It has been suggested for good sleep for centuries, as indicated by its name "somnifera," which means "sleep-inducing." Ashwagandha leaf or root crude powder can improve sleep quality on its own. Triethylene glycol is a sleep-promoting active component found in Ashwagandha leaves, according to studies, and animal testing has shown its ability to induce sleep [32].

Lavender *(Lavandula angustifolia*)

Lavender has been described in medieval herbs and documents to treat a variety of illnesses, including polio, head lice, migraines, epilepsy, fainting, panting, heart failure (possibly heart attacks). panic, heart palpitations or other

heart problems), colds, daydreams, bites, cramps, and congestion**.** Lavender essential oil, made in England, was also used with sphagnum moss to disinfect wounds and promote healing during the Second World War. Traditional uses of lavender oil for antifungal, antibacterial, antidepressant, anti-inflammatory, carminative, analgesic, and sedative qualities have shown potential, resulting in a renewed interest in lavender oil [33].

Pharmacotherapy

Barbiturates

Although barbiturates have many potential drawbacks such as addiction, drug interactions, lethality in overdose, and cognitive impairment that prevent them from being commonly prescribed, they may be used for short-term treatment of insomnia on rare occasions [34].

Benzodiazepines

Barbiturates are recommended than BZDs for treating short–term insomnia. Because of the development of tolerance, dependency, and hangover effects, long–term use of BDZs for insomnia is not suggested [35]. Triazolam (Halcion, Pfizer), estazolam (ProSom, Abbott), temazepam (Restoril, Mallinckrodt), quazepam (Doral, Questcor), and flurazepam are the five BZDs currently approved by the FDA for the treatment of insomnia. Because of their potential for misuse or dependency, all of these substances are classified as Schedule IV controlled substances. The major difference between them is the period they are active. Triazolam has a short half-life, estazolam and temazepam have a medium half-life, while quazepam and flurazepam have a long half-life. The most widely given BZD for insomnia is temazepam. The duration and onset of action of a BZD should be considered while selecting one. Patients' tolerance to the sedative effects of BZDs has developed quickly; so, long-term usage of these medications is not advisable [36].

Diazepam is a sedative. It's used off-label for insomnia, restless leg syndrome, and pre/post-operative sedation, among other things [37].

Nonbenzodiazepines *(BZRA or 'Z' drugs)*

Non-BZDs, commonly known as "Z drugs," was developed to reduce the negative effects and misuse potential of BZDs. When compared to placebo, the currently available Z drugs—zolpidem, zaleplon, and eszopiclone—provided small but statistically significant decreases in subjective and polysomnographic sleep latency, according to a meta-analysis of 13 studies involving over 4,000 patients. Larger dosages, longer treatment durations, and higher proportions of younger and/or female patients were associated with bigger reductions in sleep latency in studies employing larger doses, longer treatment durations, and greater proportions of younger and/or female patients [38].

Patients who have trouble falling asleep prefer zaleplon, while those who have trouble staying asleep prefer eszopiclone. Zaleplon can be used for middle insomnia if you have at least 4 hours before you need to get up. A sublingual zolpidem preparation has recently become available for insomnia symptoms in the middle of the night. Eszopiclone has been approved for long-term use. Controlled-release zolpidem is also approved for long-term use, and its slow-release formulation extends the half-life of the drug and keeps drug plasma levels stable throughout the night. Orally, zopiclone and etizolam are effective for treating short-term insomnia [34].

Antihistamine drugs

The tricyclic antidepressant doxepin, which inhibits serotonin and norepinephrine uptake pre-synaptically and is an antagonist at histamine-1, muscarinic-1, and alpha-1 adrenergic receptors at high doses (150–300 mg), is a prescription antihistamine medication approved for improving sleep maintenance in the treatment of insomnia. At low doses (3-6 mg), doxepin is very selective for antagonizing histamine-1 receptors, allowing for safe use in insomnia. The selective anti-histaminic action of mirtazapine, trazodone, and quetiapine at lower doses could theoretically provide off-label effectiveness for insomnia [39].

Melatonin agonists

Ramelteon (Rozerem, Takeda) is the only melatonin (MT) agonist approved for the treatment of insomnia characterized by difficulty falling asleep [40]. Because ramelteon is a targeted MT1 and MT2 receptor agonist, it has no affinity for GABA receptors, reducing the risk of abuse [41]. Ramelteon has been demonstrated to reduce both polysomnographic and subjective sleep latency in people with chronic insomnia in studies [42,43,44].

In more formal investigations, over-the-counter melatonin was proven to reduce sleep onset latency and improve subjective sleepiness upon awakening, but it did not improve scores of drowsiness, fatigue, and alertness throughout the day [45].

Antidepressants

Trazodone

Trazodone has been used to treat depression in large doses since it was approved by the FDA more than 30 years ago. The drug is also used off-label as a hypnotic at low doses due to its modifying effects on serotonin (5-HTA) receptors. At doses as low as 10 mg, trazodone has been proven to inhibit nearly half of the brain's 5-HTA receptors. A nightly dose of 25 to 50 mg is indicated for patients with insomnia. As stated, this can be titrated to a dose of 100 mg every night. Anticholinergic side effects including orthostatic hypotension may occur at higher doses, increasing the risk of falls and injury [46].

Mirtazapine

Mirtazapine (Merck's Remeron) belongs to the piperazinoazepine class of drugs, which contains sedative effects that may help people with insomnia. The drug's significant antagonistic action on histamine (H1) receptors cause sedation. Only for the treatment of the major depressive disorder is mirtazapine currently approved [47]. In insomnia patients, a daily dose of 30 mg is usually prescribed; higher doses may reduce the drug's sleep-inducing properties [48].

Tricyclic antidepressant: Doxepin

Doxepin (Pernix Therapeutics' Silenor) is a sedating tricyclic antidepressant (TCA) that has a high affinity for histamine (H1) receptors. It is used for the treatment of insomnia that is characterized by problems maintaining sleep [49].

Atypical Antipsychotics

Atypical antipsychotic medicines including quetiapine, olanzapine, and risperidone are recommended for sleep disturbances, even though they are not FDA-approved. The antagonistic effects of these medicines on several neurotransmitter systems, including serotonin (5-HT2) and histamine (H1) receptors, cause sedation. The most usually given antipsychotic for insomnia is quetiapine [50,51].

Orexin receptor antagonist: Suvorexant

Suvorexant (Merck's Belsomra) is the first drug in a new class of insomnia drugs known as orexin receptor antagonists. Orexins are neurotransmitters that control waking and sleeping patterns. Suvorexant was licensed in August 2014 for the treatment of insomnia characterized by sleep onset and/or maintenance difficulties. It's a controlled substance classified as Schedule IV [52].

Dependency, withdrawal symptoms, or other side effects such as burning or tingling in the hands, arms, feet, or legs, changes in appetite, constipation, problems keeping balance, dizziness, and daytime drowsiness are all common side effects of these medicines. Synaptic plasticity and sleep-dependent memory consolidation may be impaired by such hypnotics. As a result, natural substances with sleep-inducing potential can be used instead of manufactured medicines to avoid adverse effects and reliance.

Table 1 : Medications approved by the Food and Drug Administration (FDA) for insomnia [47]**.**

	Name	**Recommended Dose Before Retiring**	**Half-Life (hours)**	**Primary Indication**	**Adverse Drug Reactions**
Benzodiazepines	• Flurazepam	Initial dose: 15 mg (women); 15 or 30 mg (men)	47–100		Dizziness • Drowsiness • Lightheadedness • Staggering • Ataxia • Falling
	• Temazepam (Restoril)	• Usual adult dose: 15 mg • 7.5 mg may be sufficient for some patients; some may need 30 mg	3.5-18.4		• Drowsiness • Headache • Fatigue
		• Recommended adult dose:	1.5–5.5 10–24		• Drowsiness • Dizziness

	• Triazolam (Halcion) • Estazolam • Quazepam (Doral)	0.25 mg • 0.125 mg may be sufficient for some patients • Initial dose: 1 mg (adults) • Some patients may need 2 mg • Initial dose: 7.5 mg • May be increased to 15 mg if necessary	39–73	Sleep-onset and sleep maintenance insomnia	• Lightheadedness • Somnolence • Hypokinesia • Dizziness • Abnormal Coordination • Drowsiness • Headache • Fatigue • Dizziness • Dry mouth • Dyspepsia
Nonbenzodiazepines	• Zolpidem (Ambien) • Zaleplon (Sonata) • Eszopiclone (Lunesta)	• Initial dose: 5 mg (women); 5 or 10 mg (men) • Total daily dose should not exceed 10 mg • Initial dose: 10 mg (nonelderly adults) • 5 mg may be sufficient for some patients; others may need 20 mg • Initial dose: 1 mg • May be increased to maximum of 3 mg	2.6 ~1.0 6	Sleep-onset Insomnia Sleep-onset Insomnia Sleep-onset and sleep maintenance insomnia	• Drowsiness • Dizziness • Diarrhea • Headache • Dizziness • Drowsiness • Paresthesia • Nausea • Abdominal pain • Memory Impairment • Headache • Somnolence • Unpleasant taste
Melatonin Agonist	• Ramelteon (Rozerem)	• Recommended dose: 8 mg • Total daily dose should not exceed 8 mg	1.0–2.6	Sleep-onset Insomnia	• Somnolence • Dizziness • Fatigue • Nausea • Exacerbated insomnia
Orexin Receptor Antagonist	• Suvorexant (Belsomra)	• Recommended dose: 10 mg • Total daily dose should not exceed 20 mg	10–22	Sleep-onset and sleep maintenance insomnia	• Daytime somnolence • Headache • Dizziness
Tricyclic Antidepressant	• Doxepin (Silenor)	• Initial dose: 6 mg (adults); 3 mg (elderly) • Total daily dose should not	15.3	Sleep maintenance insomnia	• Somnolence • Sedation • Nausea • Upper respiratory tract

		exceed 6 mg			infection
Barbiturates	• Butabarbital (Butisol Sodium) • Secobarbital (Seconal Sodium)	• Initial dose: 50 to 100 mg (nonelderly adults) as bedtime hypnotic • Initial dose: 100 mg (nonelderly adults) as bedtime hypnotic	100 15–40	Short-term treatment of sleep-onset and sleep maintenance insomnia	• Somnolence • Confusion • Agitation • Somnolence
Antihistamines	• Diphenhydramine (Benadryl) • Doxylamine (Unisom SleepTabs)	• Adults: 50 mg as a sleep aid • Adults: 25 mg	8–17 10–12	Sleep-onset and sleep maintenance insomnia Sleep-onset and sleep maintenance insomnia	• Somnolence • Dry mouth • Dizziness • Dyskinesia • Somnolence

Conclusion

Sleep is essential for one's personal metabolic activities as well as for person's overall health. Learning and memory, metabolism and weight, safety, mood, cardiovascular health, and disease are all affected by sleep. The most common sleep disorder, insomnia, affects 30-40% of the adult population. The sleep-wake cycle is regulated by hormones generated by the hypothalamic-pituitary-adrenal axis, such as melatonin, cortisol, and others. Insomnia is caused by a disturbance in this cycle. GABA-L-glutamic acid, Acetylcholine, Norepinephrine, Dopamine, Serotonin, Steroids, Orexin, and Adenosine are all neurotransmitters that play a role in sleep regulation. Sleep is affected by any changes or disturbances in neurotransmitter levels. The regulation of neurotransmitters is the mechanism of action of almost all plant-derived and synthetic-derived drugs. CBT-I is the most well studied non-pharmacological insomnia treatment for the elderly. We discovered strong evidence that CBT-I is an effective, safe, and long-lasting first-line treatment choice. This is notable considering the time and cost-effectiveness of BBT-I and relaxation interventions.

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