Key and Current Issues in the Management of Insomnia

ABSTRACT

There is increasing appreciation of the relevance of sleep to general well-being, especially for those with medical—including psychiatric—illnesses. This growing recognition of the relevance of sleep is reflected in the DSM-V guidelines. We endeavor to present a nuanced understanding and usage of sedative hypnotic medications in the management of insomnia. New medications that reduce wakefulness is also mapped out in this overview. In addition, we briefly discuss the intervention of cognitive behavior therapy for insomnia (CBT-I) as the mainstay of treatment for chronic insomnia.

KEYWORDS: sleep disorders, insomnia, management, treatment

Introduction

Why is sleep important?

Over the past two decades a substantial amount of research has confirmed the pivotal role of sleep in health. Sleep plays a key role in the body's recuperation and recovery. A "good night's sleep" has been shown to improve both physical and mental health.[1,2] Sleep consists of two phases: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. The NREM phase of sleep is further sub-divided into four stages. Stage 1 is referred to as transitional or light sleep. Suppression of peripheral physiological and metabolic function including blood pressure, gastrointestinal secretions, and cardiac activity occurs in stage 2 of NREM. Stage 3 and 4 are together referred to as slow wave sleep (SWS) or deep sleep with further reduction in muscle activity.[3] The amount of total SWS declines considerably with age. REM sleep accounts for 20-25% of total sleep time

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and involves brain activity which is similar to that when awake and there is accompanying muscle atonia.[2,3] The muscle atonia may prevent dream enactment.

One of the most studied functions of sleep is memory consolidation, a process that creates long term storage for newly acquired information.[4] Human and animal studies have emphasized the role of sleep in memory consolidation.[3] Different stages of sleep have been shown to be involved in memory processing and cognitive performance. Although, extensive research has implicated REM sleep in the processing of spatial and contextual memory,[4] emerging evidence is highlighting the role of SWS in learning and memory.[5] Encoding, consolidation and retrieval are 3 sub-processes of long-term memory. Perceived stimuli are encoded in the brain through changes in the strength of connections between neurons, resulting in the formation of a trace within distributed networks in the brain.[6] This concept referred to as the synaptic homeostasis hypothesis and is garnering much attention. This hypothesis provides the underpinning as to why sleep is critical for refreshing memory networks in the brain and for subsequent encoding of new learning.[5,6]

Sleep interacts with our physiology at many critical levels. For instance, a bidirectional link between sleep and immune function has been established. An inflammatory response to a pathogenic stimulation of our immune system can alter sleep duration and intensity. Similarly, sleep deprivation can lead to increased risk of infection and impact infection outcome negatively.[7] Moreover, sleep has been shown to clear metabolic waste from the brain. This is of particular importance since sleep disruption has been linked to development of neurodegenerative diseases such as certain dementias, including Alzheimer's disease.[3]

Furthermore, epidemiological evidence indicates that insomnia, short sleep duration and poor-quality sleep are associated with an increased risk of cardiovascular disease (CVD) and premature mortality.[8] Acute total sleep deprivation and continuous sleep restriction over prolonged periods alter cardiac function parameters such as heart rate and blood pressure. For example, in healthy subjects, restriction of sleep to 3.6 to 4.5 hours per night for 10 consecutive days increased heart rate by 5 beats per minute during sleep periods and by 22 beats per minute during sleep deprivation periods. Sleep deprivation results in increased blood pressure.[3] A 12-year follow-up survey of respondents with sleep problems reported positive correlation between sleep complaints and coronary artery disease in men[9] and an increased

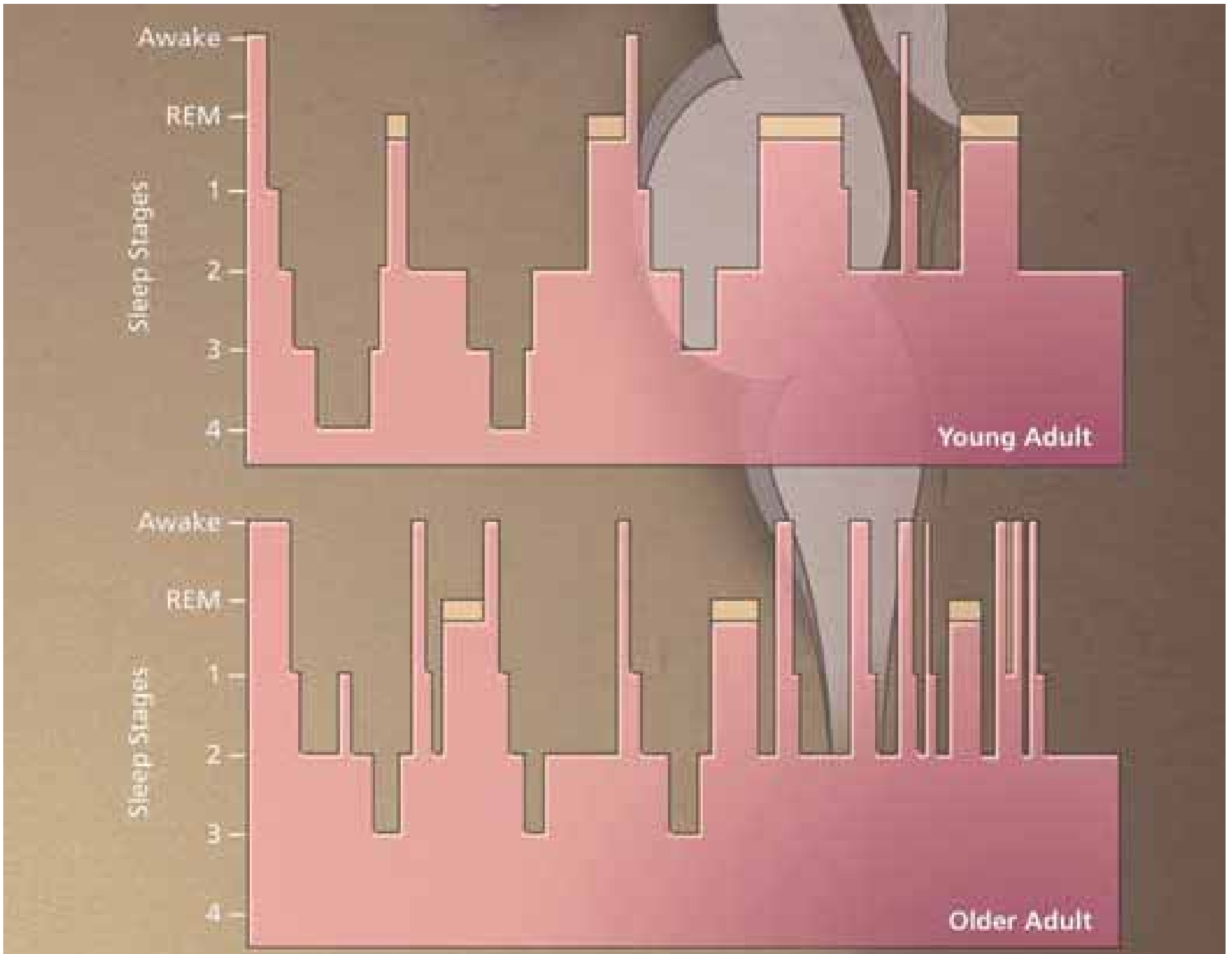
incidence of diabetes in men.[10] A better understanding of why we sleep is becoming possible as more research is uncovering the interplay between sleep and physical and mental health.

Insomnia

The essential feature of insomnia disorder is dissatisfaction with sleep quantity or quality with complaints of difficulty initiating or maintaining sleep. The sleep complaints are accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning. Persistent or chronic insomnia is specified if insomnia lasts for three months or longer.[11]

DSM-5 eliminated categories of primary and secondary insomnia

Figure 1: Sleep Changes in Older Adults



With aging, stage 1 sleep increases and stage 3 and 4 decrease. Nighttime awakenings occur more frequently.

and created the term "insomnia disorder" to cover both categories when insomnia is the predominant or stand-alone complaint. These diagnostic criteria allow for other sleep-, mental-, or physical disorders to be co-morbid. Importantly, DSM-5 requires the presence of co-morbidity to be specified as well as the duration of symptoms. Although often very difficult, identifying and treating comorbidities are paramount.

Insomnia is more common in women, older adults, and populations with medical and psychiatric disorders. Approximately 40% of individuals with insomnia have a comorbid psychiatric condition.[12,13]

Furthermore, insomnia symptoms and insomnia disorder may occur comorbidly with other primary sleep disorders and circadian rhythm disorders. In this context, insomnia symptoms may occur comorbidly with restless leg syndrome (RLS), periodic limb movement disorders (PLMD), sleep apnea hypopnea syndrome, delayed sleep-wake phase disorder and advanced sleep-wake phase disorder.[13]

Effects of Insomnia

Chronic insomnia causes substantial impairment in general quality of life. The 36-item Short Form Health Survey of the Medical Outcomes Study (SF-36) assesses 8 quality of life domains namely, physical functioning, role limitation due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitation due to emotional health problems, and mental health. Insomnia sufferers reported decreased quality of life on virtually all dimensions.[13,14]

Insomnia may lead to serious mental health issues. Studies on insomnia and related psychiatric disorders found that insomnia is a significant and independent risk factor for subsequent onset of depression. Insomniacs are 4 times more likely to suffer major depression.[15,16] Furthermore, the finding that depression is an equally strong risk factor for subsequent insomnia onset confirms a bidirectional relationship between the two conditions.[15]

Economic and COVID-19 Impact of Insomnia

There is substantial evidence that insomnia results in an enormous socioeconomic burden due to workplace productivity loss, absenteeism, and increased use of health care services. The annual cost of insomnia in Canada is an estimated $6.6 billion CAD, which includes insomnia-related health care use, prescription medications and over-the-counter medications.[17]

The COVID-19 pandemic raised significant health concerns. A 2020 study evaluating the impact of the COVID-19 pandemic on sleep and

psychological symptoms in a large sample of adults living in china demonstrated high rates of clinically significant insomnia, anxiety, and depression.[18] Social confinement, financial stress, fear, and anxiety associated with the anticipation of potential COVID-19 infection are factors that have upset simple routines of life with imminent negative mental health consequences and disruption in sleep.[19]

Treatment Options

There are essentially two modes of treatment for insomnia: pharmacotherapy and psychotherapy. Pharmacological interventions are employed in over 95% of all cases of insomnia and have shown robust effects in modulating insomnia symptomology. However, medications are frequently associated with undesirable side-effects.[20]

Currently, cognitive behavioural therapy for insomnia (CBT-I) is considered as first line in management of chronic insomnia. CBT-I is regarded as a safe treatment option because it is free of polypharmacy, adverse effects, dependency, and cognitive and psychomotor impairment.[21,22] Pharmacotherapy for chronic insomnia should be considered when CBT-I is not effective or unavailable. Combined pharmacologic treatment with CBT-I has shown better efficacy than CBT-I alone. Pharmacotherapy may be provided during the initial phases of CBT-I, but is encouraged to be discontinued in the CBT-I maintenance phase.[23]

Pharmacological Treatment of Insomnia: Benzodiazepines and Non-benzodiazepines

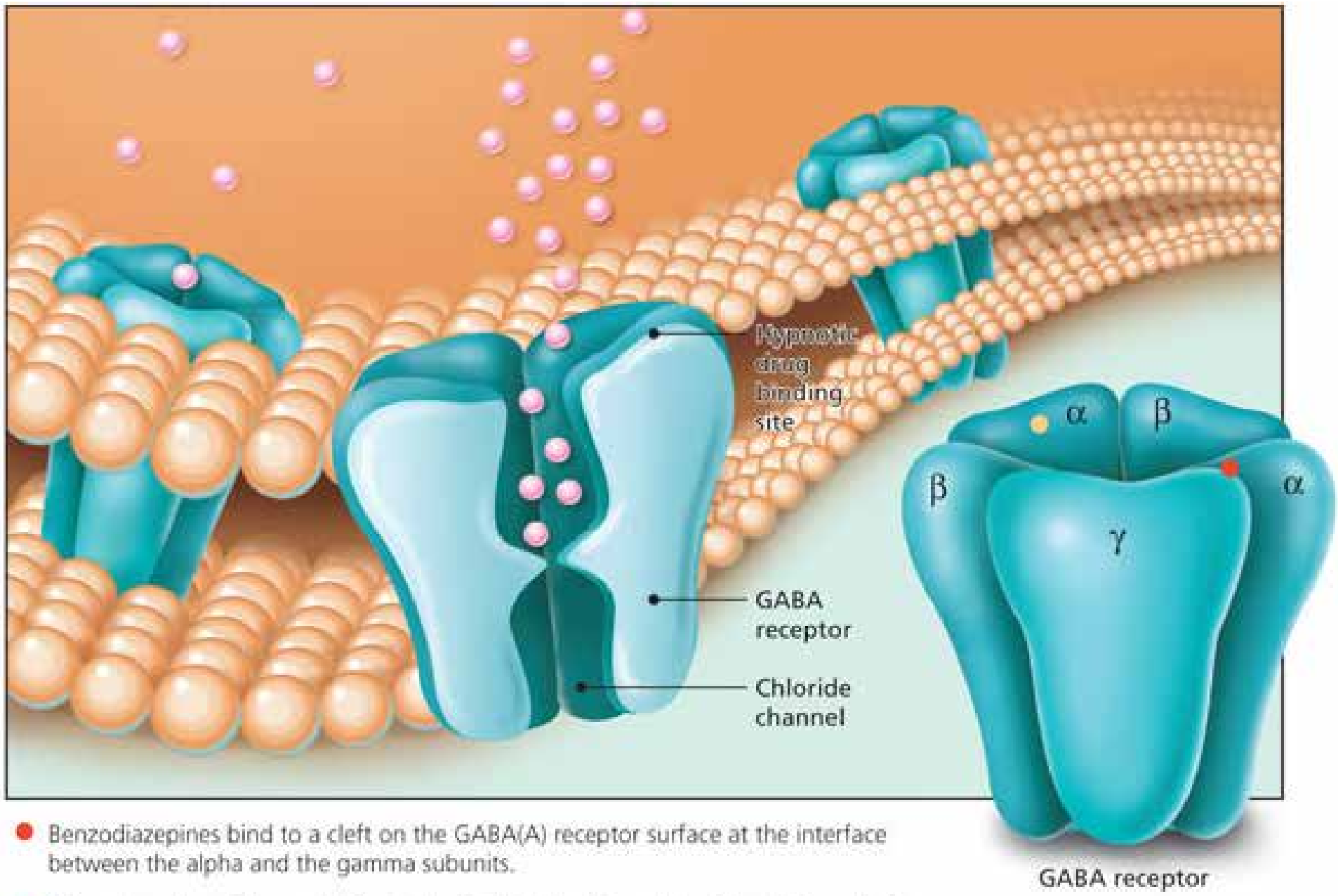
Benzodiazepines

In the 1960s the Food and Drug Administration (FDA) approved benzodiazepines that became the hypnotic of choice for treatment of insomnia. However, the addictive properties and potential withdrawal symptoms led to increasing concerns.[24,25]

Benzodiazepines can shorten sleep latency, decrease nocturnal awakenings, and increase total sleep time. Nevertheless, they also shorten REM sleep and reduce slow wave sleep. Side-effects include daytime fatigue, cognitive impairment, anterograde amnesia, respiratory depression, tolerance, dependence, and withdrawal symptoms.[26]

According to the American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents, and therefore their use in treating insomnia in the elderly should be avoided.[27] Moreover,

Figure 2: Molecular Target for Hypnotic Drugs



- Benzodiazepines bind to a cleft on the GABA(A) receptor surface at the interface between the alpha and the gamma subunits.
- Other drugs (zopiclone, zolpidem) also bind to the alpha subunit, but interact with amino acids in distinct binding domains to the benzodiazepines.

benzodiazepines have been associated with rebound insomnia that may occur after only one night of use.[26] Because of their addictive potential, benzodiazepines should be avoided in patients with a history of substance abuse.[28]

Non-benzodiazepines

The potential for harmful side-effects of benzodiazepines and off-label medications identified a need for a safer, more specific hypno-sedative for treatment of insomnia. The FDA first approved non-benzodiazepine hypnotics in 1992, and these are now referred to as "Z-drugs". These agents have since become the most prescribed hypnotic medications.[24] Structurally different from benzodiazepines, Z-drugs are positive allosteric modulators of GABAA receptors. They are considered to have higher affinity for the GABAA receptor subtypes and have more favorable treatment outcomes with lower side effects and lower abuse potential compared to benzodiazepines.

This class of medications comprise zopiclone, eszopiclone, zolpidem and zaleplon.[23]

In head-to-head comparisons with benzodiazepines, non-benzodiazepines have consistently demonstrated equivalent or even greater sedative efficacy. For instance, a large body of evidence indicates that zopiclone has similar efficacy to benzodiazepine but with good safety and tolerability profile. Compared with short-acting (triazolam, temazepam) and long-acting benzodiazepines (flurazepam, nitrazepam), zopiclone causes similar or lower residual sedation. In addition, rebound insomnia associated with benzodiazepine withdrawal is not common with zopiclone. Zopiclone has been used successfully to withdraw patients from benzodiazepines by initially switching from a benzodiazepine to zopiclone and a month later stopping zopiclone.[29]

Aside from the common adverse side-effects of headache, dizziness, and myalgia,[24] Z-drugs have been associated with cognitive impairment and parasomnias, for example, sleep driving, sleep eating, and having sex in sleep,[30] but less frequently compared to benzodiazepines.

Orexin and hypocretin receptor antagonists

Discovered in the late 1990s, the neuropeptide orexin is part of a signalling pathway in the lateral hypothalamus that plays an important role in sleep-wake cycles.[31,32] Orexin receptors regulate wakefulness and targeting these receptors to induce sleep and treat insomnia has become the subject of many experimental studies.[31] These newer agents have a very different mechanism of action. Simply, instead of increasing sleepiness, these newer agents represent a paradigm shift by decreasing arousal.[33]

There is anecdotal evidence that some patients experiencing insomnia as part of their hyperarousal symptoms associated with post-traumatic stress disorder (PTSD) may respond better with these agents that decrease arousal instead of increasing drowsiness.[34]

Common adverse effects associated with dual orexin receptor antagonists include dizziness, nasopharyngitis and headaches. No dependency or tolerance-inducing effects have been associated with these drugs. However, they are contraindicated in Narcolepsy.[24]

Suvorexant

Suvorexant was approved by the FDA in 2014 and was the first orexin antagonist released in the market.[24] Treatment with suvorexant has shown improvements in both subjective and objective polysomnography measures of sleep onset and sleep maintenance. Moreover, patients treated with

suvorexant reported better sleep quality and feeling refreshed in the morning.[31] Although clinical trials had shown that higher doses of suvorexant appeared more effective than lower doses, the higher doses caused next day somnolence. Considering the totality of the safety and tolerability data, the FDA's review of suvorexant supported the use of lower doses of 10mg to 20mg before bedtime.[31]

Lemborexant

The more recent orexin antagonist, lemborexant, was approved by the FDA in 2019.[24] A randomized double-blind trial showed that lemborexant improves sleep onset latency and sleep maintenance when compared to placebo and zolpidem.[36] Studies have shown that optimal therapeutic doses for lemborexant are between 2.5 mg and 10 mg before bedtime.[37]

Off-Label Pharmacological Treatment of Insomnia: Antidepressants

Off-label prescription of antidepressants, antipsychotics, and anticonvulsants for treatment of insomnia is a common practice. Disconcertingly, meta-analyses indicate that some off-label medications have been prescribed more than FDA-approved medications for insomnia.[38]

Doxepin

Doxepin is a tricyclic antidepressant that was approved for the treatment of insomnia by the FDA in 2010.[39] It is a potent H1 histamine blocker with significant sleep promoting effects in chronic primary insomnia.[40] A five-week study of adults with chronic primary insomnia suggests that 3mg and 6mg improve sleep maintenance without any next-day residual effects, rebound insomnia, or an increase in adverse effects as compared to placebo.[41] However, doxepin at higher doses is associated with undesirable anticholinergic side effects.[42]

Trazodone

Trazodone is one of the most widely prescribed off-label medications for treatment of sleep problems. It is an antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class that blocks post-synaptic serotonin receptors 5-HT1A, 5-HT1C, and 5-HT2, as well as post-synaptic alpha-1-adrenergic receptors.[43] Trazodone is not FDA-approved due to insufficient clinical data and is therefore used off-label for managing sleep difficulties in patients with and without depression.[44,45]

Despite it being a popular prescription choice among physicians for its sleep promoting effects, its efficacy has been deduced from small studies conducted in populations of depressed patients. These studies were usually associated with design

issues that lack showing objective efficacy.[43,45] Some adverse effects associated with trazodone include drowsiness, dizziness, tiredness, nausea, vomiting, orthostatic hypotension, and the rare occurrence of priapism.[45]

Off-Label Pharmacological Treatment of Insomnia: Antipsychotics

Quetiapine

Anecdotal evidence suggests that second-generation (atypical) antipsychotic agents are increasingly used to treat sleep problems, specifically, multi-acting receptor-targeted antipsychotics such as quetiapine and aripiprazole. Quetiapine is an antipsychotic approved for the treatment of schizophrenia, bipolar disorder, and in combination with other medications treats major depressive disorder. Its sedative and anxiolytic properties are believed to arise from antagonism at histamine type 1 (H1) and serotonin type 2A (5-HT2) receptors.[46]

Despite a lack of empirical evidence supporting the use of quetiapine for insomnia, the number of prescriptions for this indication continues to rise. Quetiapine is the most frequently prescribed antipsychotic for sleep promotion.[47] A 2011 meta-analysis found inconclusive evidence regarding quetiapine's efficacy for treating insomnia.[48]

Nevertheless, a pilot study assessing the ability of quetiapine to induce sleep found that objective and subjective parameters of sleep improved substantially. Total sleep time and sleep efficiency improved significantly from baseline to week 2 and week 6.[49]

Quetiapine is associated with adverse metabolic events, e.g., diabetes, hyperlipidemia, and obesity. Given these risks, the use of quetiapine for insomnia is not recommended.[46]

Over-the-counter medications

Melatonin and melatonin receptor agonists

Melatonin is a commonly used over the counter supplement for the treatment of insomnia and it is not FDA regulated; therefore, the stated dosages on products may not reflect actual dosages.[24] Melatonin is a hormone naturally produced in the body by the pineal gland and plays a role in maintaining and synchronizing circadian rhythm.[24]

Therapeutic use of melatonin and melatonin receptor agonists (e.g., Circadin, ramelteon, tasimelteon and agomelatine) is considered useful for jet lag, delayed sleep-wake phase disorder, and non-24-hour sleep wake disorder (more commonly seen in individuals with complete blindness). Time of melatonin administration is of critical importance[50] since optimal treatment effects are observed

SUMMARY OF KEY POINTS

Insomnia is a sleep disorder in its own right. It is no longer regarded as just a symptom. It calls for specific, targeted insomnia treatment, especially in situations where insomnia is comorbid with medical conditions.

Cognitive behavioural therapy for insomnia (CBT-I) produces moderate to large effects on insomnia measures when insomnia is comorbid with chronic medical conditions. It is the mainstay of treatment in most cases of chronic insomnia.

The use of hypnotics should be planned strategically. In general, short term hypnotic use should be the objective, but for many patients long term use may be necessary and appropriate.

when melatonin is timed and dosed individually.[51] Evidence for the use of melatonin and melatonin agonist receptors for the treatment of insomnia is vague, with short-term usage showing improvements in sleep quality and sleep latency, but its effects on total sleep time are less consistent.[52]

Adverse effects of melatonin include grogginess, irritability, nightmares, anxiety, and memory impairment, especially in higher doses.[24] Moreover, melatonin is associated with altering reproduction in animals and has recently been shown to cause early onset of puberty in girls.[53] Melatonin may be best administered as a chronobiotic, rather than for management of primary insomnia. Its precursor, tryptophan is a hypnotic and is successfully used for sleep[54] and non-rapid eye movement parasomnia in the pediatric population.[55]

Antihistamines

In addition to being involved in immune response and regulation of gastric release, antihistamines

CLINICAL PEARLS

The initial dose of sedative-hypnotics should be determined on an individual basis and titrated in accordance with the patients' needs. While too high dose is not desirable, too low a dose would result in under-treatment and is counter-productive.

Insomnia may become a chronic disorder and as such may necessitate long-term management. Prescribe carefully-chosen hypnotics for the requisite period and re-evaluate patients in follow up. Consider CBI-I as a treatment option, independently or in conjunction with pharmacotherapy.

also work as a neurotransmitter within the alerting system. Due to their side effect of drowsiness, antihistamines such as diphenhydramine have become a common over the counter sleep aid for insomnia.[24] Antihistamines have anticholinergic side effects including dry mouth, difficulty urinating, confusion and memory impairment.[24] Due to lack of demonstrated efficacy and safety concerns they are not recommended for insomnia.[25]

Cognitive Behavioural Therapy for Insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is considered the gold standard of treatment for chronic insomnia. It has been demonstrated convincingly as a very effective treatment and management option for this condition. However, there are several challenges associated with delivery of CBT-I, for instance, limited accessibility in remote areas, high cost and lack of availability of CBT-I trained therapists.[56,57] Development of digital CBT-I (dCBT-I) has overcome some of these limitations. Delivery through technological mediums such as internet, computers, smartphone applications and other devices have been explored. Recent studies have shown that dCBT-I has equally effective treatment outcomes compared to face-to face CBT-I.[56]

The role of CBT-I is to target non-adaptive thoughts and behaviours that perpetuate chronic insomnia. It consists of well-established therapeutic techniques, including cognitive therapy, stimulus control, sleep restriction, sleep hygiene and relaxation.[21,58] Once a person has learnt the techniques, they may return to it at a later stage if life events so dictate.

Cognitive therapy

The aim of cognitive therapy is to address dysfunctional beliefs and attitudes regarding one's impaired ability to fall asleep, triggering worry and anxiety that eventually lead to arousal that interferes with sleep. Cognitive therapy identifies and replaces these beliefs with more positive, adaptive, and sleep promoting beliefs and attitudes.[21,58]

Stimulus control

Stimulus control is a behavioural intervention that strengthens the association between bed and sleep and weakens the cues that have conditioned bed with anxiety and arousal leading to difficulty falling asleep. To achieve this, patients are asked to use the bed only for sleep; to leave the bedroom when they are unable to fall sleep and to return to bed only when they are sleepy.[21,58]

Sleep restriction

Sleep restriction is a misnomer and should preferably be referred to as "bed restriction." This behavioural

treatment for insomnia first establishes the average total sleep time of a patient by the patient logging their usual sleep time over a period of two weeks. The person with insomnia records their total time in bed that usually exceeds their actual total sleep time substantially. Treatment starts with the patient being given a restricted total in-bed time approximating their logged total sleep time. The goal is to increase sleep drive, consolidate sleep, and reduce time awake in bed.

The efficacy of this treatment option equates that of medication and is more enduring. However, positive results are usually experienced only after several weeks of sustained effort.[21,58]

Sleep hygiene and relaxation

Sleep hygiene aims to encourage behaviours and environmental conditions that are conducive to promote improved quality and quantity of sleep.[21] Practice of behaviours such as avoiding long daytime naps, limiting alcohol and caffeine intake before bed are recommended.[58] Similarly, the goal of relaxation techniques is to decrease physiologic and cognitive arousal through meditation, diaphragmatic breathing, and biofeedback.[21]

Sleep hygiene is not regarded as a stand-alone treatment for insomnia but forms a component in the overall management of those suffering from insomnia.

Conclusion

Insomnia is a common problem that may present in isolation or with comorbidities. Regardless of the underlying pathophysiology, treating insomnia is of paramount importance due to pivotal role of sleep in human physiological functioning. Sleep has been implicated in consolidation of memory and new learning. Sleep deprivation can have a drastic impact on physical and mental health including increased risk of cardiovascular disease, premature mortality and development of later onset depression.

Several classes of medications, including benzodiazepines, non-benzodiazepines (Z-drugs), antidepressants, antipsychotics, over the counter sleep aids and the newer class orexin receptor antagonists are employed in the management of insomnia. CBT-I remains the mainstay of treatment for chronic insomnia.

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