Original Article

Role of optimum diagnosis and treatment of insomnia in patients with hypertension and diabetes: A review

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Abstract

Sleep plays a pivotal role in regulation and function of the central nervous system (CNS) and other physiological functions of the body such as regulation of body temperature, metabolism, catabolism, learning, and memory consolidation. Therefore, sleep is not a mere passive state, but it is a highly organized interaction of neural networks and neurotransmitters of the CNS which maintain active neurobehavioral state. However, in insomnia normal physiological function is disturbed which results in several comorbidities such as depression, cardiovascular disorders, hypertension, diabetes mellitus, breathing difficulties, chronic pain, and gastrointestinal problems which affect the quality of life. Diagnosis of insomnia requires a comprehensive assessment of patient's medical history, physical examination, and sleeping pattern using various screen tools. There are several options available for the treatment of insomnia such as non-pharmacological and pharmacological that increase our understanding of the involvement of neurophysiological, neurobehavioral, neurochemical, neurocognitive, and neuroendocrine factors associated with insomnia. The pharmacological agents that are currently in use for the treatment of insomnia include benzodiazepines (BZDs), non-BZD hypnotics, and ramelteon as well as antidepressants such as doxepin. However, due to adverse events and addiction potential, use of BZDs is obsolete. Among non-BZD, zolpidem is the highly prescribed drug for the treatment of insomnia, globally. This review article focuses on prevalence, pathophysiology, diagnosis, and treatment of insomnia in patients with hypertension and diabetes. In addition, it also discusses the role of zolpidem in comparison to BZDs in the management of insomnia.

Keywords: Diabetes mellitus, hypertension, insomnia, zolpidem

Introduction

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), insomnia is the hindrance in sleep initiation and maintenance, inability to restore sleep, and early morning awakenings despite adequate sleep, resulting in impairment of daytime functioning.[1]

Various international and Indian studies have reported varied degree of insomnia prevalence.[2-9] Elderly, postmenopausal women, family or personal history of insomnia, psychological, and biological predisposition have a high risk of insomnia.[2,7,9] Insomnia affects concentration and memory, leading to deteriorated cognitive, social, and vocational well-being. It increases the risk of industrial accidents/road accidents, depression, cardiovascular disorders, hypertension, and diabetes mellitus, breathing difficulties, chronic pain, and gastrointestinal problems which in turn decrease the quality of life.[10]

This review highlights the new changes in the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) criteria of insomnia disorders, association of insomnia with hypertension and diabetes, and various management strategies for insomnia. Furthermore, this review stressed on rampant use of unapproved drugs for insomnia in India along with their disadvantages.

Methodology

We searched electronic databases, namely, PubMed and Google Scholar to identify relevant articles. The search did not filter

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Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_337_17

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How to cite this article: Garg H. Role of optimum diagnosis and treatment of insomnia in patients with hypertension and diabetes: A review. J Family Med Prim Care 2018;7:876-83.

articles based on specific time duration, however; recent articles were preferred. Articles published in English language were considered for inclusion. Articles elaborating classification, risk factors, pathology, diagnostic techniques, treatment of insomnia, and association with comorbidities such as hypertension and diabetes mellitus were searched.

Search terms were insomnia AND co-morbidities AND diabetes AND hypertension; insomnia AND diagnosis AND classification AND impact on daily activities; insomnia AND treatment AND benzodiazepines OR non-benzodiazepines OR zolpidem OR anti-depressants OR hypnotics. Two independent reviewers conducted separate searches and reviewed the articles separately.

Results

Selection and inclusion of studies

The present narrative review included studies as per the above-mentioned criteria. Overall, we identified 326 articles from PubMed and Google Scholar. Two independent reviewers then carefully read the titles and abstracts of all the articles, after which 259 articles were found relevant. The full texts of these articles were procured and evaluated for inclusion. Overall, 58 articles were found relevant for inclusion and were used for the preparation of this review.

Classification of sleep disorders based on DSM-5 criteria

DSM-5, 2013, a diagnostic tool, has comparatively similar criteria to ICSD-3. It classifies insomnia under an umbrella term "insomnia disorders" where both primary and secondary insomnia are combined. Classification of sleep disorders based on different screening criteria is described in Table 1.[1]

Insomnia with comorbidity

Glidewell *et al.* demonstrated the prevalence of insomnia with comorbid medical conditions in 86% of individuals.[11] Terzano *et al.* found that among 3284 patients with insomnia, common comorbidities were cardiovascular (35%), musculoskeletal, connective tissue (28%), digestive system (19%), and endocrine and immune system diseases (16.9%).[12] Another study reported heart disease (21.9%), hypertension (43.1%), neurologic disease (7.3%), breathing problems (24.8%), urinary problems (19.7%), chronic pain (50.4%), and gastrointestinal problems (33.6%) as comorbidities.[13] Assessment and diagnosis of insomnia with comorbidities should be thoroughly evaluated based on comorbid medical and psychological conditions. Review of complete medical and psychiatric history is essential for diagnosis of insomnia with comorbidities.[14] Commonly observed comorbidities with insomnia are presented in Table 2.[14] Hypertension and diabetes mellitus in insomnia patients have been discussed in subsequent sections.

Insomnia and hypertension

Hypertension in insomnia patients is well-established in several studies. Panda *et al.*, in a study involving South Indians with insomnia, reported hypertension in 42.6% of patients.[4] A recent Indian study reported insomnia among hypertensive population as approximately 47.2% [*N* = 310; 95% confidence interval (CI): 43.4, 51.0]. Of these, newly diagnosed with insomnia using Athens Insomnia Scale (AIS) scale was higher as compared to patients already diagnosed with insomnia [34.9% (95% CI: 31.2, 38.5) vs. 12.3% (95% CI: 9.81, 14.8)], respectively. Additionally, a total of 123 (18.7%) patients (of 657 patients) were newly diagnosed with hypertension, of which of 62 (50.4%) patients were insomniacs suggesting that insomnia is prevalent in newly diagnosed hypertensive patients.[15] Taylor *et al.* reported that the prevalence of hypertension is 43.1% in patients with insomnia as compared to 18.7% in individuals without insomnia.[13]

Association between insomnia and hypertension

Sleep maintains the body balance by suppressing stress and proinflammatory pathway. However, in insomnia, both pathways cause activation of neuroendocrine stress

Table 1: Insomnia disorder diagnostic screening criteria (DSM-5)

Diagnostic criteria
Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening.
The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, *behavioral*, or other important areas of functioning.
The sleep difficulty occurs at least three nights per week, is present for at least 3 months, and despite adequate opportunity for sleep.
Insomnia does not co-occur with another sleep disorders.
Insomnia is not explained by coexisting mental disorders or medical conditions.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Edition 5. Adapted from: Macedo PJ, *et al.* Insomnia current diagnosis: an appraisal. Rev Bras Neurol 2015;51:62-8.

Table 2: Coexisting morbidities in patients with insomnia[18]

System	Examples of disorders, conditions, and symptoms
Neurological	Stroke, dementia, Parkinson's disease, seizure disorders, headache disorders, traumatic brain injury, peripheral neuropathy, chronic pain disorders, neuromuscular disorders
Cardiovascular	Angina, congestive heart failure, dyspnoea, dysrhythmias
Pulmonary	COPD, emphysema, asthma, laryngospasm
Digestive	Reflux, peptic ulcer disease, cholelithiasis, colitis, irritable bowel syndrome
Genitourinary	Incontinence, benign prostatic hypertrophy, nocturia, enuresis, interstitial cystitis
Endocrine	Hypothyroidism, hyperthyroidism, diabetes mellitus
Musculoskeletal	Rheumatoid arthritis, osteoarthritis, fibromyalgia, Sjögren syndrome, kyphosis
Reproductive	Pregnancy, menopause, menstrual cycle variations
Sleep disorders	Obstructive sleep apnea, central sleep apnea, restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorders, parasomnias
Other	Allergies, rhinitis, sinusitis, bruxism, alcohol and other substance use/dependence/withdrawal

COPD: Chronic obstructive pulmonary disease. Adapted from: Schutte-Rodin S, *et al.* Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4:487-504.

systems, that is, autonomic sympathoadrenal system and hypothalamic–pituitary–adrenal axis.[16] Stages 3 and 4 (N3, the third stage) of non-rapid eye movement (NREM) sleep are often referred to as deep sleep or slow-wave sleep (SWS) and are considered "restorative" period of sleep. In healthy adults, ≈20% of sleep time is spent in SWS.[17] SWS is characterized by increased vagal tone and reduced sympathetic activity which decreases heart rate (HR), blood pressure (BP), and cardiac workload. On an average, BP declines by 10%/10 mmHg/more during sleep. This is referred to as "dipping" and those not experiencing this are "non-dippers."[18] In case of sleep deprivation, rapid eye movement (REM) and NREM, sleep excite sympathetic nervous system during the night, resulting in increased BP persisting during daytime.[19]

Sleep duration and hypertension

Sleep duration has an impact on onset and severity of hypertension in insomniacs. A study evaluating hypertension incidence in insomniacs demonstrated an increase in sleep onset latencies of >30 min resulting in severe hypertension (odds ratio: 0.83; CI: 0.51, 1.34) than general population. Furthermore, wake after sleep onset of >30 min significantly increased hypertension severity ($P \leq 0.05$).[20] The National Health and Nutrition Examination in the United States in a study showed that shorter sleep duration (≤5 h) increased hypertension risk (13%) in individuals (32–59 years) after controlling obesity and diabetes.[21] Fernandez-Mendoza *et al.* reported that both chronic insomnia ($P = 0.004$) and objective short sleep duration ($P = 0.003$) were significantly associated with occurrence of hypertension.[22] Inadequate quantity and poor quality of sleep leads to increased sympathetic activation and decreased parasympathetic activation leading to stress.[19]

Insomnia and diabetes

Sleep plays an important role in regulating metabolic functions and glucose homeostasis.[23] Taylor *et al.* reported that 13.1% of insomniacs have diabetes as compared to 5% patients without insomnia. Additionally, insomnia was observed in 47.4% of patients with diabetes.[13] Gottlieb *et al.* reported a significant difference ($P < 0.001$) in diabetes mellitus incidence between <5 h sleep/night (32.8%) as compared with >9 h sleep/night (24.2%).[24] A meta-analysis of 10 studies (107,756 patients), showed that diabetes risk in individuals with short sleep (≤5 or <6 h) and problem with sleep maintenance were 28% and 84%, respectively.[25] Poor sleep quality and less sleep efficiency (SE) are significantly ($P < 0.05$) associated with increased glycated hemoglobin level.[26] Another study reported that sleep of ≤4 h for six nights reduced glucose tolerance by 40%.[23]

Untreated insomnia results in fluctuating glycemic levels among diabetics. Tsai *et al.* showed that patients with diabetes ($N = 46$) being treated for over a year had poor sleep quality ($n = 16$, 34.8%) and most of these ($n = 14$, 87.5%) had poor glycemic control (A1c ≥7%). Furthermore, inefficient sleep was associated with poor glycemic control (level of A1c: $r = 0.54$, $P < 0.05$).[26]

Pathophysiology of insomnia-associated diabetes

Sleep is associated in modulating insulin production, insulin sensitivity, glucose use, and glucose tolerance through the night.[27] Inadequate sleep activates the sympathetic nervous system, which inhibits insulin release and increases glucose levels. Overactivity of the sympathetic nervous system leads to insulin resistance. Sleep deprivation is associated with disturbed secretion of counter-regulatory hormones such as cortisol and growth hormones.[23] Evidence has shown that ≤4 h of sleep for six nights changes the release pattern of growth hormone, from a normal single pulse to a biphasic pattern.[28] High growth hormones lead to higher glucose levels.[23] Partial sleep loss can increase inflammatory cytokine production or inflammation, or both contributing to increased insulin resistance. Furthermore, chronic sleep loss can cause low-grade inflammation that may lead to insulin resistance and diabetes.[23,29]

Diagnosis and treatment patterns of insomnia

Early insomnia diagnosis contributes to prevention of insomnia-related complications. Inadequate diagnosis results in aggravated insomnia-related comorbidities. A survey conducted by the National Sleep Foundation in the United States ($N = 1000$) reported that 50 (5%) of 1000 patients who participated consulted their physician for insomnia, whereas 300 (30%) patients never discussed their sleep problems with a physician.[30] In India, the scenario is no different as a cross-sectional, observational study conducted among corporate employees ($N = 602$) reported insomnia in 83 (13.8%) participants, of which only 3 (3.6%) participants were clinically diagnosed with insomnia in past and the remaining 80 (96.4%) participants were not diagnosed.[9] These studies suggest that insomnia is often undiagnosed and neglected due to lack of consultation in primary care settings. Diagnostic techniques must be adequately used for identifying insomnia to facilitate optimum management.

Diagnosis of insomnia

Diagnosis starts with collection of information, namely, sleep history, sleep-wake pattern (confirmed by patient's partner), family history especially among first-degree female relatives, psychiatric conditions, concomitant medication, and previous treatment for insomnia.[31] There are several screening tools for the diagnosis of insomnia available such as AIS, insomnia severity index, and Pittsburgh Sleep Quality Index.[2,32]

Treatment of insomnia

The primary objectives of insomnia treatment are to improve sleep quality and quantity and to improve daytime function using non-pharmacological or pharmacological treatment.[14,33]

Non-pharmacological treatment for insomnia

General psychotherapy and behavioral therapies are effective and recommended. These therapies reduce potentiated autonomic and cognitive arousal, modify bad sleeping habits, modulate wrong perception and beliefs about sleep, and promote the healthy sleeping practices.[34] These include the following:

Sleep hygiene: It involves educating patients about different behavioral and environmental factors that can affect sleep. Features in maintaining sleep hygiene are listed in Table 3.[35]

Stimulus control therapy: It is designed to eliminate negative association between the bed and undesirable outcome due to lack of sleep such as wakefulness, frustration, and worry.[14] This technique follows a specific protocol which helps the patient fall asleep. This includes going to bed only when sleepy, maintaining a regular schedule, avoiding daytime naps, using the bed only for sleep, if unable to fall asleep (or back to sleep) within 20 min, and indulge in relaxing activity until drowsy and then return to bed.[14]

Sleep restrictions: Recommended for patients with chronic insomnia, this technique restricts the amount of time in the bed to the amount of total time spent sleeping. The therapy is effective in patients with SE less than 85%. Over a period, there is increased SE and decreased sleep latency.[34]

Cognitive strategies: This strategy is designed to change the negative perception and beliefs that are responsible for insomnia. Anxiety or unrealistic expectations of sleep may cause emotional breakdown that could increase sleep disturbance and start a noxious cycle. Helping patients combat negative attitude decreases anxiety and arousal associated with insomnia. Patients must stay motivated to replace self-negative thoughts with more adaptive, realistic, and optional interpretations based on past evidence.[34]

Relaxation techniques: These techniques are recommended to mitigate heightened arousal (physiological or cognitive) during night or daytime. For somatic arousal, progressive muscle relaxation and autogenic therapies are recommended, whereas for cognitive arousal, imagery training and thought prevention therapies (e.g., meditation) are recommended.[35] Progressive muscle relaxation training involves methodical tensing and relaxing different muscle groups throughout the body.[14]

Pharmacological treatment of insomnia

While considering pharmacotherapy, choice of pharmacological agent should be based on sign and symptoms, aim of treatment, medical history, cost, feasibility of optional treatments, associated conditions, contraindications, drug–drug interactions, and adverse events (AEs).[34]

Table 3: Features of sleep hygiene

Different features of sleep hygiene
Set and maintain a regular bedtime, every night.
Avoiding exercise 3 h before bedtime.
Having dinner at least 2 h before bedtime.
Avoiding consumption of caffeine, alcohol, or smoking at least 3 h before bedtime.
Enjoy a relaxing bedtime routine for an hour before bedtime.
Make sure that the bedroom is dark, quiet, and comfortable (appropriate temperature).
Make sure that the bed is comfortable.
Avoid daytime naps.
Exercise regularly. Avoid inactivity during the day.
Avoid emotionally upsetting activities close to bedtime

As per clinical guidelines for insomnia management, the following sequence of pharmacological treatment (alone or in combination) is recommended:[34]

- Short-intermediate acting benzodiazepine receptor agonists (BZD or newer BzRAs) or the melatonin receptor agonist such as ramelteon
- Alternate short-intermediate acting BzRAs or ramelteon (ineffective initial agent)
- Sedating antidepressants such as trazodone, amitriptyline, doxepin, and mirtazapine
- Combined BzRAs or ramelteon and sedating antidepressant
- Other sedating agents, namely, anti-epileptics and atypical antipsychotics.

All Food and Drug Administration (FDA)-approved drugs for the treatment of insomnia with their pharmacokinetic properties are summarized in Table 4.[36-38]

BZD receptor agonist hypnotics

Mechanism of action of BzRAs

This class includes both BzRAs and non-BzRA hypnotic derivatives. The major difference in the mechanism of action for BZDs and non-BZDs is that the BzRAs selectively bind to any of α-subunits 1, 2, 3, and 5 of $GABA_A$ and produce hypnotic, anti-convulsant, myorelaxant, and anxiolytic effects. While non-BZDs selectively bind to a α-1 subunit of $GABA_A$ and produce only hypnotic effects.[34]

BZDs: The US FDA has approved the use of immediate-release BZDs such as triazolam (short-acting); estazolam and temazepam (intermediate-acting); and flurazepam and quazepam (long-acting) for treating insomnia.[36] BZDs are not suitable for patients with chronic insomnia as they cause dependence and tolerance on long-term use due to which they are used to treat short-term insomnia. They are also associated with excessive sedation, motor incoordination, cognitive impairment, and anterograde amnesia.[39,40]

Non-BZDs: The non-BzRA hypnotics, also known as Z-drugs, were introduced to minimize AEs and addiction associated with BZDs. The newer generation hypnotics approved by the FDA are eszopiclone, zaleplon, zolpidem, and zopiclone. These drugs decrease sleep latency, increase total sleep time (TST), and quality of sleep except for zaleplon which is effective for decreasing sleep latency.[41,42] According to a meta-analysis (13 studies, $N = 4378$), non-BZDs (Z-drugs) improved polysomnographic sleep onset (95% CI, −0.57, 0.16) and subjective sleep onset (−0.33, −0.62, 0.04).[43]

Selective melatonin receptor agonists

In 2005, FDA introduced ramelteon as a selective melatonin receptor agonist with an entirely new mechanism of action effective in reducing sleep latency among patients with chronic

Table 4: FDA-approved drugs for the treatment of insomnia with their pharmacokinetic properties

Name	Dosage (mg)	Binding receptors	Time to peak plasma concentration (h)	Major active metabolites	Elimination
BZDs					
Triazolam[36,37]	0.125, 0.25	α-1, -2,-3, and -5 of $GABA_A$	1.5-5.5	No active metabolites	Renal
Flurazepam[36,37]	15, 30	α-1, -2,-3, and -5 of $GABA_A$	0.5-2.3	N_1-hydroxyethylfurazepam and N_1-desalkylflurazepam	Renal
Quazepam[36,37]	7.5, 15	α-1, -2,-3, and -5 of $GABA_A$	0.5-2	2-oxoquazepam and N-desalkyl-2-oxoquazepam	Renal, feces
Estazolam[36,37]	1, 2	α-1, -2,-3, and -5 of $GABA_A$	0.5-6	1-oxo-estazolam and 4-hydroxy-Estazolam	Renal
Temazepam[36,37]	15, 30	α-1, -2,-3, and -5 of $GABA_A$	1.2-1.6	N-desmethyl temazepam and O-conjugate of temazepam	Renal
Non-BZDs					
Zolpidem IR[36-38]	5, 10	α-1 subunit of $GABA_A$	1.6	No active metabolites	Renal
Zolpidem MR[36-38]	6.25, 12.5	α-1 subunit of $GABA_A$	1.5	No active metabolites	Renal
Eszopiclone[36,37]	1, 2, 3,	α-1 subunit of $GABA_A$	1	(*S*)-*N*-desmethylzopiclone and (*S*)-zopiclone-*N*-oxide	Renal
Zaleplon[36,37]	5, 10, 20	α-1 subunit of $GABA_A$	1	5-oxo-zaleplon and 5-oxo-desethylzaleplon	Renal
Melatonin receptor agonist					
Ramelteon[36]	8	Melatonin receptor (MT_1 and MT_2)	0.5-1.5	M-II	Renal, feces
Sedating antidepressant					
Doxepin[37]	3, 6	Histamine receptors (H_1)	3.5	N-desmethyldoxepin	Renal
Orexin receptor antagonist					
Suvorexant[36]	5, 10, 15 20	Orexin 1- and Orexin 2-receptors	0.5-6	No active metabolites	Feces

FDA: Food and Drug Administration; MT1: Melatonin receptor 1; MT2: Melatonin receptor 2; M-II: Ramelteon metabolite; H1: Histamine receptor 1

insomnia. Ramelteon selectively binds to melatonin receptors MT_1 and MT_2 which are highly concentrated in the hypothalamic suprachiasmatic nucleus (SCN). Melatonin receptor agonist shows no signs of withdrawal symptoms or rebound insomnia on discontinuation with long-term use.[36]

Sedating antidepressants

Doxepin is an older sedating tricyclic antidepressant drug approved by the FDA and was recently reintroduced in low dose for sleep onset and sleep maintenance.[35] Doxepin selectively binds and antagonizes histamine receptors (H_1) in tuberomammillary nucleus and inhibits the arousal pathway, thus producing hypnotic effect.[43]

A study evaluating the safety and efficacy of doxepin (1, 3, and 6 mg) in adults (N = 67) revealed that all the three doxepin doses showed significant ($P < 0.0005$) increase in sleep duration, TST, and overall SE as compared to placebo.[44,45] The NIH State of Science Conference on insomnia stated that "all anti-depressants have potentially significant AEs," raising concerns about the risk–benefit ratio.[46]

Orexin receptor antagonists

In 2014, FDAa pproved suvorexant as a potent orexin receptor antagonist for the treatment of insomnia, especially for sleep onset and sleep maintenance. Orexin A (hypocretin 1) and B (hypocretin 2) are neuropeptides that regulate wakefulness and sleep by acting on Orexin-1 (OX-1) and Orexin-2 (OX-2) receptors. These neuropeptides promote wakefulness, appetite, metabolism, reward, stress, and autonomic function and regulate the sleep–wake cycle.[34,39] Suvorexant binds to these receptors reversibly to elicit its action.[47] The recommended dose is 10 mg once at night and can be upgraded to 20 mg. The most common AE is somnolence.[41]

Suvorexant [10 mg (N = 62), 20 mg (N = 61), 40 mg (N = 59), or 80 mg (N = 61)] was assessed for the treatment of primary insomnia (N = 19) in a randomized, double-blind, placebo-controlled (N = 249), 4-week crossover polysomnography study which reported significant improvement in SE ($P < 0.01$) as compared to placebo.[47]

Suicidal ideation seen with higher doses and mood-related AEs needs monitoring. Orexin-2 receptor antagonists play a major role in regulating sleep/wakefulness as compared to the OX-1 receptor. Thus, pharmacology of a more selective antagonism should be properly elucidated.[39]

Role of melatonin: Melatonin hormone is a sleep regulator released by the pineal gland at night. Its secretion is electrically activated by SCN at night and inhibited during the day. Melatonin is a weak hypnotic for non-circadian insomnia. Elderly patients with insomnia produce low levels of melatonin.[48]

Buscemi *et al.* concluded that short-term (≤4 weeks) use of melatonin is not effective for primary and secondary sleep disorders. However, they suggested that short-term (≤3 months) use of melatonin is safe and effective in treating delayed sleep phase syndrome.[49,50]

Comparison between benzodiazepines and zolpidem: Role in management of insomnia

The older BZDs and the newer non-BZDs are the most commonly used drugs for the treatment of insomnia. However, from a survey conducted in Germany and the United Kingdom, general physicians perceived that Z-drugs are more effective and safer in comparison to BZDs due to lesser side effects.[51] Here, we compare BZDs and zolpidem in the management of insomnia.

Structural difference

There is a major structural difference between BZDs and zolpidem: BZDs contain benzene ring, whereas Z-drugs lack benzene ring.[34,41]

Receptor selectivity and its action: BzRAs non-selectively bind to any of the alpha subunits 1, 2, 3, and 5 of $GABA_A$, whereas Z-drugs selectively bind to alpha 1 subunit of $GABA_A$.[34,41,52]

Hypnotic efficacy: Polysomnographic recording and subjective data indicate that zolpidem decreases sleep latency by approximately 30–40 min, increases TST by 1 h, and increases SE (TST/total time in bed) in patients with chronic and transient insomnia.[53]

Effect on sleep architecture: Effects of BZDs and Z-drugs on sleep architecture are different. BDZs are known to reduce Stage 3–4 sleep (SWS). For instance, estazolam (2 mg) and temazepam (15 and 30 mg) reduced Stage 3–4 sleep from 4% to 1% in 35-year-old insomnia patients and from 8% to 5% in 38-year-old insomnia patients, respectively.[54] Reduced SWS may result in increased HR, BP, and peripheral resistance.[18] BZDs also suppress REM sleep, and withdrawal of them results in REM rebound and may result in vivid and frightening dreams in some individual.[53,54] A meta-analysis was done on 11 studies in 579 healthy volunteers and 12 studies in 202 insomniac patients to find the effect of zolpidem on sleep architecture through polysomnography. It suggested that as compared to BZD, 10 mg of zolpidem does not alter sleep architecture: it moderately increases Stage 2 NREM, it slightly increases Stages 3 and 4 NREM (SWS), when it is reduced, and it does not decrease REM sleep.[55]

Dose and duration

The recommended dose of zolpidem for short-term insomnia in non-elderly patients is 10 mg and in elderly patients 5 mg. For the only middle of the night awakening, the recommended sublingual zolpidem tartrate dose is 1.75 and 3.5 mg, respectively.[52] According to clinical practice guidelines, hypnotics are prescribed for short (2–4 weeks) and intermittent (until the patient attains acceptable sleep cycle) duration.[54] The elimination half-life is short (2.4 ± 0.2 h) and the duration of action is up to 6 h.[56]

Safety profile

Based on persistent symptoms, many insomnia patients take hypnotics longer than 4 weeks raising long-term efficacy concerns. A placebo-controlled trial accessed the effect of zolpidem across 6 months and reported no signs of withdrawal, tolerance, rebound insomnia, or next-morning residual effects. Another placebo-controlled randomized controlled trial reported that nightly zolpidem 10 mg (5 mg for patients above 60 years) was more efficacious than placebo in patients receiving it for 8 months.[57] Roehrs *et al.* conducted a placebo-controlled trial in individuals with primary insomnia (N = 33) over 12 months against nightly zolpidem use and found no withdrawal or rebound symptoms.[58]

Regulatory status of hypnotics

According to Drug and Cosmetics Act (2nd Amendment, 2006), alprazolam, clonazepam, and zolpidem were Schedule H drugs.[59] However, to avoid the irrational drug use particularly of antibiotics and sedatives, in 2013, the Government of India, Ministry of Health and Family Welfare, introduced Schedule H1 drug and listed alprazolam and zolpidem as Schedule H1 drugs but not clonazepam.[60,61] The Central Drugs Standard Control Organization (CDSCO) approved clonazepam in the treatment of absence and myoclonic seizures (1995), alprazolam for short-term symptomatic treatment of anxiety and depression (1997), and zolpidem for short-term treatment of insomnia (1999).[62] Alprazolam and clonazepam are not approved by CDSCO for the treatment of insomnia.[63] Combination of zolpidem and melatonin is an irrational fix dose combination and not approved by Drug Controller General of India.[63]

Conclusion

In conclusion, diagnosis of insomnia at an early stage using the right technique is beneficial for the optimum management of the condition. Although all patients may not respond in a similar manner to a treatment, evaluating risk–benefit ratio of the drug being used is extremely important. In addition, administration of the right drug after a careful evaluation of the risk groups and dependence factor is warranted to achieve maximal benefit from the drug. Studies showed that insomnia is commonly seen in patients with hypertension and diabetes which demand the need to assess all hypertensive and diabetes patients for insomnia to avoid undiagnosed cases of insomnia.

This review has discussed in detail regarding comorbidities associated with insomnia and effect of insomnia on patients with diabetes and hypertension. However; being a narrative review, it did not include exhaustive analysis of the literature included unlike systematic reviews and meta-analyses which may be considered as a limitation of this review. Although there are limitations to this review, discussion of various aspects of insomnia in this review may be considered as a strength. The

review has elaborated the impact of insomnia treatment in patients with diabetes and hypertension by highlighting impact of specific outcomes among these patients.

Development of a treatment protocol for the management of insomnia may improve outcomes which may be considered as future directions for further advance in insomnia. These strategies are particularly important to prevent the progression of the related comorbidities associated with insomnia which in turn improves the overall well-being and quality of life of the patient. In addition, larger studies evaluating the association of insomnia with diabetes mellitus and hypertension may prove helpful.

Acknowledgement

The authors acknowledge Turacoz Healthcare Solutions (www.Turacoz.com), Gurugram, India, for their writing support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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