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Pharmacological Treatment of Insomnia – Drug Classes, Mechanisms, Risk Factors for Dependence and Clinical Consequences of Long-Term Therapy

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ABSTRACT

Introduction

Insomnia is a widespread sleep disorder impacting quality of life and overall health. While non-pharmacological approaches are effective, pharmacological treatment remains essential, especially in chronic or severe cases. Over time, various sleep-inducing drugs have been developed, targeting different neurochemical pathways. However, prolonged use may lead to tolerance, dependence, cognitive decline, and rebound insomnia.

Aim of the Study

This review aims to provide an overview of pharmacological treatment of insomnia, emphasizing drug mechanisms, dependence risk factors, and the clinical consequences of long-term therapy. Understanding these elements is vital for optimizing treatment and minimizing harm.

Materials and Methods

The review is based on literature from PubMed and Google Scholar, using search terms such as “Sleep Disorders Treatment,” “Insomnia,” and “Sleep Drug Dependence.”

Conclusion

Pharmacotherapy plays a key role in insomnia management when non-drug methods are insufficient. Though effective short-term, these medications pose risks if used long-term. Clinicians must understand the pharmacodynamics and associated risks to guide safe, informed treatment. This review underscores the need for cautious prescribing, routine monitoring, and combining drug therapy with behavioral interventions. Future research should prioritize safer options that retain efficacy while minimizing addiction potential.

Keywords

Insomnia; Sleep Disorders; Drug Dependence; Tolerance; Withdrawal Syndrome; Cognitive Impairment

Introduction

Among the most frequently observed clinical issues are sleep disorders, which, when left untreated, can impair essential aspects of daily functioning, including physical health, mental well-being, social interactions, and emotional stability (1). A lack of proper sleep has been linked to an increased risk of developing conditions such as obesity(2), diabetes(2), cardiovascular disease(3), and depression (4). Additionally, inadequate sleep and sleep disorders impact metabolic health, and metabolic dysfunction can likewise impair sleep quality (2).These disorders include a wide range of issues related to sleep, such as trouble falling asleep, poor sleep quality, waking up too early, disruptions in circadian rhythms, parasomnias, movement-related sleep disorders, and breathing disorders during sleep (5). A common result of these conditions is excessive tiredness during the day. Moreover, people suffering from sleep problems often experience difficulties in carrying out daily cognitive tasks including memory, attention, alertness, judgment, decision-making (6).

In light of the critical role that sleep plays in maintaining optimal cognitive and physiological functioning, the widespread use of pharmacological agents in the management of sleep disorders is not unexpected. Although Cognitive Behavioral Therapy for Insomnia (CBT-I) is regarded as the first-line treatment due to its demonstrated efficacy and sustained long-term benefits, access to CBT-I remains limited, as it is primarily offered in specialized centers. Consequently, pharmacological treatments continue to be commonly used in clinical practice, particularly for patients who do not respond sufficiently to CBT-I or fail to achieve full remission (7).

The latest edition of the *International Classification of Sleep Disorders* (ICSD), designated as version 3 and published in 2014, provides a detailed specification of sleep disorders, categorizing them into distinct groups. However, the authors emphasize that many aspects in this field still require further clarification. The classification identifies seven main categories of sleep disorders (listed in Table 1), each of which is further divided into more specific diagnostic units (8). In the following paper, We primarily focus on pharmacotherapy and its consequences in the context of Insomnia.

Table 1. ICSD -3 Major Diagnostic Sections
Insomnia
Sleep-related breathing disorders
Central disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Parasomnias
Sleep-related movement disorders
Other sleep disorders
Source: Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387–94. (8)

Classification of Drugs Used in the Treatment of Sleep Disorders

1. Benzodiazepines

Benzodiazepines are among the most commonly used hypnotics and exert their effects by enhancing GABAergic neurotransmission. Experimental evidence from animal models and human studies demonstrates that they reduce sleep latency and increase stage 2 NREM sleep, while suppressing REM and slow-wave sleep (SWS). EEG findings indicate a decrease in low-frequency activity and an increase in sleep spindle frequency during NREM sleep (9).The use of benzodiazepines is further restricted due to adverse effects such as the quick onset of tolerance, potential for abuse and dependence, rebound insomnia following discontinuation, and cognitive dysfunction (10).

2. Benzodiazepine Receptor Agonists – Z-drugs

Non-benzodiazepine hypnotics, also known as Z-drugs, are prescribed for managing acute and short-term insomnia (1). The most frequently reported adverse effects include memory loss, dizziness, drowsiness, and headaches (11).

3. Orexin Receptor Antagonists

Suvorexant, a dual orexin receptor antagonist, is used to treat both sleep onset and sleep maintenance insomnia effectively (10). Suvorexant is generally well tolerated, with mild side effects such as drowsiness, fatigue, headache, and dry mouth being the most frequently reported (12).

4. Antihistamine Drugs

Doxepin, a tricyclic antidepressant, enhances total sleep duration, reduces wakefulness after sleep onset, and increases sleep efficiency. It functions as a selective H1 receptor antagonist. It enhances overall sleep duration, reduces wakefulness after initially falling asleep, and increases sleep efficiency (10).

5. Melatonin and Melatonin Receptor Agonists (e.g. Ramelteon)

Due to its natural origin, low toxicity, and minimal side effect profile, melatonin is considered suitable for long-term use in older adults. It is suggested that in this group, reduced endogenous melatonin production may contribute to the development of sleep disorders (13).Melatonin receptor agonists, such as Ramelton, target the MT1 and MT2 receptors. By stimulating these receptors, these medications enhance sleep by supporting the body's internal regulatory mechanisms. They are commonly used to treat circadian rhythm sleep disorders, including jet lag and delayed sleep-wake phase disorder (1).

6. Antidepressants and other Off-Label medications

Low-dose sedating antidepressants may be utilized to manage insomnia, particularly in patients with coexisting depression or when other treatments have proven ineffective (12). Trazodone, mirtazapine, and amitriptyline are frequently prescribed at low doses for insomnia due to their strong antihistaminic properties (10). Trazodone is an oral antidepressant, with sedative effects likely due to α-adrenergic and histamine receptor blockade. It also enhances deep sleep by prolonging stages III and IV of slow-wave sleep. Trazodone's most frequently reported side effects are generally mild and encompass dizziness, sedation, fatigue, headache, dry mouth, nausea, and vomiting (12). Mirtazapine is a noradrenergic and specific serotonergic antidepressant. Its most common side effects include drowsiness, sedation, increased appetite, weight gain, and dry mouth (12). Quetiapine may be beneficial for managing insomnia in patients with co-occurring psychotic disorders. Quetiapine's sleep-promoting effects may involve multiple mechanisms, such as its antihistaminergic, antidopaminergic, and antiadrenergic activities (14).

Mechanisms of Action of Individual Drug Classes:

1. $GABA_A$ Modulation (Benzodiazepines, Z-drugs)

The **$GABA_A$ receptor** is the most extensively studied target in the treatment of insomnia. **GABA** is the brain's primary inhibitory neurotransmitter(15). It also plays a vital role in intitiating and maintaining sleep by causing chloride ion influx, which suppresses the activity of neurons that promote wakefulness(9). **Benzodiazepines (BZDs)** and **Z-drugs** act as **positive allosteric modulators** at the $GABA_A$ receptor, enhancing GABA's effect by increasing the frequency of chloride channel openings, which results in **neuronal inhibition**.
The **$GABA_A$ receptor** is a **ligand-gated ion channel** composed of five subunits (α1–6, β1–3, γ1–3, δ, etc.) with variable distribution across the brain. This subunit composition affects how different drugs bind and act:

- **BZDs** bind with similar affinity to α1, α2, α3, and α5 subunits, explaining their broad effects (sedative, anxiolytic, anticonvulsant, muscle relaxant).
- **Z-drugs** (zolpidem, zaleplon, zopiclone) show **selectivity** for the **α1 subunit**, which is primarily involved in **sleep induction** rather than anxiety relief.
- **Eszopiclone** differs by having higher affinity for **α2 and α3** subunits, linked to anxiolytic effects.

This **selectivity** gives Z-drugs a **more focused sedative-hypnotic profile** and **potentially better tolerability** compared to BZDs (15,16).

2. Regulation of Circadian Rhythm

Melatonin is an endogenous hormone synthesized by the pineal gland, plays a central role in regulating circadian rhythms and the sleep-wake cycle in humans. Its production is controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus and typically increases in the evening, aligning with heightened sleepiness and sleep propensity. Melatonin acts primarily through high-affinity membrane receptors, MT1 and MT2, both of which are found in the SCN and are implicated in circadian rhythm regulation (17). Melatonin and compounds that act on both MT1 and MT2 receptors primarily influence the latency to sleep onset, with minimal impact on total sleep duration or overall sleep structure (15).

3. Inhibition of Orexin Receptors

Orexins, comprising orexin-A and orexin-B, are excitatory neuropeptides produced exclusively by neurons in the lateral hypothalamus, which are acting on both receptors called OX_1 and OX_2. The orexin system is involved in promoting wakefulness, arousal, feeding behavior, locomotion, stress response, and mood regulation. Animal studies show that the absence of orexin signaling, especially via OX_2, leads to narcolepsy-like symptoms, highlighting its critical role in sleep-wake regulation. While OX_1 seems less essential for maintaining arousal, blocking OX_2 selectively increases REM and NREM sleep. Combined OX_1 and OX_2 receptor antagonism further enhances these effects(15,18).Suvorexant is a dual antagonist of both orexin receptors mentioned above, targeting the orexin/hypocretin signaling pathway, which is crucial for the maintenance of wakefulness (19).

4. Inhibition of Histamine Receptors

Neurons located in the tuberomammillary nuclei of the hypothalamus serve as the brain's exclusive source of histamine. Histamine exerts its effects via four receptor subtypes: H1, H2, H3, and H4. Among the receptors, the H1 subtype plays a crucial role in maintaining wakefulness. Clinically, several sedative medications, including **mirtazapine, quetiapine, hydroxyzine**, and **diphenhydramine**, exert their sleep-promoting effects through antagonism of histaminergic receptors (15).

Risk factors for dependence and tolerance

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), no longer distinguishes between substance dependence and substance abuse as separate diagnostic units. Instead, these conditions are integrated into a singular diagnosis termed Substance Use Disorder (SUD), which is conceptualized along a continuum of severity ranging from mild to severe. This classification is based on the presence of eleven specific diagnostic criteria. Historically, the construct of dependence primarily encompassed physiological adaptations to substance use, notably tolerance, defined as the need for increased amounts of the substance to achieve the desired effect, and withdrawal symptoms experienced upon cessation or reduction of use. In the DSM-5 framework, these physiological components are subsumed within the broader SUD diagnosis under the category of pharmacological criteria, reflecting a more comprehensive understanding of substance-related disorders (20).

- **Duration of therapy and risk of addiction**

Even short-term use of benzodiazepines (BZDs), lasting just a few days, can lead to the development of physical dependence (12).European guidelines recommend using benzodiazepines only for short-term treatment of insomnia, with intermittent dosing advised. Long-term use is discouraged due to limited evidence of efficacy and the risks of side effects, tolerance, and dependence (11). Z-drugs, such as Zolpidem or Zaleplon, also should be use in short-term treatment. Intermittent dosing of Zolpidem, typically up to three nights per week, has been supported by multiple studies as an effective and well-tolerated strategy for the management of insomnia. This dosing approach is associated with a low risk of escalating use over time. As for Zaleplon, due to its ultra-short action, it produces a rapid but brief high. Its abuse is often linked to hallucinations and anterograde amnesia, which impair self-control and awareness of escalating use (21). The European Sleep Research Society recommends the short-term use (up to 4 weeks) of benzodiazepines, z-drugs, and select antidepressants for the treatment of insomnia (22).

Clinical consequences of long-term therapy

The reviewed pharmacological literature primarily addresses short-term insomnia treatment (≤4 weeks). However, long-term treatment is clinically relevant since insomnia often recurs after withdrawal. Studies of hypnotic use for 12 weeks or more indicate that efficacy may remain stable over time, though some report decreased effects. To reduce risks like dependence and rebound insomnia, intermittent use of benzodiazepines (BDZs) and benzodiazepine receptor agonists (BZRAs) has been proposed, though meta-analyses on this approach are lacking (22).

- **Development of tolerance**

Tolerance to hypnotic effects of BDZs nad Z-drugs typically develops within 1–2 months. Intermittent use may mitigate tolerance, and anxiolytic benefits often persist beyond this period. However, rebound insomnia can occur upon discontinuation in up to 71% of patients (11).Over-the-counter antihistamines can be used for short-term management of insomnia in younger adults, however, their effectiveness diminishes quickly due to the rapid development of tolerance (23).

- **Withdrawal syndrome**

Suddenly stopping the use of benzodiazepines can trigger withdrawal symptoms. Common manifestations include restlessness, heightened anxiety, low mood, return of insomnia, rapid heartbeat, gastrointestinal issues like diarrhea, heightened sensitivity to sensory input, visual or auditory disturbances, feelings of detachment from reality, mental confusion, delirium, and in severe cases, seizures (12).Withdrawal from Z**-drugs** has also been linked to complex sleep behaviors such as **sleep driving**, sometimes with fatal outcomes. Acute withdrawal usually lasts 2–4 weeks but may be prolonged for months or even years after long-term use, presenting as **persistent symptoms** (24). Rebound or withdrawal symptoms were not observed with the discontinuation of Suvorexant or Ramelton (12).

- **Cognitive disturbances and memory impairment**

Prolonged use of benzodiazepines has been associated with a slight yet meaningful reduction in fluid intelligence. Moreover, extended duration of use appears to be more strongly linked to cognitive decline than the impact of high-dose usage alone (25).

- **Risk of falls and fractures**

Benzodiazepines are known to increase risks of car accidents, cognitive decline, and falls or fractures. Short-acting BDZs have less hangover effect but a higher fracture risk (26–28).Falls and fractures are a major concern in the elderly, with studies showing significantly elevated risks, particularly among individuals aged 80 and above. In dementia patients, the use of sleep medications was linked to a 33–96% increase in fractures, falls, and stroke risk compared to non-users (29).Z-drugs likely raise fracture risk by affecting gait and balance, supported by trials showing impaired walking after zolpidem use. Although initially thought to cause fewer falls than benzodiazepines, Z-drugs have been associated with similar or higher fall risks, especially at higher doses, with increased fall-related injuries seen in older adults, including those with dementia (29).

- **Potential deterioration of sleep quality (Rebound Effect)**

Rebound syndrome involves more intense symptoms than baseline and occurs within days to weeks after discontinuation of treatment, especially with short-acting agents like triazolam. Rebound insomnia following the discontinuation of long-term benzodiazepine therapy is further exacerbated by disturbances in the body's natural melatonin secretion patterns (24).

Alternatives and risk minimization strategies/Therapeutic recommendations

- **Guidelines for the Safe Use of Pharmacotherapy**

CBT-I is strongly recommended as the first-line treatment for chronic insomnia across all adult age groups, supported by high-quality evidence. Pharmacological treatments may be considered when CBT-I is ineffective or unavailable. Benzodiazepines and benzodiazepine receptor agonists demonstrate efficacy for short-term use (≤4 weeks). Sedating antidepressants show moderate efficacy for short-term insomnia treatment but are not recommended for long-term use due to limited evidence and possible adverse effects. Antihistamines and antipsychotics are not recommended for insomnia treatment owing to insufficient efficacy data and safety concerns. Melatonin and phytotherapeutics such as valerian have low efficacy and weak supporting evidence, thus are not generally advised (1,22).

- **Hypnotic Discontinuation Strategies**

Prevention of withdrawal syndrome after long-term benzodiapine intake relies on **slow tapering** over 3–6 months or longer. If symptoms emerge, treatment may include reinstating the prior dose, switching to a long-acting benzodiazepine, or using adjunctive therapies like **melatonin agonists**, **carbamazepine**, **pregabalin**, or **CBT**. Discontinuation of **alprazolam** is particularly difficult due to paradoxical receptor changes at low doses; substitution with clonazepam may help but is not always effective (30).

Generally, hypnotic discontinuation should involve gradual tapering and supportive interventions, including counseling, CBT-I, or alternative medications when necessary. Overall, benzodiazepines and BZRAs are not recommended for long-term insomnia treatment, based on low-quality evidence but with a strong recommendation against their prolonged use (22).

- **Crucial Role of the Healthcare Providers**

The primary duty of healthcare providers is to avoid causing additional harm to patients beyond their underlying illness. The physician coordinating treatment in sleep medicine plays a crucial role in delivering comprehensive, patient-centered care. As the primary clinical decision-maker, the physician is responsible for making an accurate diagnosis, integrating multidisciplinary information, and tailoring individualized treatment plans that address both the primary sleep disorder and any co-morbid conditions. Therefore, the coordinating physician is essential for optimizing clinical outcomes and ensuring ethically sound, high-quality care within the evolving field of sleep medicine (31).

Summary

Insomnia is a prevalent sleep disorder with significant health implications, often requiring pharmacological intervention when non-pharmacological treatments, such as Cognitive Behavioral Therapy for Insomnia (CBT-I), are ineffective or inaccessible. While these agents offer short-term relief, long-term use is associated with risks such as tolerance, dependence, withdrawal symptoms, cognitive decline, and increased risk of falls, particularly in older adults. Safe prescribing practices emphasize short-term use, intermittent dosing, and the integration of behavioral interventions to reduce harm. Gradual tapering strategies and the

use of supportive therapies are recommended for discontinuation. Overall, careful selection and monitoring of sleep medications are essential to minimize adverse outcomes and ensure effective, safe insomnia management.

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2. Data were obtained from

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