Review Article

Roadblocks and Innovations in Sedative-Hypnotic Treatments

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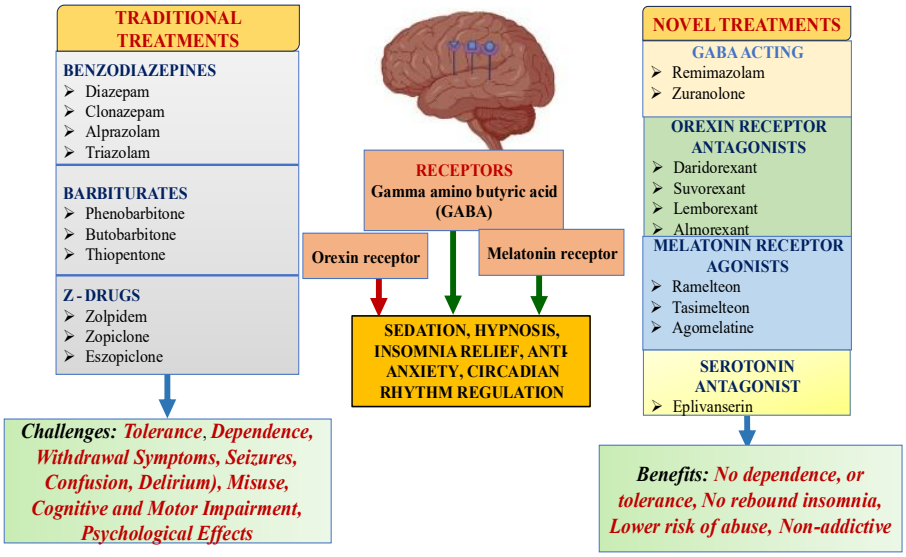
Received: 03-02-2026; **Revised:** 28-03-2026; **Accepted:** 05-04-2026; **Published online:** 20-04-2026.

ABSTRACT

Sedatives and hypnotics play a crucial role in the management of anxiety, insomnia, and related neuropsychiatric conditions. While sedatives primarily exert calming effects without necessarily inducing sleep, thus alleviating anxiety and agitation, hypnotics are specifically employed to initiate and maintain sleep. Both drug classes exert their effects by modulating central neurotransmitter systems, particularly by enhancing the activity of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter that reduces neuronal excitability. Conventional medications, including benzodiazepines and non-benzodiazepine "Z-drugs," remain widely prescribed due to their established efficacy. However, these agents have come under increasing scrutiny owing to their association with tolerance, dependence, withdrawal symptoms, and cognitive impairment, especially with prolonged use. Consequently, there is a growing emphasis on developing novel pharmacological interventions that maintain therapeutic benefits while minimizing adverse effects. Recent research has focused on alternative therapeutic targets, including melatonergic agents (e.g., ramelteon, tasimelteon), orexin receptor antagonists (e.g., almorexant, suvorexant), and newer GABAergic modulators with refined mechanisms of action. These agents are designed to mitigate the limitations of traditional sedative-hypnotics by reducing abuse potential, enhancing safety profiles, and minimizing drug interactions and cognitive side effects. This narrative review aims to examine the evolution of sedative-hypnotic pharmacotherapy over the past decades, with an emphasis on emerging therapeutic strategies that offer safer, non-addictive alternatives and address the challenges associated with conventional agents.

Keywords: GABA, Benzodiazepines, Barbiturates, Z-Drugs, Remimazolam, Almorexant, Ramelteon, Tasimelteon.

Graphical Abstract



INTRODUCTION

Mental health disorders have emerged as leading contributors to non-fatal disease burden in the 21st century, accounting for nearly 7% of the global burden of disease and approximately one-third of total years lived with disability worldwide. This burden has been exacerbated by the COVID-19 pandemic, which significantly elevated psychological suffering across populations. Epidemiological estimates indicate that since the start of the epidemic, over 70 million people have experienced depressive symptoms, approximately 90 million have experienced symptoms of anxiety disorders, and hundreds of millions have reported sleep difficulties, including sleeplessness[1,2]. The World Health Organization has documented an increase in global rates of anxiety and depressive symptoms by 25% after only the first year of the pandemic[3].

The COVID-19 pandemic has also had a substantial influence on individuals' well-being and quality of life, owing to social isolation, unpredictable economic conditions, disrupted routines, and limited access to medical care. These psychosocial stressors have

disproportionately affected those with pre-existing mental health illnesses and cognitive dysfunctions, increasing their vulnerability to anxiety, sleeplessness, and maladaptive stress reactivity. According to recent research, the pandemic's psychosocial adversity has significantly diminished emotional resilience and coping mechanisms, leading to an increase in psychological distress and sleep problems[4]. When analyzed collectively, these findings highlight the need for therapeutic strategies that improve sleep quality while reducing the neuropsychiatric effects of stress. In this context, a growing body of evidence suggests that modern psychoactive therapies, such as antipsychotic drugs, can help vulnerable patient populations reduce psychological stress, emotional dysregulation, and suicide ideation. Indeed, prior studies have indicated that contemporary psychopharmacological therapies may reduce the risk of suicide, particularly when paired with an integrated treatment strategy[5].

Major population-based epidemiological investigations in the US and UK indicated that approximately 20 to 25% of patients suffering from insomnia also experience depressive symptoms; this data supports the significant bidirectional linkages between sleeping disorders and psychological disorders[6]. The substantially elevated risk of depression, suicidal thoughts, and poor psychosocial outcomes for individuals with severe anxiety and chronic sleep disruption underscores the therapeutic significance of addressing sleep disruptions as a modifiable risk factor in mental health care.

Insomnia has traditionally been treated pharmacologically using sedative-hypnotic medications, mainly benzodiazepines (such as clonazepam and diazepam) and non-benzodiazepine GABA_A receptor modulators. Although these medicines are effective at easing symptoms temporarily, their long-term use is limited by well-established hazards such as tolerance, dependency, withdrawal symptoms, cognitive impairment, and an increased risk of falls, particularly in older populations[7]. Consequently, clinical practice guidelines recommend the use of non-pharmacological therapies whenever possible and recommend that pharmacological agents be used for brief periods. In the late 20th century, attempts to improve the safety profile of hypnotic medications led to the development of newer medicines. Zopiclone, a third-generation cyclopyrrolone derivative, was designed as a fast-acting hypnotic with the primary goal of inducing sleep[8,9]. It is one of the "Z-drugs," along with eszopiclone and zolpidem. These medications were formerly believed to be safer alternatives to benzodiazepines due to their relative receptor specificity. Subsequent regulatory reviews and clinical evaluations have raised concerns about these medications' moderate efficacy and safety, suggesting that they may have hazards comparable to those of traditional benzodiazepines with little long-term benefit[10].

Despite growing global understanding of mental health concerns, there persists an enormous discrepancy between established standards of care and treatment outcomes. Nearly 1 billion people worldwide suffer from mental health issues, and current treatment approaches are of insufficient to meet their varied and complicated needs. Such a claim necessitates an urgent appeal for pharmaceutical innovation that may be safer, more functional, and more effective.

While benzodiazepines and barbiturates have traditionally served as the primary sedative-hypnotic medicines for treating insomnia, anxiety, seizures, procedural sedation, and alcohol dependence, the general population prefers benzodiazepines to barbiturates due to their relatively safer side effect profile. Given these limitations of conventional agents, the purpose of this review is to critically evaluate the clinical efficacy and medical potential of new sedative-hypnotic medicines such as orexin receptor antagonists, melatonin receptor agonists, and a variety of non-GABAergic mechanism-based drugs. This article is primarily based on the theory that specific modulation of sleep-wake regulatory pathways, such as dual orexin receptor type 1 and type 2 antagonism (OX1/OX2), melatonin MT1 and MT2 receptor activation, and selected non-benzodiazepine and non-5-HT2A receptor mechanisms could represent efficacious and safer therapeutic options for patients who cannot tolerate or are nonresponsive to current hypnotics. These innovative treatments can address the major unmet needs of treating insomnia and improve both the quality of sleep at night and daytime functioning by reducing off-target effects and dependence risk.

Building upon this theoretical foundation, it is hypothesised that these emerging modalities, acting through the diverse mechanisms including dual orexin receptor type 1 and type 2 (OX1 and OX2) antagonist (DORA), MT1 and MT2 receptors activation with minimal affinity for benzodiazepine sites and 5-HT2A receptor antagonist for insomnia treatment, may offer effective and safer adjunct therapies for patients who are intolerant to conventional medications. Specifically, we hypothesize that these targeted mechanisms will demonstrate reduced risk of tolerance, dependency, cognitive impairment, and next-day residual effects compared to traditional GABAergic hypnotics, while maintaining or improving efficacy in sleep onset, sleep maintenance, and daytime functioning.

To address these unmet needs in sedative-hypnotic pharmacotherapy, this narrative review critically evaluates emerging sleep-modulating agents including orexin receptor antagonists, melatonin receptor agonists, and novel GABAergic modulators in comparison with traditional benzodiazepines, barbiturates, and Z-drugs. The review systematically examines differences in mechanisms of action, clinical efficacy, safety and tolerability profiles, and therapeutic positioning. By integrating evidence on dependence potential, cognitive and psychomotor effects, next-day residual sedation, and the durability of long-term treatment outcomes, this work aims to provide an evidence-based framework to support rational drug selection and personalized optimization of sedative-

hypnotic therapy across heterogeneous insomnia and sleep–wake disorder populations.

1. THERAPEUTIC APPLICATIONS OF SEDATIVE-HYPNOTICS

Sedative-hypnotics, particularly benzodiazepines and barbiturates, are integral to the pharmacological management of various neuropsychiatric and medical conditions. Their common applications include the treatment of insomnia, anxiety disorders, seizure control, procedural sedation, management of alcohol withdrawal, and acute agitation. Despite overlapping uses, benzodiazepines have largely supplanted barbiturates in most clinical settings due to their wider therapeutic index and more favorable safety profile[11].

Benzodiazepines are extensively used in psychiatric, neurological, and critical care practice. In the management of anxiety disorders, alprazolam, lorazepam, and clonazepam are commonly prescribed agents due to their intermediate to long half-lives and anxiolytic potency. For acute panic attacks or severe agitation, diazepam and lorazepam are preferred for their rapid onset of action. In sleep disorders, temazepam and triazolam are indicated for short-term management of insomnia, with triazolam being more suitable for sleep-onset difficulties and temazepam for sleep maintenance[12]. In seizure emergencies, lorazepam and diazepam are first-line agents for status epilepticus due to their rapid CNS penetration and potent anticonvulsant effects. Clonazepam and clobazam are used for long-term seizure control, particularly in patients with Lennox–Gastaut syndrome and myoclonic epilepsy[13]. For alcohol withdrawal management, chlordiazepoxide and diazepam are commonly employed in symptom-triggered protocols to prevent withdrawal seizures and delirium tremens. In procedural sedation and preoperative settings, midazolam, a short-acting benzodiazepine with amnestic properties, is favored for its predictable pharmacokinetics. Diazepam is also used for muscle relaxation in conditions such as spasticity associated with cerebral palsy or spinal cord injury[14].

Barbiturates, though now less commonly prescribed, retain utility in selected clinical scenarios. Phenobarbital remains a key agent for long-term management of generalized tonic–clonic and partial seizures, especially in pediatric populations or in low-resource settings. It is also used in refractory status epilepticus when benzodiazepines and other anticonvulsants fail to provide seizure control[15]. In anesthetic practice, thiopental and methohexital are ultra–short-acting barbiturates used for induction of general anesthesia and in neurocritical care to reduce intracranial pressure or induce coma in cases of traumatic brain injury. Methohexital is also preferred for procedural sedation in electroconvulsive therapy (ECT) due to its rapid onset and short duration[16]. Butalbital, a short-acting barbiturate, is used in combination with acetaminophen or aspirin and caffeine for the management of tension-type headaches and migraines; however, its use is limited by risk of dependence and medication-overuse headache. Barbiturates have also been employed in physician-assisted dying protocols and certain cases of intractable insomnia, though such use is rare and ethically regulated[17].

2. LIMITATIONS OF CONVENTIONAL THERAPIES

2.1 General Adverse Effects

While sedative-hypnotics, particularly benzodiazepines and non-benzodiazepine hypnotics (nBHs), have demonstrated therapeutic utility in treating sleep and anxiety disorders, growing evidence has highlighted significant concerns regarding their safety and tolerability. These concerns are especially pronounced in vulnerable populations such as older adults. Despite their initial promise, both drug classes are associated with a range of adverse effects that limit their long-term clinical use[18].

In elderly patients, the use of sedative-hypnotics has been consistently linked to an increased risk of falls, hip fractures, and overall functional decline. These complications have prompted clinical and geriatric guidelines to recommend avoiding routine use of such agents in this demographic. Furthermore, regulatory bodies such as the U.S. Food and Drug Administration have issued black box warnings for commonly used nBHs in response to reports of complex and potentially dangerous sleep-related behaviors, including sleepwalking, sleep driving, and other automatisms resulting in injury[19].

Beyond physical safety concerns, cognitive impairment represents a major drawback of chronic sedative-hypnotic use. Long-term benzodiazepine exposure has been associated with diminished memory, slowed processing speed, impaired attention, and reduced visuospatial abilities. Several longitudinal studies have also raised the possibility of a link between prolonged benzodiazepine use and the onset of neurodegenerative conditions such as Alzheimer's disease and related dementias, although the evidence remains inconclusive[20].

2.2 Dependence and Discontinuation challenges

Cessation of benzodiazepine receptor agonists is associated with a spectrum of clinically relevant discontinuation phenomena, each reflecting different neuroadaptive responses to long-term use. These include relapse, rebound, and withdrawal, which may vary in timing, severity, and clinical presentation[21]. Relapse refers to the reemergence of the original condition, typically insomnia or anxiety, over a period of weeks to months after discontinuation, mirroring the chronicity of the underlying disorder rather than pharmacologic dependence. In contrast, rebound describes a transient exacerbation of the original symptoms to levels exceeding baseline severity, typically manifesting within days to a few weeks post-cessation and resolving within three weeks. This phenomenon is particularly pronounced following abrupt discontinuation of sedative-hypnotics, especially those with short half-lives[22,23].

Withdrawal, a more complex syndrome, may involve heightened anxiety, restlessness, and anticipatory distress, often mischaracterized as drug dependence. Notably,

individuals withdrawing from short-acting benzodiazepines, such as alprazolam, frequently report time-focused anxiety and discomfort between doses, which may reflect inter-dose withdrawal symptoms rather than true addiction[24]. Tolerance to benzodiazepine receptor agonists typically develops in relation to their sedative and psychomotor effects, necessitating increased doses to achieve equivalent pharmacodynamic responses. However, tolerance to the anxiolytic properties remains uncommon. For instance, long-acting agents such as clonazepam have demonstrated sustained therapeutic efficacy comparable to antidepressants in some studies, with minimal evidence of escalating dose requirements or functional decline over time[25,26].

The discontinuation of short-acting hypnotics, including triazolam, may precipitate unusual behaviors such as nocturnal automatisms, which are frequently followed by episodes of retrograde amnesia. Furthermore, withdrawal of non-benzodiazepine hypnotics, such as zolpidem, zaleplon, zopiclone, and eszopiclone, has been implicated in complex parasomnias, including sleepwalking, sleep eating, and sleep driving. These behaviors have, in some cases, resulted in serious consequences, including traumatic injuries, motor vehicle accidents, exposure-related hypothermia, drug overdoses, falls, and even fatal incidents such as gunshot wounds[27,28,29].

2.3 Specific Drug Class Toxicity

2.3.1 Z-Drugs

Non-benzodiazepine hypnotics—commonly referred to as Z-drugs, including zolpidem, zopiclone, and eszopiclone are widely prescribed for the short-term management of insomnia. While generally perceived as safer alternatives to classical benzodiazepines, Z-drugs are not devoid of risk and require judicious use, especially in vulnerable populations.

i. **Central Nervous System and Cognitive Risks**: Z-drugs exert their sedative effects via modulation of the GABA-A receptor complex. However, their action can result in adverse central nervous system effects, such as residual drowsiness, dizziness, cognitive slowing, and confusion, which may persist into the daytime. Chronic exposure may induce physiological dependence, and abrupt discontinuation frequently results in rebound insomnia, withdrawal symptoms, and mood disturbances. Furthermore, impaired attention and executive functioning have been reported with continued use[30].

ii. **Complex Sleep Behaviors and Safety Hazards**: A major safety concern associated with Z-drugs is the emergence of parasomnias, or complex sleep-related behaviors—including sleepwalking, sleep driving, and nocturnal food preparation—performed in a semi-conscious state, often with no memory of the event. These episodes can lead to significant injury, especially when compounded by co-administration of other CNS depressants like alcohol or opioids, which markedly elevate the risk of severe respiratory depression or accidental overdose[31].

iii. **Somatic and Gastrointestinal Complaints**: Commonly reported adverse effects include morning sedation, dizziness, light-headedness, headaches, dry mouth, and gastrointestinal discomfort such as diarrhea. Dermatological reactions, including skin rashes, though infrequent, may also occur[32].

iv. **Geriatric Implications and Dementia-Related Concerns**: In older adults—particularly those diagnosed with dementia—Z-drug exposure has been associated with significantly increased risks of adverse outcomes. These include reduced physical activity, cognitive disturbances (e.g., confusion, personality changes), and a higher incidence of falls and fractures. One study reported a 40% rise in fracture risk, a 59% increase in hip fractures, and a 34% elevation in all-cause mortality within two years of continued hypnotic use. Notably, such drugs are not approved for the treatment of sleep disturbances in dementia, yet are still frequently prescribed off label, raising concerns about inappropriate use[33].

2.3.2 Benzodiazepines

Benzodiazepines (BZDs) are used for those struggling with sleep, anxiety, spasticity due to CNS pathology, muscle relaxation, and epilepsy. One of the debilitating side effects of BZDs is their addictive potential. The dependence on BZDs generally leads to withdrawal symptoms, requiring careful tapering of the medication when prescribed. Regular use of BZDs has been shown to cause severe, harmful psychological and physical dependence, leading to withdrawal symptoms like that of alcohol withdrawal. Some of these withdrawal symptoms can be life threatening[34].

i. **Central Nervous System Effects and Psychomotor Impairment:** BZDs have been shown to impair balance, coordination, and visual processing. These impairments significantly elevate the risk of falls, syncope, and fractures, especially in geriatric populations[35,36]. The risk appears dose-dependent and is particularly elevated with long-acting agents and chronic administration[37,38].

ii. **Cognitive Dysfunction and Dementia Risk:** Long-term benzodiazepine use has been implicated in increased susceptibility to cognitive decline and dementia. This may lead to diminished neuronal adaptability, compromised cognitive reserve, and impaired network compensation[39].

iii. **Driving Impairment and Public Safety Concerns:** Both benzodiazepine anxiolytics and hypnotics are known to impair executive function, sustained attention, and reaction time—parameters essential for safe driving. These effects may persist

despite tolerance development during long-term use[40]. Notably, in suspected impaired drivers aged over 65, benzodiazepines and Z-drugs were detected in 15% and 13% of cases, respectively, with zopiclone and diazepam being most frequently identified[41].

iv. **Behavioral Disinhibition and Agitation:** In a minority of users, BZDs can paradoxically induce behavioral disinhibition characterized by impulsivity, irritability, agitation, and in rare cases, aggression. Predisposing factors include concurrent alcohol use, higher dosages, younger or older age, heightened baseline anxiety, and prior history of impulsive behavior[42,43]. This phenomenon affects approximately 1% of users, with higher rates noted in pediatric and geriatric cohorts[44].

v. **Geriatric Risks and Falls:** Benzodiazepine-associated falls and resultant injuries are especially problematic in patients aged over 80 years. This age group exhibits heightened sensitivity to CNS depressants due to altered pharmacokinetics and pharmacodynamics. The extended sedative effects, particularly from long-acting agents, substantially increase fall risk in this population.

vi. **Teratogenic and Perinatal Outcomes:** Maternal use of benzodiazepines during pregnancy has been linked to adverse perinatal outcomes including preterm birth and reduced birth weight. Although some studies have reported potential teratogenic effects, confounding by co-administered drugs (e.g., antidepressants) complicates the interpretation of these findings[45].

vii. **Amnesia and Sleep-Related Abnormal Behaviors:** Benzodiazepines are known to cause anterograde amnesia, characterized by an impaired ability to form new memories. Triazolam (Halcion) is particularly associated with this adverse effect. In addition, unusual sleep-related behaviors—such as sleepwalking or performing complex activities while not fully awake—have been observed with both benzodiazepines and Z-drugs.

viii. **Next-Day Sedation and the "Hangover" Effect:** Sedation extending into the following day ("hangover effect") is a recognized concern with long-acting benzodiazepines such as diazepam and flurazepam. Residual drowsiness can interfere with daily activities, particularly driving and occupational tasks, and is especially hazardous in older adults due to increased fall and injury risk[46].

ix. **Long-Term Use, Tolerance, Dependence, and Withdrawal:** Prolonged benzodiazepine therapy can lead to the development of tolerance, physiological dependence, and substance use disorder. Short-acting, high-potency benzodiazepines—such as triazolam, alprazolam, and lorazepam—are particularly implicated in rapid tolerance development and dependence. Sudden cessation may trigger withdrawal symptoms, including rebound insomnia, anxiety, and in severe cases, seizures. Therefore, gradual tapering under medical supervision is recommended to mitigate these risks.

x. **Intravenous Administration–Associated Adverse Events:** Rapid intravenous (IV) administration of benzodiazepines carries a risk of serious cardiorespiratory complications, including respiratory depression, apnea, hypotension, bradycardia, and cardiac arrhythmias. Other adverse effects linked to IV administration include nausea, vomiting, visual disturbances (e.g., blurred or double vision), cutaneous reactions, and localized injection site reactions[47].

2.3.3 Barbiturates

Barbiturate toxicity is characterized by dose-dependent central nervous system depression, ranging from drowsiness and ataxia to deep coma. Severe poisoning can progress to respiratory depression or arrest, hypotension, hypothermia, and cardiovascular collapse. Among this class, phenobarbital poses a particularly high risk in overdose because of its long elimination half-life and substantial lipid solubility, which contribute to prolonged toxicity[48].

i. **Physical Dependence and Misuse Potential:** Chronic use of barbiturates is strongly associated with the development of physical dependence, necessitating progressive dose escalation to maintain therapeutic efficacy. This tolerance increases the risk of cumulative toxicity and accidental overdose[49]. Barbiturates also possess a high misuse potential and have historically been involved in intentional self-poisoning and suicide attempts[50].

ii. **Iatrogenic Toxicity in Comorbid Conditions:** The risk of iatrogenic toxicity is substantially heightened in patients with pre-existing medical comorbidities. For instance, patients with congestive heart failure may exhibit amplified barbiturate-induced cardiovascular depression. Individuals with chronic obstructive pulmonary disease (COPD) are particularly sensitive to the respiratory depressant effects of barbiturates, even at standard therapeutic doses[51]. Barbiturate metabolism is significantly reduced in patients with liver disease, prolonging drug half-life and increasing systemic accumulation[52]. Iatrogenic toxicity is further exacerbated by inappropriate prescribing patterns and pharmacodynamic interactions with other CNS depressants, such as opioids, sedatives, or anticholinergic agents, which can potentiate barbiturate effects.

iii. **Teratogenicity and Reproductive Safety:** Phenobarbital monotherapy in pregnant individuals has been associated with an increased incidence of congenital malformations in neonates. The risk

appears dose-dependent and underscores the importance of careful benefit–risk assessment when prescribing barbiturates during pregnancy[53,54,55].

iv. **Hemodynamic and Respiratory Effects of IV Anesthetic Use:** When administered intravenously for anesthetic purposes, barbiturates commonly induce hemodynamic changes such as hypotension accompanied by compensatory tachycardia. Additionally, respiratory depression and, in some cases, apnea may occur following rapid administration[56].

v. **Hepatotoxic and Hypersensitivity Reactions:** Barbiturates, particularly phenobarbital, are known to cause drug-induced liver injury (DILI), often accompanied by hypersensitivity manifestations such as skin rashes. Severe cutaneous adverse reactions (SCARs) linked to phenobarbital include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)[57].

vi. **Overdose and Life-Threatening Toxicity:** At supratherapeutic doses or in overdose settings, barbiturates exert profound CNS depressant effects, often resulting in coma, irreversible brain injury, multiorgan dysfunction, or fatal respiratory arrest. The narrow therapeutic index of barbiturates mandates vigilant dosing and monitoring to prevent accidental or intentional overdose[58].

3. Emerging Therapies and Novel Agents

Taken together, all the limitations underscore the importance of cautious prescribing practices and highlight the urgent need for the development of safer, targeted, and more sustainable therapeutic options for managing anxiety and sleep disorders across diverse patient populations. The development of novel sedative-hypnotic medications is essential to enhance efficacy, reduce dependence potential, and improve safety profiles[59]. Conventional medications such as barbiturates and benzodiazepines carry significant risks of addiction, overdose, and respiratory depression[60]. Extended use frequently results in tolerance development, necessitating dose escalation, and produces withdrawal symptoms upon discontinuation[61]. Cognitive impairment and other adverse effects make these agents suboptimal for long-term management[62].

Modern drug development aims to target specific brain receptors with greater precision to minimize cognitive impairment while providing rapid onset and shorter duration to enhance sleep quality without residual sedation[63]. Alternative neurotransmitter pathways, particularly orexin receptor antagonists, offer promising therapeutic approaches for patients unresponsive to conventional GABA-ergic sedatives[64]. Reducing drug interaction potential is particularly important for geriatric populations with polypharmacy considerations[65]. Advances in personalized medicine accounting for genetic factors and innovative delivery systems such as extended-release or sublingual formulations enhance convenience and efficacy[66]. Continued innovation in sedative-hypnotic pharmacology remains essential for developing safer, more effective, and targeted treatments for sleep disorders[67].

3.1 Novel GABAergic Agent: Remimazolam is an ultra–short-acting intravenous benzodiazepine developed for procedural sedation and the induction and maintenance of general anesthesia. It acts as a positive allosteric modulator at the γ-aminobutyric acid type A (GABAA) receptor, enhancing inhibitory neurotransmission in the central nervous system by increasing the frequency of chloride channel opening. This produces anxiolytic, sedative, hypnotic, and amnestic effects characteristic of benzodiazepines and underpins its clinical utility in short procedures requiring rapid onset and predictable offset of sedation[68].

Unlike traditional longer-acting benzodiazepines such as midazolam, remimazolam contains an ester linkage that permits rapid metabolism by non-specific tissue esterases to an inactive carboxylic acid metabolite, resulting in a high systemic clearance and short elimination and context-sensitive half-times. This organ-independent metabolism reduces the likelihood of drug accumulation, limits the influence of hepatic or renal impairment on drug disposition, and allows for a rapid and predictable recovery profile compared with older agents[69].

Pharmacokinetic and pharmacodynamic studies have shown that remimazolam has a rapid onset of sedation following intravenous administration, with loss of consciousness typically occurring within a few minutes. Its context-sensitive half-time remains short (approximately 6–11 minutes) even after prolonged infusion, supporting its use for continuous sedation without prolonged residual effects. High clearance and a relatively small volume of distribution further contribute to its predictable elimination[70].

Remimazolam is compared to midazolam for procedural sedation by pooled estimates of meta-analyses. The pooled data show statistically significant differences in the outcome of procedure success. The use of remimazolam has resulted in less administration of rescue medication, less time to recovery, and better cognitive recovery compared with the use of midazolam during procedural sedation[71].

Despite its rapid metabolism and reduced propensity for prolonged sedation compared with older benzodiazepines, remimazolam retains class-related risks such as respiratory depression and requires careful monitoring. Its abuse liability and dependence potential have not been fully characterized but are considered like other benzodiazepines given its GABAergic mechanism. Long-term safety, effects in special populations, and comparative outcomes in complex anesthesia settings continue to be subjects of ongoing research[72].

3.2 Orexin Receptor Antagonists: Orexin receptors (OX1R and OX2R) are seven-transmembrane domain G-protein-

coupled receptors (HCRTR1 and HCRTR2). Orexin A binds to both OX1R and OX2R, while orexin B preferentially binds OX2R. Both receptors are activated by orexins, which are neuropeptides derived from the precursor protein prepro-orexin. These receptors play key roles in regulating wakefulness, appetite, and energy balance, increase calcium levels and activate protein kinase C and adenyl cyclases. They are involved in controlling sleep-wake cycles and arousal, and their dysfunction is linked to disorders like narcolepsy. In vitro studies demonstrate OX1R coupling affinity to Gi and Gs protein families[73].

3.2.1 Daridorexant: Daridorexant is an oral DORA that has been approved for the treatment of insomnia. It was developed by Idorsia Pharmaceuticals Ltd. and is supplied under the brand name Quviviq. It selectively targets the G protein-coupled OX1R and OX2R, both of which are substantially expressed in brain regions responsible for wakefulness and arousal control. By competitively inhibiting orexin signalling, daridorexant suppresses wake-promoting pathways, thereby facilitating both sleep initiation and sleep maintenance[74].

Unlike conventional hypnotics that enhance γ-aminobutyric acid (GABA)-mediated neurotransmission, daridorexant does not interact with GABA_A receptors or associated neuronal circuits associated with cognitive impairment, tolerance, dependency, or abuse liability. This receptor-selective approach has a distinct pharmacological benefit over traditional sedative-hypnotics as it allows for tailored control of the sleep-wake cycle without producing widespread central nervous system depression[75].

Pharmacokinetic and pharmacodynamic investigations have shown that daridorexant is rapidly absorbed after oral treatment. Within an hour, measurable effects on the central nervous system manifest, such as decreased vigilance, attention, visuomotor coordination, and postural stability. Peak pharmacodynamic effects are often observed 1.5 hours after the intake, even at doses as high as 100 mg. The dose-dependent resolution of sedative effects at clinically relevant dosages, which return to baseline in 3–6 hours for 25 mg and 6–8 hours for 50 mg, supports its acceptability for administration at night[76].

Following extensive clinical research, daridorexant (ACT-541468) exhibited comparable in vitro affinity to suvorexant for OX1R and OX2R[77]. Data from multiple Phase 1 and Phase 2 studies have revealed a favorable pharmacokinetic profile with rapid absorption and an elimination half-life of around 6–10 hours. Both single-dose and multiple-dose investigations revealed a strong correlation between pharmacokinetic exposure and pharmacodynamic effects. Importantly, for doses up to 50 mg administered in the morning, drug-related effects on the central nervous system subsided after roughly eight hours. Furthermore, based on objective performance measurements and subjective drowsiness assessments, 25 mg administered in the evening had no detectable residual effects the next morning in either younger or older persons[78,79].

In Phase 1 trials, daridorexant was generally well tolerated, with fatigue and dose-dependent somnolence being the most frequently reported adverse events. These findings supported the selection of a dose range of 10–50 mg for subsequent Phase 2 clinical trials[80]. In a randomized Phase 2 research, 359 people with insomnia received daridorexant at dosages of 5, 10, 25, or 50 mg for 30 days. Daridorexant demonstrated widespread improvements in sleep characteristics without indication of residual impairment the next day, according to many visual analog and sleepiness scales and neurological exams. Additionally, during a run-out period following therapy, there were no indications of rebound sleeplessness or withdrawal symptoms[81].

Daridorexant's Phase 3 clinical research program comprised three major trials that evaluated the drug's long-term safety and efficacy at doses of 10, 25, and 50 mg for up to a year. In addition to objective and subjective sleep outcomes, these trials concentrated on next-day functioning, which they identified as a crucial aspect of daytime impairment in insomnia. The Phase 3 trial found that daridorexant improved both nocturnal sleep metrics and daytime functioning, highlighting its clinical relevance as a well-tolerated therapeutic agent for chronic insomnia[82].

In a subsequent double-blind extension trial, adults with insomnia who had completed the initial 12-week studies either continued daridorexant therapy at doses of 10, 25, or 50 mg, or were re-randomized to receive daridorexant 25 mg or placebo. Following a 40-week treatment period, participants underwent a 7-day placebo run-out phase. Across 804 enrolled patients, daridorexant demonstrated a tolerability and safety profile comparable to placebo, with no evidence of rebound insomnia, withdrawal phenomena, or residual next-morning sedation. Among the evaluated doses, daridorexant 50 mg was associated with the greatest and most consistent improvements in nocturnal sleep parameters and daytime functioning, with benefits sustained for up to 12 months. This higher dose significantly prolonged total sleep time and led to meaningful improvements in daytime symptom measures. Overall, daridorexant was found to be safe, well tolerated, and effective for management of insomnia. During the 40-week double-blind period, 91.2% of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. Nasopharyngitis was the most frequently reported TEAE across all groups during double-blind treatment. Less than 3% of patients reported any other TEAEs, such as falls, headaches, and somnolence; less than 2% of patients in any group reported dizziness and fatigue. Only single patients in each group were reported to have treatment-emergent adverse events that resulted in stopping double-blind treatment[83].

Although daridorexant has a relatively low potential for abuse when compared to the traditional GABAergic hypnotics, its long-term effects on sleep architecture remain insufficiently characterized. Consequently, continued pharmacovigilance and long-term observational

studies are necessary to fully reveal its long-term safety profile. Furthermore, evidence supporting daridorexant's efficacy in treating insomnia linked to neurodegenerative illnesses, mental disorders, or chronic pain problems remains limited, highlighting the need for further targeted clinical investigations.

3.2.2 Suvorexant: Suvorexant was approved by the U.S. Food and Drug Administration in 2014 as the first-in-class DORA for the treatment of insomnia characterized by difficulties in sleep onset and/or sleep maintenance. Due to its relatively low abuse potential compared with conventional sedative–hypnotics, suvorexant is classified as a Schedule IV controlled substance. Clinically, treatment is initiated at a dose of 10 mg once nightly, administered at least 30 minutes before bedtime with a minimum of seven hours available for sleep, with the option to increase to 20 mg if clinically indicated; however, higher doses have been associated with an increased risk of next-day impairment, particularly affecting driving performance. Unlike traditional hypnotics that induce generalized central nervous system depression, suvorexant selectively attenuates wake-promoting orexin signaling, thereby offering a favorable clinical profile that includes reduced risk of dependence, absence of rebound insomnia or withdrawal symptoms, limited next-day sedation and cognitive impairment, minimal respiratory suppression, and lower abuse liability[84,85,86].

The clinical efficacy and safety of suvorexant have been established through an extensive development program encompassing Phase II, Phase III, and post-marketing studies in patients with primary insomnia and selected comorbid conditions. In an early Phase II randomized crossover dose-finding study involving 254 patients with primary insomnia, suvorexant administered at doses ranging from 10 to 80 mg over four weeks significantly improved sleep efficiency and reduced wake after sleep onset compared with placebo from the first night of treatment, with effects sustained through week four; however, no statistically significant improvement was observed for latency to persistent sleep. The drug was generally well tolerated, with somnolence, headache, dizziness, abnormal dreams, and mild laboratory abnormalities reported as the most common adverse events[87]. These findings were further corroborated in large placebo-controlled Phase III trials enrolling more than 2,000 patients, including a substantial elderly population, where suvorexant demonstrated dose-dependent increases in subjective total sleep time and consistent reductions in wake after sleep onset and sleep onset latency at one and three months, with sustained subjective efficacy observed for up to twelve months and no clinically meaningful evidence of rebound insomnia or withdrawal following abrupt discontinuation[88].

Pooled analyses of Phase III data revealed that suvorexant-associated increases in total sleep time were distributed across all sleep stages, with a relative increase in rapid eye movement sleep, suggesting a shift toward a more physiological sleep architecture; however, the long-term clinical implications of REM enhancement remain incompletely defined. Safety data derived from a regulatory database comprising nearly 3,000 patients identified somnolence, headache, and fatigue as the most frequently reported adverse events. Dedicated on-the-road driving and psychomotor performance studies demonstrated minimal next-day impairment at approved doses, although transient balance and reaction time impairments were observed shortly after administration of supratherapeutic doses in elderly subjects. These exposure-dependent tolerability concerns ultimately influenced regulatory decisions to approve lower therapeutic doses of 10–20 mg[89].

More recent investigations have expanded the evaluation of suvorexant to special populations and comorbid conditions. In patients with mild-to-moderate Alzheimer's disease dementia, suvorexant produced significant improvements in total sleep time, wake after sleep onset, and sleep latency without detectable impairment in next-day cognitive or psychomotor performance. In contrast, a randomized, double-blind, placebo-controlled crossover study in patients with Parkinson disease–associated insomnia, involving two four-week treatment periods separated by a washout phase, did not demonstrate a statistically significant improvement in the primary endpoint of sleep efficiency. Nevertheless, secondary analyses revealed favorable trends, including reductions in wake after sleep onset and latency to persistent sleep, suggesting potential benefits for sleep maintenance and initiation; notably, this trial represents the first randomized clinical evaluation of suvorexant in Parkinson disease[90].

Despite these encouraging findings, several limitations remain evident across the existing body of evidence, including modest and inconsistent effects on sleep onset in early trials, unresolved clinical implications of REM sleep alterations, dose restrictions driven by safety considerations, and a relative scarcity of adequately powered studies assessing long-term cognitive outcomes and disease-modifying potential in neurologically vulnerable populations.

In a separate randomized, double-blind, placebo-controlled crossover study evaluating suvorexant in patients with Parkinson disease–associated insomnia, participants underwent two 4-week treatment phases separated by a 2-week washout period, receiving either nightly suvorexant (10 or 15 mg) or placebo. Among the 21 enrolled participants, suvorexant did not produce a statistically significant improvement in the primary endpoint of sleep efficiency relative to placebo. Nevertheless, secondary analyses indicated a favorable trend with suvorexant, including reductions in wake after sleep onset (WASO) and latency to persistent sleep (LPS), suggesting potential benefits for sleep maintenance and sleep initiation. Notably, this investigation represents the first randomized clinical trial assessing suvorexant in individuals with Parkinson disease. Although the primary efficacy outcome

was not achieved, several secondary sleep parameters demonstrated trends supporting suvorexant compared with placebo[91].

Mori et al. analyzed data from 48 and 57 patients taking suvorexant and lemborexant, respectively. When compared with that in the pre-treatment period, sleep duration was significantly longer on days 2 and 3 in the suvorexant group, and on all three days in the lemborexant group. On day 1 of drug administration, the lemborexant group had a significantly longer sleep duration than the suvorexant group (5.10 ± 1.84 vs. 5.93 ± 1.90 h, respectively; P = 0.017). Zero (0.0%) and three (5.3%) falls occurred in the suvorexant and lemborexant groups, respectively (P = 0.248). Lemborexant exerted a potent inhibitory effect on orexin 2 receptors, which could explain the longer sleep duration experienced by patients taking this drug on the first day of treatment. Based on the results of this study, lemborexant appears to be more effective than suvorexant in prolonging sleep duration from the first day of drug administration. Although lemborexant may increase the risk of falls, both lemborexant and suvorexant are typically considered to exert a limited effect on fall risk, compared with other sleep medications. These findings indicate that among ORAs, lemborexant showed quicker improvement in sleep duration, while suvorexant may be beneficial for patients concerned with fall risk[92].

3.2.3 Lemborexant (LEM): Lemborexant is a competitive DORA that selectively inhibits both OX1R and OX2R receptors. It has received regulatory approval for the treatment of insomnia disorder in adults across several regions, including the United States, Canada, Australia, Japan, and multiple countries in Asia and the Middle East[93].

Pharmacokinetically, lemborexant is predominantly metabolized by cytochrome P450 3A4 (CYP3A4), generating M10 as its major circulating metabolite. Notably, M10 demonstrates binding affinity to OX1R and OX2R comparable to that of the parent compound, suggesting a sustained pharmacodynamic contribution to clinical efficacy[94].

Two Phase 2 clinical studies have evaluated the efficacy and safety profile of lemborexant. The first was a two-week, randomized, proof-of-concept trial designed to establish optimal dosing for insomnia treatment. Results demonstrated that lemborexant doses ranging from 2.5 to 10 mg produced clinically meaningful improvements in sleep parameters while limiting next-morning residual effects. Doses of 5 mg and above were associated with statistically significant enhancements in sleep efficiency (SE), subjective sleep efficiency (sSE), latency to persistent sleep (LPS), and subjective latency to sleep onset (sLSO). Improvements in wake after sleep onset (WASO) and subjective WASO (sWASO) were numerically greater at doses exceeding 1 mg. Overall tolerability was favorable, with somnolence emerging as the most frequently reported treatment-emergent adverse event.

The second Phase 2 study investigated lemborexant in a more complex clinical population, comprising individuals with irregular sleep–wake rhythm disorder (ISWRD) and mild-to-moderate Alzheimer's disease (AD). Participants received lemborexant at doses between 2.5 and 15 mg or placebo once nightly. Treatment was well tolerated and resulted in improvements in both circadian rhythm markers and nocturnal sleep parameters. Additionally, lemborexant significantly reduced the mean duration of daytime sleep episodes, highlighting its potential benefit in managing sleep–wake fragmentation in neurodegenerative conditions[95].

The Phase 3 clinical development of lemborexant included two pivotal trials, SUNRISE 1 and SUNRISE 2, conducted in patients with insomnia disorder. SUNRISE 1 was a randomized, placebo-controlled, one-month study evaluating lemborexant at doses of 5 and 10 mg, with zolpidem included as an active comparator. Both lemborexant doses significantly improved sleep onset and sleep maintenance outcomes compared with placebo and zolpidem. The treatment was generally well tolerated, with headache and somnolence being the most reported adverse events[96,97].

SUNRISE 2 was a long-term, placebo-controlled, 12-month study designed to assess the sustained efficacy and safety of lemborexant at 5 and 10 mg. Both doses demonstrated superiority over placebo for sLSO at one month, with benefits maintained throughout the 12-month treatment period. Key secondary endpoints related to sleep maintenance also showed significant and durable improvements at one, six, and twelve months. Somnolence remained the most frequently reported adverse event, and overall tolerability was consistent with findings from short-term studies[98].

Importantly, across both SUNRISE trials, no evidence of rebound insomnia was observed following treatment discontinuation, as assessed by sleep diary-based measures of sLSO and sWASO. Furthermore, there were no indications of withdrawal symptoms after cessation of lemborexant therapy at either the 5 or 10 mg dose, supporting its favorable discontinuation profile. The effects of lemborexant on next-day functioning have been evaluated in several dedicated studies. In a randomized, double-blind, placebo- and active-controlled, four-period crossover trial, next-morning on-road driving performance in healthy volunteers was not significantly impaired at doses of 5 or 10 mg compared with placebo, based on changes in the standard deviation of lateral position (SDLP). However, symmetry analysis revealed that a subset of individuals receiving the 10 mg dose exhibited clinically relevant impairment, indicating interindividual variability in sensitivity[99].

In an open-label, multicenter investigation involving 90 participants, the majority of patients (95.6%) were successfully transitioned to lemborexant therapy by Week 2, with high treatment persistence observed at the end of the titration phase (97.8%) and through Week 14 (82.2%).

Treatment-emergent adverse events were reported in 47.8% of participants, although no serious adverse events were documented. Patient-reported outcome measures indicated favorable treatment responses, and sustained reductions in Insomnia Severity Index scores were maintained throughout the maintenance period[100].

Additional long-term evidence was provided by Study 303, a Phase 3, multicenter, randomized, double-blind, parallel-group trial conducted over 12 months. In this study, 949 participants in the full analysis set were randomized to receive placebo, lemborexant 5 mg (LEM5), or lemborexant 10 mg (LEM10) during the initial six-month treatment period. Both lemborexant doses produced statistically significant improvements in measures of sleep initiation and sleep maintenance compared with placebo. Importantly, therapeutic benefits were sustained across the full duration of the study, supporting the long-term efficacy of lemborexant in the management of chronic insomnia[101].

Despite robust evidence supporting the efficacy and tolerability of lemborexant, several limitations warrant consideration. Most pivotal trials excluded patients with severe psychiatric or neurological comorbidities, potentially limiting generalizability. Additionally, while next-day impairment was minimal at recommended doses, individual susceptibility—particularly at 10 mg—highlights the importance of dose personalization, especially in older adults. Long-term real-world data in cognitively impaired populations remain limited and merit further investigation.

3.2.4 Almorexant: Almorexant (ACT-078573) is an orally active dual orexin receptor antagonist that is being developed by Actelion Ltd, in collaboration with GlaxoSmithKline plc, for the treatment of primary insomnia. Almorexant is a first-in-class compound that targets the orexin system, which plays a key role in wake promotion and stabilization, in addition to having other regulatory functions. Preclinical studies and phase I clinical trials have demonstrated that almorexant decreases alertness and increases sleep in healthy rats, dogs and humans when administered during the active phase of the circadian cycle, at peak endogenous orexin tone[102].

The pharmacokinetic profile of almorexant was characterized by a median time to the maximum concentration of 1.5 hours, quick disposition with a distribution half-life of 1.6 hours, and rapidly decreasing concentrations to approximately 20% of the maximum concentration over 8 hours, with a terminal half-life of 32 hours. Objective pharmacodynamic measures showed decreases in saccadic peak velocity and adaptive tracking performance and increases in body sway with the 400-mg dose of almorexant. Subjective assessments revealed a dose-dependent decrease in alertness[103].

In a randomized study involving 112 participants, almorexant produced significant, dose-dependent reductions in mean wake after sleep onset (WASO). Total sleep time increased significantly across all almorexant dose groups compared with placebo. A statistically significant reduction in latency to persistent sleep was observed only with the 200 mg dose relative to placebo, with a treatment effect of −10.2 minutes. No unexpected safety signals were detected, and the incidence of adverse events was comparable between almorexant-treated groups and placebo. Short-term oral administration over two nights demonstrated that almorexant was both effective and well tolerated for the management of primary insomnia in elderly individuals[104].

Additional evidence was provided by a prospective, randomized, double-blind, placebo-controlled trial with an active comparator, conducted in adult men and women aged 18–64 years with chronic primary insomnia. Participants were assigned in a 1:1:1:1 ratio to receive placebo, almorexant 100 mg, almorexant 200 mg, or zolpidem 10 mg for 16 days. Treatment with almorexant significantly shortened sleep onset latency and improved sleep maintenance, without evidence of next-day performance impairment or safety concerns. Collectively, these findings further support the involvement of the endogenous orexin signaling system in the pathophysiology and treatment of insomnia disorder. From the initial screening single-blind placebo dose until 28 days following the conclusion of the double-blind study treatment, adverse events (AEs) were documented. Possible narcolepsy-like symptoms (sleep paralysis, narcolepsy, muscular weakness, jaw disorder, cataplexy, hypnopompic hallucination, and hypnagogic hallucination) were among the adverse events of particular interest. Vital signs, significant clinical laboratory abnormalities, orthostatic hypotension, and electrocardiogram (ECG) results were noted. Additionally evaluated were changes in body weight from baseline to Days 15 and 16 (Visit 4) and Epworth Sleepiness Scale scores from baseline to Day 16[105].

3.2.5 Seltorexant (JNJ-42847922): Seltorexant (JNJ-42847922) is a highly potent and selective orexin-2 receptor (OX2R) antagonist developed primarily for the treatment of insomnia, with additional investigation into its therapeutic potential in major depressive disorder (MDD). Unlike dual orexin receptor antagonists, seltorexant selectively targets OX2R, enabling focused modulation of orexin-mediated wakefulness pathways implicated in sleep initiation and maintenance while potentially minimizing off-target effects associated with broader orexin blockade[106].

The pharmacodynamic effects of seltorexant have been well characterized in preclinical models, where it consistently promoted sleep by increasing total sleep duration, reducing latency to persistent sleep, and decreasing wakefulness after sleep onset. In Sprague–Dawley rats, seltorexant produced dose-dependent sleep enhancement during both light and dark phases, characterized by reduced non-rapid eye movement (NREM) sleep latency and a marked increase in NREM sleep duration within two hours of administration. An effective dose of approximately 3 mg/kg was sufficient to support both sleep initiation and maintenance through selective

OX2R antagonism, providing a strong translational rationale for clinical development[107].

Early clinical pharmacology studies in healthy volunteers demonstrated favorable pharmacokinetic and tolerability profiles. Following single-dose and multiple-dose administration (once daily for up to 10 days) at doses up to 80 mg and 60 mg, respectively, seltorexant exhibited rapid absorption, good tolerability, and a relatively short elimination half-life of approximately 2–3 hours. Importantly, no residual neurocognitive or psychomotor impairment was detected four hours after daytime dosing, although the short duration of action has raised questions regarding its ability to sustain sleep continuity across the entire night.

Clinical efficacy was subsequently evaluated across multiple Phase 2a and Phase 2b randomized, double-blind, placebo-controlled studies in patients with insomnia disorder and depressive disorders. In early crossover trials involving patients with insomnia without psychiatric comorbidity, seltorexant administered at doses of 40 mg once daily significantly improved sleep efficiency compared with placebo, with favorable trends observed across secondary endpoints including total sleep time, latency to persistent sleep, and wake after sleep onset. These findings were supported by objective sleep measures demonstrating improved sleep continuity and architecture, including reductions in REM sleep latency and increases in overall REM duration[108].

Larger randomized trials further clarified dose–response relationships. In a clinical study involving 364 adults with insomnia disorder, seltorexant demonstrated clear dose-dependent improvements in sleep initiation and maintenance, with significant reductions in latency to persistent sleep and wake after sleep onset observed at 10 mg and 20 mg during the first six hours of treatment. Notably, the 20 mg dose produced numerically greater improvements in key sleep parameters compared with zolpidem, indicating robust efficacy for sleep initiation in patients without comorbid psychiatric illness. These results were reinforced in a subsequent Phase 2b trial, where seltorexant at doses of 10 mg and 20 mg reduced latency to persistent sleep by approximately 32 and 37 minutes, respectively, and decreased wake after sleep onset by nearly 29 minutes relative to placebo. Across studies, the safety profile remained consistent, with headache, somnolence, dizziness, fatigue, and abnormal dreams reported as the most common adverse events[109].

Seltorexant has also been evaluated in patients with major depressive disorder receiving stable antidepressant therapy. In crossover studies assessing single doses ranging from 10 to 40 mg, seltorexant produced dose-dependent reductions in sleep latency and increases in total sleep time, although effects on wake after sleep onset were less pronounced in this population. In a separate investigation involving patients with MDD treated with seltorexant 20 mg for up to 28 days, improvements were observed not only in sleep parameters but also in core depressive symptoms, suggesting a potential dual benefit in patients with comorbid insomnia and depression. Treatment was generally well tolerated, with adverse events consistent with those observed in insomnia-focused trials[110].

Despite these promising findings, several limitations remain within the current evidence base for seltorexant. Most clinical trials were of relatively short duration, limiting conclusions regarding long-term efficacy, safety, and relapse prevention. The frequent exclusion of patients with complex psychiatric or medical comorbidities restricts generalizability to real-world populations, and the short elimination half-life raises questions regarding sustained nocturnal sleep maintenance. Consequently, longer-term, adequately powered, and pragmatic studies are required to define optimal dosing strategies, clarify comparative effectiveness relative to dual orexin receptor antagonists, and establish the precise therapeutic role of seltorexant in patients with comorbid insomnia and mood disorders[111].

3.3 Melatonin receptor agonists

3.3.1 Ramelteon: Ramelteon received approval from the U.S. Food and Drug Administration (FDA) in July 2005 and was subsequently launched in the United States under the brand name *Rozerem* in September 2005. It is a highly selective agonist of the melatonin MT_1 and MT_2 receptors, which are predominantly expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus the central regulator of circadian rhythms. Activation of MT_1 receptors primarily facilitates sleep initiation, whereas MT_2 receptor stimulation contributes to circadian phase shifting, thereby promoting physiological alignment of the sleep–wake cycle[112,113].

Unlike conventional sedative–hypnotic agents, ramelteon does not interact with γ-aminobutyric acid (GABA)ergic neurotransmission or other central nervous system depressant pathways commonly associated with tolerance, dependence, cognitive impairment, or abuse liability. This receptor-selective, chronobiotic mechanism enables ramelteon to induce sleep in a manner that closely resembles endogenous melatonin signaling, representing a pharmacologically distinct and safety-oriented approach to the management of insomnia.

Following oral administration, ramelteon is rapidly absorbed; however, extensive first-pass hepatic metabolism results in a low mean systemic bioavailability of approximately 1.8%. Peak plasma concentrations are typically achieved within 45 minutes of dosing. Depending on the administered dose (ranging from 4 to 64 mg), the elimination half-life—longer than that of endogenous melatonin—varies between approximately 0.8 and 1.9 hours[114,115,116].

The clinical efficacy of ramelteon has been evaluated in several large-scale analyses. Kuriyama et al. conducted a meta-analysis of 13 randomized, placebo-controlled trials involving a total of 5,812 patients with primary, chronic, or psychophysiological insomnia. Most participants received ramelteon 8 mg orally before bedtime. The analysis

demonstrated statistically significant improvements in subjective sleep latency (sSL) and reductions in latency to persistent sleep (LPS). Sleep efficiency (SE) showed moderate improvement, along with a modest increase in total sleep time (TST) of approximately 7.26 minutes. Overall, ramelteon was well tolerated, with somnolence being the most reported adverse effect[117].

Similarly, Maruani et al. evaluated data from 1,804 patients treated with ramelteon or placebo. Doses ranged from 4 to 16 mg/day, with 8 mg once nightly before bedtime serving as the standard regimen. After four weeks of treatment, ramelteon significantly reduced both objective and subjective measures of sleep onset latency, while also producing significant increases in objective and subjective total sleep time. These benefits were maintained during long-term treatment (>4 weeks) compared with placebo. Although the magnitude of effect was modest, ramelteon consistently demonstrated excellent safety and tolerability[118].

Additional evidence regarding dosing optimization has emerged from studies in circadian rhythm sleep–wake disorders. In a study aimed at identifying the optimal dosing strategy for delayed sleep–wake phase disorder (DSPWD), a strategically timed low-dose regimen was found to be most effective. Administration of approximately 2 mg of ramelteon at an appropriate circadian phase provided the most favorable balance between therapeutic efficacy and treatment adherence. Overall, the effective dose window for improved adherence appeared to center around 2 mg[119].

Collectively, these findings position ramelteon as a chronobiotic hypnotic with a favorable safety and tolerability profile. It is particularly well suited for patients with sleep-onset insomnia, older adults, and individuals for whom GABAergic sedatives are contraindicated. Its unique mechanism of action, coupled with the absence of abuse potential, supports its role as a first-line or adjunctive option in the long-term management of insomnia and circadian rhythm sleep–wake disorders.

3.3.2 Tasimelteon: Tasimelteon is currently the only medication with orphan drug designation approved by both the U.S. Food and Drug Administration (FDA, 2014) and the European Medicines Agency (EMA, 2015) for the treatment of non-24-h sleep–wake rhythm disorder (non-24), particularly in totally blind individuals[120]. Interest in tasimelteon has been driven by its potent agonistic activity at melatonin MT1 and MT2 receptors, along with reported interactions with serotonin 5-HT2C and 5-HT2B receptors, which may contribute to its circadian phase-shifting properties[121].

Pharmacokinetically, tasimelteon undergoes extensive first-pass metabolism in the liver and intestine, primarily mediated by CYP1A2 and CYP3A4/5. Its absolute oral bioavailability is approximately 38% and remains linear across a dose range of 3–300 mg. The major metabolites (M9 and M11–M14) exhibit markedly reduced affinity for melatonin receptors and do not contribute meaningfully to clinical efficacy. Importantly, neither tasimelteon nor its metabolites demonstrate clinically relevant off-target receptor binding[122].

The clinical efficacy of tasimelteon was established in the randomized withdrawal Safety and Efficacy of Tasimelteon (RESET) study conducted by Lockley et al.[123]. Continued treatment maintained circadian synchrony in 90% of participants, whereas only 20% of subjects retained synchrony following drug discontinuation. The favorable safety and tolerability profile observed in this trial formed the basis for regulatory approval. Subsequent analyses have suggested that tasimelteon may offer superior efficacy compared with ramelteon and may also be beneficial in sighted individuals with non-24[124,125].

Tasimelteon has also been evaluated for other circadian rhythm–related sleep disorders. Polymeropoulos et al.[126] conducted a twelve-center, randomized, double-blind study assessing the effects of 20 mg tasimelteon in patients with jet lag disorder. Treatment significantly improved alertness reduced subjective drowsiness, and shortened sleep latency by approximately 15 minutes.

Further evidence of efficacy comes from two multicenter randomized controlled trials conducted by Rajaratnam et al.[127]. In the Phase II study (n = 39), doses ranging from 10 to 100 mg administered following a 5-h sleep phase shift resulted in reduced sleep latency and improved sleep efficiency compared with placebo. These findings were confirmed in the Phase III trial (n = 411), in which tasimelteon (20–100 mg) significantly decreased sleep onset latency, enhanced sleep efficiency, and reduced wake time after sleep onset.

Tasimelteon has also been investigated in primary insomnia. In a randomized, double-blind, placebo-controlled multicenter study involving 322 patients, nightly doses of 20 mg or 50 mg administered over five weeks produced significant improvements in polysomnography-derived sleep parameters. Notably, tasimelteon improved sleep from the first night of treatment, with sustained benefits throughout the study period. No cognitive or mood impairments, rebound insomnia, or withdrawal effects were observed following treatment discontinuation, supporting its potential utility in chronic sleep-onset insomnia[128].

Overall, tasimelteon is considered highly safe and well tolerated in both oral and intravenous formulations. A 20 mg bedtime dose does not result in clinically significant next-day driving impairment and, unlike ramelteon, lacks long-acting active metabolites that could adversely affect cognition or psychomotor performance. Pharmacokinetic studies indicate that dose adjustment is not required in patients with mild-to-moderate hepatic impairment or in those with severe renal impairment, including individuals undergoing dialysis.

The reported adverse events were predominantly mild to moderate in severity and included headache, elevations in

alanine aminotransferase (ALT), somnolence, abnormal dreams, sleep disturbances, and infections. In the study by Bonacci et al., headache was the most frequently observed adverse event (15.4%), followed by elevated ALT levels (9.6%), upper respiratory and urinary tract infections (5.8%), along with somnolence, sleep-related disorders, and abnormal dreaming[129,130]. More recently, Zuo et al. identified additional sleep-related adverse events, including insomnia and sleep disorders, not previously described in manufacturer-reported safety data[131].

3.4 Investigational and alternative agents

3.4.1 Eplivanserin: Eplivanserin, a propenone ether derivative, has potent 5-HT2A receptor blocking properties and a relatively long half-life. Its affinities for the 5-HT2B, 5-HT2C, and 5-HT2A receptors are low, moderate, and high, respectively. The binding of in vivo [3H] eplivanserin, which was found to bind mainly in mouse brain regions containing the 5-HT2A receptor, was found to be disrupted by the nonselective 5-HT2A/2C receptor antagonists ritanserin and ketanserin. Additionally, the agent stopped the 5-hydroxytryptophan-induced head twitches in mice. The effects of eplivanserin administered three hours after the beginning of the light phase on the sleep-wake cycle were examined in male rats prepared for long-term sleep recordings[132]. The average number and duration of SWS episodes were considerably elevated by eplivanserin. The effects of eplivanserin (1 mg, p.o.) on sleep EEG and power spectra in young, healthy men were examined by Landolt et al. A randomized, double-blind, crossover design was used to administer either eplivanserin or a placebo three hours before the start of the recording session. While N2 sleep was decreased, eplivanserin significantly increased N3 sleep. SOL, REM sleep latency, TST, SE, and REM sleep in minutes did not significantly differ between the 5-HT2A receptor antagonist and placebo. While the power associated with spindle activity (12.5–15 Hz) was decreased, NREM sleep power within 0.75–4.5 Hz was increased. The compound had no effect on subjective sleep quality. Eplivanserin selectively enhanced deep sleep by significantly increasing slow-wave (N3) sleep and NREM delta power without affecting total sleep time, sleep efficiency, REM sleep, or subjective sleep quality, indicating targeted improvement of sleep architecture rather than general sedation[133].

3.4.2 Daidzin: Daidzin (DZN), a naturally occurring soy isoflavone, has attracted considerable interest due to its broad spectrum of neuropharmacological properties demonstrated in preclinical models, including anxiolytic, cognitive-enhancing, and anticonvulsant effects. Despite these documented central nervous system activities, its potential role as a sedative–hypnotic agent has remained relatively unexplored. Recent experimental investigations have therefore sought to elucidate the sedative and sleep-promoting effects of daidzin and to clarify the molecular mechanisms underlying these actions.

In vivo studies conducted in male Swiss albino mice evaluated the sedative–hypnotic profile of daidzin administered intraperitoneally at doses of 5, 10, and 20 mg/kg. Sleep induction and maintenance were assessed using thiopental sodium– and diazepam-induced sleep paradigms. To determine the involvement of the GABAergic system, daidzin was administered alone and in combination with the benzodiazepine diazepam and the benzodiazepine antagonist flumazenil. Behavioral outcomes were measured in terms of sleep latency and total sleep duration. The results demonstrated that daidzin produced a dose-dependent and statistically significant reduction in sleep onset latency, accompanied by a prolongation of sleep duration. Notably, co-administration with diazepam resulted in synergistic enhancement of sedative–hypnotic effects, including further shortening of sleep latency and extension of sleep time. Partial attenuation of these effects by flumazenil suggests the involvement of benzodiazepine-sensitive GABAA receptor sites.

To support the behavioral findings, in silico molecular docking and molecular dynamics simulations were performed to evaluate the interaction of daidzin with the α1 and β2 subunits of the GABAA receptor. Daidzin exhibited a strong binding affinity (−7.2 kcal/mol), comparable to that of diazepam (−8.3 kcal/mol), and demonstrated stable binding conformations within the receptor complex. Molecular dynamics analyses further confirmed the stability of daidzin–receptor interactions and revealed binding patterns similar to those observed with diazepam[134].

Collectively, these findings indicate that daidzin exerts significant sedative–hypnotic effects in experimental models, likely mediated through modulation of the GABAA receptor complex. The observed pharmacological and molecular interactions support its potential as a naturally derived sedative–hypnotic candidate and warrant further investigation to determine its translational relevance in sleep disorders.

3.4.3 Zuranolone: Zuranolone (SAGE-217) is a rationally developed, orally bioavailable neuroactive steroid that represents a novel class of sedative–hypnotic agents. Structurally related to endogenous neurosteroids such as allopregnanolone, zuranolone functions as a positive allosteric modulator of both synaptic and extrasynaptic γ-aminobutyric acid type A receptors ($GABA_AR$s). This dual modulatory action distinguishes it pharmacologically from conventional hypnotics, including benzodiazepines and non-benzodiazepine "Z-drugs," which primarily target synaptic $GABA_AR$. Importantly, neuroactive steroids interact with binding sites on the $GABA_AR$ that are distinct from those utilized by benzodiazepines and barbiturates, contributing to their unique pharmacodynamic profile[135].

From a pharmacokinetic perspective, zuranolone exposure is significantly influenced by cytochrome P450 3A4 (CYP3A4) activity. Concomitant administration with strong CYP3A4 inhibitors results in increased systemic exposure and may elevate the risk of adverse effects, whereas CYP3A4 inducers reduce drug levels and may compromise therapeutic efficacy. Consequently, dose modification to 30

mg administered once daily in the evening for 14 days is recommended when zuranolone is co-administered with strong CYP3A4 inhibitors, while concurrent use with CYP3A4 inducers is generally discouraged[136].

The sedative–hypnotic efficacy of zuranolone has been demonstrated in clinical studies involving patients with insomnia. In a randomized, double-blind, three-way crossover trial, participants received a single oral dose of zuranolone (30 mg or 45 mg) or placebo. Treatment with zuranolone produced significant improvements in both subjective sleep quality and objective polysomnographic parameters. Notable enhancements were observed in sleep efficiency, total sleep time, wake after sleep onset, and the duration of nocturnal awakenings, with more pronounced effects at the higher dose. In general, zuranolone was well tolerated; no serious or severe adverse events occurred, and no adverse event-related discontinuations occurred. Every treatment-emergent adverse event (TEAE) was mild. 9.8% of participants experienced TEAEs during the placebo treatment period, 11.4% during the zuranolone 30-mg treatment period, and 4.8% during the zuranolone 45-mg treatment period. Fatigue and headache were the most common TEAEs (zuranolone 30 mg). One participant reported each of the remaining TEAEs[137].

Further analysis of sleep architecture revealed a significant increase in time spent in non-rapid eye movement (NREM) sleep stages N2 and N3, suggesting a favorable effect on restorative sleep. In contrast, no significant alterations were detected in light sleep (N1) or rapid eye movement (REM) sleep duration. Zuranolone was generally well tolerated, with headache and fatigue being the most frequently reported adverse events.

Overall, the ability of zuranolone to modulate both synaptic and extrasynaptic $GABA_AR$, improve sleep continuity, and enhance deeper stages of NREM sleep supports its potential role as a next-generation sedative–hypnotic agent. Its distinct mechanism of action and favorable sleep architecture profile highlight its promise as an alternative to traditional GABAergic hypnotics.

3.4.4 Agomelatine: Agomelatine, approved by the European Medicines Agency in 2009 for the treatment of major depressive episodes, is an atypical antidepressant distinguished by its pronounced sleep-regulatory properties. It belongs to the class of melatonergic agonists and selective serotonin antagonists (MASS), acting as an agonist at melatonin MT1 and MT2 receptors while simultaneously antagonizing serotonin 5-HT2C and 5-HT2B receptors. Melatonergic activity occurs at relatively low plasma concentrations and is considered central to its chronobiotic and sleep-promoting effects, whereas serotonergic antagonism emerges at higher concentrations and may contribute to its antidepressant and pro-cognitive actions. Blockade of 5-HT2C receptors enhances norepinephrine and dopamine release in the prefrontal cortex, while melatonin receptor activation facilitates circadian rhythm resynchronization and sleep–wake regulation[138].

Following oral administration, agomelatine is rapidly absorbed; however, extensive first-pass hepatic metabolism results in low absolute bioavailability (<5% at therapeutic doses) and marked interindividual variability. Peak plasma concentrations are typically achieved within 1–2 hours after dosing[139].

The sleep-modulating effects of agomelatine have been explored in both circadian rhythm disorders and depressive populations. In a non-blinded randomized controlled study involving 60 adolescents and young adults diagnosed with delayed sleep–wake phase disorder (DSWPD), participants received four weeks of agomelatine therapy either alone or in combination with cognitive behavioral therapy. Both treatment arms demonstrated a significant phase advance of the sleep–wake rhythm, with improvements largely attributed to the intrinsic sleep-promoting effects of agomelatine. The addition of cognitive behavioral therapy appeared to support maintenance of the adjusted circadian rhythm.

In patients with major depressive disorder, Lemoine et al. conducted a six-week randomized, double-blind trial comparing agomelatine (25–50 mg/day) with venlafaxine (75–150 mg/day) in 332 participants. While antidepressant efficacy was comparable between treatments, agomelatine produced faster and more pronounced improvements in subjective sleep quality, as assessed by the Leeds Sleep Evaluation Questionnaire, highlighting its favorable impact on sleep in unipolar depression[140].

Quera-Salva et al. further substantiated these findings in a 24-week multicenter, randomized, double-blind study, which compared agomelatine with escitalopram in 138 patients with major depressive disorder[141]. Agomelatine significantly reduced sleep onset latency from the second week of treatment onward and preserved normal sleep architecture. In contrast, escitalopram was associated with prolonged REM latency and reduced sleep cycles. Patients receiving agomelatine also reported superior morning alertness and reduced daytime sleepiness.

Hsing et al. examined the association between agomelatine use and the requirement for additional sedative–hypnotic medication in a large observational cohort of 7,961 patients[142]. After adjustment for confounding variables, agomelatine was not associated with an increased likelihood of concomitant sedative–hypnotic use compared with other antidepressants, indicating comparable sleep-medication requirements and suggesting that its sleep benefits do not necessitate adjunctive hypnotic therapy.

Grosshans et al. reported further support for agomelatine's hypnotic effects based on off-label administration (25–50 mg nightly) in nine patients with alcohol dependence and chronic insomnia[143]. After six weeks of treatment, sleep quality improved substantially, with mean Pittsburgh Sleep Quality Index scores decreasing from 13.1 to 7.8, reflecting a clinically meaningful reduction in insomnia severity.

Table 1: Comparative Overview of Innovative Agents

Drug Name	Class	Mechanism of Action	Indication	Duration of Action	Risk of Dependence	Notable features
Remimazolam	Benzodiazepine	Enhances GABA-A receptor activity	Procedural sedation	Ultra-short-acting	Ultra-short-acting	Rapid onset and recovery; used for short procedures; lower sedation hangover compared to older benzodiazepines[68].
Daridorexant (Quviviq)	Dual Orexin Receptor Antagonist	Blocks orexin-1 and orexin-2 receptors	Insomnia	Moderate	Low	Improves sleep onset and maintenance with minimal next-day impairment[74].
Suvorexant	Dual Orexin Receptor Antagonist	Blocks orexin-1 and orexin-2 receptors	Insomnia	Moderate	Low	FDA-approved DORA with good safety profile but may cause sleep paralysis in some individuals[84].
Lemborexant	Dual Orexin Receptor Antagonist	Blocks orexin-1 and orexin-2 receptors	Insomnia	Moderate	Low	Reduces sleep onset latency; may have fewer cognitive side effects compared to older sedatives[94].
Seltorexant	Selective orexin-2 receptor (OX2R) antagonist	Selectively blocks orexin-2 (OX2) receptors	Insomnia disorder	Short duration of action	Low risk	Improved sleep continuity: reduced REM latency and increased overall REM duration[106]
Ramelteon	Melatonin Receptor Agonist	Activates melatonin receptors (MT1, MT2)	Insomnia (sleep onset)	Short	None	Non-sedative profile; promotes natural sleep cycle with minimal risk of dependency[112].
Eplivanserin	Serotonin Receptor Antagonist	Blocks serotonin 5-HT2A receptors	Investigational (insomnia)	Short	Low	Development was discontinued; aimed to improve sleep quality without next-day sedation[133].
Tasimelteon	Melatonin Receptor Agonist	Activates melatonin receptors (MT1, MT2)	Non-24-hour sleep-wake disorder	Short	None	Specifically for blind individuals, regulates circadian rhythm effectively[121].
Almorexant	Dual Orexin Receptor Antagonist	Blocks orexin-1 and orexin-2 receptors	Investigational (insomnia)	Moderate	Low	Discontinued due to safety concerns despite promising effects on sleep maintenance[102].
Zuranolone	GABA-A receptor positive allosteric modulator	Enhances GABA-A receptor activity	Postpartum depression	Rapid (within days)	Low to moderate	Rapid antidepressant effect after short-course use[135].
Agomelatine	Melatonergic(MT1/MT2 agonist, 5-HT2C antagonist	Agonist at melatonin MT1 and MT2 receptors	Major depressive disorder	Delayed	Minimal to none	Resynchronization of circadian rhythms[138].

In general, agomelatine was well tolerated. Most side effects, such as headache, nausea, lightheadedness, exhaustion, and gastrointestinal distress, were mild and temporary. It demonstrated reduced rates of sexual dysfunction, weight gain, daytime sedation, and sleep disturbance when compared to SSRIs and SNRIs. Dose-related, typically asymptomatic increases in liver transaminases were a significant safety concern, underscoring the necessity of regular monitoring of liver function. Rebound insomnia, dependence, or serious adverse events were uncommon[144].

Overall, agomelatine emerges as a well-tolerated and effective agent for improving sleep disturbances, particularly in individuals with comorbid depressive disorders. Through combined melatonergic agonism and serotonergic antagonism, it promotes circadian realignment, enhances sleep initiation and continuity, and preserves physiological sleep architecture. Importantly, clinical benefits on sleep often appear early in treatment and are achieved without increasing reliance on conventional sedative–hypnotic medications, supporting agomelatine as a promising alternative for sleep dysfunction associated with depression.

3.5 Limitations of Current Evidence

Despite notable progress in the development of novel sedative–hypnotic agents, the interpretation and broader applicability of current evidence remain constrained by several methodological limitations. A substantial proportion of pivotal clinical trials have enrolled highly selected populations, applying stringent exclusion criteria that omit individuals with severe psychiatric comorbidities, neurodegenerative disorders, substance use disorders, significant hepatic or renal dysfunction, and those receiving multiple concomitant medications. Such selection practices limit external validity, as real-world insomnia frequently occurs in complex, multimorbid patients who are underrepresented in controlled trial settings.

Another important limitation relates to trial duration. Most Phase II and III randomized controlled studies have been conducted over short to intermediate timeframes, typically ranging from 4 to 12 weeks, with relatively few investigations extending beyond one year. Consequently, long-term efficacy, safety, and durability of therapeutic response remain insufficiently characterized. Although polysomnographic parameters often serve as primary endpoints, improvements in objective sleep architecture do not consistently translate into meaningful gains in patient-reported outcomes such as functional status, quality of life, and daytime performance. Furthermore, critical long-term outcomes, including cognitive trajectories, risk of falls or accidents, and occupational functioning, have not been comprehensively evaluated.

Comparative effectiveness data are also limited. The majority of trials rely on placebo-controlled designs, while direct head-to-head comparisons with established pharmacotherapies are scarce and inconsistently implemented. Evidence gaps are particularly pronounced in vulnerable and understudied subgroups, including pediatric populations, pregnant and lactating women, and adults aged 75 years and older. Additionally, dosing strategies have rarely incorporated pharmacogenomic variability in drug metabolism, despite its potential relevance to interindividual differences in efficacy and tolerability.

Finally, the predominance of industry-sponsored trials raises concerns regarding reporting transparency. Selective outcome reporting and restricted access to individual-level data may hinder independent meta-analyses and robust subgroup evaluations, thereby limiting the completeness and reproducibility of the available evidence base.

3.6 Critical Analysis

Collectively the agents reviewed underscore a clear paradigm shift in sleep and sedation pharmacotherapy transitioning from nonspecific GABAergic suppression to receptor and circuit selective modulation of sleep wake neurobiology. This evolution reflects a more nuanced conceptualization of insomnia as a disorder of dysregulated neural circuitry and hyperarousal rather than a simple deficit in sedation. Nevertheless, despite substantial mechanistic advances no therapeutic class has fully succeeded in simultaneously restoring physiological sleep architecture, preserving next day functional performance and ensuring long term safety. Persistent trade-offs among efficacy tolerability interindividual variability, and suitability for complex clinical populations remain evident across drug classes underscoring the continued need for refined personalizes pharmacologic strategies.

By selectively attenuating wake-promoting circuitry rather than causing global CNS suppression, orexin receptor antagonists represent the most significant advancement in insomnia pharmacotherapy. While maintaining sleep architecture and lowering the risk of dependence and rebound insomnia, dual orexin receptor antagonists such as daridorexant, suvorexant and lemborexant consistently improve sleep onset and maintenance daridorexant exhibit the strongest evidence for sustained efficacy and improvement in next day functioning. However, universal applicability is limited by interindividual variability, dose related residual somnolence and insufficient data in severe neuropsychiatric comorbidity. Seltorexant, a selective OX2 receptor antagonist, is positioned as a supplementary rather than replacement strategy within orexin-based therapies due to its short half-life, inconsistent sleep maintenance effects, and lact of long-term functional outcome data. However, it offers greater mechanistic precision and potential antidepressant synergy.

In contrast to direct hypnotic action, melatonin receptor agonists, such as ramelteon and tasimelteon represent a radically different therapeutic philosophy focused on circadian realignment. Clear clinical advantages include their excellent safety profile lack of abuse liability, and suitability for long term use, especially in older adults. Tasimelteon's potent effectiveness in treating non-24-hour

sleep wake rhythm disorder validates circadian targeting as a viable treatment approach. However, melatonin receptor agonists consistently show modest hypnotic efficacy in primary insomnia, which is characterized by increased physiologic and cognitive arousal. The difference between circadian misalignment and hyperarousal-driven sleep pathology is highlighted by their limited effect on sleep maintenance and fragmentation, which makes them ineffective as monotherapy in patients with severe or multifactorial insomnia.

By combining melatonergic agonism with 5-HT_2C antagonism, agomelatine integrates circadian regulation with antidepressant activity, occupying a distinct pharmacological niche. Agomelatine's dual mechanism enables it to normalize sleep architecture and enhance subjective sleep quality in patients with depressive disorders without causing sedation or cognitive impairment.

Its ability to enhance slow-wave sleep while preserving REM architecture distinguishes it from conventional hypnotics. However, the indirect hypnotic effects of agomelatine limit its usage in primary insomnia, and the requirement for routine liver monitoring hinders its wider clinical acceptance. Therefore, it is better to think of agomelatine as a sleep-modulating antidepressant rather than a true hypnotic.

Remimazolam is an example of optimization within the conventional GABAergic paradigm rather than a departure from it, in contrast to these mechanistically novel approaches. Significant benefits in procedural sedation and anesthesia are provided by its ultra-short action, quick metabolism by tissue esterases, and predictable recovery profile, especially in patients with complex medical conditions. Remimazolam does not, however, avoid the basic drawbacks of benzodiazepine receptor activation, such as dose-dependent sedation, amnestic effects, and cognitive suppression. Its intravenous formulation and unsuitability for long-term administration further limit its use in treating insomnia, highlighting the limitations of pharmacokinetic refinement in resolving class-wide mechanistic issues.

By acting as positive allosteric modulators of both synaptic and extrasynaptic GABA receptors, neuroactive steroids such as zuranolone offer an alternative GABAergic approach that enhances NREM sleep and improves sleep continuity. These drugs show quick antidepressant and sleep-promoting effects, which may be useful in acute neuropsychiatric conditions. Concerns about long-term use are raised by their GABAergic mechanism, the possibility of drug interactions, and the paucity of long-term safety data. Furthermore, despite their mechanistic novelty, it is still unclear how much their sleep effects reflect physiologic restoration versus pharmacologically induced sedation, which makes it difficult to distinguish them from conventional hypnotics.

Lastly, the conceptual appeal of selectively altering sleep architecture, especially slow-wave sleep, without lengthening overall sleep duration or causing sedation is highlighted by experimental drugs like eplivanserin and daidzin. These substances target metabolic or serotonergic pathways to improve the quality of sleep rather than its quantity. However, a persistent disconnect between significant improvements in subjective sleep quality or daytime functioning and objective EEG changes has impeded clinical development. This translational gap highlights a fundamental problem in sleep pharmacology: changes in sleep microarchitecture do not always result in functional recovery or patient-perceived benefit.

Overall, even though orexin receptor antagonists currently provide the best combination of safety, effectiveness, and preservation of daytime function for chronic insomnia, phenotype-driven medication selection is required due to the significant heterogeneity of sleep disorders. A one-size-fits-all approach is impossible due to variations in circadian alignment, hyperarousal, psychiatric comorbidity, and neurobiological vulnerability. The need for individualized, mechanism-informed therapeutic approaches and ongoing innovation beyond current pharmacologic frameworks is highlighted by the fact that no single agent has yet to achieve optimal restoration of both nocturnal sleep and daytime functioning.

4. CONCLUSION AND FUTURE PERSPECTIVES

Sedative–hypnotic agents remain essential in the management of insomnia and anxiety-related disorders; however, the therapeutic framework governing their use has undergone a substantial transformation. The field has shifted from non-selective GABA_A receptor–mediated sedation toward mechanistically targeted modulation of discrete sleep–wake pathways. Accumulating clinical evidence indicates that DORAs, including daridorexant, lemborexant, and suvorexant, provide a more physiologically aligned approach to chronic insomnia by attenuating wake drive without globally suppressing central nervous system activity. These agents demonstrate sustained improvements in sleep initiation and maintenance, preservation of sleep architecture, reduced dependence liability, and better next-day functional outcomes compared with traditional benzodiazepine-based therapies.

Melatonin receptor agonists, such as ramelteon, although modest in hypnotic potency, offer important chronobiotic benefits and maintain the most favorable safety profile, particularly in older adults and individuals with circadian rhythm disturbances. In contrast, conventional GABAergic hypnotics may retain a role in short-term or acute settings but should no longer be considered routine first-line options for chronic insomnia requiring long-term management.

The central take-home message of this review is that insomnia pharmacotherapy must evolve from broad symptom-suppressive sedation to phenotype-driven, mechanism-based intervention. For most adults with chronic insomnia, orexin receptor antagonists currently offer the optimal balance between efficacy, safety, and

preservation of daytime functioning, while melatonin agonists remain the safest choice in older or circadian-vulnerable populations. Clinicians should therefore prioritize agents that minimize cognitive impairment, reduce fall risk, limit dependence potential, and maintain functional integrity. This paradigm shift carries significant implications for long-term patient safety, healthcare resource utilization, and the overall quality of sleep disorder management.

Limitations of This Review: This narrative review has several methodological limitations that should be acknowledged. The literature search was not conducted using a fully systematic strategy, and formal risk-of-bias assessment tools were not applied, which introduces the possibility of selection bias. In addition, standardized evidence-grading frameworks were not used, and quantitative meta-analytic synthesis was not performed; therefore, the conclusions are based on qualitative interpretation rather than pooled statistical estimates. Direct comparisons across studies were further complicated by heterogeneity in patient populations, diagnostic criteria, outcome measures, treatment durations, and trial designs. Moreover, reliance on published data may predispose the analysis to publication bias, as negative trials and adverse event findings are often underreported. Future investigations incorporating systematic review methodology, structured quality appraisal, and meta-analytic techniques would strengthen the evidentiary basis and support more robust, evidence-based clinical recommendations.

Declarations

Author contributions: AB and SR played a pivotal role in conceptualizing and designing the study. AB conducted an exhaustive literature review, and shaping the methodological framework. As a guide and supervisor, SR, provided valuable insights, guidance, and oversight throughout the entire process. Together, AB and SR collaborated to ensure the depth and coherence of the manuscript. All authors reviewed and approved the manuscript.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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