mhc MENTAL HEALTH CLINICIAN

REVIEW OF DRUGS/PHARMACOTHERAPY Open Access

Efficacy and safety of pharmacotherapy in chronic insomnia: A review of clinical guidelines and case reports

Alejandro Del Rio Verduzco, PharmD, MS[1]
Ahva Salari, BS[2]
Parna Haghparast, PharmD, BCPS[3]

How to cite: Del Rio Verduzco A, Salari A, Haghparast P. Efficacy and safety of pharmacotherapy in chronic insomnia: A review of clinical guidelines and case reports. Ment Health Clin [Internet]. 2023;13(5):244-54. DOI: 10.9740/mhc.2023.10.244.

Submitted for Publication: March 16, 2023; **Accepted for Publication:** July 20, 2023

Abstract

Introduction: Chronic insomnia affects 5% to 10% of the US population, increasing the demand for treatment options and the corresponding research to prove their validity.[1] This review compares recommendations from 3 clinical guidelines and summarizes hypnotic medications, including their newly reported side effects not mentioned in the guidelines. In addition, we aim to provide an overview of what pharmacotherapies are available for prescribers and patients.

Methods: A literature search was conducted for articles published prior to January 10, 2022, and case reports and clinical studies were retrieved from PubMed and Google Scholar.

Results: Definitive conclusions cannot be drawn regarding the safety and efficacy of medications reviewed; however, trends are apparent. All 3 guidelines included in this review remarked most treatment recommendations as weak except for cognitive behavioral therapy for insomnia, which is effective but not readily available. Furthermore, based on the 15 case reports and 13 clinical studies presented in this review, many of the medications used for treatment of insomnia present safety concerns.

Discussion: Benzodiazepines and benzodiazepine receptor agonists are commonly used hypnotic agents with the "Z-drugs" having robust data establishing their efficacy for the short-term treatment of chronic insomnia. However, significant adverse effects related to the central nervous system (CNS), including developing tolerance, addiction, CNS depression, and amnesia, remain barriers to their long-term use. In comparison, newer agents present more favorable side-effect profiles although with less established efficacy. Additionally, off-label agents, including antidepressants, antihistamines, and natural supplements, are discussed due to their prominent use.

Keywords: chronic insomnia, zolpidem, eszopiclone, melatonin, ramelteon, suvorexant

[1] PGY1 Resident, Mayo Clinic Health Systems, Eau Claire, Wisconsin; [2] Student, University of California–San Diego, San Diego, California; [3] (Corresponding author) Assistant Professor and Psychiatric Pharmacist, Department of Pharmacy Practice, West Coast University School of Pharmacy, Los Angeles, California; Aurora Charter Oak Behavioral Health Center, Covina, California, Phaghparast@westcoastuniversity.edu

Disclosures: The authors declare no potential conflict of interest.

Introduction

Chronic insomnia, a significant public health problem, affects 5% to 10% of the US population.[1] Common insomnia-related sleep difficulties include trouble initiating and/or maintaining sleep. Per the *International Classification of Sleep Disorders*, 3rd edition,[2] chronic insomnia occurs at least 3 times a week and lasts > 3 months, accompanied by daytime consequences despite adequate opportunity to sleep. Lack of sufficient sleep may cause impaired cognitive

© 2023 AAPP. The Mental Health Clinician is a publication of the American Association of Psychiatric Pharmacists. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

functioning, mood disturbances, behavioral issues, and difficulty staying awake during the daytime.[2] Given its high prevalence, pharmacologic therapy is widely sought after.[2] The expansion of approved pharmacotherapies in recent years allows for personalized medication treatments addressing the unique needs of highly diverse patient populations.[2] This is important as providers seek to tailor treatments that minimize patient risk for complex clinical presentations, including those with multiple comorbid mental health and medical comorbidities. Understanding the potential adverse effects (AEs) of hypnotic agents commonly used for treating chronic insomnia in the United States allows prescribers to make strategic decisions about prescribing these medications.

The purpose of this review is to provide clinicians with an overview of the main hypnotic classes, their mechanism of action (MOA) (Table 1), and guideline recommendations based on their efficacy and safety (Table 2). The authors of this review compare 3 guidelines in a readily available format and summarize recent case reports on the rare AEs of hypnotics and the AEs that were not previously described in the guidelines.

Methods

We conducted a literature search for articles published prior to January 10, 2022. The article types included were guidelines, clinical studies, and case reports on the AEs of hypnotics. The purpose of reviewing the guidelines was to compare recommendations for treating chronic insomnia (Table 2), whereas case reports and clinical studies are included to review AEs that are not well-known or covered in the guidelines. For retrieving case reports and clinical studies, PubMed and Google Scholar with the search terms [medication] AND side effects AND insomnia as well as [medication] AND adverse effects AND insomnia. The following filters were used: English language, practice guidelines, case reports, clinical studies, and clinical trials phases 3 and 4. Articles discussing AEs of hypnotics on adolescents and medications not available in the United States were excluded from the review. The 3 most recent guidelines published in the United States as well as 15 case reports and 13 clinical studies reporting new AEs are included in this review.

Guideline Recommendations

The 3 guidelines included in this review are from the 2016 American College of Physicians (ACP), the 2017 American Academy of Sleep Medicine (AASM), and the 2019 Veterans Affairs and Department of Defense (VA/DoD).[1,3,4] All 3 guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment. The addition of pharmacotherapy is recommended for a short-course if CBT-I alone is ineffective.[1,3,4] However, there are some differences regarding pharmacologic and nonpharmacologic recommendations for the treatment of insomnia. Refer to Table 2 for a detailed comparison of the guidelines.

Insomnia Pharmacotherapy and Adverse Effects Overview

Benzodiazepines

Description

Benzodiazepines (BZDs), a form of gamma-aminobutyric acid-A (GABA-A) agonists, belong to a major class of sedative and hypnotic drugs that slow brain and bodily functions by binding to a specific allosteric site (BZD receptor) in the GABA-A receptor complex, increasing GABA's inhibitory activity in the central nervous system (CNS).[5] In short, BZDs binding to GABA-A receptors allow for a chloride ion influx that reaches the postsynaptic neuron, creating a slowing of nerve impulses.[5] This class treats insomnia effectively because BZDs create amnesic and anxiolytic effects, allowing patients to experience shorter times for sleep onset and better sleep maintenance overall.[5] Of the 3 guidelines, only the 2017 AASM recommends the use of BZDs, namely, triazolam and temazepam. The 2019 VA/DoD guideline weakly recommends against the use of BZD due to the AEs, risk of diversion, and interactions with alcohol or CNS depressants.[4] The ACP guideline does not fully address the use of BZDs for sleep as many of the studies do not meet the inclusion criteria for review.[1] Although not individually discussed in any of the 3 guidelines, flurazepam, quazepam, and estazolam are additional FDA-approved BZDs for the treatment of insomnia.[6]

Adverse Effects

Commonly reported AEs of BZDs include disinhibition, delirium, fatigue, anterograde amnesia, and depression, especially over long-time use.[5–7] For example, temazepam has a reported incidence rate of 1.3%, 4.8%, and 1.7% for delirium, fatigue, and depression, respectively.[8] Long-acting BZDs report a larger propensity for daytime sedation and impairment, demonstrating a lower potential for rebound insomnia or tolerance.[5] In contrast, short-acting agents have less reported daytime sedation and overall incidence of side effects. However, rebound insomnia and tolerance appears to be more frequently reported.

The 2019 American Geriatrics Society (AGS) Beers criteria suggest avoiding BZDs in elderly patients with dementia or cognitive impairment or those at increased risk of falls and fractures as this population has an increased sensitivity to CNS depressants.[9] Similarly, the 2019 VA/DoD guideline has a weak recommendation against this medication class due to side effects, including impaired daytime function, risks of dependency especially in elderly patients, and possible stigma.[4] Additionally, in 2016, a large retrospective cohort study conducted in Japan

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

TABLE 1: Medications used for the treatment of insomnia[6,34,59,66,66,67,68,69]

Name	Suggested Dose	Adverse Effects	Additional Considerations
BZDs			
Triazolam	0.125 to 0.25 mg at bedtime Max dose: 0.5 mg	• Dizziness • Daytime sedation • Rebound insomnia • Falls • Headache • Reduced motor activity	• Beers criteria: Elderly patients are at increased risk of ADRs • Boxed warning: Avoid combined use of BZDs and CNS depressants • Drug schedule: IV controlled substance
Temazepam	7.5 to 15 mg at bedtime Max dose: 30 mg		
Estazolam	0.5 to 1 mg at bedtime Max dose: 2 mg		
Quazepam	7.5 mg at bedtime Max dose: 15 mg		
Flurazepam	15 to 30 mg at bedtime Max dose: 30 mg		
BZD receptor agonists			
Zolpidem	IR or oral spray: Men, 5 to 10 mg; women, 5 mg at bedtime Max dose: 10 mg ER: Men, 6.25–12.5 mg; women, 6.25 mg Max: 12.5 mg	• Headache • Dizziness • Confusion • Falls • Visual disturbances (Zolpidem) • Unpleasant taste (Eszopiclone)	• Beers criteria: Elderly patients are at increased risk of ADRs, avoid using for more than 3 months • Boxed warning: Complex sleep behaviors have been reported that may result in serious injuries and death • Drug schedule: IV Controlled substance
Eszopiclone	1 to 2 mg immediately before bedtime Max dose: 3 mg		
Zaleplon	5 to 10 mg at bedtime Max dose: 10 mg		
Dual orexin receptor antagonists			
Suvorexant	10 mg, 30 minutes before bedtime Max dose: 20 mg	• Headache • Dizziness • Cataplexy • Sleep paralysis • Suicidal ideation • Hypnagogic hallucinations	• Contraindication: Narcolepsy • Severe hepatic impairment: Use not recommended • Drug schedule: IV controlled substance • Time to sleep: Onset delayed if taken with high-fat or high-calorie food. Recommended to avoid right after a meal
Lemborexant	5 mg immediately before bedtime Max dose: 10 mg		
Daridorexant	25 to 50 mg		
Melatonin agonists			
Ramelteon	8 mg 30 minutes before bedtime Max dose: 8 mg	• Dizziness • Fatigue	• Severe hepatic impairment: Use not recommended • Drug schedule: Nonscheduled
Antidepressants			
Doxepin	3 to 6 mg 30 minutes before bedtime Max dose: 6 mg	• Nausea • Upper respiratory tract infections	• Contraindications: Within 2 weeks of MAOI use, glaucoma, urinary retention • Drug schedule: Nonscheduled
Trazodone	50 to 100 mg 1 hour before bedtime (off-label dosage)	• Headache • Orthostatic hypotension • Memory impairment • Priapism (rare)	• Contraindication: Within 2 weeks of MAOI use • Drug schedule: Nonscheduled
Mirtazapine	7.5 to 30 mg per day (off-label dosage) Max dose: 45 mg	• Xerostomia • Increased serum cholesterol • Increased Appetite • Constipation • Weight gain	• Contraindication: Within 2 weeks of MAOI use • Drug schedule: Nonscheduled
Antipsychotics			
Quetiapine	25 to 200 mg (off-label dosage)	• Weight gain • Increase in blood sugar • Increase in LDL cholesterol • Extrapyramidal symptoms	• Drug schedule: Nonscheduled

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

TABLE 1: Medications used for the treatment of insomnia[6,34,59,66,66,67,68,69] (continued)

Name	Suggested Dose	Adverse Effects	Additional Considerations
Anticonvulsants			
Tiagabine	2 to 6 mg	• Dizziness • Nausea • Tremors • Asthenia • Lack of concentration	• Drug schedule: Nonscheduled
OTC products			
Melatonin	3 to 5 mg 30 minutes to 1 hour before bedtime Max dose: 5 mg (supplement)	• Headache • Dizziness • Nausea	• Severe hepatic impairment: Use not recommended • Drug schedule: Dietary supplement
Diphenhydramine	25 to 50 mg at bedtime as needed Max dose: 300 mg	• Daytime sedation • Dizziness • Xerostomia • Paradoxical excitation	• Beers criteria: Elderly patients at increased risk of anticholinergic effects • Caution: Glaucoma, renal impairment, anticholinergic side effects and quick buildup of tolerance • Drug schedule: Over the counter
Doxylamine	25 to 50 mg taken 30 minutes before bed Max dose: 75 mg	• Daytime sedation • Dizziness • Xerostomia • Paradoxical excitation	• Beers criteria: Elderly patients at increased risk of anticholinergic effects • Caution: Glaucoma, renal impairment, anticholinergic side effects and quick buildup of tolerance • Drug schedule: OTC
L-Tryptophan	250 to 1000 mg 30 minutes before bedtime Max dose: 1000 mg (supplement)	• Drowsiness	• Caution: Use with other serotonergic drugs • Drug schedule: Dietary supplement
Valerian	300 to 3645 mg (supplement)	• Headache • Mental dullness • Dizziness • Depression • Hepatotoxicity (rare)	• Caution: In patients with liver disease • Drug schedule: Dietary supplement
Chamomile	270 mg orally twice daily (supplement)	• No significant side effect reported when compared to placebo	• No proven clinical efficacy but is well-tolerated • Drug schedule: Dietary supplement

ADR = adverse drug reaction; BZD = benzodiazepine; CNS = central nervous system; ER = extended release; IR = immediate release; IV = intravenous; LDL = low-density lipoprotein; MAOI = monoamine oxidase inhibitor; OTC = over the counter.

finds that elderly patients who receive at least 180 days of triazolam have an increased risk of developing pneumonia, injuries from falls, and pressure ulcers by 40% (number needed to harm [NNH] = 25), 30% (NNH = 17), and 29% (NNH = 90), respectively.[10] The authors attribute the increased risk of pneumonia to potential impairment of swallowing and immune system functioning. Increased pressure ulcers are attributed to more significant sedation and psychomotor impairment, leading to extended bed confinement.

BZD Receptor Agonists

Description

Zolpidem, eszopiclone, and zaleplon are BZD receptor agonistic modulators or GABA-A agonists also known as "Z-drugs."[11] These agents work by positively modulating the GABA-A receptor complex similar to BZDs but differ in their chemical structure and display minimal anxiolytic effects.[11] Moreover, Z-drugs are more selective than BZDs, which affect all BZD receptor subtypes. For example, zolpidem, in contrast to BZDs, displays selective binding to the BZD_1 receptor, which is speculated to be related to the maintenance of sleep stages 3 and 4.[11] Zolpidem and eszopiclone share similar pharmacodynamic and pharmacokinetic properties. Zaleplon has a shorter duration of action than zolpidem and eszopiclone, hence, its use for sleep onset insomnia only.[11] Z-drugs are found to have a lower risk of tolerance, abuse, dependence, and residual effects when compared with BZDs, displaying similar efficacy in the promotion of sleep.[11] All 3

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

TABLE 2: Summary of recommendations from the guidelines

Parameter	Guideline		
	2016 ACP	2017 AASM	2019 VA/DoD
Analyzed data	35 RCTs, 11 observational studies	Meta-analysis of 46 RCTs	23 RCTs, 44 systematic reviews, 11 observational studies, 14 non-RCTs
Recommendations	Strong for • CBT-I (moderate-quality evidence) Weak for (recommended to use for < 4 to 5 weeks) • Suvorexant (moderate-quality evidence) • Zolpidem (low- to moderate-quality evidence) • Eszopiclone (low- to moderate-quality evidence) • Doxepin (low-quality evidence) Insufficient data found for • BZDs • Diphenhydramine • Melatonin • Trazodone	Strong for • CBT-I (moderate-quality evidence) Weak for • Sleep onset and maintenance ◦ Temazepam (moderate-quality evidence) ◦ Eszopiclone (very low-quality evidence) ◦ Zolpidem (very low-quality evidence) • Sleep onset ◦ Zaleplon (low-quality evidence) ◦ Ramelteon ◦ Triazolam (high-quality evidence) • Sleep maintenance ◦ Doxepin (low-quality evidence) ◦ Suvorexant (low-quality evidence) Not recommended in general • Diphenhydramine • Melatonin • Tiagabine • Trazodone • L-tryptophan • Valerian root	Strong for • CBT-I Weak for • Doxepin[a] • Z-drugs[a] • Auricular acupuncture • BBT-I Weak against • Diphenhydramine • Melatonin • Valerian or chamomile • Antipsychotics • BZDs • Trazodone • Cranial electrical stimulation Strong against • Kava Neither for nor against • Ramelteon • Suvorexant • Acupuncture • Aerobic exercise or yoga

AASM = American Academy of Sleep Science; ACP = American College of Physicians; BZDs = benzodiazepines, BBT-I = brief behavioral therapy for insomnia; CBT-I = cognitive behavioral therapy for insomnia; RCT = randomized controlled trials; VA/DoD = Veterans Affairs and Department of Defense.
[a]Recommended for 2 to 4 weeks.

guidelines generally recommended the use of Z-drugs for short-term treatment of chronic insomnia.[1,3,4]

Adverse Effects

Despite their increased selectivity and ability to induce normal physiological sleep, Z-drugs still share several AEs common to BZDs.[11] The most prominent are daytime drowsiness, headache, dizziness, impaired concentration, confusion, and falls.[11] Individually, zolpidem uncommonly causes visual disturbances, whereas eszopiclone use is associated with taste disturbances and xerostomia.[6,11] The 2019 AGS Beers criteria recommends avoiding Z-drug use for more than 3 months in older adults because Z-drugs have similar effects on CNS in older adults as BZDs.[8] A recent 2019 study by Borchert et al[12] compares 1407 online patient reviews with 5916 cases reported in the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). This study finds that amnesia is among the top 10 most reported side effects of Z-drugs with zolpidem particularly standing out.[12] Importantly, in 2019, the US FDA issued a new boxed warning on all Z-drugs about rare but serious instances of complex sleep behaviors, such as sleepwalking and sleep driving that result in serious injury or death.[13]

Dual Orexin Receptor Antagonists

Description

Approved by the FDA in 2014, suvorexant is the first member of a new class of hypnotic drugs known as dual orexin receptor antagonists (DORAs).[14] A second drug, lemborexant, was FDA approved in 2019 for the treatment of sleep onset and maintenance.[15] The newest member of this class is daridorexant, approved in 2022.[6] DORA agents act by preventing orexin receptors OX1R and OX2R from being activated by orexins A and B. In patients with narcolepsy, these neuropeptides are found to play a critical role in arousal and promoting wakefulness.[15] This alternative MOA is believed to result in a more favorable side-effect profile compared with GABA-A agonists or BZDs. For example, DORAs appear to promote both rapid eye movement (REM) and non-REM sleep,

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

whereas GABA-A agonists, such as BZDs and Z-drugs, promote only non-REM sleep.[16,17] Of the 3 guidelines, only the 2016 ACP and 2017 AASM recommend suvorexant (Table 2), whereas the 2019 VA/DoD guideline recommends neither for nor against its use.[1,3,4]

Adverse Effects

All the dual orexin receptor antagonists carry a warning for use in compromised respiratory function (eg, sleep apnea). Additionally, there is a warning for worsening of depression or suicide, sleep paralysis, hypnagogic or hypnopompic hallucinations, and cataplexy-like symptoms.[6] Although the side-effect profile of DORAs is still being studied, they display less risk for falls, next-day sedation, and dependence than observed in GABA-A agonists.[17] All DORAs appear to be well-tolerated, but it should be noted that suvorexant, lemborexant, and daridodexant are classified as schedule IV controlled substances with an abuse potential comparable to zolpidem.[18,19] However, in a 2016 crossover study, although the results from the visual analog scale peak effect were generally similar between suvorexant and zolpidem, the overall incidence of the AE of abuse potential was lower with suvorexant (30.6% vs 58.3%). Similarly, incidences of euphoric mood (11.1% vs 19.4%) and visual hallucination (2.8% vs 11.1%) were lower with suvorexant compared with zolpidem, respectively.[20]

The most common side effects of suvorexant include dose-related somnolence (7%), headache (4%), and dizziness (3%).[21] Additionally, rare AEs, namely, suicidal ideation, sleep paralysis, and cataplexy, have been reported. Underreported side effects, such as nightmares, have also been observed though the package insert only lists abnormal dreams occurring in 1% of tested patients.[21] A 2017 case report by Tabata et al[22] describes a 72-year-old man with Parkinson disease that experienced vivid, disruptive nightmares after taking suvorexant for 7 weeks.[22] His described behavior included yelling, kicking, and pulling his wife's hair. The vocalizations and abnormal behaviors promptly disappeared after suvorexant cessation.[22] Whereas this was the only detailed case report found, it should be noted that the previously described study by Borchert notes that nightmares were the most frequently reported side effects of suvorexant by patients in both online reviews and the FAERS report.[12]

Melatonin Agonist

Description

Ramelteon, a melatonin receptor agonist, was approved in 2005 for sleep-onset insomnia.[23] This agent has a selective affinity for melatonin receptors MT1 and MT2 located in the suprachiasmatic nucleus, and they are associated with the regulation of endogenous melatonin. Melatonin activity is found to correlate with the onset of nocturnal sleepiness in the sleep–wake cycle. Compared with exogenous melatonin, ramelteon displays 3 to 5 times the affinity to bind and activate the MT1 and MT2 receptors and has a half-life of 1 to 2.6 hours.[24] Ramelteon shows negligible activity at GABA, serotonin (5HT), histamine, and other CNS receptors, resulting in a lack of observed tolerance, dependence, withdrawal, or residual effects.[25] Despite notable advantages, the aforementioned Borchert study finds that, in patient reviews, ineffectiveness was the top complaint from those prescribed ramelteon.[11] The 3 guidelines have inconsistent recommendations for using ramelteon.[1,3,4]

Adverse Effects

Ramelteon is well tolerated with only mild to moderate AEs. The most significant and frequently reported side effects of ramelteon are dizziness (4%), fatigue (3%), and somnolence (3%).[25] Only a few case reports were found reporting notable AEs not reported by the manufacturer. A 2013 case report describes a 50-year-old man with a history of chronic alcohol consumption who developed autoimmune hepatitis (AIH) after taking ramelteon 8 mg for 7 weeks. The patient is then reported to have died due to sepsis with autopsy confirmation that the underlying cause was AIH. Due to the temporal relationship between ramelteon initiation and AIH development, authors of the case report propose ramelteon as a possible cause. Alcoholic hepatitis is deemed unlikely based on histologic and laboratory data, and the authors note that more than 4 decades of research suggests melatonin plays a role in the modulation of the immune system.[26] Another 2015 case report presents the first instance of nightmares occurring in a patient shortly after initiating ramelteon therapy. It should be noted that both case reports appear to be isolated events, and no other instances are found in the literature searched in this review.[27]

Antidepressants

Description

In the past 30 years, antidepressant use has increased for the treatment of insomnia despite a paucity of efficacy data for many agents.[3] Doxepin is a tricyclic antidepressant that strongly binds to histamine-1 (H1) receptors in the CNS, preventing histamine arousal and promoting sedation. Doxepin is selective for H1 at low doses (<6 mg) and does not inhibit serotonin or norepinephrine reuptake, thus avoiding undesirable AEs, namely, cardiac arrhythmias, hypotension, and seizures seen at higher doses (25 to 150 mg).[28]

Trazodone, an atypical antidepressant, is widely used off-label for the treatment of insomnia. Its MOA is not fully understood; however, it is known to inhibit serotonin 5-HT2A, H1, and α1 receptors at low doses (<100 mg). This combined antagonism with different receptors is expected to produce hypnotic effects without triggering the antidepressant effect observed with the simultaneous inhibition

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

of the serotonin transporter and 5-HT2A seen at higher doses (150 to 600 mg).[29] Although trazodone is widely used in clinical practice, none of the guidelines recommends its use. This is mainly due to limited evidence supporting its efficacy and lack of data on its AEs. Therefore, trazodone is weakly recommended against use as the harm may outweigh the benefits.[1,3,4]

Last, mirtazapine, an atypical antidepressant, works by enhancing the release of norepinephrine and 5-HT_{1A}-mediated serotonergic transmission. It antagonizes adrenergic α_2-autoreceptors and α_2-heteroreceptors and blocks 5-HT_2 and 5-HT_3 receptors. Low-dose mirtazapine is associated with sedation owing to its H_1 receptor blocking effect. However, in some clinical studies, the sedation was diminished despite dose increases.[30] Although it is speculated that there is an inverse dose relationship for sedation associated with mirtazapine, an exploratory analysis from 2019 does not support this theory.[31] Therefore, more studies are needed in this area. Although mirtazapine is widely used in clinical practice in patients with insomnia, none of the three guidelines address this medication.

Adverse Effects

At low doses indicated for the treatment of insomnia, doxepin is shown to be well-tolerated. AEs reported to occur for more than 2% of patients are somnolence (5%), nausea (4%), and upper respiratory tract infections (2%).[32] To date, this review has found no evidence of new or uncommon AEs regarding doxepin use at low doses. Low-dose doxepin is recommended by all 3 guidelines, especially for sleep maintenance.[1,3,4]

In contrast, trazodone appears to exhibit more significant side effects, such as somnolence, headaches, orthostatic hypotension, and impaired memory, even at low doses and rare cases of priapism.[33,34] Additionally, trazodone can cause an increase in residual morning sedation and suicidal thoughts, explaining its assignment to the "weak against" category in the VA/DoD guideline and its lack of recommendations in both the 2016 ACP and 2017 AASM guidelines.[4] A 2017 case report from Santos et al[35] describes a 60-year-old man developing distressing visual hallucinations 2 days after starting trazodone 100 mg, which promptly resolved after discontinuation. In 2018, Sarwar et al[36] report a case of an elderly patient developing bradykinetic parkinsonism after taking trazodone 100 mg with symptoms completely reversing after withdrawal. Last, in 2020, Pereira et al[37] describe the case of a 44-year-old female patient who presented with delirium to the ER after being prescribed trazodone 100 mg. Although the patient was hospitalized, discontinuation of trazodone led to the resolution of symptoms without antipsychotic medication use.

Common side effects of mirtazapine include drowsiness (54%), xerostomia (25%), increased serum cholesterol (15%), increased appetite (17%), constipation (13%), and potential weight gain (12%).[30,38,39] Furthermore, a 2017 case report from Menon et al[39] describes an experience of a 21-year-old female taking a 7.5-mg dose of mirtazapine for insomnia. The patient initially took 20 mg of escitalopram but was tapered off over 6 weeks and put on mirtazapine.[40] While participating in this treatment over a week, the patient developed distressing nightmares after 4 days, and they subsided once she stopped taking mirtazapine and switched to a 50-mg dose of sertraline.[40] Researchers conclude that the association between the drug and AEs was probable based on the Naranjo adverse drug scale. This finding agrees with the results of the pharmacovigilance report published in 2003 that describes 50 cases of nightmares associated with mirtazapine.[41] Additionally, 2 other case studies by Mathews et al in 2006 and Dang et al in 2009 report this AE.[41–43]

Antipsychotics

Description

Quetiapine is an antipsychotic used at low doses (25 to 100 mg) off-label for insomnia.[44] This drug affects H1 receptors and α-1 and α-2 receptors causing sedative effects and is known for having the shortest half-life among the second generation antipsychotics.[44] Similar to trazodone, low-dose quetiapine is not recommended by the 2019 VA/DoD guideline. This is mainly because of the lack of efficacy data and the known harms associated with antipsychotics.[4] The other 2 guidelines do not address quetiapine.

Adverse Effects

Common AEs of quetiapine include weight gain, increased blood sugar levels, and an increase in low-density lipoprotein cholesterol.[6,44] Notably, extreme AEs can be observed in elderly patients as seen in the 2016 case study by Desforges et al.[45] In this case study, an 80-year-old man was prescribed 12.5 mg of quetiapine when hospitalized to aid in sleep onset when being treated for E. coli and pyelonephritis.[45] The patient took the prescribed medication and fell into a comatose state for a 2 and a half days before returning to his precognitive state.[45] Overall, researchers in the study suggest against quetiapine use and recommend alternative methods/medications for treating insomnia falling in line with the 2017 AASM and 2019 VA/DoD guidelines.[3,4,45]

Anticonvulsants

Description

Tiagabine, uncommonly used off-label for treatment of insomnia, is a selective GABA reuptake inhibitor. It increases the GABA availability in the synapses by inhibiting the GAT-1 GABA transporter.[46] The 2017 AASM guideline recommends against tiagabine use due to lack of evidence and limited information on its AE.[3]

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

Adverse Effects

Tiagabine's side effects include nausea, dizziness, asthenia, tremors, headache, anxiety, and lack of concentration.[6] In the randomized controlled trial conducted by Walsh et al,[46] the tolerability of tiagabine 4 and 6 mg was comparable to placebo with the exception of headache.

Over-the-Counter (OTC) Medications

Description

This section covers medications or supplements that are available without a prescription for sleep promotion although they generally lack robust clinical evidence supporting their efficacy. The most studied of these medications or supplements is exogenous melatonin.[47] As previously noted when discussing the drug ramelteon, exogenous melatonin acts by activating MT1 and MT2 receptors but with less affinity and a shorter half-life (30 minutes).[23] It is essential to administer melatonin based on an individual's circadian timing. If not, it may fail to produce the desired effect or may even produce the opposite effect by causing a phase shift in the circadian clock.[4] The benefits of using melatonin approximately equal its harm.[3] However, melatonin use is weakly recommended against by all the 3 guidelines. This is mainly due to insufficient evidence for its efficacy, lack of adequate data on its AEs, poor study design, concerns about purity or contaminants of OTC medications and undesirable circadian consequences if not administered correctly.[1,3,4] Melatonin is well-tolerated with the most commonly reported side effects being headaches (< 1%), somnolence (< 1%), dizziness (< 1%), and nausea (< 1%).[6,48]

The FDA-approved OTC antihistamines for short-term treatment of insomnia include diphenhydramine and doxylamine.[6,49] These agents work by binding or blocking the action of histamine in centrally located H1 receptors, causing sedation and sleepiness. Few studies have been conducted to evaluate the efficacy and safety of these agents for insomnia treatment, especially doxylamine.[47] Diphenhydramine is well-known for its daytime sedation, dizziness, xerostomia, nausea, and nervousness. It has a Beers criteria warning for its use in elderly patients due to increased sensitivity to anticholinergic side effects.[50] Another factor limiting diphenhydramine's usefulness for insomnia is quick development of tolerance to its sedating effects (after 3 to 4 days of use). This is consistent with results of a randomized, double-blind crossover study by Richardson et al,[51] in which 15 men received either diphenhydramine 50 mg or a placebo twice a day for 4 days. By the third day, both objective and subjective measures of sleepiness were almost identical between diphenhydramine and the placebo.[51] None of the 3 guidelines recommends the use of diphenhydramine for insomnia even though benefits approximately equal its harm. The main reason behind the recommendation is lack of evidence for its benefit.[1,3,4] Patients can expect anticholinergic side effects, such as dry eyes, dry mouth, constipation, and confusion.[3,6]

L-tryptophan is an essential amino acid and serotonin precursor in many proteins, including red meat, poultry, eggs, and dairy products.[52] L-tryptophan penetrates the blood-brain barrier and is converted into serotonin, which accounts for its ability to cause sedation with minimal impairment in performance.[53] Few studies have analyzed L-tryptophan's efficacy and safety for insomnia treatment, and no significant side effects have been reported.[54] However, L-tryptophan can increase the risk of serotonin syndrome when used with selective serotonin reuptake inhibitors and other serotonergic drugs.[55,56] L-tryptophan was only addressed in the 2017 AASM guideline and was not recommended for general use.[3]

Valerian (*valerian officinalis*) is an herbal product often used for insomnia treatment. Valerian root has sedative properties believed to stimulate GABA release from nerve endings and prevent GABA reuptake back into nerve cells.[57] Furthermore, valeric acid, a constituent of valerian oil, inhibits GABA breakdown from taking place.[58] Overall, the data regarding valerian is conflicting with some studies showing efficacy, whereas others found no significant effect.[58] Notable side effects of valerian include headache, mental dullness, dizziness, and depression.[59] Valerian is implicated in a few cases of mild to moderate, reversible hepatotoxicity with typical onset of 3 to 12 weeks within 2 to 4 weeks postdiscontinuation.[60–62] Of note, usually the case reports associated with valerian involve other botanical products, such as skullcap and black cohosh, which can serve as confounders.[60] The recent 2019 VA/DoD guideline has a weak recommendation against the use of valerian, mainly due to lack of evidence to support its efficacy, concerns about the purity of herbal products, and rare cases of hepatotoxicity.[4]

Chamomile (*Matricaria recutita*) and kava (*Piper methysticum*) are both herbal products used for insomnia. Their MOA is unknown; however, they are both speculated to work on the GABA receptors.[63,64] Chamomile and kava were only addressed in the 2019 VA/DoD guideline. Although it has no known AE, chamomile use is weakly recommended against due to concerns about purity in herbal supplements, low-quality evidence, and no proven clinical efficacy. On the contrary, kava use is strongly recommended against mainly due to its lack of efficacy, low-quality studies, and potential risk of fatal liver toxicity.[4]

Discussion

The 2016 ACP, 2017 AASM, and 2019 VA/DoD guidelines address treatment options for chronic insomnia and provide comprehensive information regarding both older and more recently approved medications.[1,3,4] All of the pharmacologic

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

therapies, either for or against their use, receive a weak recommendation. The lack of strong recommendation is mainly due to insufficient efficacy or safety data or low- to moderate-quality evidence. The only strong recommendation is for CBT-I, which is not readily available to all patients.[1,3,4] Additionally, none of the three guidelines addresses place of therapy for each pharmacologic treatment option (ie, first- vs second-line options).

When comparing the guidelines, the VA/DoD guideline is the most comprehensive of all, addressing many herbals and nonpharmacologic therapies not discussed elsewhere. However, the AASM is the only guideline that breaks down the recommendations by type of insomnia (sleep onset vs maintenance).

In summary, the guidelines recommend pharmacologic therapy for treatment of insomnia if CBT-I is not accessible and using the lowest effective dose for the shortest amount of time. After evaluating the recommendations from the 3 guidelines, the Z-drugs and doxepin appear to have more consistent recommendations for the short-term treatment of insomnia. Among the guidelines, there are inconsistent recommendations for the use of ramelteon, suvorexant, and BZDs. Last, antipsychotics, trazodone, diphenhydramine, and supplements such as melatonin and valerian root are not recommended due to poor study design and safety concerns.[1,3,4] Hypnotic use is associated with dementia, fractures, motor vehicle accidents, and cognitive and behavioral issues.

References

1. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165(2):125-33. DOI: 10.7326/M15-2175
2. American Psychiatric Association. Sleep-wake disorders. In: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
3. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. JCSM. 2017;13(2):307-49. DOI: 10.5664/jcsm.6470
4. VA/DoD clinical practice guideline for the management of chronic insomnia disorder and obstructive sleep apnea [Internet]. US Department of Veterans Affairs. 2019 Oct [cited 2023 May 15]. Available from: https://www.healthquality.va.gov/guidelines/CD/insomnia/VADoDSleepCPGFinal508.pdf
5. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214-23. PMID: 23789008.
6. IBM Micromedex Solutions. Truven Health Analytics, Inc [cited 2023 May 14]. Available from: https://www.micromedexsolutions.com
7. O'Brien CP. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry. 2005;66 Suppl 2:28-33. PMID: 15762817.
8. Temazepam [Package Insert]. Mallinckrodt [cited 2023 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018163s064lbl.pdf
9. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J American Geriatrics Society [cited 2023 May 14]. Available from: https://pubmed.ncbi.nlm.nih.gov/30693946/.
10. Maeda T, Babazono A, Nishi T, Yasui M. Quantification of adverse effects of regular use of triazolam on clinical outcomes for older people with insomnia: a retrospective cohort study. Int J Geriatr Psychiatry. 2015;31(2):186-94. DOI: 10.1002/gps.4310
11. Lieberman JA III. Update on the safety considerations in the management of insomnia with hypnotics. Prim. Care Companion J. Clin. Psychiatry. 2007;09(01):25-31. DOI: 10.4088/pcc.v09n0105
12. Borchert JS, Wang B, Ramzanali M, Stein AB, Malaiyandi LM, Dineley KE. Adverse events due to insomnia drugs reported in a regulatory database and online patient reviews: comparative study. J Med Internet Res. 2019;21(11):e13371. DOI: 10.2196/13371
13. Center for Drug Evaluation and Research. Boxed warning for risk of serious injuries caused by sleepwalking. U.S. Food and Drug Administration. 2019 Apr 30 [cited 2023 May 15]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia
14. FDA approves new sleeping pill Belsomra (suvorexant) for insomnia. American Academy of Sleep Medicine – Association for Sleep Clinicians and Researchers. 2017 Feb 14 [cited 2020 Oct 28]. Available from: https://aasm.org/fda-approves-new-sleeping-pill-belsomra-suvorexant-for-insomnia/.
15. Lemborexant (Dayvigo) for insomnia: The Medical Letter Inc [cited 2020 Oct 28]. Available from: https://secure.medicalletter.org/TML-article-1601a
16. Bennett T, Bray D, Neville MW. Suvorexant, a dual orexin receptor antagonist for the management of insomnia. P T. 2014;39(4):264-6. PMID: 24757363
17. Janto K, Prichard JR, Pusalavidyasagar S. An update on dual orexin receptor antagonists and their potential role in insomnia therapeutics. J Clin Sleep Medicine. 2018;14(08):1399-408. DOI: 10.5664/jcsm.7282
18. Schedules of controlled substances: placement of suvorexant into schedule IV. Federal Register: request access. 2014 Feb 13 [cited 2020 Oct 28]. Available from: https://www.federalregister.gov/documents/2014/02/13/2014-03124/schedules-of-controlled-substances-placement-of-suvorexant-into-schedule-iv
19. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014;13(5):461-71. DOI: 10.1016/S1474-4422(14)70053-5
20. Schoedel KA, Sun H, Sellers EM, Faulknor J, Levy-Cooperman N, Li X, et al. Assessment of the abuse potential of the orexin receptor antagonist, suvorexant, compared with zolpidem in a randomized crossover study. J Clin Psychopharmacol. 2016;36(4):314-23. DOI: 10.1097/JCP.0000000000000516
21. Suvorexant [Package Insert]. Merck & Co. Inc [cited 2023 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204569s006lbl.pdf
22. Tabata H, Kuriyama A, Yamao F, Kitaguchi H, Shindo K. Suvorexant-induced dream enactment behavior in parkinson disease: a case report. J Clin Sleep Medicine. 2017;13(05):759-60. DOI: 10.5664/jcsm.6600
23. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose–response study of Ramelteon in patients with chronic primary insomnia. Sleep Medicine. 2006;7(1):17-24. DOI: 10.1016/j.sleep.2005.09.004
24. Miyamoto M. Pharmacology of ramelteon, a selective MT_1/MT_2 receptor agonist: a novel therapeutic drug for sleep disorders.

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

CNS Neurosci Ther. 2009;15(1):32-51. DOI: 10.1111/j.1755-5949.2008.00066.x
25. Ramelteon [Package Insert]. Takeda Pharmaceutical America, Inc [cited 2021 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021782s021lbl.pdf
26. Fourman LT, Robert Meyer B. Autoimmune hepatitis in association with ramelteon. J Clin Gastroenterol. 2013;47(7):651-4. DOI: 10.1097/MCG.0b013e31829174f0
27. Shah C, Kablinger A. Ramelteon-induced nightmares: a case report. Asian J Psychiatry. 2015;18(1):111-2. DOI: 10.1016/j.ajp.2015.09.004
28. Katwala J, Kumar AK, Sejpal JJ, Terrence M, Mishra M. Therapeutic rationale for low dose doxepin in insomnia patients. Asian Pac J Tropical Dis. 2013;3(4):331-6. DOI: 10.1016/S2222-1808(13)60080-8
29. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, et al. Trazodone for insomnia: a systematic review. Innov Clin Neurosci. 2017;14(7-8):24-34.
30. Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev. 2001;7(3):249-64. DOI: 10.1111/j.1527-3458.2001.tb00198.x
31. Shuman M, Chukwu A, Van Veldhuizen N, Miller SA. Relationship between mirtazapine dose and incidence of adrenergic side effects: an exploratory analysis. Ment Health Clin. 2019;9(1):41-7. DOI: 10.9740/mhc.2019.01.041
32. Doxepin [Package Insert]. Currax Pharmaceutical LLC [cited 2023 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022036s006lbl.pdf
33. Walsh JK, Erman M, Erwin CW, Jamieson A, Mahowald M, Regestein Q, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Human Psychopharmacology: Clinical and Experimental. 1998;13(3):191-8. DOI:10.1002/(sici)1099-1077(199804)13:3<191::aid-hup972>3.0.co;2-x
34. Trazodone [Package Insert]. Pragma Pharmaceuticals [cited 2021 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018207s032lbl.pdf
35. Santos G, Moreira AM. Distressing visual hallucinations after treatment with trazodone. Case Reports Psychiatry. 2017;2017(3):1-5. DOI: 10.1155/2017/6136914
36. Sarwar AI. Trazodone and parkinsonism: the link strengthens. Clin Neuropharm. 2018;41(3):106-8. DOI: 10.1097/WNF.0000000000000278
37. Pereira AT, Mota D, Ribeiro L, Rodrigues JD. Trazodone-induced delirium: case report. Revista Colombiana De Psiquiatría. 2020;49(3):199-201. DOI: 10.1016/j.rcp.2018.10.006
38. Mirtazapine [Package Insert]. Schering Corporation [cited 2023 May 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020415s023s024.pdf
39. Jilani T, Gibbons J, Faizy R, Saadabadi A. Mirtazapine. 2022 Sep 7. [cited 2023 May 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519059/.
40. Menon V, Madhavapuri P. Low-dose mirtazapine-induced nightmares necessitating its discontinuation in a young adult female. J Pharmacol Pharmacother. 2017;8(4):182-4. DOI: 10.4103/jpp.JPP_116_17
41. Biswas PN, Wilton LV, Shakir SAW. The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13554 patients in England. J Psychopharmacol. 2nd ed. 2003;17(1):121-6. DOI: 10.1177/0269881103017001716
42. Mathews M. Mirtazapine-induced nightmares. Prim. Care Companion CNS Disord. 2006;8(5). DOI: 10.4088/pcc.v08n0510b
43. Dang A, Garg G, Rataboli PV. Mirtazapine induced nightmares in an adult male. Br J Clin Pharmacol. 2009;67(1):135-6. DOI: 10.1111/j.1365-2125.2008.03305.x
44. Modesto-Lowe V, Harabasz AK, Walker SA. Quetiapine for primary insomnia: consider the risks. CCJM. 2021;88(5):286-94. DOI: 10.3949/ccjm.88a.20031
45. Desforges P, Lee TC, McDonald EG. Insomnia in the hospital—not just a bad dream. Jama Intern Med. 2016;176(9):1253. DOI: 10.1001/jamainternmed.2016.2233
46. Walsh JK, Perlis M, Rosenthal M, Krystal A, Jiang J, Roth T. Tiagabine increases slow-wave sleep in a dose-dependent fashion without affecting traditional efficacy measures in adults with primary insomnia. J Clin Sleep Med. 2006;2(1):35-41. PMID: 17557435
47. Culpepper L, Wingertzahn MA. Over-the-counter agents for the treatment of occasional disturbed sleep or transient insomnia. Prim. Care Companion CNS Disord. 2015. DOI: 10.4088/PCC.15r01798
48. Va.gov: Veterans Affairs. Clinical Guidance - Drug Monographs [Internet]. 2013 Dec 5 [cited 2020 Nov 23]. Available from: https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp
49. CFR - Code of Federal Regulations Title 21 [cited 2020 Nov 24]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=338&showfr=1
50. Diphenhydramine hydrochloride injection, USP. 2013 [cited 2023 May 15]. Available from: https://labeling.pfizer.com/ShowLabeling.aspx?id=4409
51. Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. J Clin Psychopharmacol. 2002;22(5):511-5. DOI: 10.1097/00004714-200210000-00012
52. Hartmann E, Spinweber CL. Sleep induced by L-tryptophan. Effect of dosages within the normal dietary intake. J Nerv Ment Dis. 1979;167(8):497-9. PMID: 469515
53. Lieberman HR, Corkin S, Spring BJ, Wurtman RJ, Growdon JH. The effects of dietary neurotransmitter precursors on human behavior. Am J Clin Nutrition. 1985;42(2):366-70. DOI: 10.1093/ajcn/42.2.366
54. Hudson C, Hudson SP, Hecht T, MacKenzie J. Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. Nutritional Neurosci. 2005;8(2):121-7. DOI: 10.1080/10284150500069561
55. Messiha FS. Fluoxetine: adverse effects and drug-drug interactions. J Toxicol Clin Toxicol. 1993;31(4):603-30. DOI: 10.3109/15563659309025765
56. Foong A-L, Patel T, Kellar J, Grindrod KA. The scoop on serotonin syndrome. Can Pharm J. 2018;151(4):233-9. DOI: 10.1177/1715163518779096
57. Office of dietary supplements - valerian. NIH Office of Dietary Supplements [cited 2022 Dec 1]. Available from: https://ods.od.nih.gov/factsheets/Valerian-HealthProfessional/.
58. Houghton PJ. The scientific basis for the reputed activity of valerian. J Pharm Pharmacol. 31stst ed. 2010;51(5):505-12. DOI: 10.1211/0022357991772772
59. Chemical information review document for valerian (Valeriana officinalis L.) 64. National Toxicology Program, US Department of Health and Human Services Chemical. 2009 Nov [cited 2023 May 15]. Available from: https://ntp.niehs.nih.gov/ntp/noms/support_docs/valerian_nov2009_508.pdf
60. LiverTox: clinical and research information on drug-induced liver injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
61. MacGregor FB, Abernethy VE, Dahabra S, Cobden I, Hayes PC. Hepatotoxicity of herbal remedies. BMJ. 1989;299(6708):1156-7. DOI: 10.1136/bmj.299.6708.1156
62. Cohen DL, Toro YD. A case of valerian-associated hepatotoxicity. J Clin Gastroenterology. 2008;42(8):961-2. DOI: 10.1097/MCG.0b013e3180500348

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

63. Chamomile for chronic primary insomnia–ClinicalTrials.gov. 2013 Jul 30 [cited 2023 May 14]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01286324
64. Chua HC, Christensen ETH, Hoestgaard-Jensen K, Hartiadi LY, Ramzan I, Jensen AA, et al. Kavain, the major constituent of the anxiolytic kava extract, potentiates GABAA receptors: functional characteristics and molecular mechanism. Barnes S. Plos One. 2016;11(6):e0157700. DOI: 10.1371/journal.pone.0157700
65. DailyMed. U.S. National Library of Medicine [cited 2020 Nov 5]. Available from: https://dailymed.nlm.nih.gov/dailymed/.
66. Lexi-Drugs. Wolters Kluwer Health Inc [cited 2023 May 14]. Available from: Accessed http://online.lexi.com
67. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia. The Annals of pharmacotherapy [cited 2023 May 14]. Available from: https://pubmed.ncbi.nlm.nih.gov/22510671/.
68. Leach MJ, Page AT. Herbal medicine for insomnia: a systematic review and meta-analysis. Sleep Medicine Rev. 2015;24:1-12. DOI: 10.1016/j.smrv.2014.12.003
69. Zick SM, Wright BD, Sen A, Arnedt JT. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study. Bmc Complement Altern Med. Second. 2011;11(1). DOI: 10.1186/1472-6882-11-78

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05