# A review on holistic and pharmacological management of insomnia

**C Ngomana, KD Komape, E Bronkhorst**

Department of Clinical Pharmacy, School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

**Corresponding author, email:** elmien.bronkhorst@smu.ac.za

## Abstract

Insomnia is a common sleep disorder that has negative impacts on quality of life. It significantly reduces productivity and cognitive function, and in worst cases, causes morbidity and mortality. The various types of insomnia are described according to the duration of the perceived symptoms. It is characterised by both nocturnal and daytime symptoms, with daytime symptoms often the reason for treatment. The disorder may be precipitated by several cognitive behavioural factors.

Although pharmacotherapy is a common option of treatment, clinical guidelines and literature recommend cognitive behavioural therapy as the gold standard and the first-line treatment option. Pharmacotherapeutic agents range from over-the-counter agents, e.g. antihistamines, to scheduled drugs like benzodiazepine receptor agonists. The dual orexin receptor antagonists represent the newest class of drugs indicated for the treatment of insomnia. First registered in 2014, the Food and Drug Authority regulatory body has since approved three agents in this class. Furthermore, the off-label use of medicines with sedating effects is very common in the treatment of insomnia. The popular classes of medicine include sedative antidepressants, atypical antipsychotics, and gabapentinoids. Complementary and alternative therapies, which include dietary and herbal supplements, may be considered an alternative option.

This review discusses the various available therapy options for the treatment of insomnia. The mechanisms of action and adverse effect profiles were elucidated to provide clinical guidance on considerations for the selection of sedative hypnotics to treat insomnia.

**Keywords:** insomnia, cognitive behavioural therapy, dual orexin receptor antagonists, hypnotics



https://doi.org/10.36303/SAPJ.2283

## Introduction

Insomnia is the most common sleep disorder with a significant impact on both physical and mental health.[1,2,3] The American Sleep Disorder Association (ASDA) defines insomnia as a "repeated difficulty with sleep initiation, duration, consolidation or quality that occurs despite adequate sleeping opportunity and circumstances for sleep, and results in some form of daytime impairment".[4] This means patients have trouble falling and/or staying asleep and frequent awakenings result in daytime impairment.[2,5] Daytime symptoms range from sleepiness, fatigue, impaired attention, mood swings and memory impairment.[1,6] Sometimes these patients may have difficulty maintaining social relationships.[3]

Insomnia can have far-reaching consequences, predisposing affected individuals to cardiovascular, mental, metabolic and other disorders and ultimately negatively affects their quality of life.[3,6-8] The elderly population is more at risk of suffering these consequences.[9] There is strong evidence suggesting that insomnia is a risk factor for the development of certain psychological disorders such as depression and anxiety, with these disorders proposed to increase the risk of mortality, presumably due to the high risk of self-harm and suicide.[3,10] In addition, sleep disorders can result in functional consequences including increased risk for accidents, absenteeism, increased healthcare costs, decreased work productivity and poor academic performance.[6,8,11-13] Although it is considered the second most prevalent mental health disorder, it remains underdiagnosed and undertreated.[1,14]

The diagnosis of insomnia is subjective, as it relies on the individual's perception of sleep difficulties and related daytime malfunctioning.[3,10] This subjective experience may be influenced by religious beliefs, stigma, reasoning fallacy, and differences in symptom presentation. Due to these factors, one may perceive it as a normal or an abnormal experience.[12] This can be classified as a reason for underdiagnosis and undertreatment of the condition. A thorough history of insomnia optimises evaluation of symptoms and behaviours both at night and during the day. The 24-hour history for insomnia assessment may be used to understand the diagnosis as shown in Figure 1. Daytime symptoms, as depicted in Figure 2, are usually the reason patients seek treatment. The disorder is often treated in patients with severe and more chronic insomnia, those with comorbid medical or psychiatric disorders, and those who are more educated.[12]

The reduced level of gamma-aminobutyric acid (GABA) or the impairment of GABAergic transmission is observed in the aetiology and maintenance of acute and chronic stress and acute and chronic insomnia.[15] This explains the use of hypnotics such as benzodiazepines and non-benzodiazepines (Z-drugs) to treat insomnia. Other pharmacological therapies include complementary and alternative therapies (i.e. herbal supplements), off-label use of medicine such as antidepressants,

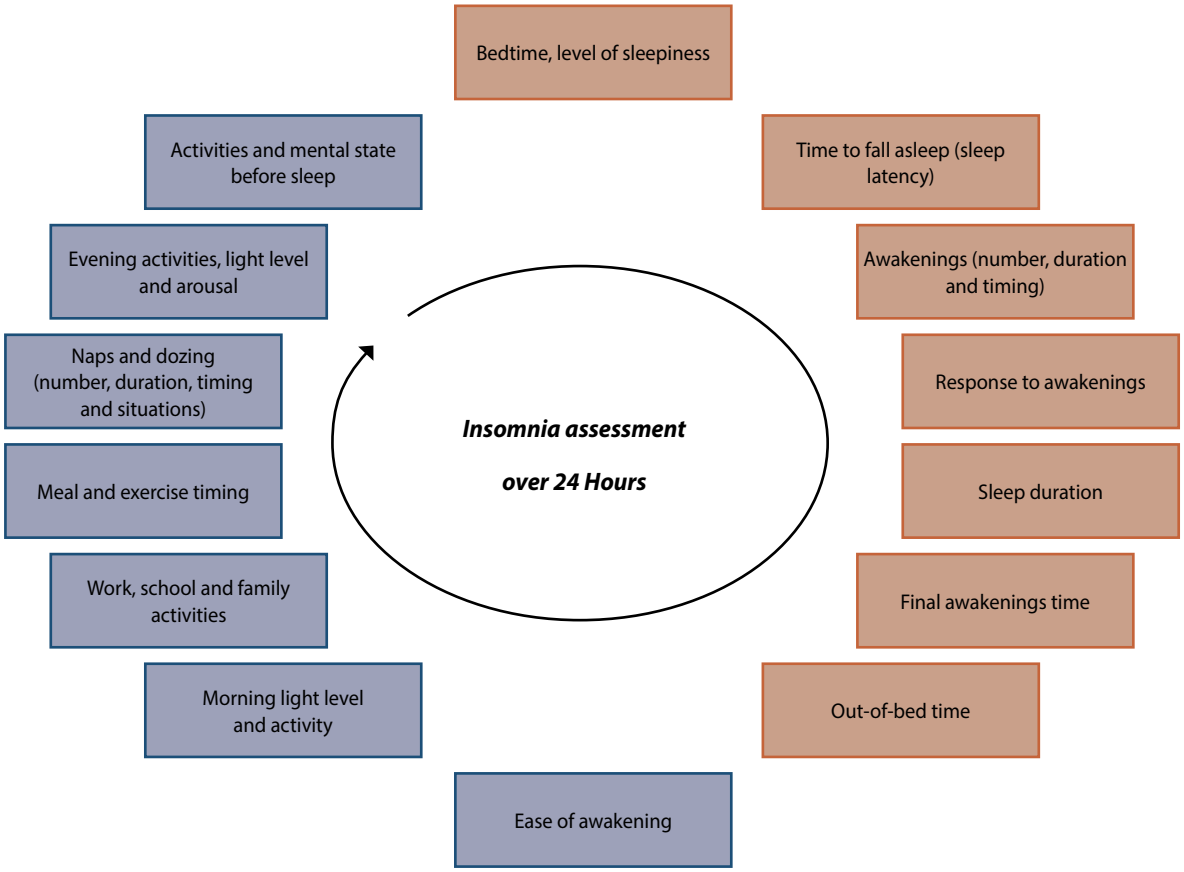


**Figure 1:** 24-hour history for insomnia assessment (Adopted from Morin and Buysse, 2024)[16]


**Figure 2:** Daytime symptoms of insomnia[17]

anticonvulsants, and atypical antipsychotics, and the emerging dual orexin receptor agonists (DORAs).[16] Non-pharmacological therapies are indicated as an integral part of insomnia treatment and cognitive behavioural therapy for insomnia (CBT-I) is the most recommended therapy.[13,16]

## Types of insomnia

Insomnia is typically classified according to the duration of symptoms. Short-term insomnia is defined as symptoms lasting for days to weeks which are usually prompted by stress. It often resolves following the resolution or mitigation of the stressor; however, it can evolve into chronic insomnia.[5] Chronic insomnia is difficulty initiating sleep, remaining asleep and inability to fall back to sleep after waking up in the early hours for at least three nights per week for a period of at least three months.[2,5,6] It can be exacerbated by excessive time spent in bed in an attempt to sleep more, which may lead to frequent awakenings at night.[5]

## Epidemiology and contributing factors

Insomnia is mostly prevalent in women, especially during peri- and post-menopause.[11,18,19] However, it affects the general population including those with poor health, low socioeconomic status and quality of life, shift workers and the elderly.[6,12,18] It affects about 10–30% of the general population,[3,13] with an estimated prevalence of 30–36% experiencing nighttime symptoms.[6] However, the inclusion of daytime symptoms yields a significant drop in the


**Figure 3:** Contributing factors of insomnia[22]

prevalence, from 10% to 15%.[6,11,12] A prevalence of about 20–48% was observed in adults who have a high risk of incidence, with aging.[20] Global statistics ranked South Africa (45.3%) second behind Brazil (79.8%) in a cross-cultural study that assessed the rate of prevalence of insomnia.[12]

According to Spielman's 3P model, the contributing factors for insomnia can be classified into predisposing, precipitating and perpetuating factors.[1,18,21] With reference to this model, predisposing factors are non-modifiable and include sex, advancing age and family history of poor sleep.[18,21] Precipitating factors, which are usually stressful life events, include perceived stress. Perpetuating factors are the maladaptive coping mechanisms and behavioural patterns that allow for the chronic progression of insomnia. These include daytime napping and excessive hours spent in bed trying to compensate for sleep.[18]

**Table I:** Non-pharmacological management for insomnia

| Therapy | Description |
|---|---|
| Sleep restriction therapy | Relies on reducing the number of sleep hours, with the idea that limited sleep time might strengthen sleep drive and result in consolidated sleep. |
| Stimulus control therapy | Involves abandoning counterproductive habits, such as eating or reading in bed, excessive screen time at night, and going to bed only when extremely drowsy. |
| Relaxation therapy | Involves adopting sleep-promoting habits such as breathing exercises, meditation, and yoga. |
| Sleep hygiene | Involves education about behavioural interventions like restricting daytime naps, refraining from nighttime smoking, and avoiding eating and drinking (alcohol or caffeine) at night.<br>Patients are encouraged to develop or maintain a healthy diet, engage in physical activity, and maintain a consistent sleep schedule. |

## Management of insomnia

### *Non-pharmacological management*

Non-pharmacological strategies are regarded as the best option to manage insomnia.[3] Clinical guidelines recommend CBT-I as the first-line treatment for insomnia.[1,5,7,9,15] CBT-I is considered the gold standard as the strategies produce robust and durable therapeutic improvement extending beyond the period of therapy.[3,13] Some of the important components of CBT-I include modification of behavioural patterns as shown in Table I and psychological factors such as excessive worries and unhelpful beliefs about

**Table II:** Pharmacological management for insomnia

| Medication | Mechanism of action and clinical use | Safety |
|---|---|---|
| **Over-the-counter medicine** | | |
| Antihistamines<br>First-generation antihistamines: sedative effects shown useful in the treatment of insomnia.<br>Examples:<br>*Over-the-counter:* diphenhydramine, chlorpheniramine and doxylamine[1,6]<br>*Prescription*: hydroxyzine[16] | Promote sleep effects by crossing the blood-brain barrier and binding to central H1.<br>Limited for use in short-term insomnia, due to rapid development of tolerance.[1]<br>Despite weak evidence of efficacy, their availability and perceived safety compared to benzodiazepine receptor agonists make them a popular option.[16] | *Common side effects*: urinary retention, blurry vision, dry mouth, prolonged sedation, and hypersomnia[1,6,16] |
| **Prescription medicine** | | |
| Melatonin and melatonin agonists<br>Ramelteon and tasimelteon are both melatonin agonists that bind to melatonin MT1 and MT2 receptors.[16] Ramelteon indicated for treatment of sleep-onset insomnia.[1,6]<br>Tasimelteon indicated for circadian-rhythm sleep-wake disorders.[16]<br>Daily dose of 8 mg 30 minutes before bedtime recommended.[6] | Melatonin is an endogenous hormone secreted by pineal gland during darkness (night).[16]<br>Exogenous melatonin, known as a sleep supplement, however, in South Africa only accessible with prescription.[23]<br>Indicated for jet lag, shift workers, and older age, due to disruptions of the circadian rhythm and reduced endogenous melatonin levels.[23]<br>Acts on the sleep-wake cycle by stimulating the MT1 receptors, depressining alert signals from the suprachiasmatic nucleus. MT2 receptors are activated leading to synchronisation of the circadian clock.[6]<br>Melatonin has limited efficacy when the endogenous melatonin levels are high. Recommended to administer an hour before bedtime and at the same time every night.[9] | *Common side effects:*<br>**Melatonin**<br>headaches and sleepiness[6]<br>**Melatonin agonists**<br>Tasimelteon: somnolence, dizziness and fatigue[11] |

| | | |
|---|---|---|
| Benzodiazepines<br>Introduced in 1950s.<br>Widely used treatment for treatment of insomnia and anxiety.[15] | Potentiate activity of GABA, by allosteric binding on GABA-A receptors, increasing GABA affinity for binding site on receptors.[15] Activation of receptors allows influx of chloride ions into neurons – hyperpolarisation produces central nervous system depression.[1,6,24]<br>Benzodiazepines show efficacy to reduce sleep-onset latency and wakefulness after sleep onset, with a small increase in the duration of sleep.[16]<br>Agents approved for management of insomnia:<br>loprazolam, lormetazepam, midazolam, nitrazepam, flurazepam, temazepam, and triazolam.[1,2] | *Common side effects*:<br>drowsiness, confusion, syncope, respiratory depression, and tremors.[24] Coadministration with other sedating medicine and longer duration of use may exacerbate side effects.[16] Abrupt discontinuation following prolonged use can lead to rebound insomnia and withdrawal symptoms.[1] Drug tolerance and physiological dependence may develop, however a severe substance disorder is relatively uncommon.[16] |
| Non-benzodiazepine BZRAs (Z-Drugs)<br>Introduced in 1980s to overcome adverse effects of benzodiazepines.[15] | Selective benzodiazepine receptor agonists enhance GABA's affinity for its binding site on the GABA-A receptor, with high affinity for alpha-1 subunit, which enables mediation of sedative effects of GABA.[1] Agents approved for treatment of insomnia: zolpidem, Zopiclone (in SA), Zaleplon and eszopiclone.[2,6,25]<br>Zolpidem recommended for acute night sleep-onset insomnia.[6] | Thought to be safer option than benzodiazepines; however, increasingly linked to misuse and dependence.[15]<br>*Common side effects:*<br>zolpidem: diarrhoea, somnolence, and visual disturbances.[2]<br>zaleplon: drowsiness, dizziness, and impaired concentration.[26] |
| Dual orexin receptor antagonists (DORAs)<br>Introduced in 2014.[16]<br>FDA approved, however not registered in South Africa. | Neurons in the lateral hypothalamus that contain orexin (hypocretin) play an important role in regulating sleep and wakefulness. When activated, they stimulate wake-promoting areas in the brainstem and hypothalamus, simultaneously suppressing sleep-promoting areas in the ventral lateral and median preoptic areas.[16]<br>Promote sleep by selectively blocking the orexin receptor-1 and receptor-2 and inhibit the binding of orexin peptides A and B to their receptors, suppressing wakefulness[1,6,27] and promoting sleep.[16]<br>The FDA-approved agents for the treatment of insomnia: suvorexant, lemborexant, and daridorexant. | *Common side effects*:<br>abnormal dreams, cough, dry mouth, upper respiratory tract infections, palpitations, psychomotor hyperactivity, and anxiety[27]<br>Lower risk of cognitive impairment compared to benzodiazepine receptor agonists[16] |
| **Sedative antidepressants – Off-label use** | | |
| Sedating antidepressants such as amitriptyline, nortriptyline, and doxepin, including the heterocyclic drugs like mirtazapine and trazodone are commonly used to treat insomnia.[16] Not approved for insomnia indication, clinicians often prefer them due to mild side effects when taken at low doses.[16] | **Doxepin**<br>A tricyclic antidepressant that exerts its sleep-promoting effects through antagonism of H1 receptors.[28] Effective in treating sleep-onset and maintenance insomnia, as well as early waking.[6]<br>**Trazodone**<br>Exerts sleep-promoting effect by blocking the 5-HT-2A receptor, H1 receptor, and alpha-1-adrenergic receptors.[29]<br>Not FDA-approved for insomnia, it is used to treat various presentations of chronic insomnia including early waking, sleep-onset, and maintenance insomnia.[6]<br>**Mirtazapine**<br>Tetracyclic antidepressant with similar sleep-promoting properties to those of trazodone.[1,9] Used off-label for treatment of insomnia, best preferred in patients with comorbid depression.[1,7,30]<br>**Amitriptyline**<br>A tricyclic antidepressant whose sedative action is attributed to its ability to antagonise muscarinic-cholinergic, alpha-1 adrenergic, and H1 receptors. No evidence supporting its use for insomnia with no comorbidities.[6] | *Adverse effects:*<br>**Doxepin**<br>Weight gain, dry mouth, blurry vision, tachycardia and QT prolongation.[28]<br>**Trazodone**<br>Prolonged half-life causes daytime sedation.[1]<br>Associated with risks such as orthostatic hypotension, syncope, priapism and QT prolongation.[29]<br>**Mirtazapine**<br>Drowsiness, increased appetite, weight gain and thrombocytopenia.[30]<br>**Amitriptyline**<br>Anticholinergic effects (blurry vision, dry mouth), weight gain, orthostatic hypotension, and dizziness. Associated with risks like slow intracardiac conduction, QTc prolongation, and arrhythmias.[31] |
| **Atypical antipsychotics** | | |
| Quetiapine and olanzapine are sometimes used off-label for insomnia due to their sedating effects.[16] | They bind to H1 receptors and alpha-1 and alpha-2 receptors to induce a sedating effect.[32] | *Potential side effects:*<br>Cardiovascular, metabolic, and neurological risks outweigh their benefits for insomnia treatment.[16] Quetiapine is commonly, reported for weight gain, increased blood sugar levels, and an increase in low-density lipoprotein cholesterol.[32] |
| Gabapentinoids | Gabapentin and pregabalin are indicated for the treatment of chronic pain and restless leg syndrome; due to their sedating effects, they are prescribed off-label for insomnia, particularly in patients with co-occurring pain.[16] | Some of the common adverse effects include somnolence, dizziness, ataxia, and fatigue.[16] |

sleep that cause and/or perpetuate insomnia.[13,16] Pharmacological interventions as presented in Table II, are considered the second-line treatment option as there is weak evidence supporting their use in insomnia.[7]

## Complementary and alternative therapies

Although there is poor evidence supporting the efficacy of cannabinoids, cannabis, cannabidiol and delta-9-tetrahydrocannabinol (THC)-containing they are widely used as an alternative treatment for insomnia.[16] There are various nutritional supplements that are marketed for sleep.[2] Valerian (*Valeriana officinalis*), chamomile (*Matricaria recutita*) and Kava (*Piper methysticum*) are the most common herbal supplements that have been found to possess sedating effects and are used to treat insomnia despite weak evidence supporting their efficacy for use.[2,16] Valerian (Valerian root) is speculated to stimulate GABA release from the nerve endings and prevent GABA reuptake back into the nerve cells, while valeric acid, an ingredient of valerian oil, inhibits the breakdown of GABA.[28,33] The mechanism of action of both chamomile and Kava are not yet established, but they are believed to work on GABA receptors. All these herbal supplements generally have a good safety profile and minimal adverse effects reported.[2,33]

## Conclusion

Insomnia is a highly prevalent sleep disorder associated with negative health outcomes in the affected individuals. Pharmacological treatment may be considered when nonpharmacological approaches have failed to yield any positive clinical outcome. For patients initiated on pharmacotherapy, it should be combined with non-pharmacological treatment to allow the use of the lowest possible doses and for optimal outcomes. Although there is poor evidence on the association between insomnia and mortality, providing psychoeducation on insomnia may also be helpful for a better outcome. Even though medications are widely used for the treatment of insomnia to produce rapid relief, their long-term use increases the risk of tolerance and dependence, and this emphasises the importance of good selection of agents and correct dosing. The comorbidities of patients must be considered to ensure a better selection of agents. As a subjective disorder, cognitive behavioural therapy remains the gold standard in the management of insomnia. Ultimately, when selecting the agent to use, duration of treatment, and available alternatives, the risk-benefit ratio should always be considered, and the patient should be informed for shared understanding and consensus.


### *ORCID*

E Bronkhorst https://orcid.org/0000-0002-6872-5417


## References


1. Naha S, Sivaraman M, Sahota P. Insomnia: A Current Review. Missouri Medicine. 2024;121(1):44-51.
2. Madari S, Golebiowski R, Meghna P. Mansukhani MP, Kolla BP. Pharmacological management of insomnia. Neurotherapeutics. 2021;18(1):44-52. https://doi.org/10.1007/s13311-021-01010-z.
3. Lovato N, Lack L. Insomnia and mortality: A meta-analysis. Sleep Medicine Reviews. 2019;43:71-83. https://doi.org/10.1016/j.smrv.2018.10.004.
4. Diaz S, Abad K, Patel SR, Unruh ML. Emerging treatments for insomnia, sleep apnea, and restless leg syndrome among dialysis patients. Seminars in Nephrology. 2021;41(6):526-33. https://doi.org/10.1016/j.semnephrol.2021.10.005.
5. Krystal AD, Ashbrook LH, Prather AA. What is insomnia? Journal of the American Medical Association. 2021;326(23):2444. https://doi.org/10.1001/jama.2021.19283.
6. Drager LF, Assis M, Bacelar AFR, et al. Guidelines on the Diagnosis and Treatment of Insomnia in Adults - Brazilian Sleep Association. Sleep Science. 2023;16(Suppl2):507-49. https://doi.org/10.1055/s-0043-1776281.
7. Paul AM, Salas RE. Insomnia. Primary Care: Clinics in Office Practice. 2024;51:299-310. https://doi.org/10.1016/j.pop.2024.02.002.
8. De Crescenzo F, D'Alò GL, Ostinelli EG, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022:400. https://doi.org/10.1016/S0140-6736(22)00878-9.
9. Cohen ZL, Eigenberger PM, Sharkey KM, Conroy ML, Wilkins KM. Insomnia and other sleep disorders in older adults. Psychiatric Clinics of North America. 2022;45:717-34. https://doi.org/10.1016/j.psc.2022.07.002.
10. Yuksel D, Prouty D, Bei B, Baker FC, De Zambotti M. Re-thinking insomnia disorder in adolescents: the importance of an accurate diagnosis. Sleep. 2021;44. https://doi.org/10.1093/sleep/zsab221.
11. Kaur H, Spurling BC, Bollu PC. Chronic insomnia. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK526136/. Accessed, 07 January 2025.
12. Morin CM, Jarrin DC. Epidemiology of insomnia prevalence, course, risk factors, and public health burden. Sleep Medicine Clinics. 2022;17:173-91. https://doi.org/10.1016/j.jsmc.2022.03.003.
13. Zhang Y, Ren R, Yang L, et al. Comparative efficacy and acceptability of psychotherapies, pharmacotherapies, and their combination for the treatment of adult insomnia: A systematic review and network meta-analysis. Sleep Medicine Reviews. 2022;65. https://doi.org/10.1016/j.smrv.2022.101687.
14. Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiological Reviews. 2021;101:995-1046. https://doi.org/10.1152/physrev.00046.2019.
15. Palagini L, Bianchini C. Pharmacotherapeutic management of insomnia and effects on sleep processes, neural plasticity, and brain systems modulating stress: A narrative review. Frontiers in Neuroscience. 2022;16. https://doi.org/10.3389/fnins.2022.893015.
16. Morin CM, Buysse DJ. Management of insomnia. New England Journal of Medicine. 2024;391(3):247-58. https://doi.org/10.1056/NEJMcp2305655.
17. Cleveland Clinic. Insomnia. 2023 Available at: https://my.clevelandclinic.org/health/diseases/12119-insomnia. Accessed 15 February 2025.
18. Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. American Journal of Managed Care. 2020;26(4). https://doi.org/10.37765/ajmc.2020.42769.
19. Endomba FT, Tchebegna PY, Chiabi E, et al. Epidemiology of insomnia disorder in older persons according to the Diagnostic and Statistical Manual of Mental Disorders: a systematic review and meta-analysis. European Geriatric Medicine. 2023;14:1261-72. https://doi.org/10.1007/s41999-023-00862-2.
20. Wang YM, Chen HG, Song M, et al. Prevalence of insomnia and its risk factors in older individuals: A community-based study in four cities of Hebei Province, China. Sleep Medicine. 2016;19:116-22. https://doi.org/10.1016/j.sleep.2015.10.018.
21. Han EK, Son HK. The factors affecting sleep quality in community-dwelling older adults, based on Spielman's 3P model of insomnia. Iranian Journal of Public Health. 2024;53(12). https://doi.org/10.18502/ijph.v53i12.17317.
22. Suni E, Dimitriu A. What causes insomnia? 2024. Available at: https://www.sleepfoundation.org/insomnia/what-causes-insomnia. Accessed 15 February 2025.
23. Marais A, Osuch E. Insomnia: what is currently available. South African General Practitioner Journal. 2020;1(1):39-41.
24. Bounds CG, Patel P. Benzodiazepines. 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK470159/. Accessed 07 January 2025.
25. Moch S. Sleepless in South Africa: Insomnia is not just a night-time problem. South African Family Practice. 2012;54(4). https://doi.org/10.1080/20786204.2012.10874236.
26. Bhandari P, Sapra A. Zaleplon. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK551571/. Accessed 07 January 2025.
27. Perlis ML, Posner D, Riemann D, et al. Sleep and sleep disorders 2. Lancet. 2022;400:1047-60. https://doi.org/10.1016/S0140-6736(22)00879-0.
28. Almasi A, Patel P, Meza CE. Doxepin. 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK542306/. Accessed 08 January 2025.
29. Shin JJ, Saadabadi A. Trazodone. 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK470560/. Accessed 08 January 2025.
30. Jilani TN, Gibbons JR, Faizy RM, Saadabadi A. Mirtazapine. 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519059/. Accessed 08 January 2025.
31. Thour A, Marwaha R. Amitriptyline. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537225/. Accessed 08 January 2025.
32. Verduzco ADR, Salari A, Haghparast P. Efficacy and safety of pharmacotherapy in chronic insomnia: A review of clinical guidelines and case reports. Mental Health Clinician. 2023;13(5). https://doi.org/10.9740/mhc.2023.10.244.
33. Yeom JW, Cho CH. Herbal and natural supplements for improving sleep: a literature review. Psychiatry Investigation. 2024;21:810-21. https://doi.org/10.30773/pi.2024.0121.