Sleepless in South Africa: insomnia is not just a night-time problem

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Abstract

Sleep is necessary for normal growth and development. Lack of sleep causes considerable personal impairment that may impose a substantial societal burden on productivity and quality of life. Insomnia, whether transient or chronic, responds to both pharmacological and non-pharmacological interventions. Cognitive behaviour therapy can effect sustained improvement in insomnia but requires motivation and commitment on the part of the patient and a trained therapist to guide the process. Benzodiazepine receptor agonists and benzodiazepines reduce sleep latency and increase total sleep time in insomniacs. However, their effects are not sustained after stopping the medication. Long-term safety of these medications has not been formally established. Combination of psychological and pharmacological therapies reduces the effect of psychological interventions. Thus, in determined patients psychological therapy should precede drug therapy.

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Introduction

Sleep is a universal need that is essential for well-being. Processes which are regulated during sleep include tissue growth and healing, synaptic function and memory, temperature regulation, energy metabolism and immune regulation. Lack of sleep causes significant distress, with increased irritability, reduced capacity for judgement and motor skills, compromised cognitive function and an increased drive to sleep. In the long term, lack of sleep may promote weight gain, enhance insulin resistance, compromise immune function and increase the risk of depression.[1] It is no wonder that people view an inability to sleep as an alarming symptom, and avidly search for interventions to alleviate their problem.

What is "normal" sleep?

Healthy individuals usually sleep for seven to nine hours each night, although the timing, duration and internal structure of the sleeping period may vary. Normally we experience two distinct brain states during sleep. Firstly, rapid eye movement (REM) sleep, a state in which dreaming occurs, accompanied by rapid eye movements but overall reduced body muscle tone. All other sleep during the night is classified as non-rapid eye movement (NREM) sleep. There are four distinct phases within the NREM state. Stage 1 indicates the transition from wakefulness to the onset of sleep. Stage 2 is classified as light sleep, during which the body temperature drops and the muscles relax. Stages 3 and 4 of NREM sleep are known as "slow-wave" sleep or deep sleep, and are a prerequisite for feeling refreshed on awakening.

Normally, sleep progresses through NREM stages 1–4 within about 60–90 minutes. This is followed by a period of REM sleep, after which the cycle repeats. In general, a standard night's sleep comprises 50% NREM stage 1–2 (light), 25% NREM stage 3–4 (deep) sleep and 25% REM sleep. Changes in the quantity (duration) and intensity (proportion of REM/light/slow wave sleep) of sleep occur across the life cycle: REM sleep is increased in babies, while geriatrics exhibit reduced REM and increased NREM stages 1-2 sleep.[2]

What is insomnia?

Insomnia is a general term defined as "complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep." "Disturbed sleep" is further explained as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime functioning. Thus, patients with insomnia have difficulty falling asleep and difficulty staying asleep (i.e. waking before a desired wake time). They also experience a reduction in restorative sleep, contributing to a feeling of tiredness during the day.

Depending on the persistence of symptoms, insomnia is categorised as transient insomnia, which lasts less than one week; short-term insomnia lasting one to four weeks; and chronic insomnia where symptoms last longer than one month.

Transient insomnia usually occurs in response to a specific stimulus such as a minor medical problem (e.g. toothache) or an immediate stressor such as friction with a colleague at work. More than 75% of adults report such symptoms, but usually the insomnia is quickly resolved once the stimulus has been ameliorated.

Chronic insomnia is more common in women, the elderly and patients with other chronic medical or psychiatric illnesses. It has a prevalence of 10–15% and is associated with mood disturbance, occupational difficulties, interpersonal problems with concomitant social and economic consequences and a reduced quality of life.[3,4]

Pathophysiology

Current theories of the pathophysiology of insomnia have in common the premise that insomnia is a disorder of hyperarousal that is experienced throughout the day. In the cognitive model, sleep disruption occurs as a result of worrying about life stressors. A vicious cycle ensues when disrupted sleep adds to existent anxiety. People literally cannot sleep because they are worried about the consequences of not sleeping (on top of all their other worries). In contrast, the physiological model proposes an imbalance between alerting neuromediators and sleep-promoting agents in the brain which results in higher brain glucose metabolism during sleep and increased cardiac and metabolic rates throughout the day. The daytime state of hyperarousal may be masked by fatigue due to lost sleep, making the 24-hour nature of insomnia less apparent.[5]

These two theories combine in the psychophysiological model of insomnia, which hypothesises that after developing acute (short-term) insomnia following a specific triggering event, patients associate the bed environment with wakefulness. This is a maladaptive conditioned response which perpetuates the cycle of hyperarousal, despite resolution of the precipitating factor. This presentation is classified as primary insomnia, since the sleep disorder occurs in the absence of a current secondary cause.[6]

Secondary causes of insomnia

Insomnia resulting from a definitive source occurs more commonly than primary insomnia.[7] Treatment of the secondary causes can resolve the sleep problem, but sometimes there is value in treating the insomnia concurrently with the primary problem (e.g. in depressed patients), since resolution of the sleep difficulty may speed up recovery.[8] However, this is not always the case, and caution is advised when treating conditions such as gastro-oesophageal reflux (GORD) and benign prostatic hyperplasia (BPH). In patients with sleep-related GORD, insomnia improves following treatment with proton-pump inhibitors, while hypnotics such as zolpidem exacerbate the acid reflux problem and may perpetuate the insomnia.[9]

Another example where care should be taken in treating insomnia concurrent with its cause is in patients with BPH, who wake up multiple times during the night to go to the bathroom as the condition causes incomplete emptying of the bladder. This disturbed sleep contributes to daytime tiredness, since the frequent night-time awakenings derange the sleep pattern. If the patient uses over-the-counter sleep aids (such as the antihistamine diphenhydramine), this could exacerbate urinary retention and thus night time awakenings.[10] Accurate diagnosis and treatment of a primary problem causing secondary insomnia (listed in Table1) is essential in the management of such cases. However, health care practitioners should remain sensitive to the patient's sleep needs.

Table I: Secondary causes of insomnia[6]

Type of secondary insomnia	Examples
Adjustment insomnia	Insomnia associated with active psychosocial stressors, e.g. divorce, job stress
Inadequate sleep hygiene	Insomnia associated with lifestyle habits that impair sleep
Insomnia due to a psychiatric disorder	Active anxiety or depression
Insomnia due to a medical condition	Restless leg syndrome, chronic pain, fibromyalgia, nocturnal cough, sleep apnoea, menopause (hot flushes), gastro-oesophageal reflux disease, benign prostatic hyperplasia, hyperthyroidism, pregnancy, heart failure
Insomnia due to a drug or substance	See Table II for further details

Several sleep problems that result in impaired quality and quantity of sleep are not considered forms of secondary insomnia, but are rather classified as sleep disorders themselves. These include disorders of the circadian rhythm such as jet lag and shift work sleep disorder, and parasomnias such as sleepwalking and night eating syndrome.[3]

An additional frequent secondary cause of insomnia is drug use. The general practitioner can provide a useful service in conducting a review of the medication to determine if drug use is contributing to a patient's insomnia. The following medicines and substances listed in Table II are known to reduce sleep and stimulate brain hyperarousal.[11]

Of interest is that while alcohol may reduce sleep latency (the time taken to fall asleep), it also reduces NREM stages 3 and 4 (deep sleep) and increases the number of night time awakenings, thus reducing both the quality and quantity of "refreshing" sleep. This contributes to daytime fatigue and worsens insomnia. It is ironical that many patients use alcohol to help themselves fall asleep, not appreciating the fact that the substance itself is perpetuating their sleep problems. In addition, if patients mix alcohol with other drugs for insomnia such as benzodiazepines or benzodiazepine receptor agonists, they further shorten sleep latency but also aggravate sleep cycle disturbances and intensify sleep-related breathing disorders such as sleep apnoea. This

Table II: Drugs which cause secondary insomnia[1-3,6]

Drug	Examples
Alcohol	Beer, wine, liquor
Antidepressants	SSRIs (e.g. fluoxetine), SNRIs (e.g. venlafaxine), MAOIs (e.g. moclobemide)
Beta blockers	More common with lipophilic drugs, e.g. propranolol
Bronchodilators	Theophylline
Corticosteroids	Prednisolone
Decongestants	Phenylephrine
Diuretics	Increase thirst and increase the need to go to the bathroom, both exacerbating insomnia
HMG-CoA reductase inhibitors	More common with lipophilic drugs, e.g. simvastatin
Stimulants	Caffeine, nicotine, modafinil, methylphenidate, levodopa, d-norpseudoephedrine, amphetamine, cocaine

SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin and noradrenaline reuptake inhibitor, MAOI monoamine oxidase inhibitor, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A

dangerous practice should be discouraged, and general practitioners should take opportunities to counsel patients against the use of alcohol as a sleep aid.[11]

Sleep study terminology

The following are some of the terms employed in the study of sleep disorders.

- *Sleep latency:* The time it takes to fall asleep after the lights have been turned out. Sleep latency may be prolonged in insomnia, and treatments for insomnia aim to reduce sleep latency.
- *Sleep efficiency:* The ratio between total sleep time and total time spent in bed (which is ideally more than 85%).
- *Total sleep time:* The cumulative time spent asleep.
- *Polysomnogram:* A test conducted in a sleep laboratory which measures brain activity, eye movements, heart rate, blood pressure, blood oxygenation, air inflow (through the nose), snoring, and chest effort during breathing. Polysomnography is used to diagnose sleep apnoea and other sleep-related breathing disorders, sleep-related seizure disorders and narcolepsy.
- *Multiple sleep latency test:* A daytime sleep study where the patient relaxes in a quiet room and brain activity is measured to document if the patient falls asleep and what phases and stages of sleep occur. The test is carried out multiple times through the day, since ability to fall asleep changes throughout the day. This is usually one of the tests for narcolepsy.

Nonpharmacological therapy

Nonpharmacological therapy should precede medication, as patient education regarding good lifestyle habits in relation to sleep can improve insomnia.

Sleep hygiene education

Most patients benefit from education concerning appropriate sleep habits and behaviours regardless of the cause of their insomnia, since poor sleep habits can perpetuate sleep disturbances and impede recovery.

Good sleep hygiene practices should include the following:[12]

- Maintaining a regular sleep-wake cycle (even on weekends).
- Using the bedroom only for sleep and sex.
- Comfortable, quiet, and dark bedroom environment.
- Developing a relaxing bedtime routine.
- Regular exercise but not within a few hours of bedtime.
- Avoidance of alcohol, caffeine and nicotine, especially a few hours before bedtime.
- No late, heavy meals before bedtime.
- No daytime napping.
- No disturbances at bedtime (e.g. disruptive noises).
- No clock close to the bed, to prevent clock watching.
- Avoiding excessive wakeful time in bed (more than 20 minutes).

In addition to advice on sleep hygiene, patients should be encouraged to keep a "sleep diary" to document their progress in implementing better sleeping practices and to highlight further areas for intervention. Since insomnia is largely a self-reported phenomenon, it may be instructive for patients to quantify their sleep in relation to their lifestyle habits, as this can help them to develop a perspective on the severity of their symptoms. A sleep diary could include information on bedtime, time to sleep onset, total sleep time, number of night time awakenings, level of refreshment, daytime sleepiness, daytime naps, use of medications, and related events.[13]

Cognitive-behavioural therapy

Cognitive therapy aims to increase patients' awareness of their specific unrealistic expectations about sleep and misconceptions surrounding the cause of insomnia. A combination of cognitive and behavioural techniques (Table III) may assist the patient to confront the individual issues and deal with them from a psychological standpoint, thus interrupting the chronicity of the insomnia cycle. The advantages of using cognitive/behavioural strategies include a low adverse-effect profile and good evidence of sustained improvement in sleep parameters over six months. However, such strategies produce only slow improvement of symptoms, require personnel trained in provision of the techniques, necessitate firm commitment from the patient to adhere to the long-term regimen, may incur out-of-pocket costs to the patient, and are hampered by the perception that pharmacological interventions are more efficacious.[14,15]

Table III: Cognitive behavioural therapy for insomnia[6,16]

Type of cognitive behavioural therapy	Description
Stimulus-control therapy	Encompasses aspects of the good sleep hygiene routine: training the patient to associate their bed with restful sleep rather than reading, watching TV or working in bed.
Sleep-restriction therapy	Reduce time in bed to estimated total sleep time (minimum five hours), then increase time in bed by 15 minutes per week. This "retraining" decreases performance anxiety about falling asleep and incrementally extends total sleep time
Relaxation therapy	Physical component: progressive muscle relaxation, biofeedback Mental component: imagery training, meditation, hypnosis
Cognitive therapy	Education to alter faulty beliefs and attitudes about sleep

Pharmacological therapy

When sleep disturbance causes significant distress or impairment, pharmacotherapy is usually the modality of choice owing to the short time to clinical effect in comparison with psychotherapy. While pharmacotherapy for short-term insomnia can be successful in breaking the cycle of sleeplessness, long-term pharmacotherapy for chronic insomnia is currently limited by the dependence potential of the medications used, tolerance to their clinical effects (with concomitant loss of efficacy) and adverse effects of prolonged use.[17]

In order to reduce the possibility of adverse occurrences with the long-term use of hypnotic agents, the following principles of drug use should be implemented:

- Identification of secondary causes and initiation of their appropriate treatment before attempting drug therapy for sleeplessness.
- Initiate insomnia pharmacotherapy at low dose, then titrate to clinical effect.
- Use short duration of therapy (two to four weeks) and/or intermittent dosing (alternate nights or three times a week).
- Be aware of escalating doses or patient resistance to stopping therapy.
- When discontinuing hypnotic agents, gradually taper doses downwards.

Although in theory these principles are sound, it has been reported that the majority of sleep medication is used over long periods of time, usually on a nightly basis for several years.[18] The problem with this is that clinical trials demonstrating efficacy of hypnotic medications were conducted over short periods (not more than six months) thus long-term value of such medications has not been established.[19] The only exception is the new drug eszopiclone (not yet available in South Africa) for which a clinical trial showing improved sleep on self-report measures was conducted over 12 months.[20] Further research on "real world" use of medications to aid sleep is necessary to inform how we advise patients with chronic sleep difficulties.

Table IV is a compilation of drugs which induce sleepiness. Where acceptable evidence has been published for clinical use of the drug in the management of insomnia, the drugs are listed in bold typeface. Where the drugs are being used "off label", or there is currently insufficient evidence, the drugs have been included for completeness, since many patients turn to these substances to augment insomnia treatment.

Combined therapy for insomnia

If used according to recommendations, current literature suggests that benzodiazepine-receptor agonist (BZRA) hypnotics and benzodiazepines (BZDs) are effective in the short-term treatment of insomnia and can maintain their efficacy over extended time periods (years) with little harm.[19] However, as soon as the medicines are stopped, insomnia recurs.[22] In contrast, cognitive behaviour interventions can improve insomnia in the short term, and these improvements are sustained over a two-year follow-up period.[23] It would seem ideal to be able to combine these two therapies. However, studies of such combined regimens have yielded disappointing results. In these combined protocols, benefit was maintained over 24 months in the group that received cognitive therapy alone but was not sustained in the group that had both medication and cognitive behavioural therapy.[24,25] Silber speculates that "patients are less committed to learning and practicing cognitive behavioural therapy techniques if they can control insomnia with medications."[6] In support of this theory, it has been shown that in patients with chronic insomnia who are attempting to stop BZD therapy, patients who received cognitive behavioural therapy during the drug tapering process managed to achieve and maintain drug freedom, compared with patients who did not receive cognitive therapy.[26,27] In our "fast-fix" society, it is understandable that patients are attracted to therapies that assure rapid results, but responsible healthcare practitioners should ensure that the issue of long-term, sustainable benefit is addressed, before therapy is commenced.

Insomnia and good medical practice

The occurrence of insomnia may be alarming for patients, and the general practitioner is ideally placed to give supportive advice concerning management of the problem.[28]

The general practitioner can assist patients to:

- Recognise insomnia and reasons for daytime fatigue.
- Investigate possible secondary causes for insomnia including social habits and drug usage.
- Make the decision to investigate further causes of the insomnia.

Table IV: Drugs which increase sleepiness (drugs with proven benefit in the management of insomnia are indicated in **bold** type)[2,3,6,11,17,21]

Drug name	Trade names	Type	Mechanism of action	Clinical use	Adverse effects
Zolpidem	Adco-zolpidem®, Ivedal®, Mylan zolpidem®, Noxidem®, Stilnox®, Zolnoxs®, Zolpihexal®	BZRAs	These hypnotic agents bind to benzodiazepine receptors (even though they are structurally different from benzodiazepines) and cause postsynaptic hyperpolarisation.	Effective for decreasing the time to sleep onset zolpidem and eszopiclone have longer half-lives and therefore are also useful for sleep maintenance; both can be used for longer than 30 days.	Proposed less rebound insomnia and better safety profile than benzodiazepines Although less than benzodiazepines, these drugs are still implicated in causing withdrawal symptoms, physical dependence and tolerance to chronic therapy. Use with caution in patients with sleep apnoea, respiratory disease and hepatic dysfunction. Zolpidem increases the risk of parasomnias, e.g. night eating syndrome. Zaleplon has such a short half-life that it may be administered on waking during the night, provided four more hours of sleep are intended.
Zopiclone	Adco-zopimed®, Alchera®, Austell-zopiclone®, Imovane®, Sandoz zopiclone®, Z-dorm®, Zopigen®, Zopivane®				
Eszopiclone	Not available in South Africa				
Zaleplon					
Brotizolam	Lendormin®	BZDs	Enhance the effects of GABA, causing post-synaptic hyperpolarisation which reduces neuronal transmission.	Effective for decreasing the time to sleep onset and prolonging sleep duration. However, efficacy declines when used continuously for more than 30 days. Intermittent use (alternate nights or three times a week) is therefore recommended.	BZDs have largely been superseded by BZRAs in the management of insomnia because of their superior tolerability. Although long half-life drugs (e.g. diazepam) are useful for concomitant anxiety, they cause daytime sedation and impair motor skills and are therefore not recommended for chronic insomnia. Short half-life drugs, e.g. Temazepam cause rebound insomnia and anxiety. All benzodiazepines impair memory. BZD use increases the risk of falls and hip fractures in elderly patients. CYP3A4 inhibitors, e.g. azole antifungals, macrolide antibiotics, protease inhibitors and grapefruit juice may increase BZD toxicity. CYP3A4 inducers, e.g. carbamazepine and St John's wort can decrease BZD effectiveness. BZDs are potentially addictive. Use with caution in patients with sleep apnoea, depression, psychosis, respiratory disease, hepatic or renal impairment and the elderly. Alcohol or other CNS depressants potentiate BZD effects and concomitant use could lead to toxicity.
Diazepam	A-Lennon Diazepam®, Valium®				
Flunitrazepam	Hypnor®, Rohypnol®, Sandoz flunitrazepam®				
Flurazepam	Dalmadorm®				
Loprazolam	Dormonoct®				
Lormetazepam	Loramet®, Noctamid®				
Midazolam	Adco-Midazolam®, Dormicum®, Midacum®, Midanium®, Midazoject®				
Nitrazepam	Arem®, Mogadon®, Sandoz- nitrazepam®				
Temazepam	Normison®				
Triazolam	Halcion®				
Diphenhydramine	Betasleep®	First-generation antihistamines	Block histamine-1 receptors.	Available over-the counter for treatment of short-term insomnia. Not indicated for chronic insomnia.	Tolerance develops to the sedative effects of antihistamines. Caution in patients with glaucoma and ↑BPH (owing to anticholinergic effects of antihistamines). Increased risk of orthostatic hypotension (exacerbating the risk of falls in the elderly). Not recommended for use in children. Daytime sedation may occur.
Doxylamine	Restwel®, Somnil®				
Phenobarbitone	Lethyl®, in various pain combinations, e.g. Propain Forte®	Barbiturates	Allosterically modulates the effects of GABA, causing postsynaptic hyperpolarisation.	Not recommended for insomnia management.	Narrow therapeutic index. Lethal in overdose. Quick development of tolerance. High abuse potential. Many drug interactions. Induces hepatic microsomal enzymes.

Drug name	Trade names	Type	Mechanism of action	Clinical use	Adverse effects
Amitriptyline	Trepiline®, Tryptanol®, Sandoz Amitriptyline®	Antidepressant drugs	Tricyclic antidepressant: inhibits reuptake of both serotonin and noradrenaline.	There is no evidence for use of these agents for insomnia that is not associated with depression. In depressed patients with insomnia, these agents may be used if "alerting" antidepressants render insomnia resistant to treatment. More research is warranted to examine the promising effects of antidepressants on reducing stress hormones and hyperarousal in chronic insomnia.	Exercise caution with amitriptyline, dothiepin and trazodone in elderly patients with prostatic enlargement, since these drugs increase urinary retention. Tricyclic antidepressants cause cardiac toxicity and can be lethal in overdose. Trazodone increases the risk of priapism. CYP3A4 inhibitors, e.g. azole antifungals, macrolide antibiotics, protease inhibitors and grapefruit juice, may increase trazodone toxicity. CYP3A4 inducers, e.g. carbamazepine and St John's wort, can decrease trazodone efficacy. Trazodone has a shorter half-life than amitriptyline, and therefore has a smaller risk of morning hangover effect. Owing to their lack of addictive potential, these drugs are used in patients with a history of substance abuse co-morbid with insomnia.
Trazodone	Molipaxin®		Inhibits re-uptake of serotonin.		
Mirtazapine	Adco-Mirteron®, Aspen Mirtazapine®, Beron®, Mylan Mirtazapine®, Remeron®, Sandoz Mirtazapine®		Blocks α_2 receptors presynaptically, which results in disinhibition of noradrenergic and serotonergic neurons, thus increasing neurotransmission. Histamine blockade contributes to sedative effects.		
Dothiepin	Prothiaden®, Sandoz Dothiepin®, Thaden®		Tricyclic antidepressant: inhibits reuptake of both serotonin and noradrenaline.		
Chloral hydrate	No longer available in South Africa	Alcohol-related hypnotic agent	Chloral hydrate is rapidly converted by alcohol dehydrogenase to trichloroethanol, which is a strong hypnotic.	Poor evidence of either safety or efficacy (especially in children, where use of hypnotic agents is problematic).	Nausea and vomiting are common. Ataxia. Headache. Nightmares. Respiratory depression in overdose.
Meprobamate	Equanil®, analgesic combinations, e.g. Stopayne®	Carbamate	Suppresses multiple CNS sites.	Not recommended for use in patients with insomnia.	Strong abuse potential. Adverse effects: Ataxia, dizziness, hypotension, syncope (which increases the risk of falls in the elderly).
Chlorpromazine	Largactil®	Antipsychotic agents	Sedative effects of these drugs are attributable to blockade of α_1 receptors in the CNS, as well as histamine-1 receptor blockade.	Off-label use; insufficient evidence of safety and efficacy in management of chronic insomnia.	Postural hypotension (which increases the risk of falls in the elderly). Weight gain. Constipation. Dizziness. Akathisia.
Risperidone	Aspen-Risperidone®, DRL Risperidone®, Mylan Risperidone®, Perizal®, Rispacor®, Risperdal®, Risperidone Hexal®, Risperlet®, Risponz®, Zoxadon®				
Olanzapine	Zyprexa®				
Quetiapine	Seroquel®				

Drug name	Trade names	Type	Mechanism of action	Clinical use	Adverse effects
Pregabalin	Lyrica®	Used for pain of diabetic neuropathy and postherpetic neuralgia	Reduces neuronal transmission through binding to the α2δ subunit on voltage-gated calcium channels	Insufficient evidence of safety and efficacy in management of chronic insomnia (used in patients with chronic pain, who report improved sleep).	Weight gain. Peripheral oedema. Neurocognitive disturbances such as confusion, disturbed attention, abnormal thinking, and euphoric mood.
Gabapentin	Epleptin®, Neurexal®, Neurontin®, Ran-Gabapentin®	Antiepileptic drug			
Ramelteon	Not available in South Africa	Melatonin-receptor agonist	Binds to M_1 and M_2 receptors, helping to maintain circadian rhythm to support the normal sleep-wake cycle. Has a higher affinity for melatonin receptors than natural melatonin	Effective for decreasing the time to sleep onset. Data are lacking on head-to-head trials with other hypnotic agents.	No documented dependence, tolerance, withdrawal syndrome, motor or cognitive deficits or rebound insomnia. Not to be taken with or immediately after high-fat meals, as this delays absorption and retards clinical effects. Avoid in patients with severe hepatic impairment. Take immediately before bedtime or while in bed, since this drug has a rapid onset of action.
Agomelatine	Valdoxane®	Anxiolytic antidepressant agent	Exerts an antidepressant effect by blocking serotonin receptors. In addition, it stimulates M_1 and M_2 receptors, helping to maintain circadian rhythm to support the normal sleep-wake cycle.	Improves sleep efficiency and slow-wave sleep. Proposed as an adjunct to treatment of co-morbid depression and insomnia. Clinical evidence remains anecdotal.	Headache. Dry mouth. Diarrhoea. Fatigue.
L-tryptophan	L-tryptophan is biotransformed to 5-hydroxytryptophan, and is sold as either formulation	Biosynthesised amino acid	Tryptophan is the amino acid precursor to serotonin, which is a precursor of melatonin.	L-tryptophan is proposed to improve both mood and sleep, owing to its potential conversion to serotonin and melatonin. Clinical studies remain inconclusive.	Orally ingested tryptophan is broken down peripherally to serotonin. Raised levels of peripheral serotonin contribute to adverse effects, such as diarrhoea and stomach cramping. Small amounts cross the blood-brain barrier (which may explain its lack of efficacy).
Melatonin		Synthetically manufactured neurohormone	Stimulates M_1 and M_2 receptors (melatonin receptors). Augments endogenous melatonin.	Promotes sleep if taken in the afternoon (not at bedtime). Can assist circadian rhythm re-establishment in patients with jet-lag or shift-work sleep disorders.	There are issues with standardisation of ingredients and dose variability in herbal products. Herbal synthetic melatonin has a short half-life and is therefore only useful in reducing sleep latency, rather than in sleep maintenance. Melatonin may reduce the efficacy of calcium-channel blockers and increase the effects of warfarin. Caffeine, nicotine, alcohol and β blockers all reduce melatonin levels in the body.
Valerian	Biral®, Restin®	Root of the plant *Valeriana officinalis*	Unknown.	Evidence supporting valerian as a sleep aid remains contradictory.	There are issues with standardisation of ingredients and dose variability in herbal products.

BZRA: benzodiazepine-receptor agonist (non-benzodiazepine), BZD: benzodiazepine, GABA: gamma-aminobutyric acid, CYP: cytochrome P450, CNS: central nervous system, BPH: benign prostatic hyperplasia

- Assess lifestyle habits (including lack of exercise) which may exacerbate insomnia.
- Adhere to the treatment regimen prescribed.
- Avoid drug interactions with insomnia medications and others.
- Stop medication for insomnia when indicated.

An important practical point to note is that both sleeplessness and medications used to treat this condition (e.g. BZDs and BZRAs) can slow reaction time and judgement, and may therefore contribute to motor vehicle accidents and accidents when operation machinery. Patients should be cautioned not to engage in such activities until they feel sure that their level of alertness is sufficient.[29]

The personal cost to the patient and societal cost of insomnia can be immense. This is an area where supportive, knowledgeable counselling can achieve great impact.[30]

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