# Insomnia disorder: a hard day's night

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## Abstract

Intermittent or acute insomnia is common, and may sometimes require short-term treatment with an approved hypnotic agent. A diagnosis of insomnia disorder, however, indicates that night-time sleep is of poor quality and chronic, and accompanied by significant impairment of daytime functioning. Although insomnia disorder often co-exists with psychiatric and medical conditions, it is viewed as an independent entity with potentially serious sequelae, requiring its own treatment, usually in the form of cognitive behavioural therapy, with or without pharmacotherapy.

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## Introduction

Approximately 30% of the adult population experiences transient sleep difficulties, with acute discrete episodes of insomnia affecting approximately 10-15%.[1] Half of these follow a more severe and chronic course, and ultimately fulfil the diagnostic criteria for insomnia disorder.[2,3] Insomnia disorder is characterised by dissatisfaction with the quality or quantity of sleep, accompanied by clinically relevant distress or the impairment of daytime functioning, and occurring at least three times a week for at least three months, despite adequate opportunities to sleep. These symptoms may include difficulty falling asleep (38%), staying asleep (61%), and/or returning to sleep after frequent or early morning awakening (52%), accompanied by daytime drowsiness, fatigue, impaired concentration, and memory, behavioural or mood difficulties or disturbances in academic, occupational, social or interpersonal functioning.[4]

Insomniacs often report excessive worry and racing thoughts. Physiological signs of this nocturnal hyperarousal include increases in the metabolic rate, brain glucose consumption, cortisol levels and blood pressure, with high electroencephalogram activity during sleep.[5] Chronic insomnia is associated with distress, increased work-related absenteeism and injuries, and with perceptions of compromised health and quality of life. It may also be a risk factor for suicide, independent of a diagnosis of depression, and may potentially serve as a warning for other serious psychiatric or medical issues.[2,6]

Insomnia occurs more frequently in women than in men, in the elderly, and in those who work irregular shifts or who have disabilities.[7] Insomnia may be caused by the following types of stress:

- *Situational:* Occupational, interpersonal, financial, academic and medical
- *Environmental:* Noise
- *Drug and substance abuse:* Caffeine, nicotine, alcohol and recreational drugs
- *Certain medication:* Selective serotonin reuptake inhibitors, bupropion, serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, lamotrigine, phenytoin, beta blockers, calcium-channel blockers, corticosteroids, thyroid hormones, nonsteroidal anti-inflammatory drugs, methylphenidate, modafinil, salbutamol, salmeterol, theophylline and pseudoephedrine.

Medical symptoms associated with insomnia include shortness of breath, nocturia, gastrointestinal problems, pain and diminished mobility.[2,8,9]

Approximately half of all insomnia cases are associated with psychiatric conditions; commonly mood or anxiety disorders.[10] These relationships may be bidirectional. Insomnia often precedes the onset of depression in major depressive disorder. Prolonged insomnia may actually double the risk of this mood disorder developing.

Insomnia may also increase the risk of developing medical conditions, such as hypertension, acute myocardial infarction, heart failure and diabetes mellitus, especially when sleep occurs for less than six hours a night.[2] Determining the cause and effect of insomnia is often very difficult, and for this reason, insomnia disorder, as defined previously, is now viewed as a condition that requires independent clinical attention, regardless of other co-morbid conditions which may be present and also require

treatment.[11] Importantly, as insomnia can precipitate, exacerbate or prolong co-morbid conditions, the treatment of insomnia may also improve co-morbidities.[12,13]

## Diagnosis and treatment

The diagnosis of insomnia is made clinically, based chiefly on a careful history of nocturnal and daytime sleep-related symptoms, their duration and their associations with physical or psychological stressors. A sleep diary is invaluable in documenting these variables. Polysomnography is not indicated unless other sleep disorders, such as periodic limb movement disorder or sleep apnoea, are suspected. Because up to 80% of insomnia is associated with a co-morbidity, early identification and management of any coexistent disorder is essential.[9]

Patients with acute-onset insomnia of short duration, i.e. ≤ 4 weeks, often have an identifiable precipitant, such as the loss of a job or partner. Short-term pharmacotherapy with benzodiazepines or Z drugs is justified in these instances.[14] However, the use of these hypnotics is associated with adverse effects, including daytime sedation, poor motor coordination, cognitive impairment, anterograde amnesia and related concerns about driving accidents and injuries from falls. These safety concerns are particularly pertinent in the elderly population, where drug clearance is reduced.[15,16] Withdrawal phenomena are also potentially problematic. The lowest dose that controls symptoms should be used, for a maximum of four weeks, and intermittently, if possible.

## Cognitive behavioural therapy

Nonpharmacological interventions are established first-line therapy in patients in whom insomnia persists, despite the adequate treatment of underlying medical or psychiatric conditions. Cognitive behavioural therapy (CBT), which addresses dysfunctional beliefs and behaviours that entrench insomnia, is recommended for all patients with chronic insomnia, including those with co-morbidities.[17] CBT usually consists of 6-8 individual or group sessions. Limitations to its use include accessibility and a lack of suitably qualified facilitators. Internet-based CBT may offer an effective alternative to face-to-face delivery. Compliance is also an issue, presumably owing to the delayed onset of efficacy, lack of faith in psychological approaches, as well as the challenges of changing sleep-related behaviour. These include reducing the time spent in bed and getting out of bed when awake, relaxation therapy, limiting caffeine and alcohol intake, keeping the bedroom dark and quiet, avoiding napping, removing clocks in the bedroom, and increasing daytime activity and exercise.[18] Sleep restriction is contraindicated in patients with bipolar disorder as it may trigger mania.[19]

## Pharmacotherapy

Pharmacotherapy for insomnia is common. Approximately a fifth of the USA adult population takes medication for insomnia, and roughly 60% of these include non-approved, non-prescription sleep aids, particularly antihistamines and alcohol.[2,14]

### *Benzodiazepine receptor agonists*

Approved hypnotics include benzodiazepines (triazolam, loprazolam, lorazepam, lormetazepam and tema-zepam) and non-benzodiazepine Z drugs (zolpidem, zopiclone and zaleplon), which, like alcohol, are neuroinhibitory benzo-diazepine (γ-aminobutyric acid A) receptor agonists. Their clinical efficacy and side-effect profiles are similar, while their half-lives differ. Indirect comparisons of benzodiazepines and Z drugs suggest that they have a similar impact on sleep-onset latency.[20] However, the benzodiazepines are more likely to prolong total sleep time and produce a hangover effect because they tend to have a longer half-life.[20,21] The choice of benzodiazepine receptor agonist is often based on individual insomnia symptoms, such as difficulty initiating (short-acting triazolam, lorazepam, zolpidem and zaleplon), or maintaining (longer-acting temazepam and eszopiclone) sleep.[16] Although these drugs are licensed for bedtime use, it is feasible to take a short-acting agent (zolpidem and zaleplon) in the middle of the night, provided at least four hours are still available for sleep. Very long-acting agents, such as clonazepam, should be avoided for insomnia because of the risks associated with daytime drowsiness. These agents should also be avoided in people with a history of alcohol dependence or substance abuse, or hepatic or renal problems, as well as in the elderly. They should also be avoided in the first trimester of pregnancy. Discontinuation of long-term benzodiazepine receptor agonists should be supervised and gradual, tapering the dose by no more than 25% of the original dose every two weeks. CBT should continue during this process in order to maximise the chances of successful discontinuation. Approximately one third of these patients relapse by two years of follow-up.[2]

### *Sedating antidepressants and antihistamines*

Low-dose sedating antidepressants with significant antihistamine effects are often used for insomnia. For instance, doxepin (3-6 mg), a tricyclic antidepressant (TCA), demonstrates a significant improvement in sleep maintenance and is US Food and Drug Administration (FDA)-approved for insomnia, rather than for depression, at this low dose. Although robust clinical data are lacking, low-dose trazodone (25-50 mg), is used as a hypnotic in approximately 1% of USA adults, while other low-dose sedating TCAs, such as amitriptyline and trimipramine (25 mg), are popular worldwide.[22] These multipotent blockers may also be associated with potentially serious antimuscarinic and alpha 1 antagonistic side-effects, including urinary retention and postural hypotension, respectively. Evidence-based recommendations for the use of these sedating antidepressants for insomnia are thwarted by a lack of comparative studies, as well as by potentially adverse risk to benefit ratio.[22]

Normal-dose mirtazapine (15-30 mg), a noradrenergic and specific serotonergic antidepressant with significant antihistamine activity,

is a reasonable option for patients with co-existent depression, particularly as it antagonises serotonin 5-hydroxytryptamine $(5\text{-HT})_2$ receptors as well.[22,23] Long-term use may be associated with antihistamine-induced increases in appetite and subsequent weight gain.

Agomelatine is a newer antidepressant, which, at therapeutic doses of 25-50 mg, improves disturbed sleep-wake cycles by stimulating the melatonin (MT) 1 and MT2 receptors, and antagonising $5\text{-HT}_{2C}$ receptors. Therefore, it is potentially invaluable in insomniacs with major depressive disorder.[24,25] It may be associated with clinically relevant hepatotoxicity, and transaminases should be monitored periodically during treatment.[26,27]

The antihistamines, diphenhydramine (25-50 mg) and doxylamine (25-50 mg), are approved for insomnia in South Africa. Yet there is little evidence that they improve insomnia, and because of their long half-life, they may cause daytime sedation. Additional side-effects include decreased cognitive function, delirium, a dry mouth, blurred vision, urinary retention, constipation and increased intraocular pressure.[28]

### *Others elsewhere*

Melatonin shows a small benefit in promoting sleep onset, as well as total sleep time, although the evidence for this is difficult to interpret owing to the different formulations and compositions of this readily available non-prescription agent. Circadin® (prolonged-release melatonin, 2 mg tablet) is the only licenced formulation of melatonin in the UK, and is particularly useful in those aged ≥ 55 years and as a short-term measure.[29]

Ramelteon, a melatonin (MT1/MT2) receptor agonist, which binds with high affinity to these suprachiasmatic nucleus receptors, is approved in the USA and Japan for insomnia, but not in the EU or South Africa. It shows small to moderate improvements in time to sleep onset. Daytime sedation may occur, but this is rare.[30]

Suvorexant, a dual orexin receptor antagonist which dampens the orexin-mediated wakefulness system of the brain that controls the transition between arousal and sleep, was granted FDA approval more recently (2014) for the treatment of insomnia.[31] It exhibits decreased time to sleep onset, decreased time awake after sleep onset and increased total sleep time. It is associated with morning sedation in 5% of patients.[32]

## Conclusion

Approved short-term hypnotic medications are indicated for those with acute insomnia resulting from a defined precipitant, while CBT is recommended as first-line therapy in those with more chronic insomnia disorder, where lack of sleep impacts significantly on daytime functioning, and on physical, psychiatric and emotional health. Long-term pharmacotherapy should be considered in patients with insomnia disorder that is unresponsive to a psychological approach.

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