

# Insomnia disorder: when sleep plays coy, aloof and disdainful

**K Outhoff**

Senior Lecturer

Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, Pretoria

Corresponding author, email: kim.outhoff@up.ac.za

## Abstract

Intermittent or acute insomnia is common and may sometimes require short term treatment with approved hypnotic agents. A diagnosis of insomnia disorder, however, indicates that poor night-time sleep is chronic and is 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 (CBT), with or without pharmacotherapy.

**Keywords:** Insomnia, hypnotics, cognitive behavioural therapy

## Background

Some (poets, writers, artists, lovers, visionaries, philosophers, over-thinkers, sheep counters) find insomnia their greatest inspiration. Yet for most, sleeplessness simply amplifies imminent worries, past embarrassments, stern memories, pain, guilt, frustrations or anguish. It diminishes perspectives and emboldens emotional and physical suffering. Approximately 30% of the adult population experiences transient sleep difficulties, with acute discrete episodes of insomnia affecting about 10-15%.<sup>1</sup> Half of these follow a more severe and chronic course, and ultimately fulfil the diagnostic criteria for insomnia disorder.<sup>2,3</sup>

Insomnia disorder is defined as dissatisfaction with the quality or quantity of sleep, accompanied by clinically relevant distress or impairment of daytime functioning, occurring at least 3 times a week for at least 3 months despite adequate opportunities for sleep. These symptoms may include difficulty falling asleep (38%), staying asleep (61%), and/or returning to sleep after frequent or early morning awakening (52%), coupled with daytime drowsiness, fatigue, impaired concentration and memory, behavioural or mood difficulties, or disturbances in academic, occupational, social or interpersonal functioning.<sup>4</sup>

Insomniacs often report excessive worry and racing thoughts. Physiological signs of this nocturnal hyper-arousal include increased metabolic rate, brain glucose consumption, cortisol levels and blood pressure, with high electroencephalogram activity during sleep.<sup>5</sup> 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.<sup>2,6</sup>

## Cause and effect

Insomnia occurs more frequently in women than in men, in the elderly, and in those who work irregular shifts or who have disabilities.<sup>7</sup> Potential precipitants of insomnia include situational stress (occupational, interpersonal, financial, academic, medical) and environmental stress (noise), drug and substance abuse, and certain medications (Table I). Medical symptoms associated with insomnia include shortness of breath, nocturia, gastro-intestinal problems, pain and diminished mobility.<sup>2,8,9</sup>

About half of all insomnia cases are associated with psychiatric conditions, most commonly mood or anxiety disorders.<sup>10</sup> These relationships may be bidirectional. Insomnia often precedes the onset of depression in major depressive disorder and prolonged insomnia may actually double the risk of developing this mood disorder. Insomnia may also increase the risk of developing medical conditions such as hypertension, acute myocardial infarction, heart failure and diabetes, especially when sleep occurs for less than 6 hours a night.<sup>2</sup> Determining the cause and effect of insomnia is often very difficult, and for this reason, insomnia disorder, as defined above, is now viewed as a condition requiring independent clinical attention, regardless of other comorbid conditions that may be present and also require treatment.<sup>11</sup> Importantly, as insomnia can precipitate, exacerbate, or prolong comorbid conditions, treatment of insomnia per se may also improve comorbidities.<sup>12,13</sup>

**Table 1:** Potential causes of drug-induced insomnia

Antidepressants	selective serotonin reuptake inhibitors (SSRI) serotonin and noradrenaline re-uptake inhibitors (SNRI) bupropion monoamine oxidase inhibitors (MAOIs)
Anticonvulsants	lamotrigine phenytoin
Cardiovascular	beta-blockers calcium-channel blockers
Anti-inflammatory	corticosteroids nonsteroidal anti-inflammatory drugs (NSAIDs)
Respiratory	salbutamol salmeterol theophylline
Hormones	thyroid hormone
Stimulants	modafinil methylphenidate pseudoephedrine
Recreational drugs	alcohol nicotine caffeine other stimulant drugs

## Diagnosis and treatment

Insomnia is diagnosed clinically, based mainly 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 comorbidity, early identification and management of any coexistent disorders is essential.<sup>9</sup>

Patients with acute onset insomnia of short duration (less than 4 weeks) often have an identifiable precipitant such as loss of a job or partner. Short term pharmacotherapy with benzodiazepines or Z-drugs is justified in these instances.<sup>14</sup> However, 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.<sup>15,16</sup> Withdrawal phenomena are also potentially problematic. The lowest dose that controls symptoms should be used, for a maximum of 4 weeks, and intermittently if possible.

## Cognitive behavioural therapy

In patients whose insomnia persists, despite adequate treatment of underlying medical or psychiatric conditions, nonpharmacological interventions are established first-line therapy. Cognitive behavioural therapy (CBT), which addresses

dysfunctional beliefs and behaviours that entrench insomnia, is recommended for all patients with chronic insomnia, including those with comorbidities.<sup>17</sup> CBT usually consists of 6-8 individual or group sessions. Limitations to its use include accessibility and lack of suitably qualified facilitators. Internet-based CBT may offer an effective alternative to face-to-face delivery. Compliance is also an issue, presumably because of delayed onset of efficacy, lack of faith in psychological approaches, and the additional challenges of changing sleep-related behaviours. These include reducing time spent in bed, 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.<sup>18</sup> Of note is that sleep restriction is contra-indicated in patients with bipolar disorder as it may trigger mania.<sup>19</sup>

## Pharmacotherapy

Although common, pharmacotherapy for insomnia may be misguided or misused. Approximately a fifth of the US adult population takes medication for insomnia, and roughly 60% of these include non-approved, non-prescription sleep aids, particularly antihistamines and alcohol.<sup>2,14</sup>

### Benzodiazepine receptor agonists

Hypnotics include benzodiazepines (triazolam, loperazolam, lorazepam, lormetazepam, temazepam) and non-benzodiazepine Z-drugs (zolpidem, zopiclone, eszopiclone, zaleplon) which, like alcohol, are neuro-inhibitory benzodiazepine (GABA<sub>A</sub>) receptor agonists. Their clinical efficacy and side effect profiles are similar, but their half-lives differ: Indirect comparisons of benzodiazepines and Z-drugs suggest that they have a comparable impact on sleep onset latency.<sup>20</sup> However, the benzodiazepines are more likely to prolong total sleep time and produce hangover effects, because they tend to have longer half-lives.<sup>20,21</sup> The choice of benzodiazepine receptor agonist is often based on individual insomnia symptoms such as difficulty initiating (short acting triazolam, lorazepam, zolpidem, zaleplon), or maintaining (longer acting temazepam, eszopiclone) sleep.<sup>16</sup> Although these drugs are licensed for bedtime use, it is feasible to take a short acting agent (zolpidem, zaleplon) in the middle of the night, provided at least 4 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. All of these agents should be avoided in people with a history of alcohol dependence or substance abuse, hepatic or renal problems, as well as in the elderly. They should also be avoided in the first trimester of pregnancy. The risk of dependence is relatively high, and discontinuation of long term benzodiazepine receptor agonist therapy should be supervised and gradual, tapering the dose by no more than 25% of the original dose every 2 weeks. CBT should continue during this process, in order to maximise the chances of successful discontinuation; approximately one third of patients relapse by 2 years of follow-up.<sup>2</sup>

### 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 significant improvements in sleep maintenance and is FDA-approved for insomnia, rather than for depression, at this low dose. Although lacking robust clinical data, low dose trazodone (25-50 mg), is used as a hypnotic in approximately 1% of US adults, while other low dose sedating TCAs such as amitriptyline and trimipramine (25 mg) are popular worldwide.<sup>22</sup> These multi-potent 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 lack of comparative studies and by potentially adverse risk-benefit ratios.<sup>22</sup>

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 insomnia-associated serotonin 5-HT<sub>2</sub> receptors as well.<sup>22,23</sup> Long term use may be accompanied by antihistamine-induced increases in appetite and subsequent weight gain.

Agomelatine is a newer antidepressant, which at therapeutic doses (25-50 mg), improves disturbed sleep-wake cycles by stimulating melatonin (MT) 1 and MT 2 receptors and antagonising 5 HT<sub>2C</sub> receptors. It is therefore potentially invaluable in insomniacs who have major depressive disorder.<sup>24,25</sup> It may be associated with clinically relevant hepatotoxicity and transaminases should be monitored periodically during treatment.<sup>26,27</sup>

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-lives, they may cause daytime sedation. Additional antimuscarinic side effects include decreased cognitive function, delirium, dry mouth, blurred vision, urinary retention, constipation and increased intraocular pressure.<sup>28</sup>

### Others and elsewhere

Melatonin shows small benefits in promoting sleep onset as well as total sleep time, although the evidence for this is difficult to interpret due 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 South Africa and the UK, and is particularly useful in those aged 55 or above, and as a short term measure.<sup>29</sup>

Ramelteon, a melatonin (MT1/MT2) receptor agonist that 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.<sup>30</sup>

Suvorexant, a dual orexin receptor antagonist that 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.<sup>31</sup> 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.<sup>32</sup>

### Conclusion

Insomnia disorder is by definition exhausting. Precipitants should be roused and removed where possible, and furtive comorbid illnesses, such as anxiety and major depressive disorders, uncovered and treated. Approved short term hypnotic medications may help those with acute insomnia, which often results from defined stressors. Conversely, CBT is the recommended first-line therapy for those burdened with chronic insomnia disorder, where lack of sleep impacts heavily on daytime functioning and on physical, psychiatric and emotional health. Additional long-term pharmacotherapy may be considered for patients whose insomnia disorder is unresponsive to psychological approaches.

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