



# Insomnia

## *Diagnosis and management*

**BACKGROUND** Insomnia is a complaint of perceived poor sleep quality resulting in impairment of daytime function. It is the commonest clinical sleep disorder with approximately 6-12% of adults complaining of chronic insomnia.

**OBJECTIVE** To review current knowledge on causes and effects of insomnia and to provide a brief evidence based review of management options for the family practitioner.

**DISCUSSION** Patients with insomnia are characterised by excessive arousal and an inability to sleep despite reported reduced sleep hours and poor sleep quality. Current management approaches are focussed on reducing this 'hyperarousal' and its behavioural manifestations by a range of behavioural treatments. Good evidence exists for the efficacy of hypnotics for short term insomnia but long term data is currently lacking. Nonbenzodiazepine hypnotics (zopiclone, zolpidem) have less adverse effects and similar efficacy to benzodiazepines.

The study of human sleep over the past 50 years has revealed a wide range of sleep disorders with significant implications for public health. Insomnia is the commonest sleep disorder and a significant health problem with major effects on quality of life, work productivity and mental health.

Insomnia is a complaint of poor quality sleep that is often associated with daytime sequelae including:

- fatigue
- irritability
- decreased memory and concentration, and
- pervasive malaise

all of which affect many aspects of daytime functioning.<sup>1</sup> There are often significant differences between what people perceive and report about their sleep and what is measured objectively (eg. by electroencephalogram [EEG] monitoring). Insomnia is not short sleep or voluntary sleep deprivation but an impairment in perceived sleep quality. Insomnia can be classified by frequency, duration or intensity, or is typically defined as either primary and secondary (Table 1).

Primary insomnia involves a predominant complaint of difficulty initiating or maintaining sleep or nonrestorative sleep for at least one month. The sleep disturbance has to cause clinically significant problems in social, occupation or other important areas of functioning. Sleep disturbance secondary to other specific sleep disorders (eg. sleep apnoea, restless legs) is excluded as is insomnia occurring exclusively during the course of a mental disorder such as a major depressive disorder or generalised anxiety disorder. Other causes of secondary insomnia include those related to medications or substance abuse. Among the commonest causes of insomnia are those related to other medical conditions such as chronic pain states or organ system failure.<sup>2</sup> Finally, some insomnias (sleep phase syndromes) involve inability to sleep at normal times but are not present if sleep is commenced either earlier or later than the usual late evening times.

### **Clinical epidemiology**

The measurement of insomnia is usually undertaken by questionnaire survey. From these types of research, the overall prevalence of insomnia is

**Ron Grunstein**



*Ron Grunstein, MBBS, MD, PhD, FRACP, is Associate Professor and Head, Sleep Research Group, Institute of Respiratory Medicine, University of Sydney, and Head, Centre for Respiratory Failure and Sleep Disorders, Royal Prince Alfred Hospital, New South Wales.*

**Table 1. Causes of insomnia**

**Primary insomnia**

Behavioural conditioning and behaviours impairing sleep

**Secondary insomnia**

Use of substances such as caffeine, nicotine or alcohol

Sleep-breathing disorders (especially in women)

Periodic limb movement disorder/restless legs syndrome

Panic attacks or recurrent nightmares during sleep

Post-traumatic stress disorder

Psychiatric disorders: mood or anxiety disorders acute or chronic stress (eg. bereavement)

Sleep phase disorders: shift work, jet lag

Concurrent medical conditions or their treatment, including any form of pain, drug intoxication or withdrawal, thyrotoxicosis, chronic end organ failure of any cause, gastric ulcer, prostate, perimenopausal symptomatology, stroke, neurodegenerative disorders, Parkinson disease, epilepsy

Prescription drugs: beta blockers, theophylline, stimulants, decongestants, thyroid hormones corticosteroids, SSRIs, MAOI drugs and phenytoin

approximately 30% with a male to female ratio of 1.3 to 1.0 in subjects aged 40 years or older.<sup>1,3,4</sup> Insomnia is also more common in the elderly, unemployed, minority and lower socioeconomic groups. Approximately one-third of patients complain of severe symptoms.<sup>5</sup> Insomnia is the most commonly reported sleep problem in industrialised nations worldwide.<sup>6</sup> Approximately 20% of patients complaining of insomnia have a co-existing well defined implantable cardioverter-defibrillator metal disorder, usually a depressive disorder or generalised anxiety. Most patients suffering from insomnia do not necessarily complain of disordered sleep but accompanying symptoms such as fatigue or daytime sleepiness. More than half of those who believe they have chronic insomnia have never discussed their problem with a medical practitioner.<sup>7</sup>

**Insomnia symptoms and daytime functioning**

Patients with insomnia tend to perform worse on tests of psychomotor performance task than those without insomnia. They also exhibit more fatigue. Despite complaining of daytime sleepiness, patients with insomnia do not have a measurable increased propensity to fall asleep during the day compared to those without insomnia.<sup>6,8</sup> This may

seem unexpected that patients with insomnia cannot fall asleep despite feeling sleepy. In effect, these patients do not fall asleep because there are excessive levels of arousal ('hyperarousal state'). This hyperarousal state is supported by elevated levels of autonomic and cerebral arousal markers such as EEG, heart rate, catecholamines, resting metabolic rate, autonomic activity and certain neuroendocrine parameters.<sup>6,8</sup>

Insomnia is both a common symptom and a syndrome, with a variable course over time. Insomnia tends to be persistent or recurrent in both clinical and community samples.<sup>9</sup> Persistent insomnia is both a risk factor for, and a precursor of, mood disorders.<sup>10,11</sup> For example, in one large population survey, persisting insomnia over one year was associated with 40-fold increase in developing new major depression.<sup>10</sup> Chronic insomnia is also associated with a higher risk of automobile accidents, greater health care utilisation, increased alcohol consumption and daytime sleepiness.<sup>11</sup> Therefore, patients with insomnia merit serious attention and effective treatment of insomnia may potentially represent an opportunity to prevent major depression.

**Management**

It is best to consider insomnia as a symptom rather than a diagnosis in the initial assessment of the patient. In this way, underlying causes of insomnia (eg. restless legs syndrome, sleep apnoea, depression, heart failure) can be assessed.

**Behavioural therapies**

Behavioural interventions seek to change maladaptive sleep habits, reduce autonomic arousal, and alter dysfunctional beliefs and attitudes that are presumed to maintain insomnia. These therapies have been shown to produce reliable and durable improvements for patients with chronic primary insomnia.<sup>11</sup>

**Relaxation therapy**

Relaxation therapy is based on observations that patients often display high levels of physiologic, cognitive and/or emotional arousal both at night and during the day. Progressive muscle relaxation aims at reducing somatic arousal whereas attention focussing techniques (imagery training, meditation) are intended to lower presleep cognitive

arousal. Relaxation therapy is useful for both sleep onset and maintenance insomnia but diligent daily practise over a period of 2-4 weeks is necessary to achieve clinical benefits.<sup>12,13</sup>

### Sleep restriction therapy

Sleep restriction therapy consists of curtailing the amount of time spent in bed to increase the percentage of time asleep.<sup>14</sup> This approach is based on the view that poor sleepers often increase their time in bed in a misguided effort to provide more opportunity for sleep, actually resulting in fragmented and poor quality sleep. Sleep restriction therapy begins by inducing a mild sleep loss to increase an individual's ability to fall asleep and stay asleep. Bedtime is delayed according to the sleep log over the preceeding two week period, and then set 15-30 minutes earlier per week. The wake up time remains unchanged. Time in bed should not be reduced to less than five hours. The goal is promoting rapid sleep onset and maintaining a sleep efficiency of 85%. The process requires approximately 4-6 weeks to be completed.

### Stimulus control therapy

Stimulus control therapy is based on the premise that insomnia is a conditioned response to temporal (bedtime) and environmental (bed/bedroom) cues associated with sleep.<sup>15</sup> The main objective of stimulus control therapy is to reassociate the bed and bedroom with rapid sleep onset. Instructions involve:

- going to bed only when sleepy
- using the bed and bedroom only for sleep
- getting out of bed and going into another room when unable to fall asleep or return to sleep easily, and returning to bed only when sleepy again
- maintaining a regular rise time in the morning regardless of sleep duration the previous night, and
- avoiding daytime napping.

Stimulus control is useful for both sleep onset and maintenance insomnia.

### Cognitive therapy

Cognitive therapy involves identifying dysfunctional beliefs and attitudes about sleep and replacing them with more adaptive substitutes.<sup>9,11,16</sup> For example, some patients have unrealistic expect-

**Table 2. Sleep hygiene tips<sup>18</sup>**

- > **A**void caffeine, nicotine, alcohol and late night exercise
- > **S**et aside time in the evening away from the bedroom to go through current problems and next days commitments - so called 'worry time'
- > **L**imit bed to sleep and sex - avoid reading, radio, TV
- > **E**xercise in the early morning sunlight to strengthen normal sleep circadian rhythms
- > **A**void sleeping in or napping
- > **P**lan for bedtime – eat a small snack, have a warm bath

tations about their sleep needs, eg. 'I must get eight hours of sleep every night', or they entertain excessive concerns about insomnia and its potential consequences, eg. 'Insomnia is always dangerous to health' or 'I am unable to function after a poor night of sleep'. The goal of cognitive therapy is to provide some reassurance to patients by informing them that sleeping less than eight hours a night is not necessarily unhealthy and does not always lead to dramatic consequences the next day. This verbal intervention may be enough to reduce the fear of insomnia, which in itself is instrumental in producing a chain reaction of sleep difficulties, fear of insomnia and its consequences, and further sleep disturbances.<sup>17</sup>

Educational efforts are always recommended, including advice on better sleep hygiene (Table 2).<sup>18</sup> In some centres, excellent outcomes have been achieved with community based nurse practitioner sleep education groups.<sup>11</sup>

Meta-analytic reviews of studies of behavioral therapies provide consistent data on the perceived efficacy of these techniques.<sup>11</sup> Importantly, different behavioural methods are not incompatible with each other, or with pharmacotherapy, and can be combined successfully. In clinical practice, it is often preferable to proceed in a sequential fashion and introduce different treatment methods according to the most important perpetuating factors of insomnia. For instance, sleep restriction is particularly useful when there is evidence of excessive amounts of time spent in bed; stimulus control therapy is indicated with patients who have irregular sleep-wake schedules and who have engaged in sleep incompatible activities. Relaxation procedures are particularly suited for individuals with tension and anxiety. Finally, when there is evidence of faulty beliefs and attitudes about sleep

and insomnia, cognitive restructuring therapy is helpful to alleviate the underlying apprehensions and anxiety.

### Pharmacological treatments

A great number of pharmacological agents (including opiates) have been used over time to promote or restore sleep. Today, the benzodiazepines and benzodiazepine-like hypnotics including zolpidem, zopiclone and zaleplon, are considered the drugs of choice for symptomatic relief of insomnia because of their safety and effectiveness.<sup>7,8</sup> These drugs target the GABA receptor and its specific subunits with variable binding. Other nonhypnotic medications such as antidepressants and antihistamines are sometimes prescribed for their sedative properties. Nonprescription agents, including herbal preparations and melatonin are widely used as self medication.<sup>8,9</sup>

### Benzodiazepines

All benzodiazepines exert five major actions:

- hypnotic
- anxiolytic
- anticonvulsant
- myorelaxant, and
- amnesic.

Depending on their predominant clinical activity, benzodiazepines are categorised as:

- hypnotics
- anxiolytics
- anticonvulsants, and
- myorelaxants.

In this article, only hypnotic benzodiazepines will be considered.

Benzodiazepines (BZDs) are the most common prescribed medication for insomnia in Australia. Temazepam is the most frequently prescribed. Benzodiazepines decrease the time to sleep onset (sleep latency), increase total sleep time and sleep continuity.<sup>19</sup> Benzodiazepines disturb sleep architecture by: decreasing stage 1 nonrapid eye movement (NREM) sleep, increasing stage 2 NREM sleep (which accounts for most of the increased sleep time), and reducing the duration of NREM stage 4 sleep and rapid eye movement (REM) sleep.<sup>9,20</sup> The onset of the first REM sleep episode is delayed and dreaming is diminished. The use of BZDs is accompanied by adverse effects that are dose dependent and related to the

pharmacokinetic properties of the agent.<sup>19,20</sup> Tolerance to the hypnotic effects of BZDs is an important issue. Benzodiazepines are initially very effective in inducing and prolonging sleep. However, tolerance to the hypnotic effects develops rapidly on repeated administration. Dose escalation may result with subsequently greater performance impairment and increased risk of physiologic dependence.<sup>19,20</sup> The efficacy of temazepam is maintained for up to one month of continuous use.

Benzodiazepines are indicated in the short term management of insomnia.<sup>7-9</sup> These compounds have all been shown to be effective in inducing, maintaining and consolidating sleep as compared with placebo. Rebound insomnia is characterised by a worsening of sleep relative to baseline. It occurs with BZD use and is more marked when the drug has been taken regularly for long periods, although it may occur after only one week of low dose administration. Benzodiazepine hypnotics often give rise to hangover effects. Even short acting BZDs may impair psychomotor performance and memory the next day. Residual effects are most likely to occur with slowly eliminated BZDs and in the elderly. Dependence on BZDs hypnotics may develop if the drugs are taken regularly for several weeks.<sup>19,20</sup>

### Zopiclone

Zopiclone is a cyclopyrrolone that exhibits some anticonvulsant, myorelaxant and antianxiety activities in addition to being a potent sedative-hypnotic agent. Oral zopiclone is rapidly absorbed (95% within 60 minutes) and its elimination half life is five hours, increasing with age up to approximately eight hours in subjects 80 years or older.<sup>21</sup> Zopiclone 7.5 mg at bedtime (usual recommended dose) decreases the sleep latency compared with placebo in patients with insomnia, and decreases the number of nocturnal awakenings. It generally increases the total sleep duration. Zopiclone does not change sleep architecture to any significant extent. Zopiclone appears to produce minimal impairment of daytime performance, short term memory and long term memory in comparison with the benzodiazepines. Some rebound insomnia on withdrawal has been reported but not to the extent of BZDs.<sup>21</sup>

## Zolpidem

Zolpidem is the most commonly prescribed hypnotic in the United States and Europe. It is a imidazopyridine derivative with specificity to the GABA<sub>A</sub> receptor, BZ<sub>1</sub> subunit. Its half life is shorter than temzepam and zopiclone.<sup>21</sup> In practical terms, this means that while zolpidem shares a similar hypnotic efficacy to BZDs, adverse effects are fewer. Zolpidem does not alter sleep architecture and is not associated with significant hangover effects, tolerance or rebound insomnia. It is one of the most widely tested drugs in patients with insomnia and currently there is emerging evidence of its efficacy in chronic insomnia, particularly with intermittent administration.<sup>22</sup> However, there are very few direct comparison studies between zolpidem 10 mg and the most commonly used hypnotic in Australia, temazepam 10 mg. At the present time, zolpidem is also more expensive and not subsidised by the Pharmaceutical Benefits Scheme.

## Antidepressants

Antidepressants with sedative effects are prescribed to avert the side effects of BZDs (ie. dependence, rebound insomnia). Amitriptyline and doxepin are prescribed as hypnotics in lower doses than those used in depression. In general, antidepressants improve sleep continuity and increase total sleep time and NREM sleep. In addition to their other side effects, antidepressants can exacerbate periodic limb movements. Most selective serotonin reuptake inhibitor (SSRI) agents will exacerbate insomnia in the first 2-4 weeks of use. There is only limited data on the use of antidepressants in patients with insomnia with milder forms of depression.<sup>8,9</sup>

## Antihistamines

Antihistamines are generally less effective than BZDs and induce significant daytime drowsiness and anticholinergic effects. Despite their over-the-counter availability, there is limited evidence of their value over placebo and clear evidence of side effects.<sup>9</sup>

## Nonprescription medication

Herbal preparations (eg. Valerian) are commonly used although no evidence of a clear efficacy is available. Melatonin is a popular dietary supplement which has not demonstrated efficacy in primary insomnia.<sup>9</sup>

## Conclusion

Although classification of insomnia into primary and secondary causes may be useful, it is still unclear why some patients with chronic disease develop insomnia and others do not. Such patients still have a problem and are appropriately managed with the same approaches as primary insomnia. Similarly, insomnia sometimes persists despite effective antidepressant therapy in depression. Basic health recommendations including specific sleep hygiene and regular exercise have positive effects on sleep.<sup>23</sup>

There is a clear role for hypnotic medications in acute situational insomnia, eg. following a sudden bereavement. The exact role for pharmacotherapy relative to behavioural treatments in the management of chronic insomnia is unclear. There is reasonable evidence that improved outcomes at one year occur with the use of behavioural therapy, however, similar studies for hypnotic therapy over that time period are limited. The approach to these patients should consist of sleep education, behavioural strategies and if necessary, intermittent use of a hypnotic. Although commonly practised, there is no evidence of benefit for long term every night use of hypnotics. Emerging data on long term intermittent use of hypnotics will be helpful in delineating the use of these drugs in patients with chronic insomnia.

### SUMMARY OF IMPORTANT POINTS

- Insomnia is very common.
- Insomnia is a complaint with heightened autonomic and cerebral arousal during sleeping hours.
- Patients with insomnia have impaired subjective and objective daytime performance.
- Behavioural treatments for insomnia are effective long term.
- Hypnotic treatments are effective in the short term and should be combined with behavioural treatments.

Conflict of interest: Dr Grunstein serves on the medical advisory board of Sanofi-Synthelabo Australia, manufacturer of zolpidem.

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### REPRINT REQUESTS

Ron Grunstein  
 Sleep Investigation Centre  
 E11, Royal Prince Alfred Hospital  
 Missenden Road  
 Camperdown, NSW 2050  
 Email: rrg@mail.med.usyd.edu.au