Managing insomnia in the primary care setting

This is a common condition.

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Primary insomnia is a common condition, occurring at a rate of approximately 10% in its chronic form in the general population.[1] It often starts with a specific problem, such as loss of a job, or a change in sleep patterns, e.g. with childbirth. It is often co-morbid with other psychiatric disturbances where the insomnia predates the other psychiatric symptoms.[2] Advancing age is associated with reduced amount of sleep, reduced sleep efficiency and more awakenings. Women are twice as likely to develop insomnia as men. The condition becomes chronic when perpetuated by the following factors: anxiety about sleep, maladaptive sleep habits, underlying vulnerability in sleep-regulating mechanisms and persistence of the precipitant stressor.[2]

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Diagnosing insomnia

Primary insomnia refers to a sleep disturbance that is not associated with a causative underlying condition. The ICD-10 diagnostic criteria for insomnia are listed in Table 1. Diagnosing insomnia requires a thorough sleep, medical, drug, alcohol, substance and psychiatric history.[1,3] The sleep history has to identify factors that precipitated the insomnia, current life stressors, a description of a typical 24-hour period of sleep behaviour, which strategies have been tried to correct the sleep disturbance and to what extent such strategies were successful.[1] Most clinicians consider >30 minutes to fall asleep and/or ≥30 minutes of wakefulness after sleep onset and total sleep time of <6.5 hours per night to represent the threshold between normal and abnormal sleep.[1] The detrimental effects of insomnia include: reduced quality of life, subjectively impaired cognitive performance, decreased ability to handle minor irritations and to enjoy family and social life, an increase in risk for a first episode of or relapse in depression, increased risk for substance abuse, hypertension, absenteeism, chronic feelings of over-arousal, road traffic accidents and activation of the hypothalamic-pituitary axis.[1,2] Commonly prescribed drugs that cause insomnia are listed in Table 2.

Table 1. ICD-10 diagnostic criteria for non-organic insomnia

- The complaint is either: difficulty falling asleep, maintaining sleep, or poor quality sleep
- The sleep disturbance has occurred at least three times per week for at least one month
- There is preoccupation with the sleeplessness and excessive concern over its consequences at night and during the day
- The unsatisfactory quantity and/or quality of sleep either causes marked distress or interferes with ordinary activities in daily living

Table 2. Drugs that cause insomnia

- Alcohol
- Anticonvulsants
- Bronchodilators
- Caffeine
- Cocaine
- Oestrogen
- Levodopa
- Monoamine oxidase inhibitors
- Ritalin
- SSRIs
- Steroids
- Sympathomimetics
- Thyroid hormone
- Theophylline
- Zolpidem and zopliclone (withdrawal syndrome in chronic use)

Differential diagnoses

Secondary insomnia differs from primary insomnia in that a specific condition can be identified as the cause of the sleep problem. Diagnostic tests for sleep disorders include oximetry and polysomnography. They are useful in detecting causes of secondary insomnia. Circadian rhythm disorder is a common condition manifested as misalignment between the sleep period and the physical/social 24-hour environmental cycle.[4] Delayed sleep phase (typical in adolescents) and advanced sleep phase (frequent in the elderly) are the two most prevalent circadian rhythm sleep disorders.[4] Others include jet lag and shift work disorder. Parasomnias are unusual episodes or behaviours that occur during sleep and disturb the patient or others. They include non-REM and REM disorders. Non-REM disorders include night terrors and sleepwalking. Night terrors are the abrupt awakening from deep non-REM sleep, usually during the first third of the night, often with a scream or signs of intense fear. Patients are unresponsive to comforting, difficult to wake, appear confused and have no recall of the experience. It is common in children but also occurs in adults and has a strong genetic component.[2] Sleepwalking often occurs in addition to night terrors where patients perform highly familiar behaviours such as walking or dressing and are difficult to wake. REM disorders include nightmares and REM sleep behaviour disorder (RBD). Unlike non-REM disorders, patients with nightmares can be woken and can recall the experience. They are common in children and reassurance about safety is paramount.

RBD presents as a lack of atonia during REM sleep and an increased vividness of dreams.[2] Narcolepsy is characterised by excessive daytime sleepiness, an irresistible desire to fall asleep and the feeling of being refreshed after daytime sleep.[3] Symptoms occurring in the early evening when the patient is lying in bed or at sleep onset may suggest a diagnosis of restless leg syndrome (RLS).[3] Repeated awakenings throughout the night, snoring and cessation of breathing during sleep may suggest a diagnosis of obstructive sleep apnoea syndrome (OSAS).[3]

Sleep-wake function

Two separate systems maintain sleep and wakefulness respectively. Projections from the brainstem to the thalamus and forebrain using noradrenalin, serotonin, acetylcholine, dopamine and the histamines maintain arousal.[2] The promotion of sleep is initiated by GABA, adenosine, melatonin and the circadian pacemaker. Benzodiazepines target the GABA A receptor. Adenosine acts at the adenosine A_2 receptor. Adenosine levels rise during the day and peak levels are associated with sleepiness. Caffeine causes insomnia by blocking this mechanism.[2] Melatonin is a hormone secreted from the pineal gland and regulates circadian rhythm. The circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus and drives melatonin synthesis.[2]

Treatment for insomnia

Insomnia that creates significant distress, with daytime symptoms, warrants intervention. Before initiating treatment, ensure good sleep hygiene practices (Table 3). Ensure that other psychiatric disorders are adequately treated and medications causing insomnia have been excluded. Typical exclusions for initiating insomnia treatment include untreated or unstable medical, psychiatric or substance abuse conditions.[1] For the majority of patients with acute insomnia spontaneous recovery does indeed occur. However, acute episodes that last 2 - 4 weeks may develop into chronic insomnia. Therefore, early intervention is warranted.[1] Referral to a sleep specialist with failure of two treatment trials and/or diagnostic tests are required.

Table 3. Sleep hygiene tips

- Have a warm bath and quiet time before going to bed
- Maintain a regular sleep routine
- Avoid naps if possible
- Don't stay in bed awake for more than 10 minutes
- Don't watch television or read in bed
- Do not drink caffeine inappropriately
- Avoid substances that interfere with sleep (cigarettes, alcohol)
- Avoid rigorous exercise before bed-time
- Have a quiet, comfortable bedroom
- Do not clock-watch

Medication

The selective benzodiazepine receptor agonists (BZRAs), zopiclone and zolpidem, are chemically similar to the benzodiazepines and were developed as hypnotic agents with a shorter half-life to avoid a hangover effect. Zopiclone, prescribed at a dose of 7.5 mg, has a longer half-life of approximately 6 hours and is useful for patients who wake throughout the night. Zolpidem, prescribed at a dose of 10 mg, is useful for sleep-onset difficulties. Initiation of a hypnotic effect is approximately 20 minutes; therefore BZRAs must be taken when already in bed to avoid amnesia and motor effects. There are many benzodiazepines available; lorazepam 1 - 2 mg (half-life 10 - 20 hours) and oxazepam 10 -15 mg (half-life 6 hours) are potential options. Tolerance and dependence with long-term benzodiazepine use is well established but is more controversial with the BZRAs. The original consensus was that they should be used for a limited period of 2 - 3 weeks based on the original trials conducted over this limited time period.[2] In reality, many patients are on chronic treatment. Tolerance does not seem to be a significant problem and many patients use the same dose for months and still report these medications to be effective.[2] However, chronic use may be associated with adaptive changes in receptors and a withdrawal syndrome occurs that includes the following symptoms: agitation, prolonged sleep-onset latency, headache, irritability, hypersensitivity to stimuli, nausea, vomiting and depersonalisation.[2] Many patients develop a psychological dependence and are unwilling to stop treatment. To avoid the development of dependence, strategies include not administering the drug every night from the beginning of treatment or periodic attempts at tapering and discontinuing medication and the co-administration of cognitive behavioural therapy techniques.[2]

Sedating antidepressants are a good option for the long-term maintenance treatment of insomnia, even in the absence of a major depressive disorder, and there are no restrictions on duration of use. The selective serotonin re-uptake inhibitors (SSRIs) disrupt sleep, except for paroxetine in those over the age of 55 years. Trazodone at a minimum dose of 50 mg may be beneficial for insomnia; side-effects include sedation and postural hypotension. Mirtazepine (15 - 45 mg) and mianserin (30 - 90 mg) are also useful as sedating antidepressants. Both are associated with weight gain and sedation. Mianserin carries a risk of neutropenia and requires measurement of the white cell count (WCC) before initiation. Low-dose amitriptyline (10 mg or 25 mg) has a long record of successful use but is contraindicated in suicidal patients or in those with cardiac risk factors. SSRIs and tricyclic antidepressants should not be used simultaneously (unless initiated and carefully monitored, preferably by a specialist) as SSRIs inhibit tricyclic metabolism which can lead to toxic levels of the latter. Antidepressants should be prescribed at therapeutic doses when insomnia coexists with a mood disorder.

Primary insomnia refers to a sleep disturbance that occurs without any specific underlying condition that causes the insomnia.

Other medications

Over-the-counter medications include antihistamine compounds such as diphenhydramine and doxylamine. These are only suitable for short-term use and are minimally effective. Melatonin is

particularly beneficial in patients over the age of 55 years and is available as 3 - 5 mg tablets without prescription, although the actual amount required is probably 0.5 mg. It should be taken one hour before bedtime or at bedtime. It has the benefit of no memory or motor effects in addition to improved daytime outcomes. However, research on its long-term effects is not available. It increases the risk of blood clotting and should not be used with warfarin. It reduces the effectiveness of antihypertensives and should be avoided in depressed patients. The antipsychotics olanzapine and quetiapine have beneficial sedating qualities but their side-effect profile of weight gain, diabetes and lipid abnormalities make them unsuitable for use in insomnia. The antihistamines only block one of the arousal systems and are therefore largely ineffectual.

Cognitive-behavioural therapy (CBT)

CBT has shown good efficacy, requires approximately six sessions and focuses on sleep-interfering behaviour, sleep hygiene, reduction of hyper-arousal features and improvement of circadian rhythm with sleep scheduling and partial sleep deprivation. An assessment for CBT includes a detailed history of sleep, a medical and mental health history, and placing an emphasis on factors that contribute to the initiation and maintenance of insomnia. The patient is requested to keep a sleep diary to document time to bed, time out of bed, minutes to fall asleep (latency) and minutes awake during time in bed. The order of treatment interventions includes sleep education, stimulus control therapy, sleep restriction and relaxation training.[5]

Patients often feel that staying in bed when awake is beneficial, but it ultimately creates conditioned arousal. The belief that extending sleep opportunity to improve insomnia often results in more frequent and longer awakenings. Stimulus control therapy addresses incorrect assumptions (Table 4).[5]

Sleep restriction therapy requires estimation of a sleep average over a 2-week period by calculating the number of hours of sleep an individual gets per night. A fixed wake time is established and a sleep window is calculated to which 30 minutes is added. A sleep diary is recorded and the sleep window is adjusted by 30 minutes as sleep efficiency improves. For example, if a patient sleeps six hours per night and sets a waking time of 06h00, they go to bed at 23h30. As sleep efficiency improves, they add an additional 30 minutes to the bedtime, which then becomes 23h00.[5]

Table 4. Stimulus control therapy

- Keep an alarm for a fixed daily wake time
- Do not nap during the day
- Keep the bed/bedroom for sleep/sexual activity
- Lie down to sleep only when sleepy
- Leave bedroom if awake for more than 15 minutes
- Return to bed only when sleepy
- No clock-watching
- Use the bed/bedroom as a strong cue for sleep

Insomnia in children and adolescents

Paediatric insomnia is a widespread problem, ranging from 1% to 6% in the general population and from 50% to 75% in children with neurodevelopmental or psychiatric co-morbidities.[6] The negative consequences of sleeplessness include hyperactivity, irritability, restlessness, poor concentration, impulsiveness, suicide risk and poor memory. Families of children with sleep disturbances also suffer, exhibiting negative effects on daytime function and well-being, as well as elevated levels of family stress.[6] A useful definition is repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family. This includes children with behavioural insomnia and those with insomnia that persists despite proper sleep hygiene. Good sleep practices (avoiding caffeinated beverages, age-appropriate sleep/wake schedules, and limit setting regarding practices such as late night television viewing) and behavioural strategies should be the first line of treatment.[6]

The three most important principles for treating bedtime resistance in young children are: creating an emotional state of calmness and safety, consistent limit setting and establishing good habits.[5] Bedtime habits include a wind-down period and a sequence of activities that begins 30 - 60 minutes before bedtime. If a child continues to test limits and does not respond to strategies to reward desirable behaviours, it may become necessary to set consequences for the undesirable behaviours, e.g. the removal of privileges. However, this can still be done within a positive framework to avoid the escalating emotional arousals of screaming and flaring tempers.[5] Pre-sleep onset worries and ruminative thinking at bedtime are a major source of difficulty. The treatment principles include: helping the child to feel emotionally and physically safe, addressing the worries and establishing a regular bedtime routine. For adolescents, multiple sleep-interfering factors (e.g. cell phones and the internet) may need to be addressed. The adolescent with difficulty waking up for school may be symptomatic of biological changes in the circadian system at puberty which shift sleep-timing preferences in the direction of the delayed sleep phase. Treatment requires gradual (15 min/day) alignment of the sleep system to the desired schedule and then to maintain that alignment. Avoid any daytime naps and be consistent during weekends and holidays.[5]

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One of the most contentious issues in the domain of treating sleep problems in children and adolescents is the use of medication to promote sleep onset.[7] There are large numbers of medications prescribed by clinicians including alpha agonists, antidepressants, atypical antipsychotics and antihistamines. There is an absence of any empirical data on risks

or benefits for most of these medications. Weiss *et al*. recommend combined sleep hygiene and melatonin as a safe and effective treatment for initial insomnia in children with ADHD taking stimulant medication.[8] Short-term side-effects of melatonin in children are minimal but little is known of the potential long-term effects, particularly on the endocrine system. It should therefore be used cautiously in this age group.

Conclusion

In adults, for the short-term treatment of insomnia where there is a precipitant stressor, use a short course of hypnotics such as zolpidem or zopiclone or a benzodiazepine. If the insomnia persists, consider melatonin in those over age 55 years, non-nightly dosing of the BZRAs and/or CBT. Further treatment may include the use of an antidepressant. Continued failure of treatment suggests that referral to a specialist may be appropriate. For children and adolescents, behavioural intervention is the treatment of choice.

References available at: www.cmej.org.za

IN A NUTSHELL

- Insomnia is common and often chronic.
- Insomnia often starts with a specific problem.
- Insomnia is often co-morbid with other psychiatric problems.
- Diagnosing insomnia includes a thorough sleep, medical, drug, alcohol, substance and psychiatric history.
- Many commonly prescribed drugs cause insomnia.
- Before initiating treatment, ensure good sleep hygiene practices and that other psychiatric disorders have been adequately treated.
- Early intervention is important.
- Medication options include BZRAs and benzodiazepines in the short term and anti-depressants, melatonin or non-nightly dosing of BZRAs in the longer term.
- CBT is a highly effective treatment for insomnia.
- Behavioural intervention remains the treatment of choice in paediatric insomnia.

SINGLE SUTURE

Blood tests won't stop gene cheats

Athletes trying to cheat by loading their bodies with genes that make muscles bigger and more efficient could be caught if forced to supply muscle biopsies, but not through the analysis of urine or blood samples.

So says Mauro Giacca of theInternational Centre for Genetic Engineering and Biotechnology in Trieste, Italy, who was asked by the World Anti-Doping Agency to look into how to screen for gene doping.

To do so, Giacca's team created mice loaded with extra copies of the muscle-boosting gene *IGF-1*, which codes for the protein insulin-like growth factor 1, by injecting their limbs with a virus that implants *IGF-1* into muscle cells. They then tested the animals' endurance by recording how long they could swim before exhaustion. The doped mice swam for three times as long as mice that received the virus but not *IGF-1*.

Autopsies showed that the extra *IGF-1* triggered the production of 10 times more protein than normal in the muscles. Giacca also saw activity soar in genes controlling energy production, contraction of muscles and respiration. Also detectable in the muscle were traces of the virus used to deliver the genes. However, the gene, protein and virus were undetectable in blood or urine from the mice.

Giacca doubts it is possible to achieve such results through exercise alone. So 'from a muscle biopsy, it would be possible to distinguish a well-trained athlete from one who'd been gene-doping for a month,' he says.

'It may be possible to look for unusual changes in gene profiles, but if this relies on muscle biopsies it won't happen,' says Lee Sweeney, of the University of Pennsylvania in Philadelphia, who created the world's first *IGF-1* 'supermice' in 2004.

Giacca doubts whether athletes will attempt gene doping in the run-up to this year's Olympic games, because it is technically challenging, but he says they may in the future – most likely through an illegal government programme.

He is now working on a study to identify, in blood and urine, raised levels of micro RNA related to gene doping.

Macedo A et al. Human Gene Therapy [doi: 10.1089/hum.2011.157]
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