Differential diagnoses and management of Insomnia

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Highlights / Hoogte Punte

Insomnia is the most common sleep-related complaint, and the second most common overall complaint (after pain) reported in primary care settings.[9] It affects 35% of the general population during the course of a year but, despite its high prevalence, 69% of patients suffering from sleep disorders never report it to healthcare providers.[6] The advent of the newer nonbenzodiazepine hypnotics has also led to an increased awareness of insomnia, and its treatment alternatives. *(SA Fam Pract 2003;45(1):40-47)*

EPIDEMIOLOGY OF INSOMNIA:

Because a definition for "normal" sleep is not well-established, the estimates of the prevalence and severity of insomnia vary widely, but it affects approximately one third of adult Americans during the course of a year.[2] The prevalence of insomnia increases with age and is more common among females, women in minority groups, the unemployed and those with medical or psychiatric disorders.[3] It is also associated with lower socio-economic status and lower educational levels. Depending on the diagnostic criteria, insomnia has a prevalence of between 10% and 69% in the primary care setting.[4] Comorbid psychiatric disorders are reported in 40.4% of insomniacs and the risk of developing comorbid alcohol dependence is also increased.[5,6] Insomnia is associated with significantly greater functional impairment, diminished capacity to solve problems, higher work absenteeism, more frequent use of general medical service, and poorer overall health. Sufferers have a higher risk of developing emotional difficulties, decreased enjoyment of interpersonal relationships, and decreased sense of wellbeing.[6,7] Daytime somnolence is associated with significant morbidity and mortality and causes impaired learning and cognition.[8]

A US-based study examining the performance of general practitioners managing elderly patients with insomnia reported that 53% of physicians neglected to elicit any sleep history. After asking an average of only 2.5 questions, 46% of these practitioners identified a prescription medication as the best therapy.[6] Research in Canada showed that women and elderly patients were more likely to receive a benzodiazepine, and that physicians who spent less time per patient were also more likely to prescribe benzodiazepines. This data suggest a need for training in treatment alternatives for insomnia.[3]

Age has a considerable effect on sleep duration and architecture. The need for sleep is not decreased during old age, but rather the ability to sleep. The elderly nap more frequently during the day, and experience more daytime sleepiness. Their sleep continuity is also disturbed, with almost no slow wave sleep and an increase in brief arousals fragmenting their sleep.[1]

DEFINITIONS OF INSOMNIA:

Insomnia, as classified in the DSM-IV, is associated with complaints about the quantity, quality or timing of sleep occurring at least 3 times a week for at least 1 month. The American National Heart, Lung, and Blood Institute Working Group on Insomnia defines insomnia as an experience of inadequate or poor-quality sleep characterised by a difficulty in falling asleep, difficulty maintaining sleep, waking up too early in the morning, or experiencing unrefreshing sleep.

The words "complaints", and "experience" should be emphasised here, because there are often significant differences between what people perceive and report about their sleep and what is measured objectively. The symptoms of insomnia may include daytime consequences such as tiredness, lack of energy, difficulty concentrating and irritability. Insomnia can be a symptom of an underlying medical, psychiatric, sleep or circadian disorder, or a disorder in itself.

Evaluation of a patient complaining of Insomnia:

An adequate sleep history, including sleep and wakefulness patterns, history from the bed partner, family history, and current and previous medications, should be obtained before a diagnosis of insomnia is made and treatment is considered.

DIFFERENTIAL DIAGNOSIS:

Several sleep disorder classifications exist. The disorders described here represent only a fraction of known sleep disorders, and only provide a framework for clinical assessment. The *DSM-IV*

classification is not comprehensive and includes primary sleep disorders, disorders related to other mental disorders, and other sleep disorders. The International Classification of Sleep Disorders (ICSD) has a more detailed diagnostic scheme for sleep disorders, with certain disorders overlapping with the DSM. **(Table I).**

Insomnia associated with medical and psychiatric conditions:

Patients suffering from anxiety disorders often present with initial insomnia, where the anxiety symptoms inhibit the onset of sleep. In contrast, patients with depressive disorders frequently complain of terminal insomnia signifying hypothalamic involvement. A variety of medications and substances can cause insomnia including anticonvulsants, corticosteroids, stimulating antidepressants, chemotherapy, and α-methyl dopa. Rapid withdrawal from sedative agents, especially the short half-life benzodiazepines and opiates, may also produce a rebound insomnia. **(Table II).**

Commonly occurring conditions where patients present with complaints of insomnia

Adjustment sleep disorder.

This commonly occurring disorder is caused by acute emotional stressors, such as financial difficulties or loss of employment. This results in an anxiety mediated insomnia, typically characterised by initial insomnia. The condition

Table I: Some of the disorders in the current classification systems

DSM IV	International Classification of Sleep Disorders – ICSD
Primary insomnia*	Psychophysiological insomnia*
	Sleep state misperception*
	Idiopathic insomnia
	Inadequate sleep hygiene*
Primary hypersomnia	Idiopathic hypersomnia
	Recurrent hypersomnia
Narcolepsy*	Narcolepsy*
Breathing-related disorders*	Obstructive sleep apnoea*
	Central sleep apnoea
	Central alveolar hypoventilation syndrome
Circadian rhythm disorders	Delayed sleep phase type*
Delayed sleep phase type	Time zone change syndrome
Jet lag type	Shift work sleep disorder*
Shift work type*	Advanced sleep phase syndrome*
Unspecified type	Irregular sleep phase syndrome
Dyssomnia NOS	Periodic limb movement disorder*
	Restless leg syndrome*
	Altitude insomnia
	Adjustment sleep disorder*
Nightmare disorder	Nightmares
Sleep terror disorder	Sleep terror disorder
Sleep walking disorder	Sleep walking disorder
Parasomnia NOS	Sleep starts, Sleep talking, Sleep paralysis
	Sleep bruxism, Sleep enureses, Primary snoring, Sudden infant death syndrome
	REM-sleep related sinus arrest
	Benign neonatal sleep myoclonus

Adapted from: Kaplan HI, Sadock JB.(1995) Comprehensive Textbook of Psychiatry. Sixth Edition.(Williams&Wilkins)

* *Discussed in text*

Table II: Medical and Psychiatric causes of insomnia

Medical Disorders	Psychiatric disorders	Medication
Asthma	Adjustment disorders	Alcohol
Chronic obstructive pulmonary disease	Alcohol and substance abuse	Amphetamine
	Anxiety	Antidepressants –MAOI, SSRI
Chronic pain	Post-traumatic stress	Antipsychotics
Coronary or pulmonary insufficiency	Panic disorder	Beta-blockers
Congestive heart failure	Major depression	Beta-agonists
Dementia	Bipolar disorder	Caffeine + Other Stimulants
Epilepsy	Obsessive-Compulsive disorder	Lamotrigine
Gastroesophageal reflux disease	Phobias	Nicotine
Hypertension	Psychosis	Oral contraceptives
Hyperthyroidism	Anorexia nervosa	Stimulating tricyclics
Parkinson's disease	Borderline personality disorder	Steroids and ACTH
Peptic ulcer disease		Theophylline
Nocturnal cardiac ischaemia		Thyroid hormone

is normally self-limiting, lasting less than 4 weeks, and should remit once the stressor has been removed. Treatment is warranted if daytime sleepiness and fatigue interfere with functioning. Management consists of behavioural modalities discussed below in combination with the judicious use of a hypnotic agent if necessary.

Psychophysiological insomnia

This type of insomnia is characterised by somatized tension and learned sleep-preventing associations. The disorder frequently follows an adjustment sleep disorder if the anxiety persists, but the patient now becomes concerned about the inability to sleep. After a few nights of insomnia, the bedroom becomes psychologically associated with the inability to sleep. As bedtime approaches, sleep inhibiting anticipatory anxiety increases and reaches maximum intensity after retiring. Sufferers frequently spend hours in bed awake, brooding over their sleeplessness. Rumination about the insomnia dominates the patient's whole world. Persistent psychophysiological insomnia often complicates other types of insomnia, including those associated with psychiatric disorders. Behavioural modalities are the treatment of choice, but can be combined with a hypnotic agent if necessary.

Sleep state misperception

This disorder is characterised by patients who complain of insomnia in the absence of objective evidence of disturbance in sleep quality, or daytime impairment. Patients are excessively concerned about the effects of diminished sleep. Polysomnographic investigations are normal without any objective evidence of insomnia. Reassurance and attempts to uncover possible underlying psychological concerns are frequently futile. The physician should guard against prescribing hypnotic too easily, as the risk for dependency may be high.

Conditions presenting with daytime somnolence

Obstructive Sleep Apnoea (OSA)

Symptoms of OSA include loud snoring, morning headaches, morning dry mouth, and decreased sexual functioning. There is narrowing or partial collapse of the upper airway, causing cessation of airflow for more than 10 seconds, as well as a decrease in oxyhemoglobin saturation levels. The patient is then aroused from sleep, which terminates the apnoea. The repetition of this cycle induces fragmented sleep, and causes excessive daytime sleepiness. Sleep apnoea is regularly associated with obesity and hypothyroidism, but for a definitive diagnosis, a polysomnographic evaluation is required. Weight loss is advocated, and surgical treatment and oral appliances help to reduce the airway obstruction. Continuous positive airway pressure(CPAP),and bi-level positive airway pressure (BiPAP) also attempt to maintain the airway during sleep.

Narcolepsy

Narcolepsy is a neurological disorder. Symptoms include excessive daytime sleepiness, cataplexy (episodes of abrupt decrease in muscle tone, often triggered by emotional reactions), hypnagogic hallucinations (vivid dreamlike experiences that occur while falling asleep or dozing), sleep paralysis (a temporary inability to talk or move while falling asleep or awakening), and disturbed nocturnal sleep. Stimulants like dextroamphetamine and methylphenidate are used for the treatment of narcolepsy. Modafinil is a new drug on the market with a mechanism of action similar to that of the sympathomimetics.

Circadian Rhythm Disorders

These sleep disorders are characterised by the inability to sleep at traditional times. Some individuals, especially the elderly, suffer from advanced sleep phase syndrome (excessive sleepiness in the evening and undesired early morning awakening).Delayed sleep phase syndrome is more common among adolescents (sleep-onset insomnia and difficulty waking at desired time in the morning). Most problematic is variable shift work in which shifts are changed frequently resulting in changes of sleeping schedules. This often leads to poor sleep quality immediately after the new shift in work schedule, which is followed by a period of adjustment. However, even fixed-shift workers who are forced to sleep during the daytime often experience difficulties in getting quality sleep. Daytime noise, light, and family and social responsibilities may interfere with sleeping patterns resulting in impaired job productivity and performance. It is recommended that shifts be kept constant for at least a month at a time. Melatonin and light therapy have also had varying success rates.

Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS) is a sleep disorder characterised by unpleasant sensations in the legs or feet that may be temporarily relieved by moving the limbs. The symptoms tend to increase towards the evening hours, particularly when lying down. RLS may be exacerbated during pregnancy or by medication such as selective serotonin re-uptake inhibitors (SSRI's) or tricyclic antidepressants (TCA's); it may also be associated with iron deficiency or uraemia. RLS often occurs in conjunction with periodic limb movement disorder (PLMD). Discomfort associated with RLS usually causes difficulties in sleep onset. Conservative management is preferred, but carbamazepine, benzodiazepines, levodopa, quinine and chlorpromazine have been tried with varying success rates.

Periodic Limb Movement Disorder (PLMD / Nocturnal Myoclonus)

This disorder is characterised by the repetitive (usually every 20 to 40 seconds) twitching or kicking of the lower extremities during sleep. Patients complain of either interrupted sleep or daytime somnolence. They are unaware of the movements and the brief arousals that follow and have no lasting sensation in the extremities. Therefore, bed partners should be questioned. The disorder is more common with increased age, from midlife onwards. Although often idiopathic, the disorder can be seen in association with drug withdrawal states, sleep apnoea syndrome, narcolepsy, and chronic renal and hepatic failure, as well as during treatment with certain medications (such as tricyclic antidepressants). Movements can be exacerbated by stress. Physical examination and blood tests (FBC, U+E, and LFT's) are essential to exclude treatable causes. Polysomnography generally confirms the diagnosis. Benzodiazepines, especially clonazepam, suppress the arousals, with levodopa, quinine, pergolide and oxycodone, among others, also proving effective in some patients.

Diagnostic tools:
Various procedures and investigations can be employed to diagnose specific sleep disorders. They include:

- **Keeping of Sleep Logs** – a graph on which the patient records bedtime, approximate sleep time, times and duration of awakenings, time of final awakening, and daytime naps over a period of 2 to 3 weeks. Although subjective, the graph summarises the patient's perception of the quality and quantity of sleep.[9]
- **Polysomnograph** – combines EEG, EMG, eye movements, oxygen saturation, limb movements, airflow, and chest and abdominal movement. Measurement is normally for one night under laboratory conditions. It is not indicated for routine evaluation of insomnia, but where a primary sleep disorder is suspected, or where a patient does not respond to appropriate behavioural and pharmacological management.
- **MSLT** – Multiple Sleep Latency Tests. A series of four or five daytime opportunities to take a 15-20 minute nap. The sessions are separated by 2 hours and are used to assess sleep latency and daytime drowsiness, and are of great value in diagnosing narcolepsy.
- **Actigraphy** – an actigraph is a device approximately the size of a watch worn on the wrist, containing a movement detector and considerable memory capacity. It records movements over a 1 or 2 week period. A 90%+ correlation has been seen between the minute by minute evaluation of the polysomnograph and the rest-activity findings recorded on the actigraph[9]. The advantage of the actigraph is that it is an extended recording of the patients life in his own home.

GENERAL MANAGEMENT AND TREATMENT RECOMMENDATIONS

In the primary care setting where the majority of the decisions are made, it would be helpful to follow a 3-step approach to treatment:

1. Consider underlying causes.
2. Nonpharmacological measures.
3. Pharmacological measures.

1. Consider an underlying cause of insomnia

Insomnia should always be considered as a symptom in the initial assessment, rather than a diagnosis. Therefore all emotional stressors, psychiatric, medical and pharmacological causes should be explored and treated before any other steps are taken to treat insomnia.

2. Nonpharmacological therapy

Nonpharmacological measures should be the first choice of treatment. A meta-analysis by Morin et al. found that nonpharmacological measures gave an average of 43.1% reduction in sleep latency with multicomponent therapies having the best response on average.[10] The other major advantage of psychological therapies is the long-term sustaining of newly learned sleeping skills with effects continuing for 3 months and longer. Moderate intensity

exercise also improves self-rated sleep quality and sleep duration in older adults, and benefits other chronic conditions such as arthritis. Because the majority of elderly people, particularly women, report low levels of physical activity, exercise may be one of the most cost-effective health interventions for people with insomnia. Several psychological treatments have been studied. The main approaches are discussed below.

I. Stimulus control therapy

Stimulus control refers to attempts to associate the bedroom with sleep rather than wakefulness, and restricts sleep-incompatible and anxiety provoking behaviours. These include sleep hygiene measures. Stimulus control showed a 49% reduction in sleep-onset latency and a 48% reduction in time awake after sleep onset[10].

II. Sleep restriction therapy

Sleep restriction attempts to limit the time spent in bed to the actual time spent sleeping. The time in bed is increased only if the time asleep exceeds 90% of the total time spent in bed. The time in bed is reduced if the time asleep drops below 80% of the total time spent in bed. Studies evaluating this method showed a 57% reduction in sleep-onset latency, and a 69% reduction in time awake after sleep onset[10].

III. Relaxation therapies

Relaxation procedures, such as progressive muscle relaxation and biofeedback, are designed to alleviate somatic or cognitive arousal. Attention-focusing procedures target cognitive arousal through imagery training, meditation, and thought stopping. Success of various therapies varied with results in reduction rates between 27% and 59%[10].

IV. Paradoxical intention

This method targets the patient's fear of insomnia. The fear of lying awake is removed when the patient stops trying to fall asleep, and tries to stay awake. The anxiety that previously inhibited sleep is alleviated and the sleep onset often improves within days. Paradoxical intention showed up to 50% reduction in sleep onset latency[10].

V. Sleep hygiene education

Sleep hygiene education alone reduced sleep-onset latency by an average of 27% in several trials.[10] Time awake after sleep onset also decreased by 27.3% compared to a 15% reduction in a control group . Sleep hygiene often includes the following strategies:

1. Maintaining a regular bedtime schedule and consistent wake-up time.
2. Going to bed only when sleepy.
3. Avoiding excessive time spent in bed.
4. Avoiding daytime naps.
5. Using the bed for sleeping and sex only.
6. Avoid watching the clock.
7. Establishing relaxing pre-sleep rituals, such as a warm bath, a light bedtime snack or 10 minutes of reading.
8. Making the bedroom as quiet as possible.
9. Avoiding the consumption of alcohol and caffeine within 12 hours of bedtime.

10. Avoiding large meals at night. Reducing evening fluid intake.
11. Exercising regularly. If exercising vigorously, do this at least six hours before bedtime. Mild exercise (simple stretching or walking) should not be done closer to bedtime than four hours.
12. Avoiding going to bed hungry.
13. Learning strategies to make bedtime as relaxing and tension-free as possible.

3. Pharmacological therapy

The principles of pharmacological therapy for insomnia are straightforward.

Only medications known to be efficacious and safe should be prescribed. The lowest effective dose should be used for the shortest period of time (less than 2 weeks). One should aim for intermittent dosing, as this may decrease the risk of tolerance and dependence. If use is prolonged or the dose is high, the discontinuation should be gradual.[3]

Self Medication

A substantial proportion of patients attempt to treat their insomnia themselves with 40% of patients utilising either over the counter(OTC) medications or alcohol.[11,12] These OTC sedatives have not been proven to have risk : benefit superiority when compared with placebo[3].

- *Alcohol* is one of the most commonly used substances for self medication. Alcohol does increase the ease of falling asleep but interferes with sleep quality and can aggravate daytime somnolence. It disrupts the sleep architecture, causes decreased deep sleep (stage 4), and increases sleep fragmentation. Awakenings are more frequent and of longer duration.[13]
- OTC medications also include *herbal remedies* of which the precise composition, action and efficacy are not always known.
- *Melatonin.* Slow release melatonin has been shown to be safe and effective for the treatment of insomnia in major depressive disorder.[12] Other studies have shown mild improvement, but large controlled studies are lacking. Rajput et al reported disruption of sleep in some patients using melatonin.[2]
- Many over-the-counter sleep aids contain *antihistamines.* Strong anticholinergic side effects, daytime sedation and cognitive impairment are common side effects. Long-term efficacy of these drugs have not been established.

Antidepressants

Physicians often prescribe antidepressants to good effect for the treatment of insomnia in nondepressed individuals. However, very little empirical evidence to support their efficacy exists. A number of antidespressants have been shown to have sleep-improving properties. **Nefazodone** has shown improvement in polysomnographic measures of sleep continuity in depressed patients, when compared to fluoxetine. **Trazodone and Mirtazepine** are both sedating, but there is little empirical support for its use as a hypnotic in nondepressed patients with insomnia.[8] **Tricyclic antidepressants** are often used in nondepressed individuals suffering from insomnia, due to their histaminergic activities. Most of these agents have a long half-life and daytime sedation and drowsiness are frequently experienced. The anticholinergic side effects, weight gain and increased appetite also limit the use of this group. Cardiotoxicity seen especially at high doses and in elderly patients with pre-existing cardiac histories, is of concern.

Hypnotics

This group includes the classic benzodiazepine hypnotics and the newer nonbenzodiazepines, zolpidem and zaleplon. A meta-analysis of randomised, controlled trials of benzodiazepines and zolpidem concluded that these agents are efficacious for the short-term treatment of insomnia, producing moderate, reliable improvements in subjective sleep-onset latency, and sleep quality.[7] However, the majority of studies reviewed were of a limited treatment duration (median - 7 days) and lacked follow-up data. Hypnotic agents are primarily indicated for the short-term management of insomnia, but up to 15% of individuals who use hypnotics continue taking them for longer than 1 year.[7]

Benzodiazepine receptor agonists

Benzodiazepine receptor agonists are the most commonly prescribed hypnotic agents for insomnia.[14] Their rational use has been controversial for years. There appears to be virtually no evidence to support the chronic use of benzodiazepines in the management of insomnia. Various studies have reported a higher risk for motor vehicle accidents, more falls and fractures, fatal poisonings, a general decline in functional status, and cognitive and psychomotor impairment associated with the use of benzodiazepines in the elderly. The rate of metabolism slows with age, which may result in higher drug concentrations and a longer duration of action leaving elderly patients particularly vulnerable to the deleterious effects of long-acting agents. Dependence on these medications is an important consideration and may explain the lower discontinuation rate among patients taking benzodiazepines than among those on placebo, despite a lack of evidence of clear-cut benefits.[7,8] Benzodiazepines may also cause vertigo, dysarthria, and ataxia, and they often have additive effects when used in conjunction with other central nervous system depressants. Tolerance following repeat administration is a potential problem, and severe rebound symptoms occur after rapid cessation of use.

A meta-analysis of studies indicated that the sleep-onset latency for patients receiving a benzodiazepine was 4.2 minutes shorter than for those receiving placebo, and total sleep time was 61.8 minutes longer than the placebo group. Very few nonpharmacological comparison trials have been done, which is disappointing given the concern about the adverse effects of benzodiazepines. The research that is available does indicate that cognitive behavioural therapies should be preferred over benzodiazepines. For physicians faced with the rare patient in whom other treatments have been exhausted and they feel they must prescribe a benzodiazepine, the drug should be discontinued within 2 to 4 weeks because it is unlikely to remain effective in the long-term. Zopiclone has often been touted as a safer sedative, but a meta-analysis by Holbrook et al does not suggest any superiority of this agent.[7]

Zolpidem and zaleplon:

These are newer nonbenzodiazepines that possess many of the benzodiaze-

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