

Chronic insomnia

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Insomnia is a prevalent complaint in clinical practice that can present independently or comorbidly with another medical or psychiatric disorder. In either case, it might need treatment of its own. Of the different therapeutic options available, benzodiazepine-receptor agonists (BzRAs) and cognitive-behavioural therapy (CBT) are supported by the best empirical evidence. BzRAs are readily available and effective in the short-term management of insomnia, but evidence of long-term efficacy is scarce and most hypnotic drugs are associated with potential adverse effects. CBT is an effective alternative for chronic insomnia. Although more time consuming than drug management, CBT produces sleep improvements that are sustained over time, and this therapy is accepted by patients. Although CBT is not readily available in most clinical settings, access and delivery can be made easier through use of innovative methods such as telephone consultations, group therapy, and self-help approaches. Combined CBT and drug treatment can optimise outcomes, although evidence to guide clinical practice on the best way to integrate these approaches is scarce.

Introduction

Insomnia is a common complaint that can present independently or comorbidly with another medical disorder (eg, pain) or psychiatric disorder (eg, depression). Insomnia is the most prevalent sleep disorder and affects large proportions of the population on a situational, recurrent, or persistent basis. It carries a heavy burden for both patients and the health-care system as evidenced by its effect on quality of life, and on psychological, occupational, and economic domains.¹⁻⁴ Insomnia is often unrecognised and untreated because of barriers to assessment and management.

Clinical presentation and findings

Insomnia is characterised by subjective complaints about dissatisfaction with sleep quality or duration, difficulty falling asleep at bedtime, waking up in the middle of the night or too early in the morning, or non-restorative or poor quality sleep. Insomnia also includes subjective reports of daytime symptoms such as fatigue or low energy, difficulties with cognitive functions (eg, attention, concentration, and memory), and mood disturbances (eg, irritability, dysphoria), all of which can produce functional impairments and are often the primary concerns that prompt patients to seek treatment.⁵⁻⁸

Polysomnographic assessment can show objective sleep impairments (eg, longer sleep latencies, reduced sleep time), but severity does not always match the patient's complaint of poor sleep. The cortex is more active in people with insomnia than in good sleepers, both around sleep onset and during non-rapid eye movement sleep;⁹ this is consistent with the general state of hyperarousal in people with insomnia. For daytime symptoms, assessment of neurobehavioural performance with objective tests shows selective performance deficits (eg, attention, memory) in individuals with primary insomnia.^{10,11} Nonetheless, most patients perceive their global functioning as greatly impaired. The patient's appraisal of sleep and daytime functioning is crucial since a diagnosis of insomnia is based on clinical symptoms rather than on objective laboratory findings.

Epidemiology

Prevalence

About 25% of adults are dissatisfied with their sleep, 10–15% report symptoms of insomnia associated with daytime consequences, and 6–10% meet criteria for an insomnia disorder.^{8,12-14} Insomnia is one of the most prevalent complaints in primary care;¹⁵⁻¹⁷ complaints increase with age and are twice as prevalent in women as in men.^{8,12}

Comorbidity

A high rate of comorbidity exists between chronic insomnia and medical and psychiatric disorders.¹³⁻¹⁸ In the 2002 US National Health Interview Survey,¹⁸ individuals with insomnia were more than five times (odds ratio [OR] 5.64, 99% CI 5.07–6.29) as likely to present anxiety or depression, and more than twice (OR 2.24, 99% CI 1.60–3.14) as likely to present congestive heart failures as individuals without insomnia. Likewise, the US National Comorbidity Survey¹³ showed that insomnia was frequently comorbid with anxiety, mood, impulse-control, and substance misuse disorders (median OR 3.4, IQR 2.8–3.9). A strong association between sleep disturbances and pain has been reported.¹⁹

Although insomnia has traditionally been conceptualised as a symptom of another disorder, longitudinal studies

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Search strategy and selection criteria

We searched PubMed, PsychNet, Embase, CINAHL, and the Cochrane Library from January, 2005, to April, 2010, with the search term "Insomnia". The search was restricted to human beings and to English and French languages. The main focus was on original contributions, meta-analyses, and systematic reviews reported during this period, but we also cited older publications that were judged to be relevant and to add new information. Because of the large number of citations, we selected those that were most relevant to epidemiology, assessment, diagnosis, and treatment (behavioural and pharmacological) of insomnia.

suggest that it can be a risk factor for new onset psychiatric disorders, most notably depression, anxiety, and substance misuse disorders.^{20,21} Findings from one study showed that

individuals with insomnia were four times more likely to develop new major depression over the next 3·5 years than were individuals without insomnia; risks to develop anxiety and substance misuse disorders were twice and seven times higher, respectively.²¹ Jansson-Frojmark and colleagues²² reported a bidirectional relation between insomnia and anxiety and depression. Insomnia and fatigue are the most common residual symptoms in patients treated for depression^{23,24} and increase the risk of relapse for future depressive episodes.²⁵

Panel 1: Assessment of insomnia (adapted from Schutte-Rodin⁴⁶)

Insomnia complaint:

Symptoms

- Difficulty falling asleep
- Number and duration of nocturnal awakenings
- Early morning awakening
- Non-restorative sleep

Onset

- Gradual or abrupt
- Circumstances (eg, changes in health, stressors, drugs)

Duration

- Days, weeks, months, years

Severity

- Frequency, intensity, effect on daytime functioning

Course

- Acute, episodic, persistent
- Precipitants and perpetuating factors (eg, stress, pain, illness)
- Previous treatments and response

Presleep conditions:

- Presleep activities (including before bedtime and in bed)
- Bedroom environment
- Psychological state before bedtime (eg, worries about sleep, thoughts and emotions)

Sleep-wake schedule:

- Bedtime and time needed to fall asleep
- Wake-up time and time out of bed
- Regularity of schedule (weekdays and weekends)
- Behaviours during nocturnal arousals (eg, use of toilet, eating or drinking)

Daytime function

- Sleepiness versus fatigue*
- Cognitive functions; mood disturbances (panel 2)
- Daytime activities including exercise; regularity of schedule

Drug and substance use

- Over-the-counter agents
- Prescription drugs
- Recreational drugs including alcohol, tobacco, and caffeine

Other sleep-related symptoms

- Respiratory (eg, snoring, witnessed apnoeas, waking gasping for breath)
- Motor (eg, restless legs, kicking/twitching during sleep, sleepwalking)
- Other medical (eg, pain, reflux, urinary frequency)

Medical history and examination, psychiatric history and examination, sleep log or diary (at least 2 weeks)

Polysomnography

- Only in cases of suspected sleep apnoea, movement disorder, or parasomnia

*Patients with insomnia almost always report fatigue and can sometimes report sleepiness, with the sleepiness being more common when insomnia is associated with medical comorbidity. Patients might confuse these two symptoms; fatigue, which can be mental or physical, does not necessarily imply sleepiness, whereas sleepiness is a physiological marker suggesting that sleep is imminent.

Course and prognosis

Insomnia can be a situational, recurrent, or persistent problem. Acute insomnia is often associated with life events or sleep schedule changes (eg, jet lag or shift work) and usually remits once the precipitating event has subsided.²⁶ For some individuals, sleep disturbance can persist even after the initial cause has disappeared. Insomnia can follow an intermittent course, with recurrent episodes of sleep difficulties associated with stressful events. Even in persistent insomnia, night-to-night variability in sleep is often reported, with an occasional good night's sleep intertwined with periods of disrupted sleep.²⁷

Results of longitudinal studies show that nearly 70% of individuals with insomnia at baseline continue to report insomnia a year later, and 50% still have insomnia up to 3 years later.^{28–30} The prognosis of untreated insomnia is not well documented; however, chronic insomnia raises the risks for depression,^{21,28} hypertension,³¹ and, possibly, mortality in older adults.^{32,33} These associations reinforce the need to identify and treat insomnia early to prevent chronicity and morbidity.

The course of insomnia is best understood by considering three types of contributing factors.³⁴ Predisposing factors increase vulnerability to insomnia—eg, age, sex, hyperarousability, anxiety-prone personality, family or personal history of insomnia, and genetic factors, such as the presence of the short allele of the serotonin transporter gene.³⁵ Sleep disturbances are more likely to arise in such individuals when exposed to stressful life events (eg, illness, separation) or to less severe but more chronic daily struggles (eg, occupational stress). Whereas most individuals resume normal sleep patterns after the triggering event has disappeared, some continue experiencing persistent sleep difficulties. Factors such as irregular sleep scheduling and the fear of not sleeping feed into and perpetuate the insomnia. Since psychological and behavioural factors are involved in perpetuation of insomnia, they need to be targeted in treatment.

Pathophysiological mechanisms

Definitive pathophysiological mechanisms have not been identified, although several neurobiological abnormalities are associated with insomnia. Patients with insomnia show increased activation of the autonomic nervous system, as evidenced by sleep-related elevations in heart rate and heart rate variability, metabolic rate, body

temperature, activity of the hypothalamic-pituitary-adrenal axis activity, and norepinephrine secretion.^{36,37} In one study, night-time blood pressure was higher in patients with insomnia than in controls.³⁸

Changes in brain activity consistent with hyperarousal occur in insomnia.^{36,37} Spectral analyses of electroencephalogram power during sleep show increased activity in faster frequencies (beta and gamma), which are thought to be associated with increased cognitive activity. Slow wave sleep is generally decreased compared with age-matched controls,³⁹ but this finding has not been reported consistently.³⁷ PET studies show raised brain glucose metabolism in sleep and waking, and smaller sleep-related reductions in brain glucose metabolism in wake-promoting regions.⁴⁰

Individuals with insomnia are more likely to have a family history of the disorder,⁴¹ which suggests a genetic vulnerability, a common environmental factor, or a learned component. Abnormalities related to sleep-wake regulatory genes have not yet been identified in insomnia.

Most studies investigating the role of hyperarousal in insomnia are correlational and thus the reported abnormalities could be the result of insomnia, associated sleep loss, or comorbidities such as depression. For example, patients with insomnia show reduced grey matter volume in the left orbitofrontal cortex and hippocampus,^{42,43} and a greater frequency of the short allele of 5-HTTLPR (the 5' regulatory region of serotonin transporter gene);³⁵ these markers have also been reported in depression. Further studies are needed to clarify the role of arousal in the pathogenesis of insomnia and its specific genetic and neurobiological mechanisms.

Assessment and diagnosis

In view of the high prevalence and substantial morbidities of insomnia, patients should routinely be asked about sleep problems by health-care providers.^{44,45} Patients who report difficulty sleeping should be questioned about the specific symptoms of insomnia, and their frequency and severity (panel 1). Although no standardised quantitative definitions for insomnia exist, several criteria are suggested: average reported sleep latency of more than 30 min, wakefulness after sleep onset of more than 30 min, sleep efficiency of less than 85% or total sleep time of less than 6·5 h.⁴⁶ A key element for the diagnosis of insomnia is the presence of distress or daytime consequences, or both. Individuals who complain about inability to sleep at night but without daytime impairment might merely be short sleepers.

Daily sleep diaries are helpful to obtain an accurate report of the sleep complaint over time; these should include bedtime and time arising from bed, time to fall asleep, number and duration of awakenings during the night, time of final awakening in the morning, and daytime naps.⁴⁶ Although polysomnography is the gold standard for measuring sleep, this test is not routinely indicated in the assessment of insomnia, except in cases

of suspected sleep apnoea or sleep-related movement disorders, or when violent or potentially self-injurious behaviour occurs during sleep,⁴⁷ or for patients who are treatment resistant.

Patients with chronic insomnia should be screened for comorbid disorders that might be contributory, such as psychiatric illnesses and medical problems. Insomnia can be a symptom of other sleep disorders, including sleep apnoea, sleep related movement disorders, and circadian rhythm disorders. For example, findings of a review of studies into the comorbidity of insomnia and sleep apnoea showed that 29–67% of older adults with insomnia (n=674 across three studies) have obstructive sleep apnoea with an apnoea-hypopnoea index greater than five.⁴⁸ Treatment of apnoea can improve sleep, whereas many hypnotic drugs can worsen sleep apnoea. Panel 2 lists common disorders that present with insomnia.

Use of prescription, over-the-counter, or recreational drugs frequently contributes to sleep disturbance; these include stimulants, antidepressants, methylxanthines, decongestants, diuretics, corticosteroids, and anti-hypertensives. Patients often use alcohol to induce sleep. However, alcohol can cause sleep disruption during the latter part of the night when blood alcohol concentrations drop. Long-term use of alcohol can lead to chronic insomnia that might not fully resolve with abstinence. Recreational drugs can contribute to insomnia related to use (stimulants) or upon withdrawal (sedatives).

Two of the main nosologies for diagnosis are the International Classification of Sleep Disorders: Diagnostic

Panel 2: Disorders that present with symptoms of insomnia

Circadian rhythm disorders

- Inability to sleep at the desired time, but able to sleep at other times.
- Delayed sleep phase: difficulty falling asleep until several hours after desired bedtime, with difficulty waking up on time for school or work. Common in young adults.
- Advanced sleep phase: difficulty staying up until desired bedtime, accompanied by early morning awakening. More common in elderly people.
- Shift work sleep disorder: difficulty sleeping at scheduled time and difficulty maintaining alertness while working. Usually seen with night shift or rotating shift work.

Sleep apnoea

- Complaints of fragmented or non-restorative sleep; daytime sleepiness can also be present.
- History of apnoea symptoms: snoring, witnessed apnoeas, waking choking or gasping, morning headaches, nocturia, fatigue or sleepiness. More common in men and those with obesity, crowded upper airway, hypertension, diabetes.

Restless legs

- Uncomfortable sensation that occurs during rest, usually worst at night, and relieved by movement. Can lead to great difficulty falling asleep and staying asleep.

Psychiatric disorders

- Insomnia is often associated with anxiety and mood disorders but can be present with any psychiatric disorder. Insomnia usually worsens when psychiatric disorder is more symptomatic. All patients with chronic insomnia should be screened for psychiatric disorders.

Panel 3: Criteria for diagnosis of insomnia (ICSD-2⁵)

- A. One or more of the following symptoms:
- Difficulty initiating sleep
 - Difficulty maintaining sleep
 - Waking up too early
 - Non-restorative sleep
- B. Sleep difficulty occurs despite adequate opportunity for sleep
- C. At least one of the following daytime symptoms related to the night-time sleep difficulty reported:
- Fatigue or malaise
 - Attention, concentration, or memory impairment
 - Social or vocational dysfunction or poor school performance
 - Mood disturbance or irritability
 - Daytime sleepiness
 - Motivation or energy or initiative reduction
 - Proneness for errors or accidents
 - Tension headaches or gastrointestinal symptoms, or both
 - Concerns or worries about sleep

A+B+C defines insomnia.

and Coding Manual 2nd edition (ICSD-2) (panel 3),⁵ and the Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th edition (panel 4), with the 5th edition expected in 2013.⁴⁹ The ICSD-2 states that acute or adjustment insomnia is associated with an identifiable stressor, remits when the stressor is removed, and lasts no more than 3 months. Insomnia of at least a month's duration is deemed chronic and is diagnosed on the basis of its presumed causes, either primary or comorbid with other conditions. In comorbid insomnia, disorders or substances contribute to the insomnia⁵⁰ and the insomnia is severe enough to cause distress or require specific treatment, separate from treatment for the primary disorder.⁵ The DSM-5 proposes to use the same criteria to define insomnia as DSM-IV and the ICSD-2, but does not have separate categories for insomnias with presumed underlying causes. Furthermore, the sleep disturbance needs to be present at least 3 nights per week for at least 3 months to meet criteria as a chronic insomnia disorder.⁴⁹

Cognitive behavioural therapy

Rationale and indication

Cognitive behavioural therapy (CBT) for insomnia is a brief, sleep-focused, multimodal intervention that includes psychological and behavioural procedures such as sleep restriction, stimulus control, relaxation, cognitive strategies, and education about sleep hygiene (panel 5).^{51,52} These therapies can be used singly, although a combined approach is preferred because several dimensions of insomnia can be addressed. The most common approach includes a behavioural (stimulus control, sleep restriction,

relaxation) component combined with a cognitive and an educational (sleep hygiene) component. The objective of CBT is to change factors that perpetuate insomnia, including behavioural factors (poor sleep habits, irregular sleep schedules), psychological factors (unrealistic expectations, worry, unhelpful beliefs), and physiological factors (mental and somatic tension, hyperarousal). The main CBT indications include persistent insomnia, primary or comorbid, and insomnia in young and older adults. Caution is advised for use of sleep restriction, which could produce daytime sleepiness or exacerbate mania in a bipolar patient. Evidence of daytime sleepiness should prompt a warning against driving or operating dangerous machinery.

Evidence for efficacy

The 2005 US National Institutes of Health state-of-the-science conference on insomnia concluded that only two treatment modalities (CBT and benzodiazepine-receptor agonists [BzRAs]) had adequate evidence to support their use in the management of chronic insomnia.³ Evidence from meta-analyses^{53–55} and systematic reviews^{56–60} suggest that CBT produces moderate to large effect sizes for sleep onset latency (range from 0.41 to 1.05) and sleep quality (0.94–1.14), and small to moderate effect sizes for the number of awakenings (0.25–0.83), duration of awakenings (0.61–1.03), and total sleep time (0.15–0.49). 70–80% of patients achieve a therapeutic response, whereas about 40% achieve clinical remission.⁶¹ In terms of symptom reductions, subjective sleep latency and time awake after sleep onset are reduced from an average baseline of 60–70 min to about 35 min, and total sleep time is increased by 30 min, from 6 h to 6.5 h. Evidence that CBT improves fatigue, quality of life, and psychological symptoms is limited.^{59,62}

Clinical evidence suggests that behavioural interventions aimed at curtailing time spent in bed are especially effective for improvement of sleep continuity, whereas cognitive strategies are instrumental for reduction of psychological distress³⁹ and dysfunctional beliefs.⁶³ Education about sleep hygiene is incorporated in most treatments, but it should be seen as a minimum intervention, since alone it produces little effect on sleep.

Long-term outcomes

CBT produces sleep improvements that are sustained over time,^{59,64} which is a clear advantage compared with drug treatment. Although interventions that restrict the amount of time spent in bed can yield slight increases (or even a reduction) of sleep time during initial treatment, this situation usually improves with time, with total sleep time often exceeding 6.5 h at 6-month follow-ups. Even patients who respond well to short-term therapy can be vulnerable to recurrent episodes of insomnia. Long-term, maintenance therapies to prevent or minimise insomnia recurrence need to be developed and assessed.

CBT for comorbid insomnia

Patients with a range of medical and psychiatric disorders can benefit from CBT for insomnia.⁶⁵ For example, CBT is effective for insomnia associated with chronic pain,⁶⁶ fibromyalgia,⁶⁷ cancer,^{68,69} and various medical conditions in older adults.^{70,71} Likewise, treatment of insomnia in the context of co-occurring major depression^{72,73} or substance misuse⁷⁴ can be helpful. In a study that examined the effect of augmentation of an antidepressant drug with a brief, symptom focused, CBT for insomnia in patients with major depressive disorder, the augmented therapy regimen produced higher remission rates for both depression (62% vs 33% for antidepressant drugs plus placebo) and insomnia (50% vs 8%).⁷⁵

Thus, the presence of a comorbid disorder should not preclude the targeting of insomnia for treatment. Insomnia can be more severe at baseline in patients with comorbid disorders, but the absolute changes on sleep outcomes during treatment are similar to those obtained by patients with primary insomnia. For some conditions, addition of CBT to other treatment regimens or adaptation of CBT to disease specific conditions is necessary; for example, the addition of fatigue management to standard CBT has been helpful for insomnia patients with cancer⁶⁹ and traumatic brain injury.⁷⁵

CBT for older adults

Insomnia is more prevalent in older adults and is more likely to be associated with other medical disorders. Findings from a meta-analysis⁵⁷ showed that treatment effect sizes were similar (moderate to large) for middle-aged and older adults for subjective measures of sleep latency, wake after sleep onset, and sleep quality. In a systematic review McCurry and colleagues⁵⁸ concluded that multimodal CBT and sleep restriction therapy alone met criteria for empirically validated therapies, whereas evidence was insufficient to support cognitive therapy, relaxation, or education about sleep hygiene as stand-alone therapies for insomnia in older adults. Results of some studies show that older adults with comorbid medical or psychological disorders can benefit from sleep-specific treatment.^{70,71,76} Rybarczyk and colleagues⁷¹ reported that older adults with chronic obstructive pulmonary disease, osteoarthritis, or coronary artery disease benefited from group CBT, as evidenced by improved sleep continuity and satisfaction and enhanced quality of life.

Discontinuation of hypnotic agents can be difficult especially after longlasting use. A supervised and time-limited withdrawal programme can ease discontinuation of hypnotic drugs in long-term users.⁷⁷⁻⁷⁹ For example, in a study of 76 older adults who had used benzodiazepines for insomnia for nearly 20 years, treatment was effective to reduce the quantity (90% reduction) and frequency (80% reduction) of drug use, and 63% were drug-free within the 10-week intervention.⁷⁸ The addition of CBT to supervised drug withdrawal minimised rebound insomnia.

Panel 4: DSM-5 insomnia disorder 307.42 (proposed⁴⁹)

- A. The predominant complaint is dissatisfaction with sleep quantity or quality made by the patient (or by a caregiver or family in the case of children or elderly people)
- B. Report of one or more of the following symptoms:
 - Difficulty initiating sleep; in children this symptom might be manifested as difficulty initiating sleep without caregiver intervention
 - Difficulty maintaining sleep characterised by frequent awakenings or trouble returning to sleep after awakenings (in children this symptom might be manifested as difficulty returning to sleep without caregiver intervention)
 - Early morning awakening with inability to return to sleep
 - Non-restorative sleep
 - Persistent resistance to going to bed or bedtime struggles (children)
- C. The sleep complaint is accompanied by great distress or impairment in daytime functioning as shown by the report of at least one of the following:
 - Fatigue or low energy
 - Daytime sleepiness
 - Cognitive impairments (eg, attention, concentration, memory)
 - Mood disturbance (eg, irritability, dysphoria)
 - Behavioural difficulties (eg, hyperactivity, impulsivity, aggression)
 - Impaired occupational or academic function
 - Impaired interpersonal/social function
 - Negative effect on caregiver or family functioning (eg, fatigue, sleepiness)
- D. The sleep difficulty occurs at least 3 nights per week
- E. The sleep difficulty is present for at least 3 months
- F. The sleep difficulty occurs despite adequate opportunity for sleep

Duration

- Acute insomnia (<1 month)
- Sub chronic insomnia (1–3 months)
- Persistent insomnia (>3 months)

Clinically comorbid disorders:

- Psychiatric (specify)
- Medical (specify)
- Another (specify)

Practical considerations for CBT implementation

CBT is typically delivered in the context of four to six therapy sessions at weekly intervals, although the number of follow-up visits can vary as a function of insomnia severity, comorbidity, and patient motivation. Acute and milder forms of insomnia might need less time and be manageable in primary care clinics, but more complex cases might need to be handled by behavioural sleep medicine specialists.

CBT is generally well accepted by patients,⁸⁰ but barriers to implementation include time and scarce availability of clinicians with CBT skills. Since individual, face-to-face therapy with a sleep specialist is not always feasible, alternative treatment delivery models can improve access to CBT. With training and supervision, nurses can deliver effective CBT for insomnia in primary care settings.^{62,68} Group therapy and telephone consultations represent other cost-effective methods.^{74,81} Self-help approaches using printed materials,^{82,83} videos,⁸⁴ or internet-based programmes⁸⁵ are helpful as stand-alone

Panel 5: Psychological and behavioural therapies for insomnia⁵¹**Treatment (level of endorsement)⁶⁰***Stimulus control therapy (standard)*

Behavioural recommendations designed to reinforce the association between the bed or bedroom and sleep, and to strengthen a consistent sleep-wake schedule: (a) go to bed only when sleepy; (b) get out of bed when unable to sleep; (c) use the bed for sleep only (no reading, problem-solving in bed); (d) arise at the same time every morning; (e) avoid napping.

Sleep restriction therapy (guideline)

A method that limits the time spent in bed as close as possible to the actual sleep time, thereby producing a mild sleep deprivation, which results in more consolidated sleep. The sleep window is gradually increased throughout a few days or weeks until optimum sleep duration is achieved.

Relaxation training (standard)

Clinical procedures aimed at reduction of somatic tension (eg, progressive muscle relaxation, autogenic training) or intrusive thoughts (eg, imagery training, meditation) interfering with sleep. Most relaxation techniques need professional guidance initially and daily practice for a few weeks.

Cognitive therapy (insufficient evidence as single therapy)

Psychotherapeutic method aimed at alleviating excessive worries and revising misconceptions about sleep, insomnia, and daytime consequences. Specific targets include unrealistic sleep expectations, fear of the consequences of insomnia, and misconceptions of the causes of insomnia.

Sleep hygiene education (insufficient evidence as single therapy)

General guidelines about health practices (eg, diet, exercise, substance use) and environmental factors (eg, light, noise, temperature) that might promote or interfere with sleep: (a) avoid stimulants (eg, caffeine, nicotine) for several hours before bedtime; (b) avoid alcohol around bedtime as it fragments sleep during the second half of the night; (c) exercise regularly, it can deepen sleep; (d) do not watch the clock; (e) keep the bedroom environment dark, quiet, and comfortable.

Cognitive behavioural therapy (standard)

A combination of any of the above behavioural (eg, sleep restriction, stimulus control instructions, relaxation) and cognitive procedures.

treatments or as additions to professionally administered therapy.⁸⁶ Although these different treatment delivery models can ease treatment access, they should be judged in the larger context of a stepped-care approach.⁸⁷ Some patients might need little guidance whereas others might need more intensive and structured therapy. Ultimately, the success of CBT depends on the patient's willingness to comply with treatment recommendations. To optimise outcome, follow-up visits are often necessary to monitor progress, address compliance issues, and provide guidance and support.

Pharmacotherapy

Various drugs are used to treat insomnia, including over-the-counter agents (OTCs; antihistamines, melatonin, and herbal preparations), prescription hypnotic drugs for insomnia (BzRAs, chronobiotic agents, and low-dose doxepin hydrochloride), and other prescription agents not specifically indicated for insomnia (antidepressants, antipsychotics, and anticonvulsants) (table).

For agents not approved by the US Food and Drug Administration (FDA), scarce data exist about efficacy for improvement of sleep, and little or no data exist about improvement of daytime functions or medical outcomes for any prescription drugs. Furthermore, all agents used for promotion of sleep can potentially produce adverse effects, some of them severe, particularly in elderly people.

OTC agents

Antihistamines used as sleep-inducing agents include diphenhydramine or doxylamine succinate, which are often combined with pain-relieving drugs such as paracetamol or ibuprofen. Antihistamines can cause drowsiness but there are few data about their efficacy for insomnia. Side-effects include agitation, anticholinergic effects (eg, dry mouth, urinary retention), and exacerbation of restless legs syndrome.⁸⁸ Tolerance can develop⁸⁹ and abrupt withdrawal can lead to rebound insomnia.

Melatonin is a hormone produced by the pineal gland that contributes to reinforcement of circadian and seasonal rhythms. Synthetic melatonin is sold as a dietary supplement in the USA, but in some countries it is deemed a prescription drug. Results from studies into the efficacy of melatonin as a hypnotic agent are inconclusive; findings from a meta-analysis showed a reduction in sleep latency of only 7.2 min.⁹⁰ Some evidence supports use of synthetic melatonin for insomnia related to circadian rhythm disorders such as delayed sleep phase and shift work sleep disorder.⁹¹ Side-effects can include drowsiness, dizziness, headache, nausea, and nightmares.

A range of herbal preparations are used for insomnia, most commonly valerian. Valerian binds to gamma-aminobutyric acid (GABA) type A receptors to improve response to GABA.⁹² Results of a meta-analysis showed subjective improvement in sleep quality, although improvement in quantitative measures of sleep has not been shown.⁹³ Side-effects can include drowsiness, dizziness, and allergic reactions.

Hypnotic agents

Most prescription hypnotic agents act as agonists at the benzodiazepine receptor; these include several benzodiazepines and the structurally distinct BzRAs (table). These agents act by binding to the GABA type A receptor and are effective in promotion of sleep onset. Hypnotic agents with short half-lives (eg, triazolam, zaleplon, and zolpidem) mainly reduce latency to sleep. Zaleplon, with its ultra-short half-life, can even be used after awakening during the night without substantial risk of daytime effects, whereas zolpidem is more likely to produce residual effects the next day after middle-of-the-night dosing.^{94,95} Agents with longer half-lives are effective in reduction of wakefulness during sleep⁹⁴ but can lead to hangover and daytime impairment, especially with regular nightly use.⁹⁶ Side-effects include sedation,

cognitive impairment, motor incoordination, ataxia, dizziness, and gastrointestinal upset. Long-term use can lead to dependence or misuse in some individuals. Abrupt discontinuation can lead to transient rebound insomnia, which can be more severe than the initial insomnia disorder.^{97,98} Adverse effects are probably more severe with use of benzodiazepines than with the newer BzRAs.³

Chronobiotic agents for insomnia include prolonged-release melatonin and ramelteon. Prolonged-release melatonin is indicated for poor quality sleep in adults aged 55 years or older. Ramelteon, a melatonin receptor agonist, reduces latency to sleep, but does not increase total sleep time. It has no demonstrable misuse potential, does not seem to cause next-day impairment and does

	Dose range (mg)	Dose in elderly people (mg)	Half-life (h)	Peak plasma concentration (h after administration)	Side-effects
Benzodiazepine receptor agonists: benzodiazepines					
Estazolam	1-2	0.5	10-24	2	Dizziness, drowsiness, lightheadedness, ataxia, amnesia, gastrointestinal (GI) symptoms
Flurazepam	15-30	15	47-100	2	As for estazolam
Quazepam	7.5-15	7.5	25-41	1.5	As for estazolam
Temazepam	7.5-30	7.5	6-16	1	As for estazolam
Triazolam	0.25-0.50	0.125-0.250	1.5-5.5	2	As for estazolam
Benzodiazepine receptor agonists: non-benzodiazepines					
Eszopiclone [‡]	2-3	1-2	5-6	1	Unpleasant taste, dry mouth, dizziness, drowsiness, amnesia, GI symptoms
Zopiclone* [†]	3.75-7.5	7.5	5	>2	As for eszopiclone
Zaleplon	10-20	5-10	1	1	Dizziness, headache, GI symptoms, drowsiness, amnesia
Zolpidem	10	5	2.5	1.6	As for zaleplon
Melatonin receptor agonist					
Melatonin, prolonged release* [†]	2 (1-2 hours before bedtime and after food)	2	3.5-4	3	Headache, pharyngitis, back pain, asthenia, irritability, nervousness, dizziness, somnolence, abdominal pain, constipation
Ramelteon [‡]	8	8	1-2.6	0.75	Drowsiness, dizziness, interaction with fluvoxamine
Antidepressants					
Amitriptyline* [†]	50-100	20	10-28 (including the metabolite nortriptyline)	4-8	Drowsiness, dizziness, confusion, blurred vision, dry mouth, constipation, urinary retention, arrhythmias, orthostatic hypotension, weight gain, exacerbation of restless legs, periodic limb movements, or rapid eye movement-sleep behaviour disorder
Doxepin	75-100	25-50	8-24	2-3	As for amitriptyline
Trimipramine* [†]	25-200	25-100	11-23	2	As for amitriptyline
Mirtazapine* [†]	15-45	7.5-15	20-40	2	Drowsiness, dizziness, increased appetite, constipation, weight gain
Agomelatine* [†]	25-50		1-2	1-2	Can raise liver enzymes; check liver functions prior to initiation and at 6, 12, 24 weeks, and periodically thereafter Nausea, dizziness, headache, somnolence, anxiety, abdominal pain, back pain, interaction with fluvoxamine
Trazodone* [†]	150-400	150	7	1	Drowsiness, dizziness, headache, blurred vision, dry mouth, arrhythmias, orthostatic hypotension, priapism
Anticonvulsants*					
Clonazepam	0.25-0.50	0.25	30-40	1-4	Drowsiness, dizziness, ataxia, depression, nervousness, reduced intellectual ability
Gabapentin	300-600	300	5-7	2-4	Drowsiness, dizziness, emotional lability, ataxia, tremor, blurred vision, diplopia, nystagmus, myalgia, peripheral edema
Tiagabine	4-8	4	7-9	0-75	Drowsiness, dizziness, ataxia, tremor, new-onset seizures in patients without epilepsy, difficulty in concentration or attention, nervousness, asthenia, abdominal pain, diarrhoea, nausea
Antipsychotics*					
Olanzapine	5-10	5	21-54	6	Drowsiness, dizziness, tremor, agitation, asthenia, extrapyramidal symptoms, dry mouth, dyspepsia, constipation, orthostatic hypotension, weight gain, new-onset diabetes mellitus
Quetiapine	25-200	25	6	15	As for olanzapine

*Not approved for treatment of insomnia by the US Food and Drug Administration. †Not available in the USA. ‡Not available in European Union.

Table: Pharmacological treatment for insomnia

not lead to rebound insomnia, by contrast with the benzodiazepines and BzRAs.⁹⁸ Ramelteon might help to promote circadian rhythm entrainment at lower doses,⁹⁹ although it is not specifically indicated for this aim.

Rare but potentially serious side-effects, including abnormal sleep-related behaviours (eg, eating, driving, or sexual activity during sleep) and severe allergic reactions can occur with use of hypnotic agents.^{98,100} Abnormal behaviours during sleep are more likely when hypnotic agents are taken at higher doses or in combination with alcohol or other sedating drugs. A concern for elderly people is whether the use of hypnotic agents could increase the risk of falls; the evidence, however, suggests that both insomnia and use of sedating drugs are associated with increased falls in older adults.^{101–104}

A major issue regarding the use of hypnotic agents for chronic insomnia is duration of treatment. Although insomnia is a disorder that often lasts for years or decades, relatively few long term, randomised controlled trials have been done. Results from studies of eszopiclone for 6 months in adults¹⁰⁵ and 12 weeks in elderly patients¹⁰⁶ show continued efficacy with no rebound insomnia. Results of a 24-week study of extended-release zolpidem showed long term efficacy, without evidence of statistically significant tolerance or rebound insomnia.¹⁰⁷ Ramelteon consistently reduced latency to sleep onset in a 6-month trial in adults with chronic insomnia, without evidence of tolerance, rebound insomnia, or residual daytime effects.¹⁰⁸

Most studies into the efficacy of hypnotic drugs have been undertaken in patients with primary insomnia, but clinical trials for comorbid insomnia have been done with some of the newer agents. Eszopiclone improves insomnia when given with selective serotonin reuptake inhibitors in patients with either major depression (given fluoxetine) or generalised anxiety disorder (given escitalopram);^{109,110} symptoms of depression and anxiety seemed to resolve more quickly in patients receiving eszopiclone than in those given placebo. A trial of extended-release zolpidem with escitalopram showed statistically and clinically significant improvement in insomnia, but no additional reduction of anxiety symptoms, compared with the group given escitalopram and placebo.¹¹¹ Hypnotic drugs seemed to decrease symptoms of insomnia in patients with chronic pain but had no consistent effects in reduction of pain.¹¹²

Other prescription agents

Antidepressants with sedating effects are some of the most commonly prescribed drugs for insomnia although data about efficacy are generally scarce. The doses of antidepressants typically used to induce sleep are substantially less than antidepressant doses. A sedating antidepressant might be appropriate for a patient with insomnia and major depression, either when used at a therapeutic dose or in combination with another

antidepressant. Antidepressants might be considered for patients with a history of substance misuse or other contraindications to use of a controlled substance.

Antidepressants prescribed for insomnia include trazodone hydrochloride, mirtazapine, tricyclic antidepressants such as doxepin, and agomelatine.¹¹³ These agents can improve sleep in patients with comorbid depression and can have sleep-promoting effects in individuals with primary insomnia, although scarce data are available.^{113,114} Agomelatine might be helpful in patients with insomnia and circadian rhythm disorders, since it is a melatonin receptor agonist.¹¹⁵ In Buscemi and colleagues' meta-analysis,¹¹⁶ both self-reported and objectively measured sleep latency were reduced with antidepressants, although the improvements were smaller than with hypnotic agents.

Several studies have assessed the efficacy of very low dose doxepin (up to 6 mg) for insomnia;^{117,118} doxepin is one of the most potent antihistamines available, at doses far lower than those required for the antidepressant effect. Polysomnographically defined wake after sleep onset was reduced, total sleep time and sleep efficiency were improved, and subjective latency to sleep was decreased; no significant side-effects were noted compared with placebo. The US FDA has approved low dose doxepin for the indication of insomnia.

Although antidepressants do not have misuse potential, they can lead to pronounced side-effects such as weight gain, increased suicidal ideation, hypomania or mania in patients with bipolar disorder, cardiac toxicity, and orthostatic hypotension. Withdrawal effects from rapid eye movement (REM) sleep-suppressing drugs (eg, tricyclics) include REM sleep rebound with excessive dreaming and possible rebound insomnia.¹¹⁹ Other effects on sleep include possible exacerbation of restless legs syndrome or appearance of REM sleep behaviour disorder, in which patients do not remain atonic during REM sleep and act out dreams.¹¹⁹

Some anticonvulsants are used for potential sleep-promoting effects, particularly those with effects on GABA neurotransmission. Tiagabine hydrochloride and pregabalin, which increase slow wave sleep, might be helpful for insomnia since the disorder is often associated with a deficit in slow wave sleep.¹²⁰ Results from studies of tiagabine in patients with primary insomnia show consistent effects of increasing slow wave sleep, decreasing wakefulness after sleep onset, and decreasing sleep latency.^{121–123} Pregabalin has been reported to decrease insomnia and anxiety in patients with comorbid generalised anxiety and insomnia,¹²⁴ and to reduce insomnia and pain in patients with fibromyalgia.^{125,126} Side-effects can include weight gain, daytime sedation, dizziness, and cognitive impairment.

Atypical antipsychotics are used for chronic insomnia, particularly quetiapine and olanzapine; most of these agents tend to increase total sleep time or sleep efficiency, or both.¹²⁷ Their sleep-inducing effects might be related to

blockade of histamine and 5-HT_{2C} receptors.^{127,128} Side-effects can be serious and include substantial weight gain, abnormal lipid and glucose regulation, and increased mortality, particularly in elderly people. They can exacerbate restless leg syndrome and, possibly, increase rates of parasomnias such as sleep walking and eating during the night.

Choice of drug

The choice of drug for insomnia treatment should be based on the pharmacological characteristics of the agent (table) and clinical factors related to the patient (panel 6).^{46,129} Drugs with shorter time to peak blood concentration (t_{max}) will probably have a more rapid onset of action and aid sleep onset, whereas those with longer half-lives ($t_{1/2}$) can provide better sleep maintenance but have the potential for daytime hangover. Mechanism of action is relevant to explain side-effects; it might have increasing relevance as underlying mechanisms for sleep disorders are identified and better understood (eg, insomnia due to a circadian rhythm disorder could benefit from an agent that can synchronise the circadian clock).

Patient-related factors that affect drug choice include nature of insomnia symptoms (sleep initiation vs maintenance), age (doses might need to be lowered for elderly patients), response to previous treatments, and cost. Patients might have disorders that are contraindications for some choices (eg, benzodiazepines in patients with severe sleep apnoea or pulmonary disease), or disorders that make a non-first-line agent more desirable (eg, a sedating antidepressant in a patient with major depression). Other drugs that are being taken can preclude certain choices (eg, ramelteon should not be given to patients taking fluvoxamine).

Duration of treatment and frequency of dose depend on the clinical situation. Patients should be reassessed within a month of starting a hypnotic drug and then at intervals of at least every 6 months to assess continued effectiveness and potential side-effects. In general, hypnotic drugs should be used at the lowest effective dose and the need for continued use should be determined by attempts to wean patients from the drug periodically. However, some patients might need and benefit from long-term treatment with hypnotic drugs without pronounced adverse effects. Some patients might need nightly dosing, although intermittent dosing could be sufficient for episodic insomnia and might reduce the risks for tolerance or daytime sedation due to increased drug concentrations of longer-acting agents.

Combined CBT and drug treatment

CBT and drug treatment can have complementary roles in the management of insomnia. For instance, no single treatment is effective for all forms of insomnia or acceptable to all patients and, even in those who respond to treatment, few reach complete remission. Combined approaches should optimise outcome by taking advantage

Panel 6: Guidelines for choice of pharmacotherapy agent

The American Academy of Sleep Medicine clinical guideline for management of insomnia recommends the following sequence of choices for pharmacotherapy⁴⁶

- Short or intermediate-acting benzodiazepine-receptor agonists (BzRA) or ramelteon. No particular drug recommended; choice should depend on clinical factors.
- Alternative BzRA or ramelteon. Choice based on response to first drug—eg, if duration of action insufficient, choose an agent with a longer half life.
- Sedating low-dose antidepressant. For patients with depressive symptoms, treatment failures.
- Combination of BzRA and antidepressant. Combination therapy might improve efficacy while minimising toxicity by use of agents at lower doses.

Evidence for efficacy of other prescription drugs (eg, tiagabine, pregabalin, quetiapine, olanzapine) is insufficient to recommend their use for primary insomnia, but they could be helpful in patients who have other indications for their use (eg, chronic pain conditions, psychiatric disorders).

Agents not recommended for use include alcohol, chloral hydrate, and non-barbiturate non-benzodiazepine drugs such as meprobamate because of adverse effects, toxic effects, and risk for misuse and dependence. Antihistamines should be avoided because of their potential for adverse effects and scarce efficacy data. Long-term use of over-the-counter agents such as valerian and melatonin is generally not recommended because of the absence of safety or efficacy data.

of the more immediate and potent effects of hypnotic agents and the more sustained effects of behavioural interventions. Comparisons of effect sizes derived from meta-analyses of these two treatment modalities suggest that CBT might have a slight advantage for measures of sleep latency and sleep quality, whereas pharmacotherapy (BZRAs) produces a more favourable outcome on total sleep time.^{54,55,130}

Findings from studies that directly contrast the effects of CBT and drug treatment for insomnia^{61,64,131–136} show that these two therapies are effective in the short-term, with drugs producing faster results in the acute (first week) phase of treatment, whereas they are equally effective in the short-term (4–8 weeks). Patients given CBT maintain their improvements with time, whereas those given drugs alone tend to relapse after discontinuation. Combined interventions have a slight advantage compared with single modalities during initial treatment, but this advantage does not always persist with time. Long-term effects are more equivocal with some studies suggesting that a combined intervention produces more sustained benefits than drugs alone,^{131,132} whereas others suggest more variability across patients for long-term outcomes.^{64,135}

Two studies have examined the effect of sequential therapies. In a small investigation,¹³³ the best outcome was obtained when CBT was introduced first in the sequence, irrespective of whether it was used alone or with drug treatment. In a larger study of 160 patients with persistent insomnia, a two-stage treatment approach was used to assess the added benefit of drugs to CBT and the effect of different maintenance therapies on long-term

outcomes.⁶¹ CBT used singly or combined with drug treatment produced similar rates of treatment responders (60% vs 61%) and remitters (39% vs 44%) after the acute 6-week treatment phase. After the 6-month extended treatment, a higher remission rate was reported for combined therapy than for CBT alone (57% vs 45%) and this higher remission rate was sustained throughout the 24-month follow-ups. In patients initially given combined therapy, those who continued with maintenance CBT but discontinued drug treatment during extended therapy achieved better long-term outcomes than those who continued using drugs intermittently. This finding suggests that, although drugs can provide an initial added benefit, discontinuation of drug treatment while patients are still receiving CBT is the best option.

A potential explanation of these findings is that behavioural and attitudinal changes are often essential to sustain sleep improvements. Attribution of therapeutic benefits to the hypnotic drug alone, without integration of self-management skills, could place a patient at greater risk for recurrence of insomnia once drug treatment is discontinued. Availability of drugs might undermine a patient's efforts and motivation for behavioural changes. Additional research is needed to assess the effects of combined therapies and examine the best methods for their integration.

Conclusion

Insomnia is a prevalent and costly public health problem. It is associated with substantial long-term effects on psychological, occupational, and physical functioning. Despite advances in diagnosis and management, insomnia is still under-recognised and often goes untreated. Although insomnia often presents with a comorbid medical or psychiatric disorder, it usually warrants separate treatment. Two therapeutic options—CBT and approved hypnotic drugs—have adequate evidence from clinical trials to support their use in the management of insomnia. Nonetheless, not all patients respond to these interventions. Important challenges for the future include the need to validate treatment algorithms that would take into account insomnia phenotypes, patient preference, and second line therapies for patients who do not respond to first line treatment. There is also an urgent need for more public education about sleep and broader dissemination of evidence-based therapies for insomnia, and education and training to prepare health-practitioners to attend and treat insomnia complaints according to clinical guidelines.

Contributors

Both authors participated equally in conception and writing of the article. CMM did the search for relevant references. Both authors revised and approved the final version of the article.

Conflicts of interest

CMM has served as a consultant for Eli-Lilly, Merck, and Sanofi-Aventis and has received research grants from Organon, Merck, and Sanofi-Aventis. RB has served as a consultant for Merck and Sanofi-Aventis.

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