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Primer

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Insomnia disorder

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Abstract

Insomnia disorder (ID) causes both night-time and daytime symptoms. Night-time symptoms include subjective difficulties initiating and maintaining sleep and early morning awakenings, whereas fatigue, perceived impairments in cognitive functioning, and mood disturbances are common daytime symptoms. The prevalence of ID in adults is high (10–16%) and the condition represents a substantial burden for both patients and society. ID is also an independent risk factor for other mental disorders and physical diseases. Diagnosis relies on self-report, as a biomarker for the disorder has not yet been established. The aetiological and pathophysiological understanding of ID spans from epigenetic and genetic research to cognitive behavioural and psychophysiological approaches. Clinical guidelines recommend cognitive behavioural therapy for insomnia (CBT-I) as the first-line treatment. However, CBT-I still requires widespread implementation, with digital CBT-I offering a scalable solution to improve treatment accessibility. Most available hypnotic agents are recommended solely for short-term use, owing to their limited efficacy and potential adverse effects. Given the considerable proportion of patients who respond insufficiently to medications and the need for further research on CBT-I, the development of novel interventions and the refinement of existing treatments is urgently required.

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Introduction

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1], insomnia disorder (ID) is defined as complaints of difficulties falling asleep, maintaining sleep and/or waking up too early from sleep. These difficulties must occur at least three nights per week for a minimum duration of 3 months and must be associated with complaints of daytime impairments, such as fatigue, irritability and reduced cognitive function. ID is a common disorder[2] with substantial economic and societal costs[3]. ID is an independent risk factor for other mental disorders and physical diseases[4–6], including depression, anxiety disorders and cardiovascular disease, raising the possibility that adequate treatment of ID could help to prevent the onset of such conditions. The pathophysiology of ID involves psychophysiological hyperarousal and cognitive behavioural factors, such as maladaptive behaviours (for example, excessive time in bed and daytime napping), nocturnal rumination and dysfunctional beliefs about sleep[7]. More recent research has started to identify involved epigenetic and genetic factors and neurobiological aspects.

In routine clinical practice, ID is frequently overlooked or not explicitly assessed[8], even though asking about sleep complaints is relatively straightforward. This may reflect the historical view within medical education that insomnia is merely a nuisance symptom or secondary to other medical conditions. Assessment is primarily based on clinical interview identifying patient-reported sleep difficulties and related daytime impairments. The first-line treatment is cognitive behavioural therapy for insomnia (CBT-I)[9–12], although sleep medications are the most commonly prescribed treatment in practice[13].

This Primer summarizes the epidemiology, pathophysiology, diagnosis and treatment of ID, and introduces possible directions for future research and clinical care.

Epidemiology

Prevalence and natural history

ID is the most prevalent sleep disorder and affects individuals of all ages and genders. It is estimated that 10–16% of adults meet the diagnostic criteria for ID and another 15–20% report subsyndromal insomnia[2,14,15]. In adolescents, the estimated prevalence of ID ranges from 10% to 24%[16,17].

ID is a global problem. One systematic review of studies in 19 countries estimated a prevalence of 16.2% for chronic ID in adults (lasting at least 3 months) and 7.9% for severe ID (at least two nocturnal symptoms and daytime consequences)[18]. Prevalence varies between countries and regions, with a higher reported prevalence in Brazil, China and the USA than in other countries[18]. These differences probably reflect multiple factors, including variations in study methodologies, although the full reasons for the disparities remain unclear. In Canada, the annual incidence of new-onset ID is approximately 2.8%, and 37.5% of individuals continue to meet the diagnostic criteria after 5 years[19]. The perception of ID may also be influenced by cultural factors as evidenced by the much lower prevalence estimates (<3%) of insomnia symptoms in pre-industrial societies such as those of nomadic hunter–gatherers in Bolivia and Namibia[20]. Some studies have suggested a 20–30% increase in the prevalence of ID since 2000 (refs. 21–23).

The impact of age and sex

Age and sex influence the prevalence of ID across the lifetime[24–26]. Few studies have focused specifically on childhood ID. Most of the available studies found no significant sex differences in participants at 5 years of age[26–29]. The prevalence of ID increases during puberty[16,26,27], at which time sex differences also begin to emerge, especially after menarche[16,26,27]. Psychological, social and environmental factors may contribute to these sex differences. During adolescence, insomnia symptoms rise in both sexes[17], with higher rates in girls (23.6%) than in boys (12.5%) aged 16–18 years[30].

The prevalence of ID is stable between 15 and 44 years, then increases after 45 years of age[26]. In adults, a higher prevalence in women is consistently reported across all age groups[26,31]. The prevalence of insomnia symptoms is particularly high during pregnancy and the postpartum period, affecting >70% of women[32,33]. Moreover, the prevalence of insomnia symptoms in menopausal women is around 45%[34–36]. In adults aged 60 years or above, the prevalence of ID is 19.6%, with higher rates linked to female sex and comorbid mental or physical health conditions[37]. Physiological changes may trigger ID during puberty, pregnancy and menopause, and psychosocial factors probably contribute to its maintenance.

Comorbidity

ID is frequently comorbid with a range of health conditions. For example, around 35% of people with ID also have obstructive sleep apnoea (known as comorbid insomnia and obstructive sleep apnoea (COMISA))[38,39]. COMISA is associated with poorer outcomes, including a 45–50% higher mortality risk and 70–88% higher cardiovascular disease risk than ID alone[40,41]. ID is also commonly comorbid with mental health conditions, such as depression, anxiety disorders, bipolar disorder, psychosis and substance use disorders. Of these, comorbidity rates are highest with depression and anxiety, with some estimates close to 50%[42]. ID is also associated with cardiovascular, respiratory and metabolic conditions[43,44], especially when ID co-occurs with polysomnographically measured short sleep duration[45]. The increased risk of comorbidity adds to the burden on individuals with ID.

Health consequences of insomnia

In the 1970s, various sleep alterations were identified as potential early biomarkers of mental disorders[46]. These include shortened rapid eye movement (REM) latency, increased non-REM (NREM) sleep and reduced NREM sleep. A landmark meta-analysis demonstrated that sleep disturbances are common across various psychiatric conditions and not specific to any single disorder[47]. Years later, this work was reframed as evidence that sleep disruption is a transdiagnostic feature of psychopathology[48]. These findings were confirmed in a more recent meta-analysis that found that impaired sleep continuity is a common characteristic of mental disorders[49]. Nevertheless, these studies could not establish causality. A subsequent meta-analysis showed that baseline insomnia symptoms in people without depression is associated with an increased risk of subsequent depression[50]. Moreover, another meta-analysis demonstrated that insomnia symptoms predict depression, anxiety disorders, alcohol abuse and psychosis, with high consistency across studies[6]. Further research is needed to evaluate the link between ID and other less-studied disorders, such as eating disorders and personality disorders.

ID can also increase the risk of some physical diseases. An umbrella review linked insomnia symptoms to cardiovascular disease, hypertension and thyroid cancer[5]. Moreover, this review found longitudinal associations with obesity, cognitive decline and dementia, although evidence was less robust for these associations. Importantly, individuals with insomnia symptoms exhibit poorer cognitive performance than healthy individuals across several domains, including memory, alertness and attention[51].

Economic burden

ID is associated with high economic costs. Healthcare utilization is increased in people with untreated ID, equating to almost US$64,000 in additional healthcare costs per patient with ID per year in the USA[3]. Indirect costs of ID include absenteeism from work, lower work performance ratings, disability, difficulties in daily activities and life dissatisfaction, all of which increase the economic and societal burden of this disorder[52]. In high-income countries, the estimated indirect cost of ID ranges from 0.6% to 1.3% of national gross domestic product per year[53]. These high direct and indirect costs add up, exceeding US$100 billion per year in the USA[54]. Both psychotherapeutic and pharmacological treatments for ID are cost-effective, with treatment costs recouped within 6–12 months of treatment initiation[54].

Mechanisms/pathophysiology

A substantial body of research has sought to elucidate the mechanisms and pathophysiology of ID, leading to the development of several influential models that have informed clinical interventions.

Predisposing, precipitating and perpetuating factors

The three-factor model describes the development and maintenance of ID in terms of predisposing, precipitating and perpetuating factors[55]. Predisposing factors relate to an individual's initial vulnerability for developing ID, and include biological factors (such as genetics and stress reactivity (the degree to which stress disrupts sleep)), psychological factors (personality traits such as neuroticism, introversion and perfectionism, and a tendency to worry or ruminate) and social factors (such as child rearing and shift work)[56–58]. Adverse childhood experiences (such as emotional, physical and sexual abuse) may also increase vulnerability to insomnia through heightened sleep reactivity[59–61]. Some predisposing factors are adjustable, and thus are suitable targets for prevention. Precipitating factors are acute events that trigger stress and result in the initial acute sleep complaints. The primary precipitating factors are often illness, bereavement, financial stress or even 'positive' factors such as commencing a new job[62–65]. The type of precipitating factor is not relevant per se, but the factor results in increased subjective stress, which in turn causes sleep difficulties.

Acute insomnia (insomnia symptoms for <3 months) is very common, but dissatisfaction with sleep can persist and develop into a chronic sleep disorder in a smaller number of individuals[63,66]. According to the theory, the reason for this transition is the presence of perpetuating factors, which are 'safety' behaviours adopted by the individual to compensate for sleep difficulties but that instead reinforce the sleep problem. Examples of such factors are extending time in bed or staying in bed while awake in (failed) attempts to obtain more sleep. These behaviours associate the bed and bedroom with wakefulness and other non-sleep behaviours and, as such, the bed and bedroom are no longer strongly associated with sleep. Targeting and reducing perpetuating factors is a key component of behavioural treatments for ID (that is, sleep restriction therapy and stimulus control therapy). Indeed, reducing the amount of time spent in bed awake, combined with increased homeostatic sleep pressure[67], is thought to be partially (but critically) responsible for treatment efficacy[68].

Genetics

Genetic factors have a role in the development of ID. Twin and family studies have indicated a moderate heritability of ID, with estimates ranging from 0.30 to 0.60 (refs. 69,70), with higher heritability in female than in male individuals[71]. Genetic predisposition may also underlie sleep reactivity with heritability estimates ranging from 0.29 to 0.40 (ref. 72). Findings from candidate gene studies have largely not been replicated in genome-wide association studies (GWAS) and may therefore represent false-positive results and/or effects limited to selected samples of individuals with ID. Unconfirmed associations have been found for the 3111T/C polymorphism of *CLOCK*[73,74], and polymorphisms in the circadian genes *PER1* and *PER2* (ref. 75) and the orexin receptors (*ORX1* and *ORX2*)[76]. Individuals with certain variants of *ORX1* develop insomnia symptoms at a rate 2.1 times higher than those without these variants[77]. Additional research has highlighted the relevance of polymorphisms in genes encoding $GABA_A$ receptor subunits (*GABRA1*, *GABRB3* and *GABRG2*)[78], the serotonin transporter region (*SLC6A4*)[79], neuropeptide S receptor (*NPSR1*)[80], brain-derived neurotrophic factor (*BDNF*)[81] and oestrogen receptor (*ESR1*)[82].

The number of GWAS has increased substantially in the past few years. These studies support the notion that ID has a polygenic origin. ID is considered the third most polygenic trait, following major depressive disorder and educational attainment[83]. GWAS suggest a substantial genetic overlap between insomnia symptoms and psychiatric traits (such as depression and anxiety), which may contribute to the association between ID and mental disorders[84,85]. GWAS findings account for only approximately 17.3% of the total heritability of ID, suggesting that additional factors, such as interactions between genes and environmental influences, probably contribute to the development of the disorder[83]. Specific patterns of DNA methylation are associated with disturbed sleep following psychosocial stressors in humans[69]. These findings suggest an epigenetic regulation of endocrine arousal responses to stressors[86]. However, epigenetic data on ID remain limited. In a pilot study, dysfunctional DNA methylation patterns were found in genes regulating sleep and brain development in individuals with ID compared with healthy controls[87]. Further epigenetic research is needed to elucidate the complex mechanisms underlying ID and its long-term effects on the brain[88].

Neurobiological perspectives

An early PET study found that people with ID have increased global cerebral metabolism during both NREM sleep and wakefulness compared with people without ID[89]. However, the findings of subsequent studies were largely inconsistent; the studies were limited by small sample sizes, divergent analytical approaches and the lack of independent replication[90]. A meta-analysis found a significant convergence of structural and functional neuroimaging findings in the subgenual anterior cingulate cortex, which is involved in fear-related emotional and cognitive processing[91]. Notably, other meta-analyses found similar abnormalities in different sleep disorders[92] and mental disorders[93]. Further supporting the close link between ID and mental health, a large multimodal brain imaging study found reduced cortical surface area, smaller thalamic volumes and weaker functional connectivity in three groups of individuals: those with insomnia symptoms, those with depression and those with anxiety[94].

Animal models of ID are used to study the mechanisms of sleep disturbances and to test potential treatments. In a rat model of acute stress-induced insomnia[95], exposure to a stressor prolonged sleep-onset latency and increased the frequency of nocturnal awakenings. In this model, stress led to increased activation of the cerebral cortex, limbic system (infralimbic cortex, bed nucleus of the stria terminalis and amygdala) and arousal-related areas (locus coeruleus and tuberomammillary nucleus) during sleep. Surprisingly, sleep-promoting areas (median and ventrolateral preoptic nucleus)

were also activated. Under normal conditions, reciprocal inhibition between sleep-promoting and arousal systems creates a bistable circuit with rapid transitions between wake and sleep, analogous to a 'flip–flop' switch[96]. However, these findings – although independent replication is pending – tentatively suggest that during stress-induced insomnia, both systems are simultaneously activated, causing instability and a hybrid sleep–wake state.

Arousal: hyperarousal or failure to inhibit arousal?

A prevailing concept across several models is that arousal is implicated in ID[97–99]. According to the theory, individuals with ID experience a level of physiological activity before or during the preferred sleep opportunity that is incompatible with the experience of good sleep, often conceptualized as 'hyperarousal'. Supporting evidence of a role for hyperarousal in ID includes increased activity of the hypothalamic–pituitary–adrenal axis as indicated by increased cortisol levels[100], small increases in metabolic rate[101], increased body temperature[102], and a potential neurotransmitter imbalance with reduced levels of γ-aminobutyric acid[103]. There is evidence that hyperarousal in ID occurs during NREM sleep[104] and REM sleep[105,106], resulting in increased awakenings and faster electroencephalography (EEG) frequencies[107]. These faster EEG frequencies are thought to be associated with increased sensorimotor and cognitive activity, which may explain the common phenomenon of sleep–wake state discrepancy in ID[108–111] (wherein patients overestimate wakefulness and underestimate sleep duration in comparison with estimates obtained from polysomnography).

By contrast, the psychobiological inhibition model suggests that physiological arousal is not heightened in ID but rather that ID arises from an inability to 'de-arouse'[112]. In this model, stressful life events are thought to initially trigger hyperarousal, and ID persists due to the inability to return to 'normal' arousal levels during the evening and night. Three key mechanisms are responsible for this shift, known as the attention–intention–effort pathway[113]. In this pathway, an individual becomes focused on sleep-related cues (attention), consciously intends to sleep (intention), and finally increases effort towards falling asleep (effort), which result in the inhibition of normal de-arousal processes. This pathway may thus perpetuate ID, whereby arousal and cognitive processes drive the inability to sleep by inhibiting de-arousal.

Cognitive perspectives

Maladaptive cognitions and beliefs about sleep are a key feature of ID. Individuals prone to worry and rumination are more likely to develop acute insomnia[114]. Additionally, worry and rumination can act as perpetuating factors when the inability to sleep restfully and the consequences of perceived sleep loss become targets of this cognitive activity, fuelling further worry and vice versa[115]. According to the cognitive model of ID, these cognitive processes during acute insomnia trigger arousal and distress[116]. This response leads to selective attention towards sleep-related threats, creates distorted perceptions about the daytime functioning deficits being experienced, encourages unrealistic expectations about sleep and leads to safety behaviours, such as daytime napping or cancelling appointments to reduce demands, all of which exacerbate insomnia symptoms. Attitudes, expectations and beliefs about sleep (also known as sleep-interpreting processes) are key to ID and appear to moderate the effects of worry on sleep[117–119]. For example, if an individual believes that sleeping for 8 hours is necessary, then when faced with the prospect of getting less than 8 hours of sleep, the individual will be more prone to worry. This worry contributes to the sleep continuity disturbance, which creates more worry, and thus the cycle of ID continues. Maladaptive cognitions and beliefs are the primary targets of cognitive therapy for ID.

Emotional perspectives

Poor sleep affects both children and adults emotionally, often resulting in irritability or overexcitement. Although this effect is common knowledge, the role of emotions in ID has only recently attracted systematic scientific attention. Since then, both theoretical models and empirical evidence have suggested that emotional processes and emotion dysregulation contribute to the development and maintenance of ID and may also link it to affective disorders[98,99,120–122]. For example, physiological[123,124] and neuroimaging studies[125] have shown heightened emotional reactivity in individuals with ID to disorder-related stimuli (such as images of people lying awake in bed at night and appearing frustrated). Moreover, REM sleep, which is crucial for emotion regulation, is often unstable in individuals with ID, with reduced REM duration, an increased number of arousals and an association with increased perception of wakefulness during REM sleep[105,110,126–128]. Such disruptions may hinder the overnight dissolving of emotional distress[129,130] by impairing overnight amygdala adaptation[131] and may result in an inability to dissociate anterior cingulate cortex activity from emotional memory traces[132]. Ultimately, these changes may link ID to depression and anxiety disorders[98,99,105]. At the behavioural level, emotion regulation is also impaired in individuals with ID, who rely more on dysfunctional strategies, such as rumination, avoidance or suppression, compared with healthy controls[133].

The cycle of ID

ID is an unrelenting condition that persists remarkably well over time, often for several years[134]. The microanalytic model[115] may explain this persistence and implicates four factors: arousal (physiological, emotional and cognitive arousal)[97], dysfunctional cognitions (such as worry and unrealistic expectations)[135], maladaptive habits (such as excessive time in bed and napping)[136] and consequences (such as fatigue and mood disturbances). Each factor has bidirectional relationships with each of the others, together creating the 'cycle of ID'[115] (Fig. 1). That is, each occurrence of insomnia symptoms results in consequences which promote dysfunctional sleep-related cognitions and maladaptive behaviours, which increases arousal and the likelihood of insomnia symptoms re-occurring, and thus the disorder is self-reinforcing. Breaking this cycle is therefore key to ID remission and forms the cornerstone of cognitive and behavioural treatments for ID.

Diagnosis, screening and prevention

Nosology

DSM-IV distinguished between primary and secondary insomnia[137], in which primary insomnia was defined as insomnia occurring in the absence of another medical, psychiatric or sleep disorder, and secondary insomnia was defined as insomnia that arises as a consequence of an underlying condition. The tenth revision of the International Classification of Diseases (ICD-10) distinguished organic and non-organic insomnia[138], in which organic insomnia was defined as insomnia caused by a medical condition, and non-organic insomnia was defined as insomnia not attributable to any medical condition. In DSM-5 (ref. 1), the distinction between primary and secondary insomnia was removed and both entities are now included under the single diagnostic category of ID, regardless of whether it occurs on its own or alongside other comorbid conditions (such as depression or chronic pain). The change was based on evidence that 'secondary' insomnia often persists after the

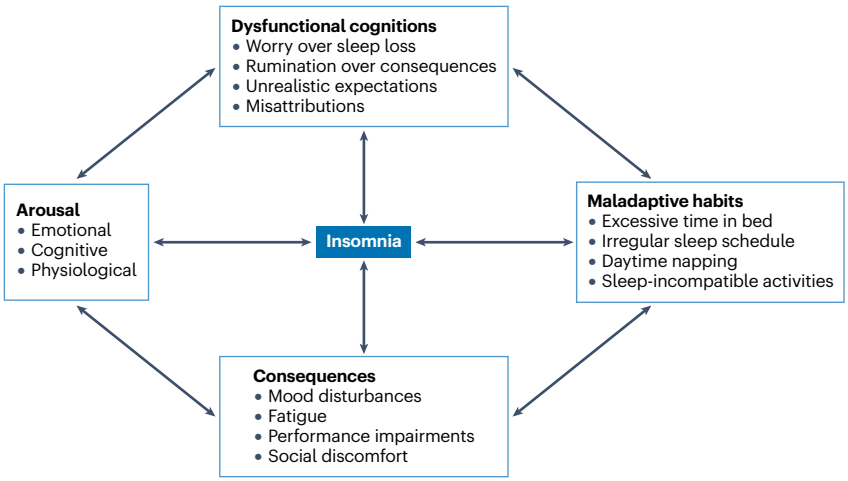

Fig. 1 | The 'cycle of insomnia' according to the microanalytic model. The microanalytic model explains the mechanisms through which insomnia becomes self-sustaining through four bidirectionally related factors: arousal, dysfunctional cognitions, maladaptive habits and consequences. Insomnia symptoms lead to consequences that reinforce unhelpful thoughts and behaviours, increase arousal and elevate the risk of symptom recurrence, thereby maintaining the disorder. Reprinted with permission from ref. 115, Guilford Press.

'primary' condition has been treated, making the separation more artificial than clinically useful. Likewise, the distinction between organic and non-organic insomnia was removed in ICD-11, and the International Classification of Sleep Disorders, third edition (ICSD-3) also uses the unifying entity of chronic ID. The diagnostic criteria for ID according to DSM-5, ICD-11 and ICSD-3 are now largely harmonized and presented, using ICSD-3 as an example, in Box 1.

Despite the shift towards a single diagnostic category for ID, numerous efforts have been made to identify reliable ID subtypes based on clinical characteristics[45,139,140]. More specifically, ID with objective short sleep duration is characterized by physiological hyperarousal, impaired neurocognitive function, and an increased risk of cardiometabolic diseases[45]. Moreover, five stable subtypes of ID have been identified based on analyses of personality traits, life history and affect[139]. To date, however, evidence supporting differential treatment recommendations for these subtypes has been insufficient for their inclusion in formal diagnostic nosologies.

Diagnostic procedure and screening

In Europe, the European Insomnia Guideline[10] provides a commonly cited framework for the diagnosis of ID, with recommendations that are similar to those of other diagnostic guidelines[9,11].

Diagnosis of ID relies mainly on a clinical interview and patient (or caregiver) reports of sleep difficulties and associated daytime dysfunction. Clinical assessment should include discussion of previous or current medical or mental disorders, personality and social factors, and substance use. Sleep history should include the history of sleep complaints, associated daytime impairment, and sleep–wake patterns, including daytime sleep and sleep timing. Moreover, sleep diaries for a duration of at least 7 days are recommended for monitoring daily sleep patterns[141] (Fig. 2). Diagnostic assessment should also incorporate information from bed partners or caregivers regarding sleep behaviours (such as snoring, apnoea and periodic limb movements). Physical examination, laboratory tests (such as blood count, thyroid, hepatic and renal parameters, C-reactive protein, haemoglobin, ferritin and vitamin B_{12}) or other medical diagnostic tools may be needed in some patients based on the clinical presentation. If indicated and available in clinical practice, additional tests may include electrocardiography, EEG, and CT or MRI (for example, when a neurological disease is suspected), as well as the evaluation of circadian markers (for example, melatonin and core body temperature) when a circadian rhythm sleep disorder is suspected. Questionnaires such as the Insomnia Severity Index[142], the Sleep Condition Indicator[143] and the Pittsburgh Sleep Quality Index[144] may help to evaluate symptoms and treatment outcomes. Polysomnography (Fig. 3) and actigraphy are reserved for people with treatment-resistant ID and those with suspected comorbid sleep disorders such as sleep-related breathing or movement disorders. Commercial sleep trackers that rely on body movement and/or cardiorespiratory signals are increasingly used to monitor sleep. However, many have not been validated according to scientific standards and may provide feedback that induces unnecessary worry and stress[145].

Prevention

Research on the prevention of ID, and mental disorders more broadly, remains limited[146–148]. Preventive approaches targeting infants may include the dissemination of knowledge about infant sleep and the promotion of positive bedtime routines[147]; however, a review of mostly psychoeducational school-based preventive sleep interventions found no clear benefits on sleep-related outcomes suggesting a need for more complex, tailored programmes[149]. In line with this finding, sleep psychoeducation alone is also not highly effective in treating ID[150–152]. Effective ID treatment might also prevent other mental disorders and physical illnesses. Indeed, this has been demonstrated by the prevention of incident major depression among older adults[153] and adolescents with ID through CBT-I[154]. However, evidence for the preventive effects of ID treatments on other disorders and diseases remains more limited.

Management

Clinical guidelines

Several clinical guidelines for the management of ID have been published in the past 10 years[9–12,155–160]. These evidence-based guidelines, including the 2023 European Sleep Research Society guidelines[10], suggest that CBT-I should be used as the first-line treatment for ID (Box 2). Pharmacological treatment is considered as a secondary option for patients in whom CBT-I has not been effective. Although expert statements agree that the treatment of ID in children and adolescents should also primarily rely on non-pharmacological interventions based on CBT-I principles[161–163], the evidence supporting both psychotherapeutic

and pharmacological treatments in this age group remains limited. Furthermore, there is a lack of high-quality insomnia guidelines specifically developed for children and adolescents.

Psychotherapeutic treatment

CBT-I is an umbrella term encompassing evidence-based therapeutics for the treatment of ID[115,164]. CBT-I comprises different cognitive behavioural techniques, and the choice of one or more techniques is made by the expert clinician according to professional competence and patient goals and preferences.

CBT-I is a multicomponent intervention addressing different contributing factors to ID. The behavioural components, sleep restriction therapy and stimulus control therapy, aim to consolidate and regularize sleep, increase sleep pressure[67] and create positive sleep-related associations. Sleep restriction therapy requires individuals to limit their time in bed to the actual amount of sleep obtained (determined from 1 week of sleep diary data), following which, the sleep window is adjusted weekly by increasing time in bed by 15 min when sleep efficiency calculated from sleep diaries (proportion of time spent asleep relative to the total time spent in bed) is above 85–90% or decreasing time in bed by 15 min when sleep efficiency is below 80%, until an optimal sleep duration is reached. No adjustments are made for the following week if sleep efficiency is above the lower limit (80%) and below the upper limit (85% or 90%). Stimulus control consists of behavioural instructions designed to re-associate the bed and bedroom with sleep and to re-establish a consistent sleep–wake schedule as follows: go to bed only when sleepy; get out of bed when unable to sleep; use the bed or bedroom only for sleep and sex (for example, no reading or watching TV); get up at the same time every morning; and avoid daytime napping. Both sleep restriction therapy and stimulus control therapy can produce clinically meaningful adverse effects, in particular increased tiredness and sleepiness during the first weeks of treatment[165,166]. Cognitive techniques, such as cognitive restructuring, aim to change dysfunctional beliefs and attitudes about sleep and alleviate worry and rumination at bedtime. These techniques are supported by psychoeducation, and are aimed at improving knowledge of sleep regulation and individual differences in sleep. Relaxation therapy is another component of CBT-I and may also be used to help reduce somatic tension and intrusive thoughts at bedtime.

Meta-analyses have demonstrated both the short-term and long-term efficacy of CBT-I in reducing insomnia severity[167,168]. However, effect sizes decline over time[168]. In clinical trials, CBT-I is usually administered in four to eight treatment sessions[167]. Remission rates are around 45% at the end of treatment for individual face-to-face CBT-I[169]. However, there is limited evidence suggesting that CBT-I improves objective sleep parameters[170] or objectively assessed cognitive performance[171] (Fig. 4). The most effective components of CBT-I are sleep restriction therapy, stimulus control therapy and cognitive therapy[150,151].

Largely due to the suboptimal availability of face-to-face CBT-I, digital CBT-I interventions have been developed and these approaches have reasonable efficacy for ID, especially when delivered with personalized guidance[172,173]. However, drop-out rates from digital CBT-I have ranged from approximately 5% to 50% in clinical trials[166,174]. Stepped care models for ID have been proposed, in which treatment intensity is progressively tailored to patient needs[175] (Fig. 5). In these models, digital CBT-I is the initial step, providing broad accessibility to treatment at relatively low cost, then group-based CBT-I is delivered to patients who do not achieve sufficient benefit from digital CBT-I[176]. The final step is individual CBT-I, which is the most resource-intensive form of care. Clinical trials evaluating stratified care in patients with ID are needed, in which those with uncomplicated ID receive low-intensity treatments and those with complicated ID receive high-intensity interventions[177].

CBT-I is effective in addressing the behavioural and cognitive factors that contribute to the development of ID[178]. Some initial evidence also indicates an effect on hyperarousal[179], although the evidence is not unequivocal[180]. Other psychotherapeutic treatment approaches target the heightened emotional reactivity and emotional dysregulation that are associated with ID. For example, mindfulness-based therapy for insomnia (MBTI) addresses metacognitions[181], integrating CBT-I techniques and mindfulness-based cognitive therapy for depression[182]. MBTI leads to acute improvements in insomnia severity, arousal and depressive symptoms, although evidence of long-term benefits remains limited[183]. Acceptance and commitment therapy (ACT) is another emerging approach focusing on emotional functioning. ACT emphasizes psychological acceptance (acknowledging thoughts and feelings without attempting to suppress or avoid them), commitment

Box 1 | Diagnostic criteria of chronic ID according to ICSD-3

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep
   2. Difficulty maintaining sleep
   3. Waking up earlier than desired
   4. Resistance to going to bed on an appropriate schedule
   5. Difficulty sleeping without parent or caregiver intervention
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the night-time sleep difficulty:
   1. Fatigue or malaise
   2. Attention, concentration or memory impairment
   3. Impaired social, family, occupational or academic performance
   4. Mood disturbance or irritability
   5. Daytime sleepiness
   6. Behavioural problems (for example, hyperactivity, impulsivity and aggression)
   7. Reduced motivation, energy or initiative
   8. Proneness to errors and accidents
   9. Concerns about or dissatisfaction with sleep
C. The reported sleep–wake complaints cannot be explained purely by inadequate opportunity (that is, enough time is allotted for sleep) or inadequate circumstances (that is, the environment is safe, dark, quiet and comfortable) for sleep.
D. The sleep disturbance and associated daytime symptoms occur at least three times per week.
E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months.
F. The sleep–wake difficulty is not better explained by another sleep disorder.

ICSD-3, International Classification of Sleep Disorders, third edition; ID, insomnia disorder. Adapted from the International Classification of Sleep Disorders, third edition (ref. 267) copyright American Academy of Sleep Medicine. Used with permission.

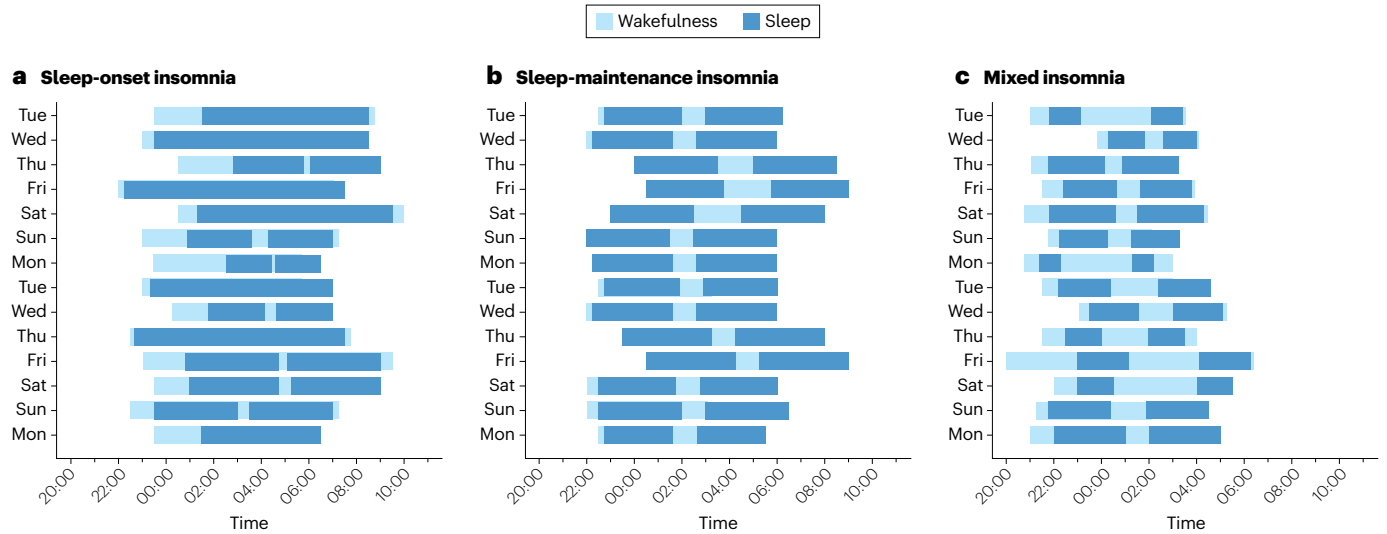

Fig. 2 | Representative sleep diary data. a, A patient with insomnia disorder (ID) showing increased sleep onset latency. **b**, A patient with ID experiencing difficulty maintaining sleep. **c**, A patient showing difficulty with both sleep onset and sleep maintenance.

to personally meaningful, values-based action, and psychological flexibility (the ability to adapt one's behaviour in accordance with personal values)[184]. Initial evidence supports the use of ACT in individuals with ID[185–187], and potentially also in patients unresponsive to CBT-I[188].

MBTI and ACT align with a new avenue of clinical research advocating process-based psychotherapy for ID[189]. As both emotion regulation and sleep processes are commonly disrupted in patients with mental disorders[47,49], sleep may qualify as a transdiagnostic process that psychotherapy should address more broadly[48]. Another emerging topic is the use of virtual reality for the treatment of ID. Some protocols have proposed using virtual reality to support meditation and relaxation[190] and exposure techniques[191], particularly in adolescents with ID. Adapting CBT-I for complex medical settings, such as inpatient psychiatric care, are also being developed and tested with promising results[192–194]. Further adaptations of CBT-I that are used in clinical practice include abbreviated forms (for example, brief behavioural therapy[195]) or standalone treatment with sleep restriction therapy[196], and combinations of CBT-I with chronobiologically informed treatments[197,198]. According to a survey among members of the World Sleep Society, availability of CBT-I is still limited outside Europe and North America[199]. Thus, restricted access continues to be a major barrier to implementation.

Pharmacological treatment

According to European and US guidelines, pharmacological treatment can be considered when CBT-I is insufficiently effective[10,12] (Table 1). This caution reflects the similar efficacy of both approaches in acute treatment but superior long-term benefits of CBT-I[10]. This distinction is important given that ID often persists for years or decades, a perspective that should be considered when initiating treatment pathways. Discussing potential long-term benefits and risks with patients is recommended before initiating pharmacological treatment, as a prerequisite for an informed and shared decision-making process[10,12].

Meta-analyses have demonstrated that benzodiazepines and benzodiazepine receptor agonists improve both subjective and objective sleep outcomes when used for up to 4 weeks[200,201]. However, beyond this time frame, little is known about the effects of these agents, except for beneficial effects of eszopiclone with use for up to 6 months[200,202]. Negative effects on cognitive functioning are an adverse effect of benzodiazepines and benzodiazepine receptor agonists[203]. Moreover, tolerance can develop within days to weeks[204]. Dose increases are not recommended and may promote the development of dependence. Sedating antidepressants, in particular doxepin and trazodone, improve subjective and objective sleep outcomes when used for up to 4 weeks; however, there is insufficient evidence regarding long-term outcomes and their effects on cognitive function[205]. Orexin receptor antagonists improve both subjective and objective sleep outcomes with short-term treatment without cognitive adverse effects[206,207], and there is some evidence that these effects can be maintained with long-term treatment[208] (Fig. 4). Orexin receptor antagonists are not available in all countries, but can be used for up to 3 months, with longer treatment durations evaluated on an individual basis after careful consideration of potential benefits and risks. Other pharmacological therapies for ID have insufficient supporting evidence; these include antipsychotics, sedating antihistamines, melatonin receptor agonists and phytotherapeutics[10]. However, melatonin can be recommended in patients with ID in whom circadian phase delays or advances are potentially exacerbating their insomnia symptoms[209]. Moreover, prolonged-release melatonin may be effective in some patients over 55 years of age for up to 3 months[210].

In general, patients with difficulties falling asleep in the evening may benefit more from agents with shorter half-lives, whereas patients with difficulties maintaining sleep may benefit more from agents with longer half-lives. No global consensus has been reached on the pharmacological treatment with the best efficacy or risk–benefit ratio[9–12,157,158,160,211]. This lack of consensus is partly because most pharmacological studies are limited to a few weeks in duration (with only a small number including longer-term observations up to 1 year[208,212,213]), which is insufficient for making evidence-based recommendations for long-term treatment.

Another limitation of pharmacological studies is that they focus on polysomnographic parameters, such as sleep onset latency

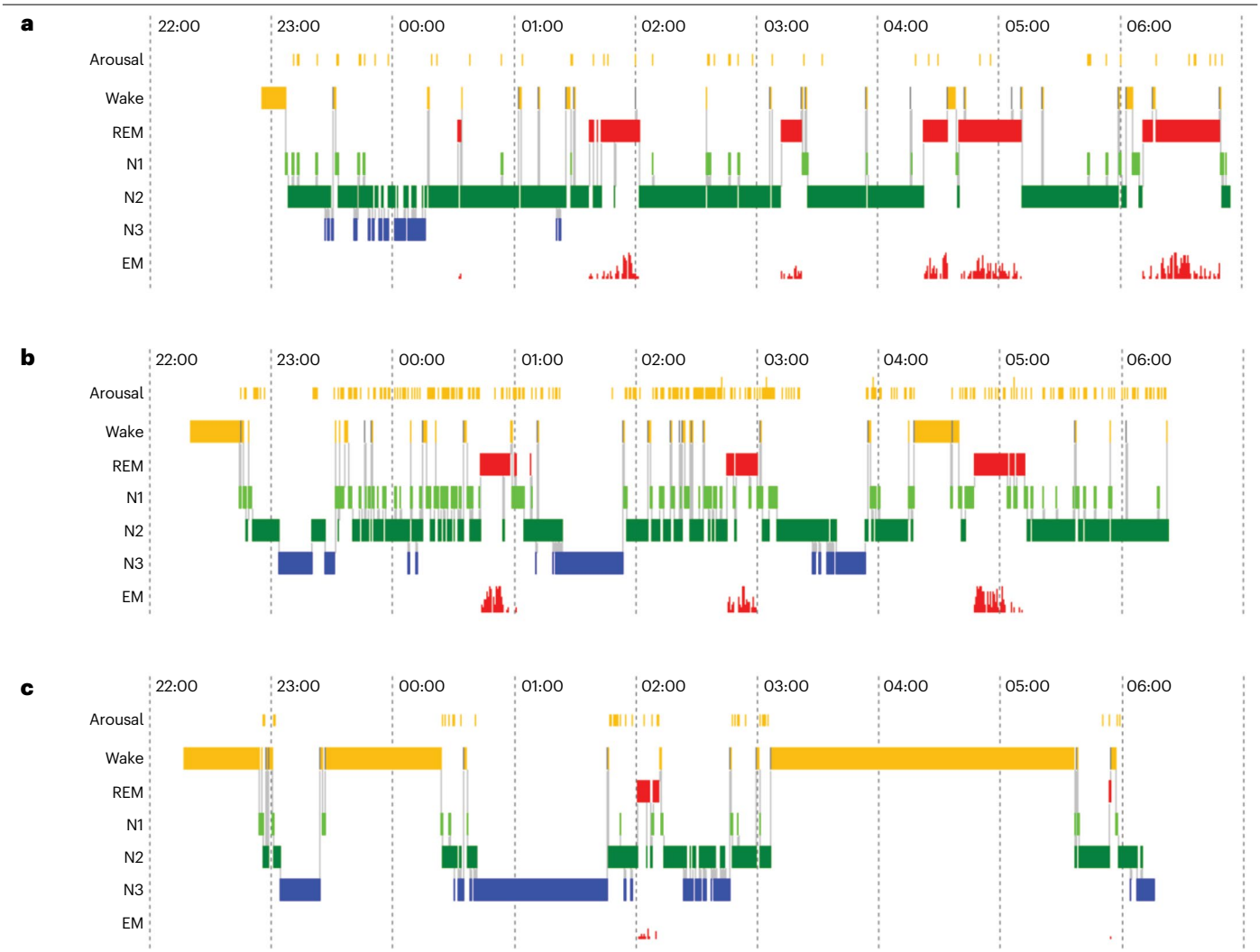

Fig. 3 | Polysomnographic data from a good sleeper and patients with insomnia disorder. a, Polysomnographic trace from a good sleeper. **b**, Polysomnographic trace from a patient with insomnia showing only slightly reduced sleep duration but frequent arousals and fragmented rapid eye movement (REM) sleep. **c**, Polysomnographic trace from a patient with insomnia disorder with objectively shortened sleep duration. EM, eye movements; N1–N3, NREM sleep stages 1–3.

or wake after sleep onset (WASO), as primary outcomes. However, many patients with ID do not exhibit marked alterations in these parameters[128], and these parameters also correlate poorly with subjective difficulties with sleep initiation and sleep maintenance. Moreover, several studies have included only patients with objective polysomnographic sleep disturbances, thereby reducing the generalizability of their findings for the full population of patients with ID. In these preselected patients, improvements in total sleep time with pharmacological treatment compared with placebo are often reported in terms of minutes. For instance, a standard dose of zolpidem – one of the most widely prescribed hypnotics worldwide – reduced polysomnographic sleep onset latency by 6 min and WASO by 16 min compared with placebo at week 2 (in 212 patients recruited from 40 centres, preselected on the basis of an objective WASO of >40 min)[214].

These considerations underpin guideline recommendations to reserve pharmacotherapy for people who do not respond to CBT-I, discuss effects of long-term treatment with patients, use low doses, avoid dose escalation, regularly re-evaluate potential benefits and risks, and discontinue whenever possible[10,12].

Dependence and withdrawal. Patients taking hypnotic medications for weeks, months or years can develop tolerance, rendering the medication less effective or ineffective. Many continue using the medication because dose reduction or discontinuation often leads to poor sleep quality (known as rebound insomnia) and, after long-term use, potentially severe withdrawal symptoms (including epileptic seizures and delirium), which require careful management and gradual dose reduction under medical supervision[215]. Although not all patients develop tolerance and dependence, these phenomena pose significant global public health concerns[216], emphasizing the need for cautious initiation, regular reassessment, avoidance of dose escalation and discontinuation whenever feasible.

Approval situation and the development of new substances. Approved pharmacotherapy for ID includes benzodiazepines, benzodiazepine receptor agonists, low-dose doxepin (in the USA), melatonin receptor agonists and dual orexin receptor antagonists[10,12]. Most of these substances are approved only for short-term treatment of ID (apart from the orexin receptor antagonists and slow-release melatonin) despite short-term pharmacotherapy often lacking efficacy after discontinuation[10]. Accordingly, off-label use is common in clinical practice. This off-label use includes prescribing approved drugs beyond their recommended duration, and recommending other non-approved substances such as sedative antidepressants, antipsychotics, antihistamines or herbal remedies.

Kinases have emerged as novel targets in sleep–wake regulation, and future pharmacological advances in sleep medicine may focus on these pathways[217]. The selective α_2-noradrenergic agonist dexmedetomidine, which attenuates locus coeruleus activity at subanaesthetic doses, has also been proposed as an alternative hypnotic based on the findings of an early-phase clinical study[218].

Other treatments

Some evidence supports the use of physical exercise[219], tai chi[220], light therapy (30–60 min of daily exposure to high-intensity bright light delivered via dedicated light-therapy devices)[221], and listening to slow music at bedtime for 30–60 min (ref. 222) for ID. Evidence is also accruing for the use of a brief behavioural therapy, intensive sleep retraining[223]. However, the number of randomized controlled trials and quality of the evidence is low, highlighting the need for larger, well-designed clinical trials. As these treatments are associated with few adverse effects, the European Insomnia Guideline suggests that elements of these treatments may be integrated with CBT-I[10].

Treatment of acute insomnia

Few clinical trials have investigated treatments for acute insomnia. Preliminary evidence from four randomized controlled trials suggests that CBT-I may be effective in preventing the progression to ID in this population[224], but further research is needed. Moreover, further studies are needed to evaluate whether pharmacotherapy can reduce the risk of developing ID in patients with acute insomnia, potentially by alleviating sleep-related worry and dysfunctional compensatory behaviours.

Combination therapies

As no single therapy is acceptable to all patients or fully effective for all forms of ID, combining therapeutic approaches may be required to optimize outcomes. Only very few studies have directly compared CBT-I and medications with combined approaches[225–228]. These studies indicated that CBT-I yields short-term improvements in sleep continuity,

Box 2 | Treatment recommendations according to the European Insomnia Guideline

Treatment considerations

- Insomnia disorder should be actively treated whenever it presents (**A**).
- In the presence of comorbidities, whether insomnia or the comorbid condition is treated first or whether both are treated at the same time is a matter of clinical judgement (**A**).

CBT-I

- CBT-I should be provided as the first-line treatment for insomnia disorder in adults of any age, regardless of comorbidities (**A**).
- CBT-I may be delivered either in-person or digitally (**A**).
- Sleep restriction and stimulus control are the most active ingredients of CBT-I (**B**).

Pharmacological interventions

- A pharmacological intervention can be proposed if CBT-I is not effective (**A**).
- BZ and BZRA can be used in the short-term treatment of insomnia (≤4 weeks) (**A**).
- Longer-term treatment (off-label use) with BZ or BZRA, either daily or preferably intermittently, may be initiated in some patients, and the advantages and disadvantages need to be discussed on an individual basis (**B**).
- Low doses of sedating antidepressants can be considered (off-label use) in the short-term treatment of insomnia; contraindications have to be carefully considered (**B**).
- Longer-term treatment of insomnia disorder (without comorbidities; off-label use) with low-dose sedating antidepressants may be initiated in some patients, and the advantages and disadvantages need to be discussed on an individual basis (**B**).
- Orexin receptor antagonists can be used for a period of up to 3 months in the treatment of insomnia (**A**).
- Longer-term treatment of insomnia disorder with orexin receptor antagonists may be initiated in some patients, and the advantages and disadvantages need to be discussed on an individual basis (**A**).
- Because of insufficient evidence and possible risks, antihistamines are not recommended for insomnia treatment (**A**).
- Because of insufficient evidence and in light of their side effects, antipsychotics are not recommended for insomnia treatment (**A**).
- Melatonin (fast-release, OTC or as a prescription drug) in general is not effective in the treatment of insomnia, if no circadian factors are involved (**A**).
- Longer-term treatment of insomnia disorder with PR melatonin (in patients >55 years of age) for up to 3 months may be effective in some patients (**B**).

Other therapies

- Herbal remedies and phytotherapeutics are not recommended for the treatment of insomnia because of insufficient evidence (**A**).
- Light therapy and exercise regimes may be useful as adjunct therapies to CBT-I (**B**).

The letters in bold type refer to the level of evidence: A, very strong recommendation; B, strong recommendation. The European Insomnia Guideline[10] provides a detailed description of the grading procedure.

BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists; CBT-I, cognitive behavioural therapy for insomnia; OTC, over the counter; PR, prolonged release. Reprinted with permission from ref. 10, Wiley.

	Subjective sleep (short-term)	Subjective sleep (long-term)	Objective sleep (short-term)	Cognitive	Quality of life	Important adverse effects
CBT-I	++	+	0	0	+	Transient daytime sleepiness early in treatment
BZ or BZRA	++	0	++	–	+	Tolerance, dependence, falls, cognitive impairment
Sedating antidepressants	+	0	+	0	0	Daytime somnolence, anticholinergic effects
Orexin receptor antagonists	+	+	+	0	0	Daytime somnolence, headache

High certainty of evidence | Moderate certainty of evidence | Low certainty of evidence

Fig. 4 | Effects of key evidence-based treatments for insomnia. 'Subjective sleep' refers to patient-reported difficulties with sleep onset and sleep maintenance, as assessed by questionnaires and sleep diary data. 'Objective sleep' refers to sleep onset and sleep maintenance, assessed using polysomnography or actigraphy. Short-term effects refer to post-treatment effects for cognitive behavioural therapy for insomnia (CBT-I) and to effects observed within the first 4 weeks of administration for pharmacological therapies. Long-term effects (6 months to 1 year) refer to follow-up effects for CBT-I and to effects observed during ongoing treatment with pharmacological agents. 'Certainty' is used in accordance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework and reflects the extent of our confidence that the estimated effects are correct. ++, pronounced positive effect; +, positive effect; 0, no clear effect; –, negative effect; BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists.

comparable to those produced by medication (mostly benzodiazepines and benzodiazepine receptor agonists), at the end of a treatment period of 4–8 weeks, and that medication increases sleep duration more than CBT-I. Combined therapy produces improvement in sleep more quickly (after 1 week of treatment) than CBT-I alone (after 2–3 weeks), but this advantage is lost by the 4th or 5th week of treatment[229].

Long-term follow-up has shown that sleep improvements are sustained to some extent with CBT-I but, with few exceptions, not with hypnotic medication when used alone[10,168,200]. An interesting approach is to introduce CBT-I and medication sequentially. This approach was evaluated in a two-stage, sequential multiple-assignment randomized controlled trial comparing CBT-I and CBT-I plus zolpidem, testing four different treatment sequences in 160 patients with chronic ID[225]. Following the initial 6-week treatment phase, a similar benefit was reported when CBT-I was used alone (59% of patients achieved a treatment response and 39% were in remission) or in combination with zolpidem (61% responders and 44% remitters). However, after extended treatment with CBT-I for 6 months, the remission rate was higher in those who received initial treatment with combined therapy (57%) than with CBT-I alone (44%). The higher remission rate was sustained throughout the 24-month follow-up. Moreover, in patients who initially received combined CBT-I plus zolpidem, those who continued with CBT-I but discontinued medication during extended therapy had achieved better long-term outcomes at the 6-month follow-up (68% remitters) than those using medication intermittently (two to three nights per week; 42% remitters).

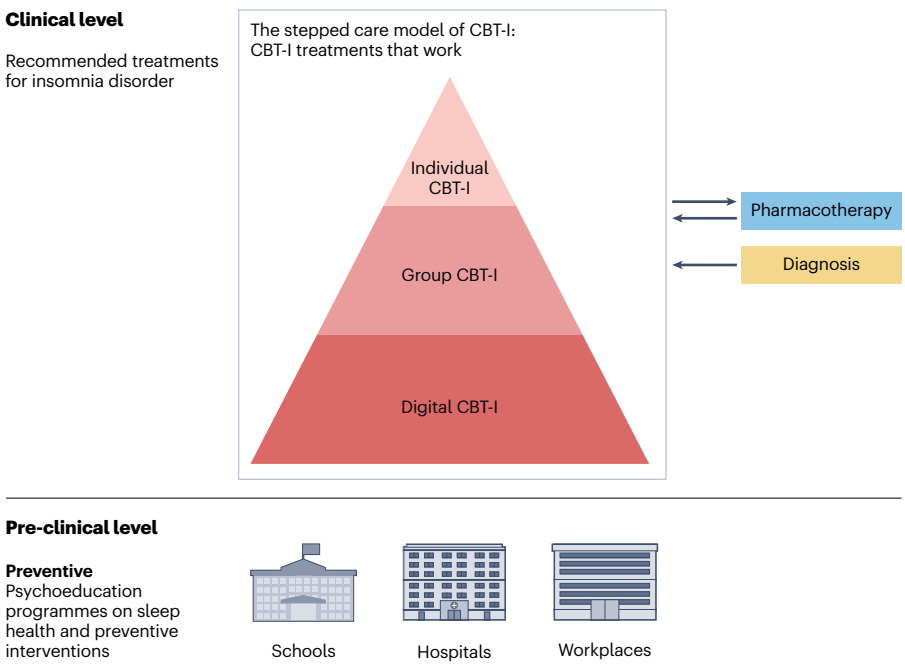

Fig. 5 | Stepped care model of cognitive behavioural therapy for insomnia within healthcare provision. In this stepped care model, treatment intensity is tailored to patient needs. Digital cognitive behavioural therapy for insomnia (CBT-I) represents the first, low-cost and widely accessible step. Patients who do not benefit sufficiently receive group-based CBT-I and, if necessary, individual CBT-I as the most resource-intensive option. Adapted from ref. 266, CC BY-NC-ND 4.0.

Another important question when combining therapies is the optimal order of treatment and how best to proceed when initial treatment fails. These issues were evaluated in one trial that assessed four treatment sequences of psychological and drug therapies in 211 adults with ID[230]. Patients received initial therapy with either behavioural therapy or zolpidem, and those who did not remit received a second treatment with medication (zolpidem or trazodone) or psychological therapy (behavioural therapy or cognitive therapy). In this trial, both initial therapies produced equivalent rates of responders and remitters (46% responders and 38% remitters with behavioural therapy; 50% responders and 30% remitters with zolpidem). Moreover, second-stage therapy in non-remitting patients further increased response rates in those who initially received behavioural therapy (from 41% to 63% with behavioural therapy followed by zolpidem; from 51% to 68% with behavioural therapy followed by cognitive therapy), but not for those who initially received zolpidem. A significant increase in the percentage of remitters was also observed with second-stage therapy sequences (from 38% to 56% with behavioural therapy followed by zolpidem; from 31% to 49% with zolpidem followed by trazodone).

Comorbidities

The European Insomnia Guideline recommends CBT-I as the first-line treatment in those with comorbid conditions[10]. Randomized controlled trials have found that CBT-I is effective for treating ID in people with common comorbid conditions including depression[231], anxiety disorders[232,233], post-traumatic stress disorder[234], cancer[235], heart failure[236], chronic pain[237] and obstructive sleep apnoea[238]. More evidence is needed for comorbid ID and bipolar or psychotic disorders, but supportive evidence is accumulating[239,240].

Despite the efficacy of CBT-I for comorbid ID, there are some contraindications to the use of CBT-I for this indication. Sleep restriction therapy should be avoided or applied with caution in patients with bipolar disorder or seizure disorders, as sleep deprivation may increase the risk of triggering manic episodes and seizures. Moreover, as CBT-I can lead to residual daytime sleepiness[165], it is not recommended for patients in whom excessive daytime sleepiness may cause accidents or critical errors, such as those who drive long distances or work in high-risk settings. Caution is also warranted in patients with higher baseline level of daytime sleepiness, such as in patients with COMISA. Additionally, certain stimulus-control instructions (such as advising individuals to get out of bed if they cannot sleep) should be used carefully in older adults or those at risk of falls.

With regard to pharmacological treatments for ID, antidepressants and antipsychotic medications are used frequently for sedation in those with comorbid mental disorders. However, sleep medications are contraindicated in some individuals. For example, benzodiazepines and benzodiazepine receptor agonists can increase the risk of falls and should be used carefully in older adults or those at higher risk of falls[241]. Moreover, these drugs are also contraindicated in pregnant women or in those with respiratory disorders (such as obstructive sleep apnoea) as they may suppress respiratory drive.

Table 1 | Major classes and examples of drugs used in the treatment of insomnia

Drug class (primary mechanism of action)	Example drugs	Half-life (h)
Benzodiazepines (agonistic activity at the $GABA_A$ receptor)	Lormetazepam	8–15
	Oxazepam	5–15
	Temazepam	8–20
	Triazolam	1.4–4.6
Benzodiazepine receptor agonists (agonistic activity at the $GABA_A$ receptor)	Zaleplon	1
	Zolpidem	2–4
	Zopiclone	5–6
	Eszopiclone	6
Sedating antidepressants (antagonistic activity at histamine receptors)	Amitriptyline	10–28
	Doxepin	8–24
	Mirtazapine	20–40
	Trazodone	4.9–8.2
	Trimipramine	15–40
Orexin receptor antagonists (antagonistic activity at orexin receptors)	Daridorexant	8
	Lemborexant	17–19
	Suvorexant	12
Antihistamines (antagonistic activity at histamine receptors)	Diphenhydramine	3–9
	Doxylamine	3–6
	Hydroxyzine	7–20
	Promethazine	10–12
Antipsychotics (different mechanisms of action)	Melperone	4–8
	Pipamperone	17–22
	Prothipendyl	2–3
	Quetiapine	7–12
Melatonin receptor agonists (agonistic activity at melatonin receptor)	Fast-release melatonin	0.4–1
	Prolonged-release melatonin	3.5–4
	Ramelteon	1–2.6

Quality of life

The chronic nature of ID and its associated sleep and daytime impairments profoundly affect the individual's quality of life[242]. Quality of life dimensions affected by ID include vitality and energy directly related to the daytime sequelae of the disorder (namely, fatigue and cognitive impairments)[243,244], but also extend to mental health and physical functioning more broadly[245]. These effects are clearly consequential to the individual, given that the most common reasons for seeking help for sleep are related to the daytime consequences of ID[246]. Many studies in this area use the Medical Outcomes Study short-form health survey 36 (SF-36) to assess quality of life[247]. These studies have consistently found that ID is associated with poorer scores on all of its eight domains (limitations in physical activities, social activities, usual role activities due to physical problems, usual role activities due to emotional problems, body pain, mental health, vitality and general health perception)[247].

ID is associated with reduced quality of life in almost all dimensions even after controlling for comorbidities[248]. In a large survey in the USA, the annual loss of quality-adjusted life years attributable to ID was found to be significantly larger than any of the 18 other medical conditions assessed, which included depression, arthritis and hypertension[249]. Moreover, more severe symptoms of ID have been associated with the poorest quality of life[250] after controlling for other conditions[251]. Multiple studies have suggested that ID increases morbidity, which in turn drives higher rates of healthcare use[52,252,253]. These higher rates may be due to comorbid chronic health conditions and motor and non-motor accidents in people with ID. ID also has

direct and indirect consequences on work. Indeed, ID leads to greater work absenteeism and presenteeism, higher risk of workplace errors and accidents, and reduced work productivity[254–257].

ID treatment has an important role in improving daily functioning and quality of life. One meta-analysis demonstrated that CBT-I has a moderate effect on quality of life[258]. This effect was smaller when ID was comorbid with another condition but was similar across face-to-face and digital CBT-I modalities. Moreover, in a large randomized controlled trial ($N = 1{,}711$), a digital CBT-I programme produced large and sustained improvements to sleep-related quality of life as assessed by the Glasgow Sleep Impact Index[166]. This effect was mediated by reductions in insomnia symptoms. With regard to work-related benefits of ID treatment, a study including digital CBT-I found that presenteeism was improved after treatment, but not absenteeism[259]. An economic evaluation found that CBT-I is highly cost-effective compared with pharmacotherapy or no treatment, particularly due to reductions in the costs associated with poor work productivity and absences[260].

The effects of benzodiazepines, benzodiazepine receptor agonists, sedating antidepressants and orexin receptor antagonists on quality of life have not been synthesized in meta-analyses[200,205,206]. However, several clinical trials have shown improvements in quality of life and work-related outcomes following treatment with benzodiazepine receptor agonists[213,261–263].

Outlook

The recognition and clinical management of ID has improved over the past decade. For the first time, all major diagnostic coding systems recognize ID as the principal overarching category, defined by largely identical criteria. This remarkable alignment provides an ideal foundation for research, enabling studies worldwide to be conducted using consistent definitions. Although most research on ID has been conducted in North America and Europe, future studies from middle-income and low-income countries will be essential to broaden the global evidence base and improve the generalizability of findings.

Regarding the mechanisms and pathophysiology of ID, identifying data-driven subtyping may improve the discovery of reliable biomarkers and clinically relevant phenotypes[45,139,198,264]. The heterogeneity of ID trajectories is evident in clinical practice, and approaches that inform differential treatment decisions would be highly valuable. Furthermore, pathophysiological models of ID should acknowledge the influence of age, sex and gender to facilitate the development of personalized therapeutic interventions. Overall, increased efforts should be directed towards replicating key findings in mechanistic research on ID and rigorously adhering to open science principles, including the pre-registration of hypotheses and analysis plans.

With respect to diagnostic procedures, the use of ambulatory sleep assessment tools is rapidly expanding, which may have both positive effects (increased diagnostic precision) and negative effects (increased focus on sleep that could fuel concerns and exacerbate the problem) on patients. Polysomnography remains costly and is performed in an artificial laboratory environment, limiting its routine use in patients with ID. Developing valid home-based methods that enable frequent central nervous system-based measurements in natural settings could be clinically and scientifically useful. Such tools would facilitate longitudinal studies of sleep characteristics (such as those related to slow-wave and REM sleep) and their response to treatment. However, a valid biomarker for ID has not been identified. Thus, subjective patient report remains the major focus of all clinical diagnostic and therapeutic efforts, paralleling the situation in other mental disorders.

Based on efficacy and safety data, clinical guidelines recommend CBT-I as first-line treatment for all patients with ID. However, a substantial number of patients do not achieve remission with CBT-I[169], and the treatment is not acceptable or available to everyone, including patients in low-income and middle-income countries[199]. Further research on CBT-I is needed to improve outcomes. Additionally, more studies on the efficacy of CBT-I in patients with specific comorbidities (such as sleep apnoea or specific mental disorders) would be valuable. Regarding pharmacological treatment, off-label use of medications for ID, such as sedative antidepressants or antipsychotics, is widespread. In this context, additional high-quality clinical trials are needed, and therapeutic innovations would be very welcome. Evidence on the relative harms associated with the use of hypnotics compared with those associated with untreated ID would also be of great interest.

In general, current clinical practice diverges from evidence-based guidelines. Moreover, ID is still under-recognized and under-treated in many individuals. These issues underscore the need for broader clinical recognition of ID within medical and related professions in order to improve access to effective treatments[265].

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Author contributions

Introduction (K.S. and D.R.); Epidemiology (C.B., C.M.M. and H.S.); Mechanisms/pathophysiology (K.S., C.B., C.M.M., L.P., M.L.P. and H.S.); Diagnosis, screening and prevention (C.B., L.P. and D.R.); Management (K.S., C.B., C.M.M., C.N., H.S. and D.R.); Quality of life (C.M.M. and H.S.); Outlook (K.S. and D.R.); overview of the Primer (K.S. and D.R.).

Competing interests

C.M.M. has served on advisory boards for Eisai, Idorsia and Haleon; has received research support from Lallemand Health; and has received royalties from Mapi Research Trust. C.N. has served on advisory boards for Lundbeck and Idorsia. L.P. served as consultant, adviser or CME speaker for Bruno, Fidia, Idorsia, Italfarmaco, Neopharmed gentili, Pfizer, Pharmanutra, Sanofi-Aventis and Viatris. D.R. has received honoraria for speaking engagements from GET.ON Institut für Online Gesundheitstrainings GmbH, Heel and Idorsia; and has received consultancy fees from GAIA.AG, Heel, Idorsia and X-trodes. K.S., C.B., M.L.P. and H.S. declare no competing interests.

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