Insomnia disorder

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Abstract

Insomnia disorder affects a large proportion of the population on a situational, recurrent or chronic basis and is among the most common complaints in medical practice. The disorder is predominantly characterized by dissatisfaction with sleep duration or quality and difficulties initiating or maintaining sleep, along with substantial distress and impairments of daytime functioning. It can present as the chief complaint or, more often, co-occurs with other medical or psychiatric disorders, such as pain and depression. Persistent insomnia has been linked with adverse long-term health outcomes, including diminished quality of life and physical and psychological morbidity. Despite its high prevalence and burden, the aetiology and pathophysiology of insomnia is poorly understood. In the past decade, important changes in classification and diagnostic paradigms have instigated a move from a purely symptom-based conceptualization to the recognition of insomnia as a disorder in its own right. These changes have been paralleled by key advances in therapy, with generic pharmacological and psychological interventions being increasingly replaced by approaches that have sleep-specific and insomnia-specific therapeutic targets. Psychological and pharmacological therapies effectively reduce the time it takes to fall asleep and the time spent awake after sleep onset, and produce a modest increase in total sleep time; these are outcomes that correlate with improvements in daytime functioning. Despite this progress, several challenges remain, including the need to improve our knowledge of the mechanisms that underlie insomnia and to develop more cost-effective, efficient and accessible therapies.

Insomnia disorder is a condition characterized by both nocturnal and diurnal symptoms. It involves a predominant complaint of dissatisfaction with sleep quality or duration and is accompanied by difficulties in initiating sleep at bedtime, frequent or prolonged awakenings, or early-morning awakening with an inability to return to sleep[1,2]. These difficulties occur despite adequate opportunity for sleep and are associated with clinically significant distress or impairment of daytime functioning including fatigue, decreased energy, mood disturbances and reduced cognitive functions, such as impaired attention, concentration and memory. Diagnosis of insomnia is made when sleep difficulties are present for ≥3 nights per week and last for >3 months[1,2].

There is an important distinction between acute sleep disturbance, which is a ubiquitous and transient phenomenon characterized by insomnia symptoms that typically last a few days or weeks, and insomnia disorder, which tends to be persistent and often lasts months or years. Insomnia disorder and insomnia symptoms have different courses and trajectories, and the most reliable duration of symptoms for defining insomnia is 3 months[3,4].

Insomnia is commonly associated with other medical and psychiatric disorders[5–8], but there is limited understanding of its mechanistic pathways; further, there is often a bidirectional relationship between insomnia and these disorders. This complexity has led current nosology (disease classification) systems to eliminate the distinction between primary insomnia, which cannot be attributed to another cause, and secondary insomnia, which is caused by a separate condition and adopts the term insomnia disorder. Where appropriate, co-morbid disorders are listed as descriptors when diagnosing insomnia (BOX 1).

The combination of the prevalence of insomnia with its effects on quality of life (QOL), occupational functioning and physical and psychological health means that the disorder inflicts a heavy burden on individuals and the broader community. However,

owing to barriers relating to treatment and management, insomnia often remains unrecognized and untreated[9,10]. This Primer summarizes the current evidence on the epidemiology, aetiology and pathophysiology of insomnia, and addresses key issues relating to its assessment, diagnosis and treatment.

Epidemiology

The worldwide prevalence of insomnia symptoms is approximately 30-35%, and epidemiological studies from different countries yield similar prevalence estimates. By contrast, depending on the diagnostic criteria used, prevalence rates of insomnia disorder range from 3.9% to 22.1%, with an average of approximately 10% for multinational studies that used the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM IV) criteria[11-14]. The 1-year incidence of insomnia varies between 7% and 15%[15-17]. Although insomnia can be situational or recurrent, its course is often chronic with a median duration of 3 years and persistence rates ranging from 56% to 74% at 1 year[17-19] and 46% at 3 years of follow-up assessment[19]. One longitudinal study found a remission rate of only 56% across 10 years for individuals reporting severe insomnia symptoms[20].

Sleep disturbances in insomnia can be characterized into sleep onset, sleep maintenance and mixed symptom phenotypes, which is the most prevalent[14]. Sleep-onset insomnia is more common in younger adults, whereas sleep-maintenance difficulties are more common in middle-aged and older adults. Of the three phenotypes, sleep-onset insomnia is the least stable and the mixed symptoms profile the most stable[18]. There are limited data on the natural course of insomnia phenotypes and even less information on the pathophysiology and clinical outcomes associated with such phenotypes. Although cross-sectional studies have shown that individuals with mixed symptom phenotypes report the most pronounced effect on daytime functioning[18,21], longitudinal studies have not confirmed these outcomes[18].

Factors that influence insomnia include age, sex and, potentially, ethnicity. Insomnia is more prevalent in women than in men and is also more commonly diagnosed in people with medical or psychiatric disorders than in the general population[5,13,22]. A potential reason for the sex difference in the prevalence of insomnia is gonadal steroid effects, as the rise in insomnia prevalence in women compared with men begins at puberty[23] and increases during and after menopause. Insomnia is also a common problem in children and adolescents[23]; however, much less information is available about its epidemiology and treatment in these younger age groups than in adults. Whereas insomnia symptoms and disturbed sleep, particularly sleep fragmentation, increase with age[24], the prevalence of insomnia itself is similar among older adults and younger people[12,15]. This discrepancy is primarily due to elderly people reporting daytime impairment or distress associated with their disturbed sleep less often than their younger peers. The prevalence of insomnia might also vary with race, but findings are currently inconsistent[12,25-27], and there have been few studies on the prevalence of this disorder outside of the United States that have examined potential racial or ethnic differences. Conclusive evidence of racial differences in insomnia will require multinational studies that account for both ethnic and racial heterogeneity while controlling for factors, such as socioeconomic status, that might moderate the observed effects.

Geography might also have a role in the development of insomnia. Northern latitude is associated with increased frequency of certain types of sleep disturbance. For instance, a comparison between people from Ghana (at 5°N) and Norway (at 69°N) found that those living in the northern latitude reported longer time to fall asleep in January and August than those living close to the equator, but no differences in waking up earlier than desired or in sleep efficiency between the two populations[28]. There are marked seasonal differences in daylight durations at northern latitudes, whereas these

differences in Ghana are very small. The possibility that people living in northern areas

of the world might experience more insomnia symptoms during the long dark periods

relative to the short dark periods has been examined, but results are equivocal. Whereas

cross-sectional studies of people living in regions with northern latitude have found

increased sleep disturbance during the winter[29], a longitudinal 2-year study conducted

in Norway did not find a relationship between rates of insomnia symptoms and

season[30].

Altitude has also been examined in relation to sleep because of the documented

increase in insomnia symptoms during acclimatization to high altitude. However, there is

no evidence of difference in the sleep architecture between individuals residing in high

altitude and those residing in low altitude[31].

Insomnia is related to a range of other disorders. For example, there is robust

evidence that insomnia is a risk factor for both incident and recurrent major depressive

disorder[32-35] and additional evidence, although weaker, that insomnia increases the risk

of developing an anxiety disorder, substance use problems and suicidality[36,37]. In

addition, cross-sectional and longitudinal studies have also shown that the phenotype of

insomnia with objective short sleep duration is a strong risk factor for hypertension[38,39],

diabetes[38] and other morbidities, whereas those with persistent insomnia have an

increased risk of mortality compared with those with recurrent insomnia and those

without insomnia[40]. Although bidirectional relationships exist between insomnia and

medical or psychiatric morbidity – for example, depression, anxiety and pain – such a

relationship does not hold for all associated disorders[18,41]. Furthermore, epidemiological

studies throughout the world have identified an association between insomnia, especially

reduced or fragmented sleep (see BOX 2 for definitions of key terms), and increased

rates of accidents[42,43] and falls in the elderly[44,45]. Accordingly, insomnia has been

proposed as a transdiagnostic contributor to the multifactorial causation of medical and psychiatric conditions[46].

Insomnia is also associated with significant direct and indirect costs[47], and in the United States accounts for 13.6% of all days out of role[48] and 4.6% of injuries requiring medical attention[42]. As such, the gross economic burden of this disorder has been estimated at up to US$107.5 billion per year[49]. In Canada, the individual economic burden of insomnia is estimated to be CA$5,010 per person per year, with nearly 90% of this amount being accounted for by indirect costs owing to work absenteeism and reduced productivity[50].

Mechanisms/pathophysiology

Despite the high prevalence of insomnia and its substantial global burden, the exact underlying mechanisms of the disorder have not been identified. Neurobiological and psychological perspectives have been elaborated that suggest alterations in brain function as well as genetic, behavioural, cognitive and emotional factors are involved in the development and maintenance of insomnia. These are conceptually classified into predisposing, precipitating and perpetuating factors[51] (FIG. 1). Predisposing factors, such as hyperarousal, make individuals vulnerable to the development of insomnia, precipitating factors, such as stressful life events, are the actual triggers of an acute episode of the disorder and perpetuating factors, including excessive worrying about sleep loss and its consequences, contribute to maintain sleep disturbances even after the initial trigger has been removed.

Unlike some other sleep disorders, such as sleep apnoea and narcolepsy, the state of research on insomnia is still in its infancy and its aetiology and pathophysiology are still unclear. Progress in this field has been hampered by the heterogeneity of the disorder, which might reflect different underlying causal mechanisms[52,53]. In addition, many studies in this area are correlational – thus making it impossible to draw valid

inferences about causal relations – and small sample sizes and a lack of independent replication for numerous findings preclude definitive conclusions.

Risk factors

A wide range of sociodemographic correlates of insomnia have been identified, and include advanced age, female sex, low socioeconomic status, unemployment, low educational attainment, psychological distress and self-rated poor health. Only a few of these meet at least one of the criteria for a true risk factor[54,55]. For instance, female sex[56], a positive family history of insomnia[57] and stress exposure in the form of severe and chronic life events represent reliable risk factors for the onset of insomnia[18,34].

The neurobiological perspective

Insomnia tends to aggregate in families, and at least 30% of affected individuals have a positive family history of the disorder[58]. Twin studies that compared monozygotic and dizygotic twins have estimated the heritability of insomnia to be between 30% and 60%[59–61]. Although these findings show that insomnia is in part attributable to genetic factors, the genes that are involved remain to be determined. Results from candidate gene studies support an association between sleep disturbances and alterations in circadian clock genes, such as period circadian clock 3 (*PER3*)[62], as well as between insomnia diagnosis and genes related to neurotransmitter function involved in sleep-wake regulation, such as the serotonin transporter solute carrier family 6 member 4 (*SLC6A4*)[63] and γ-aminobutyric acid A receptor β3 (*GABRB3*)[64]. In addition, two genome-wide association studies on insomnia have been reported[65,66]. However, potential associations that have been identified using either the candidate gene approach or genome wide association analysis await replication in independent samples. Thus, although several studies have established a moderate genetic heritability for insomnia, the underlying genes responsible for insomnia remain largely unknown[67].

Furthermore, it has been argued that epigenetic mechanisms might mediate the effect of stressful life events on stress-regulatory systems at the molecular level.[68]

A large body of evidence supports the notion that patients with insomnia are characterized by increased levels of physiological arousal during sleep and wakefulness, a phenomenon called hyperarousal.[69] This evidence includes increased activity of the hypothalamic-pituitary-adrenal axis as indicated by increased levels of cortisol,[70] increased activity of the autonomic nervous system as indicated by an increased resting heart rate and altered heart rate variability parameters,[71,72] increased metabolic rate[73] and increased body temperature[74] in people with insomnia compared with the general population (FIG. 2). Moreover, quantified sleep electroencephalography (EEG) and polysomnographic data reveal reduced sleep duration and sleep efficiency, an increased number of awakenings, a decrease in slow-wave sleep,[75] an increased number of arousals during rapid eye movement (REM) sleep[76] and an increase in fast frequencies in nocturnal EEG[77,78] in patients with insomnia. These increases in fast frequencies in EEG are assumed to be associated with an increase in sensorimotor and cognitive activity and have been suggested as a reason to explain the fact that many patients with insomnia overestimate sleep latency and underestimate sleep duration.[79] However, it is unclear exactly how the brain activity underlying increased fast frequencies interferes with sleep-promoting brain areas to result in the perception of poor sleep. Insomnia with short sleep duration (<6 hours) is a risk factor for several adverse health outcomes and, thus, has been proposed to be a distinct phenotype of the disorder.[41] In addition, patients with insomnia are characterized by increased sleep-onset latency during daytime investigations of sleepiness with the Multiple Sleep Latency Test.[73] This finding has been suggested as a potential objective marker of hyperarousal and has been linked to nocturnal sleep duration,[80] cognitive performance[81] and hypertension.[82]

An early functional brain imaging study using ^{18}F-fluorodeoxyglucose PET imaging reported increased brain metabolism in patients with insomnia in an extended brain network, including parts of the arousal system, the emotion-regulating system and the cognitive system[83]. This finding was interpreted as direct evidence for increased central nervous system arousal in patients with insomnia. Of particular importance, the only animal model of stress-induced insomnia – which involves exposing male rats to olfactory and visual cues of a competitor by placing them in a dirty cage previously occupied by another male rat – resulted in simultaneous activation of wake-promoting and sleep-promoting neuronal networks, indicating increased arousal levels and increased homeostatic sleep pressure[84]. This unique co-activation of wake-promoting and sleep-promoting brain circuits might result in instability of the so-called flip-flop switch of sleep-wake regulation[85]. In the flip-flop switch model (FIG. 3), rapid and complete transitions between wakefulness and sleep are induced by mutually inhibitory neuronal circuits. An instability of this system with an increased number of transitions and less complete transitions between wakefulness and sleep might increase the difficulty of correctly perceiving and memorizing the duration of these states of consciousness. Although speculative, this in turn might result in overestimation of wake time and underestimation of sleep duration, which are characteristic of patients with insomnia. The difficulties in perception and memory associated with instability of the flip-flop switch might be particularly true for unstable REM sleep, which has been suggested to have an important role in the discrepancy between subjective and objective sleep in insomnia[86].

Functional MRI has been used to study the neurobiological correlates of daytime performance in patients with insomnia[87,88]. These studies have shown that patients with insomnia are characterized by a reduced ability to engage task-related brain areas, in particular in frontosubcortical networks, which is possibly related to impaired attention

and arousal regulation. Of note, successful treatment did not lead to a recovery of altered caudate nucleus activity during an executive task[88], suggesting that task-related hypoactivation might be a vulnerability marker for insomnia. A further functional MRI study reported increased amygdala reactivity to sleep-related stimuli in those with insomnia[89]. Although it is clear that the experience of poor sleep is associated with negative emotional arousal, this, together with the finding of generally increased amygdala activity in individuals with insomnia[83], might also be suggestive of a vicious cycle between increased amygdala reactivity and poor sleep.

Altered brain function might also be related to changed brain morphometry in patients with insomnia. Pilot studies suggest there is a grey matter reduction in the frontal lobe[90] and hippocampus[91] and an increase in grey matter volume in the anterior cingulate cortex[92] in patients with insomnia. However, there are some concerns about the reproducibility of these findings[93]. In addition, functional impairments in frontosubcortical networks in patients with insomnia might be related to the finding of reduced integrity of white matter tracts in the anterior internal capsule[94], which contains fibres connecting the prefrontal cortex with subcortical nuclei. FIGURE 4 provides an overview of the central nervous system pathways that are potentially involved in the aetiology and pathophysiology of insomnia.

Hormones, neurotransmitters and neuropeptides have also been implicated in insomnia. The neurotransmitters that are important in sleep-wake regulation are also targeted by pharmacological therapies for insomnia. γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the central nervous system and promotes sleep by inhibiting all of the key arousal systems. For example, pronounced sleep-promoting effects can be observed when GABA activity is locally facilitated in the median preoptic area of the hypothalamus[95]. This area inhibits the ascending reticular activating system (FIG. 5), which constitutes one of the key sleep-promoting

mechanisms of the mammalian brain[96]. Studies using proton magnetic resonance spectroscopy have shown reduced levels of GABA in patients with insomnia[97]. This reduction is likely to result in difficulties initiating and maintaining sleep. Transmission of the neurotransmitter histamine is directly involved in the ascending reticular activating system. Histaminergic neurons are located in the tuberomammillary nucleus of the posterior hypothalamus and innervate the basal forebrain and cerebral cortex in an excitatory manner[98]. Consequently, antihistaminergic agents promote sleep. In addition, the hormone melatonin is secreted by the pineal gland in darkness during the night and is involved in the timing of biological rhythms as well as in promoting sleep[99]. The sleep-inducing mechanism of melatonin is thought to involve an attenuation of the alerting signal of the suprachiasmatic nucleus of the hypothalamus, an extensively studied cell group that controls circadian rhythms throughout the body. Finally, the lateral hypothalamus contains neurons that produce the neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively)[100]. These neurons reinforce arousal pathways in the brainstem and also have an excitatory effect on the basal forebrain and cerebral cortex, thus promoting wakefulness. Moreover, it is assumed that orexinergic neurons suppress REM sleep[96].

The psychological perspective

Predisposing risk factors for insomnia include psychological and physiological characteristics. For example, longitudinal studies have demonstrated that sleep reactivity – that is, the tendency to exhibit sleep disturbances in response to stressful events – is a predisposing risk factor for insomnia[34]. Moreover, several personality traits including neuroticism, sensitivity to anxiety symptoms and the tendency to internalize problems have been shown to be risk factors for insomnia[16,101]. In addition, results from two studies support the suggestion that perfectionism is a risk factor for insomnia[102,103].

However, the magnitude of the observed effects in these studies was rather small, and the effect could be explained by a third variable (emotional distress)[103].

The most frequently reported triggers of acute episodes of insomnia (also called precipitating factors) are stressful life events with a negative emotional valence that are related to family, health, work or school[104]. In addition, there is evidence to support the notion that acute stress has a negative effect on the onset of sleep difficulties[105,106].

Behavioural perpetuating factors for insomnia include excessive time in bed, an irregular sleep-wake schedule and daytime napping[51]. Many patients with insomnia use excessive time in bed and daytime napping as compensatory strategies against their perceived sleep loss. However, these strategies lead to more-pronounced sleep difficulties[51]. Classical conditioning has also been suggested to be an important perpetuating factor in insomnia[107]. In particular, it has been suggested that the bed and the bedroom environment of patients with insomnia become conditioned to arousal and anxiety during an acute episode of insomnia, leading to sleep problems even after the removal of the initial stressor. Furthermore, a large body of evidence demonstrates that worry and rumination are involved in the maintenance of insomnia[108]. These unproductive thought processes are believed to be associated with a level of physiological arousal that is incompatible with sleep initiation and maintenance. Moreover, self-report studies on emotions in patients with insomnia have shown an increased experience of negative emotions both in general and specifically at bedtime[109].

Several integrative models of psychological mechanisms involved in the development and maintenance of insomnia have been proposed[110-112]. In addition to the above-mentioned behavioural and cognitive characteristics of patients with chronic insomnia, these models suggest that sleep-related cognitions are of particular importance. These characteristics include unrealistic expectations concerning sleep

duration and daytime functioning, excessive worry over the consequences of sleep loss and a distorted perception of one's own sleep[113]. This set of beliefs and cognitive processes might lead to selective attention to sleep-related stimuli – preferential attention allocation to sleep-related cues, such as body sensations, for a sign of poor sleep – and explicit intention and effort towards sleeping[114,115]. In turn, this might have the effect of inhibiting sleep-wake automaticity and, thus, inhibiting sleep initiation and maintenance.

Diagnosis, screening and prevention

Insomnia is characterized by nocturnal and diurnal symptoms, as well as dissatisfaction with sleep quality or duration. Although some individuals might present exclusively with nocturnal symptoms, substantial daytime impairment and/or distress is an essential feature of insomnia (BOX 1). A 30-minute rule is often used to quantify insomnia – for instance, taking >30 minutes to fall asleep, spending >30 minutes awake after sleep onset or awakening >30 minutes before the desired time and before obtaining 6.5 hours of sleep. Although arbitrary and not part of the formal description, such criteria are useful to operationalize the definition of insomnia.

Classification

Three classification systems offer specific diagnostic criteria for insomnia. DSM-5 (REF. 1) and the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems*[116] offer a small number of broad categories based on current symptoms and functioning, whereas the third edition of the *International Classification of Sleep Disorders*[2] offers a larger number of subtypes based on clinical presentations and the presumed aetiology of insomnia. Common features of insomnia across these three classification systems include difficulties initiating sleep and/or problems maintaining sleep and waking up earlier than desired. In addition, the three classification systems include a requirement for substantial distress or daytime impairment per week that lasts

for at least 1 month (3 months for DSM-5) and occurs despite adequate opportunity to sleep (BOX 1). Although not yet included as subtypes in any of the classification systems, a growing body of evidence supports the delineation of two insomnia phenotypes – first, insomnia with objectively verified short sleep duration (<6 hours) and second, insomnia with near-normal objective sleep duration. The first phenotype is associated with poorer long-term health outcomes than the second one[117]. Additional research to enhance the understanding of the underlying aetiology and pathophysiology of insomnia and the relationship between these mechanisms and treatment responses could eventually translate to a diagnostic system that enhances our ability to match patients to treatments.

Diagnostic and screening methods

Diagnosis of insomnia is based on the patient's subjective complaint of difficulties initiating or maintaining sleep, along with reports of substantial distress or daytime impairments. Polysomnography, the gold-standard measurement of sleep, provides information that is useful in ruling out other sleep disorders that might account for the insomnia complaints, such as periodic limb movement disorder (PLMD) or sleep apnoea. Nonetheless, professional practice guidelines for the use of polysomnography indicate that performing polysomnography is not necessary to make the diagnosis of insomnia nor is it recommended for routine use in the evaluation of insomnia[118–120].

Assessment of medical history, current medication use and current health issues are essential when a patient presents with insomnia symptoms. This is because pain, discomfort and adverse effects of treatment of medical and psychiatric disorders can have negative effects on sleep. Checklists can assist clinicians in identifying important factors to screen for in patients with insomnia (BOX 3). Medication type, amount, time of administration and frequency of use are relevant. For medication taken for sleep, it is

particularly important to assess the degree of tolerance, withdrawal effects on discontinuation and psychological dependence.

Along with collection of a sleep or insomnia patient history, the most helpful tool for the assessment of sleep problems is completion of a daily sleep diary by the patient[121]. Daily recording is less influenced by recall and information processing biases than a retrospective global report during a clinical assessment. Retrospective recall of sleep patterns and insomnia symptoms require patients to provide an average over the past week or month. As a result, patients' descriptions of their sleep habits might be inadvertently influenced by their most recent or most noticeable evenings. Although paper versions of these diaries are inexpensive and easy to use, increasingly available Internet-based and electronic versions improve efficiency and accuracy by time stamping data and, thereby, ensuring the diary is actually completed each morning. Sleep diaries have two key benefits. First, upon clinical review, they reveal the type of sleep difficulty that the patient is experiencing – be that a problem with sleep onset, waking up after going to sleep, early-morning waking or a combination of these issues. In addition, diary entries might reveal variability in sleep across days, especially between weekdays and weekends, and whether the patient has bedtimes and rise times that are very early or late at night, which would suggest the need to further evaluate the role of circadian tendencies in the patient's presentation. Second, keeping a sleep diary can also have a direct therapeutic benefit for the patient by providing a broader perspective of their sleep issues[110].

Several patient-reported questionnaires can complement the assessment of insomnia, and two in particular are recommended to measure insomnia severity and sleep quality. The first is the Insomnia Severity Index[122,123], which is a 7-item scale that surveys the past month for sleep difficulties, degree of interference with daytime functioning and degree of distress. Each item is rated on a 5-point scale, and the total

score ranges from 0 to 28. A score of 0-7 suggests no clinical insomnia, a score of 8-14 indicates subthreshold insomnia, a result of 15-21 is considered insomnia of moderate severity and a score of 22-28 is indicative of severe insomnia. The second is the Pittsburgh Sleep Quality Index[124], which is a 24-item scale that also surveys the past month for sleep-related impairment. Items are rated on a 0-3 scale, and the total score ranges from 0 to 21, with higher scores indicating worse sleep quality. In addition to the total score, seven component scores that align to areas routinely assessed in clinical interviews can be derived from this instrument. The following interpretation guidelines are recommended: a total score of <5 is associated with good sleep quality and >5 is associated with poor sleep quality. Overall, these instruments are useful as screening methods and are sensitive to sleep improvement following treatment[125].

Factors that hinder diagnosis

Recent classification and diagnostic changes indicate a move towards recognition of insomnia as a disorder in its own right, along with greater operationalization and quantification of its diagnostic criteria. Nonetheless, the diagnosis of insomnia continues to be based on the subjective complaints made by the patient, rather than on any laboratory-based (polysomnography) measurement of sleep. There can be substantial discrepancies between perception of sleep difficulties and objective findings derived from polysomnography. A large discordance is referred to as sleep-state misperception or paradoxical insomnia[2]. For a patient with insomnia, the subjective perception is typically of taking more time to initiate sleep and of sleeping less than what is recorded by polysomnography. This discrepancy might pose a serious challenge to clinicians who usually do not have access to a sleep evaluation derived from polysomnographic recordings.

Several other sleep disorders might present with symptoms similar to insomnia and need to be ruled out, as the diagnosis of insomnia requires that symptoms are not

better explained by other sleep disorders. For instance, patients with PLMD are not usually aware of their limb movements, but the disorder nonetheless commonly results in problems with staying asleep and sleep that is non-restorative[2]. Diagnosis of PLMD requires polysomnographic testing. Clinical symptoms include descriptions from patients' sleeping partners who have observed 'kicking' in the night or describe the patient as a 'restless sleeper'.

Restless legs syndrome (RLS) is another sleep disorder that needs to be ruled out when evaluating insomnia. RLS involves discomfort or restlessness in the limbs – usually the legs – when the patient is at rest and is more pronounced in the evening[2]. These symptoms can interfere with sleep, particularly with sleep initiation. RLS is relieved by movements such as walking, tapping or stretching[1].

Another class of sleep disorders to consider during an assessment of insomnia is sleep-related breathing disorders (SRBDs), particularly obstructive sleep apnoea. Although patients with SRBDs chiefly complain of daytime sleepiness, some report that their most prominent problem is trouble sleeping. Indeed, increasing evidence supports the notion that SRBDs and insomnia are often co-morbid[126].

When considering a differential diagnosis of insomnia, SRBDs and PLMD, it is important to be aware of a crucial distinction between fatigue and excessive daytime sleepiness. Fatigue is typically a feature of insomnia and reflects low energy levels, whereas excessive daytime sleepiness is a characteristic feature of SRBDs and PLMD and reflects a physiological propensity to fall asleep unintentionally. Excessive daytime sleepiness is measured using the Multiple Sleep Latency Test, which is conducted in a laboratory during the day and scores the average time to fall asleep over several 20-minute nap opportunities.

Preventive measures

The field of preventive health care classifies three levels of prevention: primary, secondary and tertiary. Primary prevention refers to methods aimed at avoiding the occurrence of disease. In the context of insomnia, this can be done by promoting healthy sleep practices through sleep hygiene education. For example, information on caffeine and alcohol consumption – such as when and how much alcohol can be safely consumed – sleep environment, exercise and regular sleep schedules is typically offered through non-specialist press and on the Internet. Although typically integrated with behavioural therapies for insomnia, there is little evidence that these recommendations alone are effective as primary prevention for insomnia. An example of a more-intensive approach to primary prevention is a series of eight 15-minute televised programmes designed to improve sleep that was developed by the Dutch educational broadcasting company Teleac/NOT. The programme was augmented with nine radio broadcasts that offered additional details about the information and techniques presented in the television lessons – including theories of sleep, coping with dreams, the importance of routines and breathing exercises – and an audio recording that guided the listener through relaxation procedures[127]. The programme was viewed by approximately 200,000 people in the Netherlands and 23,000 of them ordered the written course material that included sleep diaries and an information booklet. An evaluation of the programme aimed to assess its effectiveness among those with sleep problems but, to the best of our knowledge, there was no assessment of the value of this programme for the prevention of insomnia among asymptomatic individuals. For the 325 viewers who reported sleep problems, there was a 22-minute decrease in sleep latency and a 35-minute increase in total sleep time.

Secondary prevention refers to the detection and targeting of risk factors of a disorder before its emergence. In the context of insomnia, this can be done by

developing methods to identify individuals who are vulnerable or at risk for insomnia. Several vulnerabilities for insomnia have been proposed, although, as highlighted earlier, few have been clearly established. Examples of plausible risk factors that await research include unhelpful beliefs about sleep and a history of experiencing disturbed sleep in response to stress. Identification of non-symptomatic individuals with these vulnerabilities and interventions to modify unhelpful beliefs and alter their stress response have the potential to prevent the development or re-emergence of insomnia. Validated measures for the identification of these vulnerabilities already exist[128,129], but the efficacy of the proposed preventive interventions has not yet been tested.

Tertiary prevention refers to reducing the negative impact of a disease. In the context of insomnia, which tends to be a chronic or episodic disorder, this can refer to efforts to enhance tolerance of and coping with poor sleep and to prevent the occasional poor night from becoming a relapse into another insomnia episode. Metacognitive approaches to insomnia[130] are particularly promising in this regard. They are focused on changing one's relationship with one's thoughts rather than the content of the thoughts. In doing so, metacognitive therapies aim to promote psychological flexibility – in other words, expanding one's behaviour and thought options to include willingness to tolerate a negative experience – responses to stressful situations that are reflective, rather than reflexive, and commitment to values-based actions[131]. A recent study provides preliminary evidence that one such metacognitive approach, acceptance and commitment therapy[132], improves subjective sleep quality and QOL of individuals with insomnia who have not responded to cognitive–behavioural therapy for insomnia (CBT-I)[133].

Management

Treatments available for insomnia include psychological, pharmacological and alternative therapies. Alternative therapies, such as valerian root and acupuncture, have

not been adequately evaluated and are generally not recommended for the management of insomnia owing to lack of evidence about their risks and benefits[134].

Psychological therapies

Psychological interventions for insomnia involve several distinct cognitive and behavioural therapies, hence the label cognitive-behavioural therapy. These interventions are aimed at changing sleep-scheduling behaviours and unhelpful beliefs and worries that are presumed to perpetuate insomnia. They can be used in isolation, but in clinical practice are commonly combined to address different contributing factors simultaneously.

Behavioural treatment methods include sleep restriction, stimulus control and relaxation therapies (BOX 4). Sleep restriction is designed to compress the sleep window as close as possible to the actual sleep time to strengthen the homeostatic sleep drive. This window is then gradually modified, usually on a weekly basis, contingent upon sleep efficiency (the ratio of time spent asleep to time spent in bed), until an optimal sleep time is reached[135,136]. This method is often combined with stimulus-control therapy, which involves a series of behavioural instructions designed to strengthen the association between the bedtime or bedroom environment and rapid sleep onset and also to establish a consistent sleep-wake schedule[107]. These behavioural procedures are predicated on the observations that individuals with insomnia tend to spend too much time in bed, perhaps as a mechanism to cope with the disorder, and often come to associate their bedroom environment with performance anxiety and the frustration of being unable to sleep.

There are several relaxation-based interventions that can be used in isolation or in combination with sleep restriction and stimulus-control procedures. Some of these methods, such as progressive muscle relaxation, seek to reduce physical tension, whereas others focus on reducing intrusive thoughts and mental tension, such as

imagery training. The selection of a particular relaxation method should be adapted to the specific needs of the individual, but daily practice over several weeks is often necessary to achieve benefits and, in most cases, professional guidance is initially needed to derive optimal therapeutic benefits[137].

Cognitive therapy seeks to alter misconceptions about sleep, unhelpful beliefs and negative thinking patterns such as worrying. This is usually accomplished through verbal interventions and behavioural experiments in which the patient is guided to test new hypotheses to challenge some unhelpful and engrained beliefs and to reduce excessive worrying about sleep and the perceived impact of sleeplessness[138,139]. This therapy is particularly helpful in alleviating the emotional distress and stopping the cycle of insomnia that often develops[140].

CBT-I is a brief, sleep-focused and directive psychotherapeutic approach designed to guide patients to modify behavioural and thinking patterns that are presumed to perpetuate or exacerbate insomnia[138,141]. CBT-I is typically carried out over four to six individual or group therapy sessions in which the therapist, who is a psychologist or other mental-health-trained clinician, provides guidance to change sleep habits, sleep schedules and thinking patterns. Keeping a daily sleep diary is also an essential element of CBT-I. In addition to engaging the patient in the therapeutic process, it enables the clinician to evaluate insomnia symptoms, sleep schedules and exacerbating factors, and to monitor progress during the course of therapy. CBT-I can also be complemented with didactic materials available in print or on the Internet. Recent studies have yielded promising results with DVD-based[142] and Internet-based CBT-I[143,144], although such treatment delivery methods should be considered as complementary rather than a replacement for live, face-to-face CBT-I.

CBT-I is often the treatment of choice for chronic insomnia. The efficacy of CBT-I for treating younger and older adults ranging in age from early 20s to late 70s,

regardless of whether they are taking medication, has been extensively documented. Furthermore, increasing evidence supports its use in the management of insomnia that is co-morbid with medical issues, including pain and cancer[145,146], and psychiatric disorders, such as depression[134,137,147,148] (A. Van Straten, J. Lancee, A. Kleiboer, P. Cuijpers and C.M.M., unpublished observations). The effects of CBT-I include improvements in sleep continuity and sleep efficiency, which are achieved through reductions in sleep latency and time spent awake after sleep onset (average effect sizes of 0.6-0.8). Although there are extensive data supporting the benefits of CBT-I for sleep-onset and maintenance insomnia, less evidence is available for patients with insomnia that is characterized by early-morning awakenings. Based on patient-reported outcomes such as the Insomnia Severity Index, 70-80% of patients are estimated to achieve a response to CBT-I and approximately 40% to attain remission after therapy. Sleep improvements achieved with CBT-I are well maintained over time, with evidence of sustained benefits documented up to 2 years after treatment completion[125].

There are few contraindications to certain components of CBT-I. As sleep restriction might produce residual daytime sleepiness[149], it should not be used in patients with symptoms of excessive daytime sleepiness, or with individuals who drive long distance or are engaged in hazardous occupations. Sleep restriction should also be avoided or used with caution among patients with bipolar disorders or seizure disorders because of the potential risk that sleep deprivation might trigger a manic or hypomanic phase or seizure. Some stimulus-control instructions, such as getting out of bed if unable to sleep, should be used with caution with the elderly who might be at risk of falls.

Medical therapy

Many different medications are available for the management of insomnia, and have either been approved for this specific use or are used 'off label' (TABLE 1). Differences in the characteristics of these agents include their pharmacological properties, their risk-

benefit profile when used to treat insomnia and the patients for whom they are indicated and contraindicated. The optimal clinical pharmacological management of patients with insomnia requires the clinician to be aware of these medication attributes and use this knowledge to choose the medication that minimizes the treatment risk–benefit ratio for each patient on the basis of their characteristics and the specific nature of their insomnia.

US FDA-approved treatments. The benzodiazepines are a group of compounds that exert their therapeutic effect on sleep through allosteric modulation of the GABA type A receptor complex[150,151]. Benzodiazepines are capable of having broad inhibitory effects on brain function, which include: sleep enhancement, myorelaxation, anxiolysis, anticonvulsant effects, cognitive impairment, motor impairment and reinforcing effects[151]. The binding of benzodiazepines enhances the inhibition caused by GABA when it binds to its receptor. Although various benzodiazepines are used to treat insomnia, several are not indicated by the FDA for the treatment of this condition and have never been studied to determine their risk–benefit ratio in the treatment of patients with insomnia[152]. These agents are most effective for treating sleep-onset problems, although some have demonstrated efficacy for treating problems with falling asleep and staying asleep. Although most people who take benzodiazepines do so appropriately, their use might be problematic when taken by the small subset of the population who are prone to abusing these medications[152].

The 'non-benzodiazepines' are a group of agents that are not part of the benzodiazepine chemical class but act via the same mechanism: to enhance GABA-mediated inhibition through allosteric modulation of the GABA type A receptor complex[150–152]. In the United States, these agents include zolpidem (immediate release and modified release), eszopiclone and zaleplon, whereas in Canada and Europe, zopiclone and immediate-release zolpidem are available. All of these agents are

approved by the FDA for the treatment of insomnia and have a solid evidence base that has established their risk–benefit ratio in the treatment of insomnia. Similar to the benzodiazepines, these agents are among the most-effective treatments for helping people fall asleep. Eszopiclone and modified-release zolpidem have also been shown to improve sleep maintenance in patients with insomnia and have been approved by the FDA for this purpose. All of these agents might be problematic for those who are prone to abusing this class of drug[152].

Although many medications block the histamine H1 receptor (H1R) to a degree, doxepin at dosages of <6 mg is the only truly selective H1R antagonist available[98]. Studies with this agent[153,154] indicate that it has robust effects on sleep maintenance and modest effects on sleep onset. As a result, it is approved by the FDA only for improving difficulties staying asleep. Notably, it has its greatest therapeutic effects in the last third of the night including the last hour of the night, which makes this agent uniquely suited for treating patients with early-morning awakening[98]. It has minimal abuse potential so can be used in those prone to substance-use-related problems.

Ramelteon is a melatonin receptor agonist that exerts its therapeutic effect via binding to type 1 and type 2 melatonin receptors[152]. This agent is only effective in initiating sleep and, as a result, has a FDA indication only for the treatment of sleep-onset difficulties. It is generally well tolerated and is without substantial abuse potential and could be considered for use in individuals who are prone to substance abuse, although there are no studies of its use in this population. It has been demonstrated to be safe in those with obstructive sleep apnoea and those with chronic obstructive pulmonary disease[155,156].

Another agent that exerts its therapeutic effect via melatonin receptors is melatonin itself[99]. Melatonin is available over the counter in the United States and Canada, and a prolonged-release version has been approved by the European

Medicines Agency for the treatment of primary insomnia in patients >55 years of age.[157].

Melatonin is widely used by patients with insomnia, and for some is their preferred therapy.[157].. This is at least in part owing to the excellent safety profile of melatonin.[158].. Numerous studies have evaluated the effects of various dosages and preparations (immediate release and prolonged release) of melatonin in patients with sleep disorders.[159,160].. These studies indicate that melatonin has a greater therapeutic effect in patients with delayed sleep-phase syndrome than in those with insomnia, although improvements in sleep latency seem to occur in patients with insomnia as well. However, it remains unresolved as to whether the magnitude of the therapeutic effect seen in patients with insomnia is large enough to be of clinical significance for the majority of patients.

Suvorexant is the first antagonist of orexin receptors available for the treatment of insomnia. It was approved by the FDA with an indication for treating sleep-onset and sleep-maintenance problems. Suvorexant is notable for its efficacy in treating sleep difficulties in the last third of the night.[161].. Orexinergic agents vary in their affinity for orexin A and orexin B receptors, although suvorexant blocks both. Clinical trials on suvorexant indicate that it has sustained efficacy for up to a year of nightly use without significant rebound insomnia and has an overall favourable adverse-effect profile.[161,162].. Several agents that block the orexin receptors, other than suvorexant, are in development for the treatment of insomnia. Some of these agents block either orexin A or orexin B receptors, although others are dual-receptor antagonists, like suvorexant. The implications of these pharmacological differences remain unknown as there are no published data on orexin antagonists other than suvorexant.

Off-label treatments. Several agents approved for the treatment of major depressive disorder are used off label for the treatment of insomnia. The most commonly used antidepressants are trazodone, amitriptyline, mirtazapine and doxepin, although, with the

exception of doxepin, which is used at dosages of 3–6 mg for insomnia, they are used at the same or lower doses in this context than for the treatment of depression[152]. All of these agents have non-selective pharmacological effects and have adverse effects consistent with this profile. In addition, there are minimal data on the risk-benefit ratio of these agents in the treatment of insomnia. Although trazodone is one of the most widely prescribed antidepressants, the available studies provide a limited indication of the risk-benefit ratio in the treatment of patients with insomnia. By far the largest study carried out evaluating the efficacy and safety of trazodone in patients with insomnia compared 50 mg of trazodone ($n = 98$) with 10 mg of zolpidem ($n = 100$) and placebo ($n = 103$)[152]. This study found that trazodone was associated with significant improvement compared with placebo on sleep parameters that were derived from a morning diary in the first but not second week of a 2-week study. By contrast, zolpidem led to significant improvements in both weeks compared with placebo. Trazodone had significant effects on sleep in the second week of the study but on only the patient global impression ratings. This study also reported that 30% of patients who were treated with trazodone reported headache compared with 24% of those who took zolpidem. In addition, 23% of trazodone-treated patients had somnolence as an adverse effect compared with 16% of patients who were treated with zolpidem. Four smaller placebo-ontrolled studies of higher dosages in the range of 50-100 mg of trazodone have been carried out. Some of these trials found that high doses of trazodone improved sleep, which was indicated primarily by measures of sleep maintenance; however, this improvement was associated with a significant increase in next-day sleepiness and cognitive impairment based on objective tests, such as the critical flicker fusion test and a cognitive testing battery[163–165]. Doxepin has been evaluated in several placebo-controlled trials in the dosage range of 25-50 mg. In this context, its pharmacological effects are, in addition to H1R antagonism, 5-hydroxytryptamine receptor 2A antagonism, anticholinergic effects and

anti-adrenergic effects and the associated adverse effects[166-168]. Mirtazapine and amitriptyline have not been studied in placebo-controlled trials in patients with insomnia. The use of these medications carries substantial risks of daytime sedation and weight gain, and amitriptyline also has significant anticholinergic adverse effects[152]. As mirtazapine is a highly potent H1R antagonist with an affinity for this receptor that is far greater than its affinity for other receptors, at a low enough dosage, this agent probably becomes a highly selective H1R antagonist with effects that are similar to the use of doxepin at a dosage of 3-6 mg. However, there are no data available to evaluate whether this is the case.

Several antipsychotic medications are also used off label for the treatment of insomnia. No placebo-controlled trials have evaluated the use of antipsychotics to treat insomnia and, as such, their risk-benefit ratio in insomnia therapy remains unknown[152]. The most common adverse effects of these agents include daytime sedation, dizziness, anticholinergic effects and increased appetite. Less common adverse effects include parkinsonism, acute dystonic reactions, akathisia and tardive dyskinesia[152].

The antihypertensive agent prazosin, which blocks α1 adrenergic receptors, has been shown to have therapeutic effects in the treatment of nightmares and sleep disturbance in post-traumatic stress disorder[169-172]. The primary adverse effects are orthostatic hypotension, particularly when first arising from bed, and dizziness, which can be minimized by starting with a low dose and gradually increasing the dosage. Prazosin has minimal reinforcing effects and can be considered in patients who are prone to substance abuse.

Anticonvulsants that are used to treat insomnia off label include gabapentin and pregabalin. Both agents exert sleep-enhancing effects by binding to the voltage-dependent calcium channel subunit α2/δ2. This binding decreases the activity of glutamatergic and noradrenergic neurons that are involved in promoting

wakefulness[173,174]. Gabapentin was found to have sleep-promoting effects in a small placebo-controlled study of patients with insomnia and co-morbid alcohol dependence[175], and several studies have documented that pregabalin has sleep-promoting effects in patients with generalized anxiety disorder[176]. The most common adverse effects of these agents are daytime sedation and dizziness. Gabapentin can also be associated with ataxia and diplopia, and pregabalin might be associated with dry mouth, cognitive impairment and increased appetite. Pregabalin has some abuse potential, whereas gabapentin has minimal reinforcing properties.

Combined therapies

Psychological and pharmacological therapies could have complementary roles in the treatment of insomnia. Comparisons of effect sizes derived from meta-analyses[177-179] indicate that CBT-I has a slight advantage in improving measures of sleep-onset latency and sleep quality, whereas pharmacotherapy (benzodiazepine receptor agonists) produces a more favourable outcome on total sleep time. Evidence from the few randomized clinical trials that have directly contrasted the effects of CBT-I and medication for insomnia indicates that both therapies are effective in the short term, and that medication tends to lose its effects after drug discontinuation, whereas CBT-I produces the best-sustained long-term benefits[125,180,181].

Combined therapy might have a slight advantage over single-treatment modality during acute treatment of insomnia, but this initial advantage does not always persist over time. The main evidence for this conclusion comes from a sequential, two-stage treatment trial that assessed both the effect of adding drug treatment to CBT-I and the effect of different maintenance therapies on long-term outcomes[182]. Following the initial 6-week phase of the trial, similar rates of success were produced when CBT-I was used alone or in combination with zolpidem. At this stage, combined therapy resulted in 61% of patients reaching the criterion for a treatment response and 44% reaching the criterion

for remission, and single therapy produced a 60% treatment response rate and a remission proportion of 39%. After the 6-month extended treatment, a higher remission rate was reported for those who were initially treated with combined therapy (57%) than for those who used CBT-I alone (45%). This higher remission rate was sustained throughout the 24 months of follow-up study[182]. Of interest, among patients who initially received combined therapy, those who continued with maintenance CBT-I but discontinued medication during extended therapy achieved better long-term outcomes than those who continued using the drug intermittently (2-3 nights per week). Thus, although medication might provide an added value during the initial course of treatment, drug discontinuation while patients are still receiving CBT-I is the most effective long-term management strategy.

One potential explanation for these findings is that behavioural and attitude changes are important in sustaining sleep improvements over time. Conversely, a patient who receives medication might be less inclined to implement behavioural changes. In addition, patients who fail to integrate self-management skills and attribute their improvements in sleep to medication alone might be at a greater risk of recurrence of insomnia once medication is discontinued than those who only received behavioural treatment. Thus, despite the intuitive appeal of combining behavioural and medication therapies, additional research is needed to evaluate the effects of combined and sequential treatments and to examine optimal methods for integrating these therapies as, currently, it is not entirely clear how these therapies should be combined and who they should target.

Several guidelines and consensus statements[118,134,158] are available that outline how to select the most appropriate treatment to manage insomnia. The use of a hypnotic medication might be particularly indicated to provide rapid relief in acute insomnia. Conversely, CBT-I is essential to alter factors that exacerbate or perpetuate insomnia

and thus should be the first-line therapy for persistent insomnia. Although hypnotic medications should be discontinued after an initial treatment course of a few weeks, insomnia can be a recurrent problem even among those who initially benefit from treatment. Under such circumstances, the intermittent use of medication might be necessary. Additional research is required on the indications for long-term use and on optimal strategies to combine psychological and pharmacological therapies for insomnia.

Quality of life

The chronic nature of insomnia and its associated medical and psychiatric sequelae produce a profound burden on QOL. Insomnia severity is associated with reduced QOL in nearly every domain of functioning, even after controlling for medical and psychiatric disorders[48,183,184]. Both work productivity and attendance are negatively affected by insomnia[50,185,186]. Given that the outcome that insomnia has on QOL is comparable to that of other chronic conditions such as congestive heart failure and major depressive disorder[187], it is not surprising that the overall health effect of insomnia is often greater than in its common co-morbidities[12]. Several cross-sectional studies suggest that co-morbid insomnia symptoms exacerbate QOL in cancer, pain disorders and Parkinson disease[55,188-190]. Insomnia has also been shown to reduce QOL in adolescents, with prospective data indicating that insomnia poses a significant risk of impaired inter-personal functioning, problems with peers, low social support and life dissatisfaction[191].

Treatment might normalize several aspects of QOL in insomnia. Two placebo-controlled trials using benzodiazepine receptor agonists showed that 1-6 months of treatment improved sleep in patients with insomnia, and that this was accompanied by improvements in QOL including social functioning, vitality and work domains[192,193]. Measures of QOL in people with insomnia 12 months after treatment with zopiclone were no different from controls, which provides evidence for sustained improvement in QOL with continued treatment[194]. Behavioural treatment of primary insomnia has also

been shown to improve health-related QOL domains, such as vitality, physical functioning and mental health[195]. Finally, in a clinical trial of patients with insomnia co-morbid with non-metastatic breast cancer, a cognitive-behavioural intervention improved both global and cognitive measures of QOL at post-treatment and at the 6-month follow-up assessment[196].

Outlook

Substantial progress has been made in the past two decades in understanding and treating insomnia. However, there is still limited knowledge about its aetiology and pathophysiology, possible biological markers and optimal therapies, leaving many unanswered research questions wide open for future investigations.

At the epidemiological level, there is wide variability in prevalence and incidence rates of insomnia, which is partly accounted for by variable definitions and assessment methods used across studies. Recent efforts in harmonizing diagnostic criteria across nosology systems[1,2] should facilitate the use of standardized insomnia definitions and assessment procedures in future epidemiological research. Longitudinal studies have begun tracking the natural history of insomnia over time, but additional investigations are needed to document moderators and mediators of insomnia trajectories, as well as long-term outcomes associated with persistent insomnia. Such studies would create opportunities to design and evaluate prevention programmes for at-risk individuals.

With regard to mechanisms and aetiology, it is well recognized that hyperarousal is a core feature of insomnia, but it remains unclear whether this represents a cause, a consequence or an epiphenomenon of insomnia, whether hyperarousal is a state or a trait feature of insomnia and how hyperarousal is related to cognitive processes that are assumed to be involved in the development and maintenance of insomnia. More research is required to investigate the biological and psychological bases of hyperarousal and to examine how these are intertwined to produce insomnia. Along

these lines, there is also a need to determine the mechanisms by which insomnia interacts with co-morbid disorders, such as depression, pain and cardiovascular disorders. Increasing availability of neuroimaging technology should facilitate future research to search for reliable markers of insomnia. Additional research is also needed to identify clinically useful phenotypes.

Much evidence has been obtained about the burden of insomnia on QOL, occupational functioning and psychological and physical health. Additional research is necessary to examine indices of QOL that are uniquely or differentially impaired in insomnia relative to commonly occurring co-morbid disorders, such as depression. There is also a need to identify the contribution of hyperarousal, the effect of sleep loss and sleep fragmentation associated with insomnia on QOL, and whether QOL varies as a function of different factors – including onset, maintenance and objective duration phenotypes, sleep quality, patient age and sex and co-morbidities.

Several challenges with regard to the management of insomnia remain. Although effective treatment options are available, and these are safer than therapies used in the past (for example, barbiturates), no single treatment modality is effective, tolerated or acceptable to all patients with insomnia. More clinical trials are needed to examine how to best combine psychological and pharmacological therapies to optimize treatment response, while at the same time taking into account the patient's preference. Given the frequent co-morbidity between insomnia and other medical and psychiatric disorders, clinical studies are also warranted to evaluate the value of adding insomnia-specific treatment for patients who present with co-morbid psychiatric conditions, such as depression, or medical disorders, such as pain and hypertension. Likewise, given the well-documented morbidity associated with insomnia, it will be essential to document the effect of treating insomnia on long-term health outcomes. Ultimately, we need to evaluate whether we can reverse morbidity with insomnia treatment.

There is a wide gap between current clinical practice and available evidence on insomnia therapies. For instance, insomnia is often unrecognized and untreated. When treatment is initiated, it is typically with over-the-counter drugs or natural products that have unknown risks and benefits. Furthermore, there is widespread use of off-label medications, such as antipsychotics, for the management of insomnia, with little or no evidence supporting such practices. A serious challenge for the future will be to disseminate more efficiently validated therapies and practice guidelines and foster their use in various clinical settings. On the practical side, there is a definite need to develop more cost-effective, efficient and accessible therapies. Further validation of behavioural interventions through the Internet and other mobile devices is warranted.

Box 1 | **Clinical features of insomnia and changes in diagnostic criteria**

Diagnosis of insomnia requires patient dissatisfaction with sleep quality or duration along with other night-time and daytime symptoms that are present for ≥3 nights per week and last for >3 months.

Night-time insomnia symptoms

- Difficulty falling asleep at bedtime (sleep-onset insomnia)
- Frequent or prolonged awakenings (sleep-maintenance insomnia)
- Early-morning awakenings (late insomnia)

Daytime insomnia symptoms

- Fatigue and reduced energy
- Impaired attention, concentration or memory
- Mood disturbances
- Difficulty functioning in academic or occupational settings

Insomnia classification systems

Current diagnostic criteria reflect important changes that have been made in the latest versions of the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition)[1] and the *International Classification of Sleep Disorders* (third edition)[2]. They include:

- Elimination of the distinction between 'primary insomnia' and 'secondary insomnia' (that is, insomnia related to another medical or psychiatric disorder). This reduces the need to make a causal attribution between insomnia and co-existing disorders, as there is limited understanding of mechanistic pathways in chronic insomnia and thus about the nature and directions of these associations. This change also acknowledges bidirectional or interactive effects between sleep disorders and co-existing medical or psychiatric disorders, and still requires specification of clinically relevant co-morbid conditions
- Deletion of 'non-restorative sleep' from the definition of insomnia, as this is not specific to insomnia and is often reported with several other sleep disorders
- Change in the definition of chronic insomnia to include a minimum frequency of 3 nights per week with insomnia and increased minimum duration threshold from 1 month to 3 months
- Addition of the construct of 'sleep dissatisfaction' to the definition of insomnia
- Specification of 'early-morning awakening' as a nocturnal insomnia symptom

Box 2 | **Key terms**

- Fast EEG frequencies: EEG activity in the beta (16-32 Hz) or gamma (32-48 Hz) range
- Fragmented sleep: sleep that is frequently interrupted by brief arousal or awakening
- Homeostatic sleep drive: an internal pressure to sleep that increases with wakefulness and decreases with sleep. The homeostatic sleep drive is in constant interaction with the circadian clock to regulate sleep–wake cycles
- Hyperarousal: a state of increased arousal at the physiological, cortical, cognitive or emotional level
- Non-restorative sleep: sleep that is judged qualitatively to be non-refreshing or of poor quality
- Sleep efficiency: time spent asleep divided by the time spent in bed × 100
- Sleep latency: time from lights out or bedtime to sleep onset
- Sleep restriction: a behavioural treatment that consists of restricting the amount of time in bed as close as possible to the actual sleep time
- Sleep window: the amount of time between the initial time into bed and the final arising time
- Slow-wave sleep: a stage of sleep with synchronized EEG activity with a frequency of 0.5-2 Hz and a relatively high amplitude
- Stimulus-control therapy: a set of behavioural recommendations intended to strengthen the association between sleep and the bedroom or bedtime stimuli, and to establish a consistent sleep–wake schedule
- Unstable REM sleep: REM sleep that is characterized by an increased number of awakenings and sleep-stage changes compared with normal sleep patterns
- Wake after sleep onset: time spent awake between the initial sleep onset and the final arising time

EEG, electroencephalography; REM, rapid eye movement.

Box 3 | **Guidelines for assessment of insomnia***

Insomnia symptoms
- Age of onset, precipitating event (or events) and sudden or gradual onset
- Current symptoms including difficulty getting to sleep, problems staying asleep and waking up too early
- Frequency of symptoms: either every night, episodic, specific nights, situation-specific or seasonal variation
- Course since onset of symptoms, such as change in severity over time or relative emergence of symptoms (if more than one)
- Perceived daytime consequences

Factors that influence insomnia symptoms
- Past and current treatments including their efficacy
- Factors that improve or ameliorate symptoms
- Factors that exacerbate insomnia, such as stress or schedule changes
- Factors that maintain insomnia including behavioural factors, for example going to bed too early, getting extra sleep on the weekends and drinking alcohol, and cognitive, for instance unhelpful beliefs about sleep, worry about the consequences of insomnia and fear of poor sleep

Health
- Medical disorders and symptoms, including co-morbid sleep disorders
- Pain, discomfort and treatments that interfere with sleep
- Pharmacological considerations including alerting and sedating effects of medications

Social
- Work schedule that is incompatible with sleep
- Arriving home late without enough time to wind-down
- Family and social responsibilities at night, such as caretaking of a child (or children) or an elderly person
- Stressful life events: past stressful events might be precipitants and current stressful events might be perpetuators
- Sleeping with pets

*Compiled based on information from REFS 118,197.

Box 4 | **Cognitive–behavioural therapies for persistent insomnia**

Sleep restriction (level 1a*)
A method designed to restrict time spent in bed (the sleep window) as close as possible to the actual sleep time, thereby strengthening the homeostatic sleep drive. This sleep window is then gradually increased over a period of a few days or weeks until optimal sleep duration is achieved.

Stimulus control (level 1a)
A set of instructions designed to reinforce the association between the bed and bedroom with sleep and to re-establish a consistent sleep–wake schedule:
- Go to bed only when sleepy
- Get out of bed when unable to sleep
- Use the bed or bedroom for sleep only (no reading or watching television, and so on)
- Arise at the same time every morning
- No napping

Relaxation training (level 1b)
Clinical procedures, for example progressive muscle relaxation, aimed at reducing autonomic arousal, muscle tension and intrusive thoughts that interfere with sleep. Most relaxation procedures require some professional guidance initially and daily practice over a period of a few weeks.

Cognitive therapy (level 2b when used alone)
A psychological approach using Socratic questioning and behavioural experiments to reduce excessive worrying about sleep and reframe unhelpful beliefs about insomnia and its daytime consequences. This therapy usually requires a trained and skilled clinician. Additional cognitive strategies might involve a paradoxical intention technique to alleviate performance anxiety that is associated with the attempt to fall asleep.

Mindfulness-based interventions (level 3b)
The core principle of mindfulness-based interventions is non-judgemental awareness in the present moment. It is derived from meditation, and its most common variant is mindfulness-based stress reduction.

Sleep hygiene education (insufficient evidence)
General guidelines about health practices, including diet, exercise and substance use, and environmental factors, such as light, noise and excessive temperature, that might promote or interfere with sleep. This might also include some basic information about normal sleep and changes in sleep patterns with ageing.

Cognitive–behavioural therapy (level 1b[‡])
A multimodal intervention that combines some of the above cognitive and behavioural procedures, such as stimulus control, sleep restriction and relaxation training. Multicomponent behavioural therapy would include more than one behavioural procedure but without a cognitive component.

*Indicates level of evidence (University of Oxford Centre for Evidence-Based Medicine).
[‡]For cognitive-behavioural therapy with or without relaxation; level 1a for multicomponent behavioural therapy without cognitive therapy. Adapted with permission from REF. 199, Elsevier.
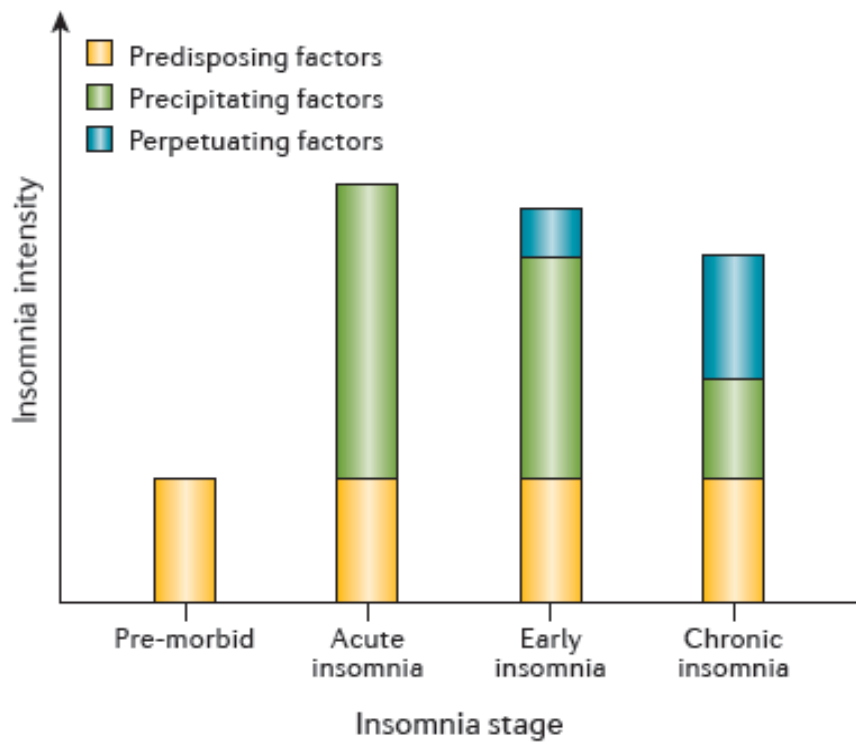
Figure 1 | **The relative importance of three types of factors in the course of insomnia.** The various stages of insomnia are influenced, to different degrees, by predisposing, precipitating and perpetuating factors. Adapted with permission from REF. 198, Springer.
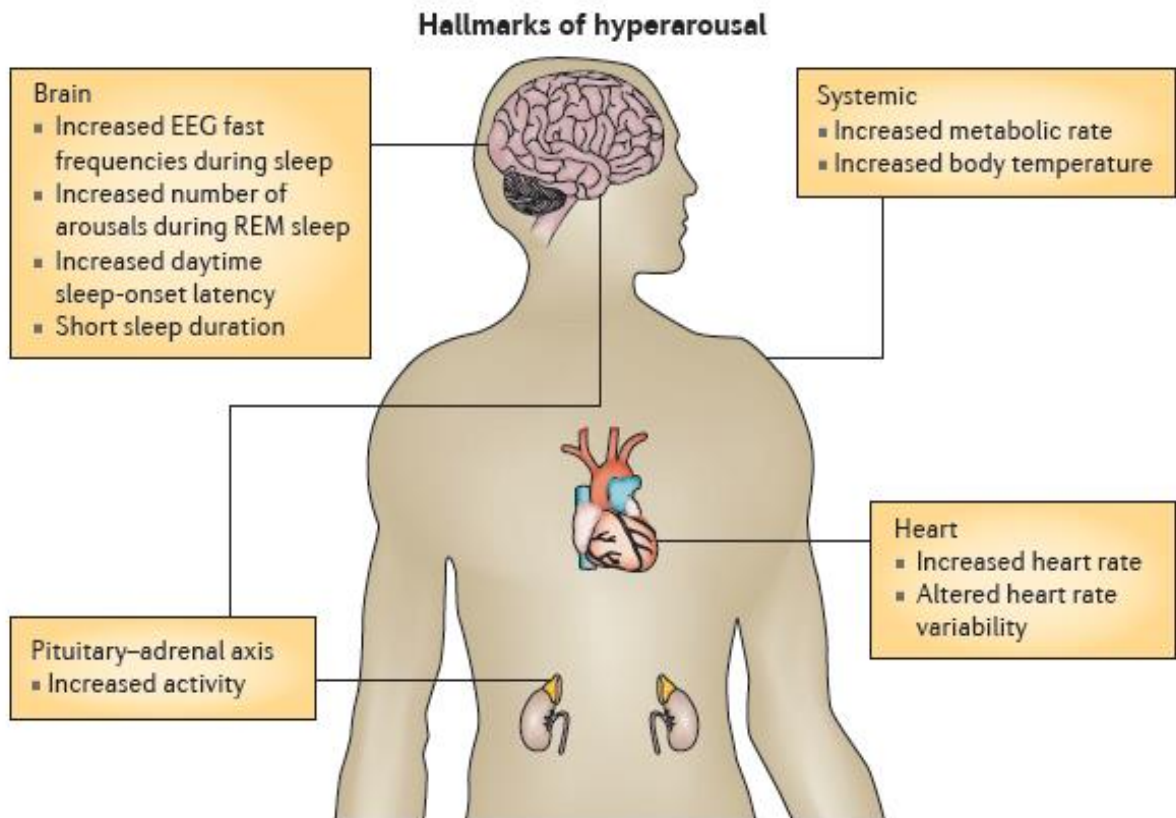
Hallmarks of hyperarousal

Brain
- Increased EEG fast frequencies during sleep
- Increased number of arousals during REM sleep
- Increased daytime sleep-onset latency
- Short sleep duration

Systemic
- Increased metabolic rate
- Increased body temperature

Heart
- Increased heart rate
- Altered heart rate variability

Pituitary–adrenal axis
- Increased activity

Figure 2 | **Indicators of hyperarousal in insomnia.** Hyperarousal can involve multiple bodily systems and functions, including electrophysiological factors, the autonomic nervous system and endocrine variables. EEG, electroencephalography; REM, rapid eye movement.
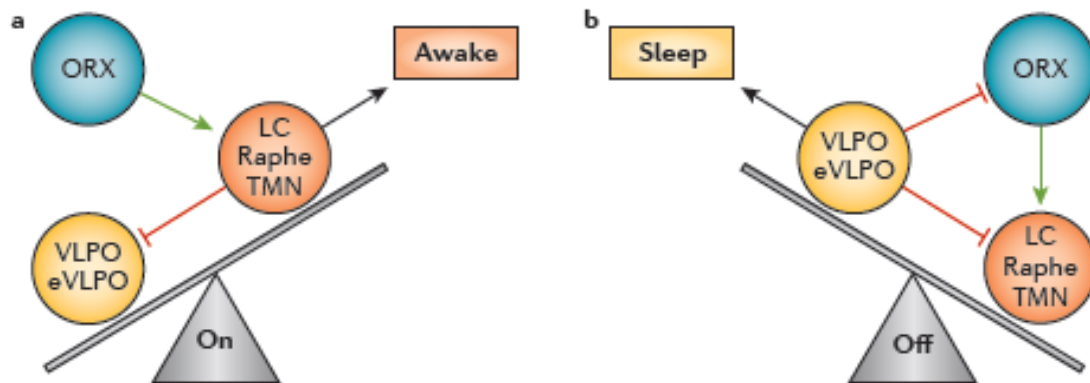
Figure 3 | **An overview of the flip-flop switch model.** The flip-flop switch prevents the existence of intermediate states between sleep and arousal, and instead produces sharp and unstable switches between states. This is achieved through direct mutual inhibition between neurons in the ventrolateral preoptic nucleus (VLPO) and the monoaminergic cell groups (nuclei). Some stability is added to the system through the action of orexin (ORX) neurons. Wakefulness is promoted through the activity of groups of monoaminergic cells such as the raphe nuclei, locus coeruleus (LC) and tuberomammillary nucleus (TMN). These regions have two key functions. First, they inhibit sleep-promoting neurons in the VLPO, which in turn relieves inhibition of the monoaminergic cells and ORX neurons. Second, these monoaminergic nuclei also directly stimulate wakefulness. In addition, ORX neurons act to promote the activity of monoaminergic nuclei. As the VLPO neurons do not have ORX receptors, the ORX neurons function primarily to reinforce the monoaminergic tone, rather than to directly inhibit the VLPO (part **a**). Sleep is maintained by the activity of the VLPO neurons. These function to inhibit the monoaminergic nuclei and thereby relieve their own inhibition. This relief, in turn, enables VLPO neurons to inhibit ORX neurons, which further prevents any activation of monoaminergic nuclei that might interrupt sleep (part **b**). eVLPO, extended VLPO. Figure from REF. 85, Nature Publishing Group.
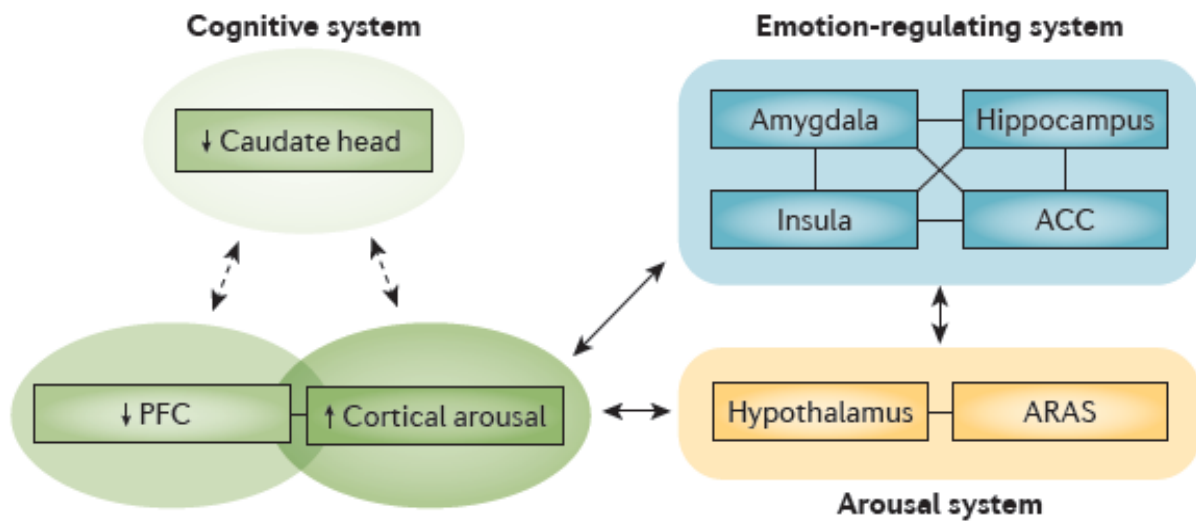
Figure 4 | **Central nervous system pathways that are potentially involved in the psychopathology of insomnia.** According to this model, overactivation of the arousal system, the emotion-regulating system and parts of the cognitive system is accompanied by reduced activation of the prefrontal cortex (PFC) and the caudate head. Prefrontal hypoactivation is assumed to be associated with daytime fatigue and reduced recruitment of the caudate head is assumed to be related to arousal regulation. Solid and dashed arrows represent pathways that are assumed to be reinforced or attenuated, respectively, in insomnia. ACC, anterior cingulate cortex; ARAS, ascending reticular activating system.
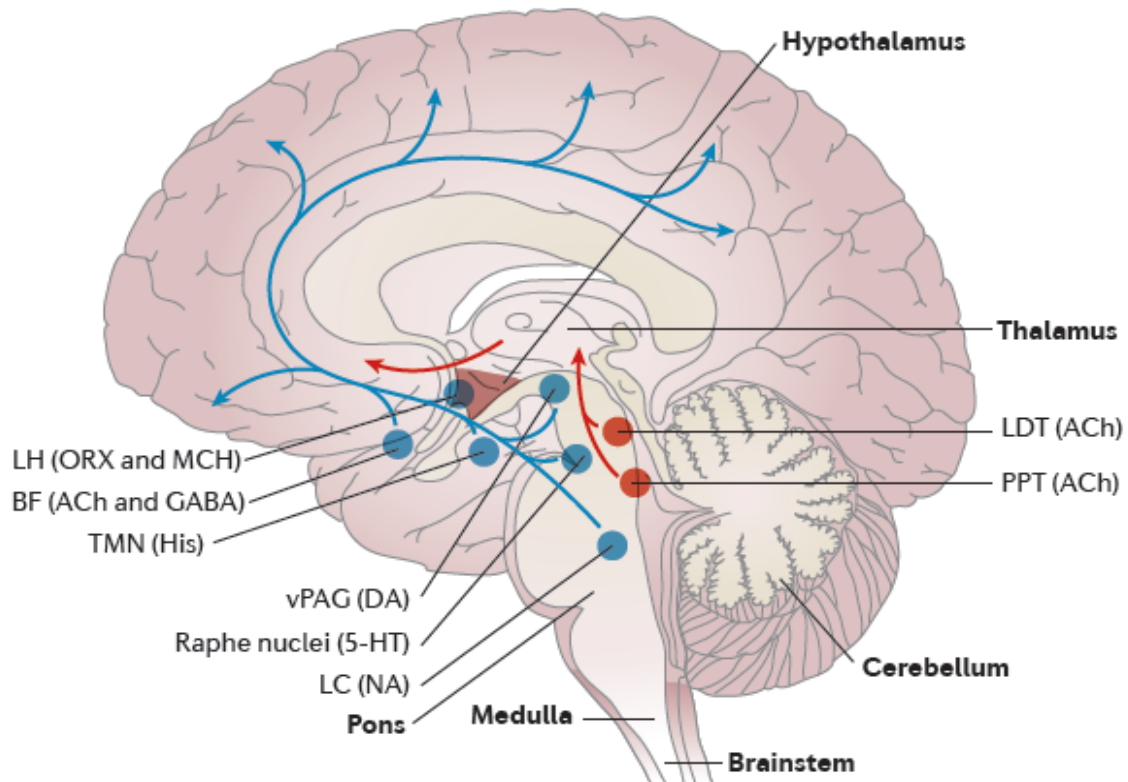
Figure 5 | **Main neurotransmitters involved in the ascending reticular activating system.** One ascending arousal pathway (blue) includes noradrenergic (NA) neurons in the locus coeruleus (LC), serotonergic (5-HT) neurons in the raphe nuclei, histaminergic (His) neurons in the tuberomammillary nucleus (TMN) and dopaminergic (DA) neurons in the ventral periaqueductal grey matter (vPAG). This pathway receives contributions from neurons in the lateral hypothalamus (LH), which contains orexin (ORX) and melanin-concentrating hormone (MCH), as well as from basal forebrain (BF) neurons that contain acetylcholine (ACh) and γ-aminobutyric acid (GABA). A second ascending arousal pathway (red) comprises cholinergic neurons in the pedunculopontine nucleus (PPT) and laterodorsal tegmental nuclei (LDT) that activate thalamic relay neurons resulting in cortical activation. Figure from REF. 85, Nature Publishing Group.

Table 1 | **Properties of medications commonly used to treat insomnia in the United States**

Medication	US FDA-approved indication	Relevant characteristics for treatment optimization
Benzodiazepines		
Triazolam	Insomnia	• Indicated for sleep-onset insomnia • Has abuse potential
Temazepam	Insomnia	• Indicated for sleep-onset and sleep-maintenance insomnia • Has abuse potential
Quazepam	Insomnia	• The very long half-life of this agent makes it unsuitable for insomnia therapy owing to the risk of daytime impairment • Has abuse potential
Flurazepam	Insomnia	• The very long half-life of this agent makes it unsuitable for insomnia therapy owing to the risk of daytime impairment • Has abuse potential
Clonazepam	Seizures and anxiety	• Minimal data on the risk–benefit in patients with insomnia • Might be useful for treating sleep problems in patients with substantial anxiety at night • Demonstrated to improve sleep in patients with MDD and co-morbid insomnia • Risk of daytime impairment • Has abuse potential
Diazepam	Seizures, anxiety and muscle spasm	• No studies on the risk–benefit in patients with insomnia • Long half-life confers substantial risk of daytime impairment • Has abuse potential
Chlordiazepoxide	Anxiety and alcohol withdrawal	• No studies on the risk–benefit in patients with insomnia • Has abuse potential
Lorazepam	Anxiety	• No studies on the risk–benefit in patients with insomnia • Might be useful for treating sleep problems in patients with substantial anxiety at night • Risk of daytime impairment • Has abuse potential
Alprazolam	Anxiety	• No studies on the risk–benefit in patients with insomnia • Might be useful for treating sleep problems in patients with substantial anxiety at night • Risk of daytime impairment • Has abuse potential
Non-benzodiazepines		
Zolpidem (IR and MR)	Insomnia	• IR indicated for sleep-onset insomnia • MR indicated for insomnia and maintenance in terms of wake time after sleep onset in the first 6 hours of the night • Improves sleep in patients with MDD and GAD with co-morbid insomnia • Has abuse potential
Eszopiclone	Insomnia	• Indicated for sleep-onset and sleep-maintenance insomnia • Improves sleep and enhances depression and anxiety outcomes in patients with MDD and GAD • Improves pain outcomes in patients with MDD and GAD with co-morbid insomnia • Has abuse potential
Zaleplon	Insomnia	• Indicated for sleep-onset insomnia • Has abuse potential
Melatonin receptor agonists		
Ramelteon	Insomnia	• Only indicated for the treatment of sleep-onset problems • Minimal abuse potential so could be considered in those at risk for substance abuse • Demonstrated safety in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease
Melatonin	Available OTC	• Excellent safety profile • Available data indicate that it has a greater therapeutic effect on

		• delayed sleep-phase syndrome than on insomnia • Data in patients with insomnia indicate a therapeutic effect on sleep-onset latency, but the clinical significance of this effect has not been established
Melatonin prolonged release	Approved by the EMA for insomnia treatment in patients >55 years of age in Europe	• Excellent safety profile • Available data indicate that it has a greater therapeutic effect on delayed sleep-phase syndrome than on insomnia • Data in patients with insomnia indicate a therapeutic effect on sleep-onset latency, but the clinical significance of this effect has not been established
Selective histamine H1 receptor antagonists		
Doxepin	Insomnia	• Indicated for sleep-maintenance insomnia only • Uniquely addresses problems relating to staying asleep, including in the last third of the night (including the last hour of the night) without increasing the risk of daytime impairment or sedation • Minimal abuse potential
Orexin (also known as hypocretin) receptor antagonists		
Suvorexant	Insomnia	• Addresses problems associated with falling asleep and staying asleep, including in the last third of the night without increasing the risk of daytime impairment or sedation • Might have abuse potential
Antihypertensives		
Prazosin	Hypertension, heart failure and benign prostatic hypertrophy	• Unique therapeutic effects on nightmares and sleep disturbance associated with post-traumatic stress disorder • Risk of orthostatic hypotension as a primary adverse effect • Minimal abuse potential
Antidepressants		
Amitriptyline	Depression	• No data on the risk–benefit for the treatment of insomnia • Significant risk of daytime sedation, weight gain and anticholinergic adverse effects • Minimal abuse potential
Doxepin	Depression	• Minimal data on the risk–benefit for the treatment of insomnia • Significant risk of daytime sedation, weight gain and anticholinergic adverse effects • Minimal abuse potential
Trazodone	Depression	• No data demonstrating efficacy in the treatment of insomnia • Minimal data on the risk–benefit for the treatment of insomnia • Highly variable therapeutic and adverse effects due to common polymorphisms of metabolic enzymes • Minimal abuse potential
Mirtazapine	Depression	• No data on the risk–benefit for the treatment of insomnia • Significant risk of daytime sedation and weight gain • Minimal abuse potential
Antipsychotics		
Olanzapine	Schizophrenia and mania	• No data on the risk–benefit for the treatment of insomnia • Significant risk of daytime sedation and weight gain • Minimal abuse potential
Quetiapine	Schizophrenia and mania	• No data on the risk–benefit for the treatment of insomnia • Minimal abuse potential
Risperidone	Schizophrenia and mania	• No data on the risk–benefit for the treatment of insomnia • Significant risk of daytime sedation and weight gain • Minimal abuse potential
Anticonvulsants		
Gabapentin	Partial seizures and pain	• No data on the risk–benefit for the treatment of insomnia • Minimal abuse potential
Pregabalin	Partial seizures, pain and fibromyalgia	• Data available supporting its use in patients with GAD and specifically demonstrating improvement in sleep in this population

EMA, European Medicines Agency; GAD, generalized anxiety disorder; IR, immediate release; MDD, major depressive disorder; MR, modified release; OTC, over the counter.

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