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REVIEW ARTICLE

Insomnia disorder: State of the science and challenges for the future

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Summary

Insomnia disorder comprises symptoms during night and day that strongly affect quality of life and wellbeing. Prolonged sleep latency, difficulties to maintain sleep and early morning wakening characterize sleep complaints, whereas fatigue, reduced attention, impaired cognitive functioning, irritability, anxiety and low mood are key daytime impairments. Insomnia disorder is well acknowledged in all relevant diagnostic systems: Diagnostic and Statistical Manual of the American Psychiatric Association, 5th revision, International Classification of Sleep Disorders, 3rd version, and International Classification of Diseases, 11th revision. Insomnia disorder as a chronic condition is frequent (up to 10% of the adult population, with a preponderance of females), and signifies an important and independent risk factor for physical and, especially, mental health. Insomnia disorder diagnosis primarily rests on self-report. Objective measures like actigraphy or polysomnography are not (yet) part of the routine diagnostic canon, but play an important role in research. Disease concepts of insomnia range from cognitive-behavioural models to (epi-) genetics and psychoneurobiological approaches. The latter is derived from knowledge about basic sleep–wake regulation and encompass theories like rapid eye movement sleep instability/restless rapid eye movement sleep. Cognitive-behavioural models of insomnia led to the conceptualization of cognitive-behavioural therapy for insomnia, which is now considered as first-line treatment for insomnia worldwide. Future research strategies will include the combination of experimental paradigms with neuroimaging and may benefit from more attention to dysfunctional overnight alleviation of distress in insomnia. With respect to therapy, cognitive-behavioural therapy for insomnia merits widespread implementation, and digital cognitive-behavioural therapy may assist delivery along treatment guidelines. However, given the still considerable proportion of patients responding insufficiently to cognitive-behavioural therapy for insomnia, fundamental studies are highly necessary to better understand the brain and behavioural mechanisms underlying insomnia. Mediators and moderators of treatment

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response/non-response and the associated development of tailored and novel interventions also require investigation. Recent studies suggest that treatment of insomnia may prove to add significantly as a preventive strategy to combat the global burden of mental disorders.

KEYWORDS
anxiety, CBT-I, depression, insomnia, insomnia models, prevention, treatment guidelines

1 | DEFINITION AND DIAGNOSIS OF INSOMNIA DISORDER (ID)—DSM-5, ICSD-3, ICD-11

In the last 50 years all medical diagnostic classification systems have included ID. DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) in its previous versions DSM-III-R/DSM-IV (American Psychiatric Association, 1987, 1998) suggested a distinction between primary and secondary insomnias, whereas DSM-5 (American Psychiatric Association, 2013) heralded a paradigmatic change by establishing ID as an overarching diagnostic category, eliminating artificial distinctions. The ICSD (International Classification of Sleep Disorders) in its third version (American Academy of Sleep Medicine, 2014) confirmed this new nosology (see Table 1; diagnostic criteria for chronic ID according to ICSD-3).

The ICD-10 (International Classification of Diseases, 10th edition; World Health Organization, 1993) distinguished between organic and non-organic sleep disorders; however, ICD-11 will follow the avenue paved by DSM-5 and ICSD-3 (World Health Organization, 2019). When analysing the "new" criteria for ID all systems list both night-time and daytime symptoms and, notably, the symptom of non-restorative sleep was dropped from the criteria due to lack of specificity.

Abandoning the distinction between primary/secondary insomnia constituted a major advance in acknowledging that insomnia frequently is not just a symptom of any other somatic or mental disorder, but constitutes an independent disorder, deserving specific consideration in clinical practice. It is important to note that insomnia probably more frequently occurs as a co-morbid condition together with somatic and mental disorders, than it does occur in its isolated form. DSM-5, ICSD-3 and ICD-11 pay respect to this by explicitly allowing co-morbidity. Furthermore, it turned out that cognitive-behavioural treatment for insomnia (CBT-I) not only has decisive effects on sleep/insomnia complaints, but also positively influences somatic/mental co-morbidities and quality of life. At present, evidence is accumulating that insomnia treatment with CBT-I may even have surplus benefits with respect to general treatment and prevention especially of mental disorders (Benz et al., 2020; Cheng et al., 2019; Hertenstein et al., 2022; Irwin et al., 2022; Leerssen et al., 2021).

Nevertheless, ID as a "one size fits all" category is seen critical by many working in the field. There is still a lively and ongoing discussion about different insomnia phenotypes, for example focussing on the main nocturnal complaint, that is, insomnia with or without "objective" short sleep (Vgontzas et al., 2013), or sleep-onset insomnia versus sleep-maintenance insomnia (Pillai et al., 2015). Indeed, the profile of dominant sleep complaints matters for the risk of developing first-onset major depressive disorder (Blanken et al., 2020). However, subtyping based on sleep characteristics may not be that robust, even across 2 nights (Johann et al., 2017), let alone across months or years (Edinger et al., 2011). Apparently, insomnia complaints change over time. More robust insomnia subtypes surfaced by multivariate profiling of personality features rather than sleep features (Blanken, Benjamins et al., 2019).

As it would be beyond the scope of this article to comprehensively describe the diagnostic and differential diagnostic procedure for insomnia, the interested reader is referred to Riemann et al. (2022) and other textbooks (Sateia & Buysse, 2010). Some important issues

TABLE 1 Diagnostic criteria for chronic ID according to ICSD-3 (AASM, 2014)

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 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/malaise.
   2. Attention, concentration or memory impairment.
   3. Impaired social, family, occupational or academic performance.
   4. Mood disturbance/irritability.
   5. Daytime sleepiness.
   6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. 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.

Abbreviation: ICSD-3, International Classification of Sleep Disorders, 3rd version.

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concerning diagnostic procedures, however, should be highlighted here. The use of sleep diaries constitutes an integral part of insomnia assessment for both research and/or clinical purposes (e.g. consensus sleep diary by Carney et al., 2012). Sleep diaries are easy to apply and to evaluate. Sleep diaries focus on the experience of sleep and can be reviewed by the clinician as they are presented, but the inherent information can also be used to create highly informative graphical displays of sleep and bedtimes (Figure 1).

Beyond sleep diaries, other insomnia-specific questionnaires like the Insomnia Severity Index (Bastien et al., 2001) or the Sleep Condition Indicator (Espie et al., 2014) should be used.

For both clinical and fundamental research, it is favourable to take note of the recommendations for a standard research assessment of insomnia (Buysse et al., 2006). Several paradigms were developed to elucidate specific aspects of insomnia, for example, the attentional bias paradigm (Espie et al., 2006; Harris et al., 2015). This paradigm suggests that patients with chronic insomnia have developed a bias in their perception and processing of stimuli related to insomnia. Other highly promising paradigms investigate failing overnight amelioration of distress, which seems key to persistence of hyperarousal (Wassing et al., 2016; Wassing, Benjamins et al., 2019; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). At present, not yet being ready for standard clinical practice, it is conceivable that these paradigms might be used in the future to measure responsiveness to CBT-I, also in combination with neuroimaging methods.

As the diagnosis of insomnia is solely based on subjective complaints and their measurement, it remains a matter of long-standing debate what the role of technical methods like actigraphy or polysomnography (PSG) might be. It is a highly controversial issue as to whether PSG should be part of the diagnostic process. Doubtlessly PSG helps to unravel suspected occult pathology of sleep, that is, periodic limb movements during sleep (periodic limb movement disorder) or sleep apnea (obstructive sleep apnea syndrome). US guidelines clearly deny the usefulness of PSG to diagnose insomnia (Kushida et al., 2005), whereas guidelines of the German and the European Sleep Research Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017) suggest that PSG be used for patients with therapy-refractory insomnia who have not responded to a previous adequate "dose" of pharmaco- or psychotherapy.

The frequently described discrepancy between subjective (i.e. data from sleep diaries) and objective data (PSG) called paradoxical insomnia or sleep state misperception is seen as a major clinical and scientific challenge. PSG contrasted with subjective data does not reveal as pronounced disturbances of sleep as indicated by subjective data (Feige et al., 2008). A PSG meta-analysis revealed mean total sleep time differences between insomnia and good sleepers of about 25 min, whereas subjective estimates demonstrated an almost 2-hr difference (Baglioni, Regen, et al., 2014; Baglioni, Spiegelhalder, et al., 2014). Traditional PSG reveals only a glimpse of the brain activity during sleep. Advanced analyses have commenced to reveal electroencephalogram (EEG) correlates of subjective wakefulness during sleep, like simultaneous wake-like and sleep-like brain activity in people with insomnia (Christensen et al., 2019; Stephan et al., 2021). Furthermore, classification of individual insomnia patients based on their PSG and EEG power-spectral variables can distinguish between those with objective short sleep and those with sleep state misperception (Kao et al., 2021). Accordingly, the "misperception" may in fact be "mismeasurement": an inappropriate use or interpretation of traditional PSG features by clinicians, rather than inappropriate interpretation of subjective experiences by people with insomnia. It is important to bear in mind that these same challenges apply to mental disorders in general. There is no objective "test" for depression, anxiety or psychosis. The validation of any such tests needs to apply self-report coupled with clinical judgement as the "gold-standard."

Vgontzas and colleagues have postulated that the long-term health consequences of insomnia may be related specifically to objective short sleep duration of less than 6 hr (Vgontzas et al., 2013). However, patients with short sleep insomnia during one night do not fulfil that criteria on another night, and an increased risk of hypertension in short sleeping insomnia could not be replicated (Johann et al., 2017). Also, the hypothesis that the presence of objectively documented short sleep may be of relevance for the choice of therapy (Riemann et al., 2011), that is, pharmacotherapy for insomnia patients with objective short sleep duration versus psychotherapy for insomnia patients with objective normal sleep duration, has yet to be resolved and deserves further consideration (Vgontzas et al., 2013). More details will be provided in the aetiology/pathophysiology section. Figure 2 gives some examples of PSG determined sleep profiles of a good sleeper and two patients with ID.

2 | EPIDEMIOLOGY OF INSOMNIA AND INSOMNIA AS A RISK FACTOR FOR OTHER DISORDERS

Insomnia more frequently afflicts females than males (60% versus 40%), and its prevalence increases with age (for an overview, see Ohayon, 2002). The European Academy for CBT-I has summarized prevalence data for ID across some European countries (Baglioni et al., 2020), varying strongly from country to country. Data for Germany indicate a prevalence of 5.7%, whereas French surveys indicate figures up to 20%. On average, approximately 10% of the adult European population suffer from chronic insomnia. The heterogenous data clearly stress the need for the prospective collection of pan-European samples with state-of-the-art methods to obtain the full picture for planning of insomnia healthcare services.

The costs of insomnia for the individual and society are staggering: it was demonstrated that insomnia conveys increased risks for cardiovascular diseases (Li et al., 2014), obesity and diabetes (Anothaisintawee et al., 2016; Chan et al., 2018), depression (Baglioni et al., 2011; Hertenstein et al., 2019), anxiety (Hertenstein et al., 2019) and suicide (Pigeon et al., 2012). Wickwire (2019) reported that untreated insomnia leads to increased all-cause healthcare utilization based on a randomly selected and nationally representative sample from the USA. Data from Norway indicate that insomnia strongly predicts sick leave and disability pension (Overland

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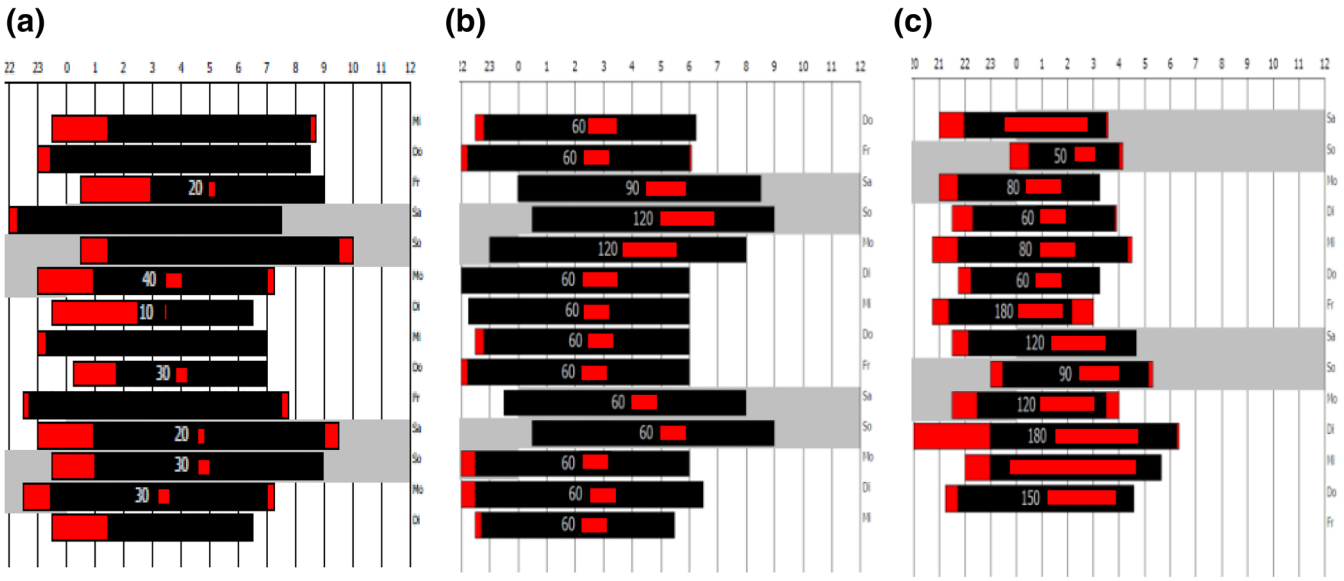

FIGURE 1 Sleep diary data from different patients with insomnia. (a) An insomnia patient who shows an increased sleep-onset latency. (b) A patient with insomnia experiencing difficulty in maintaining sleep. (c) A patient with mixed insomnia showing difficulty in both sleep onset and sleep maintenance

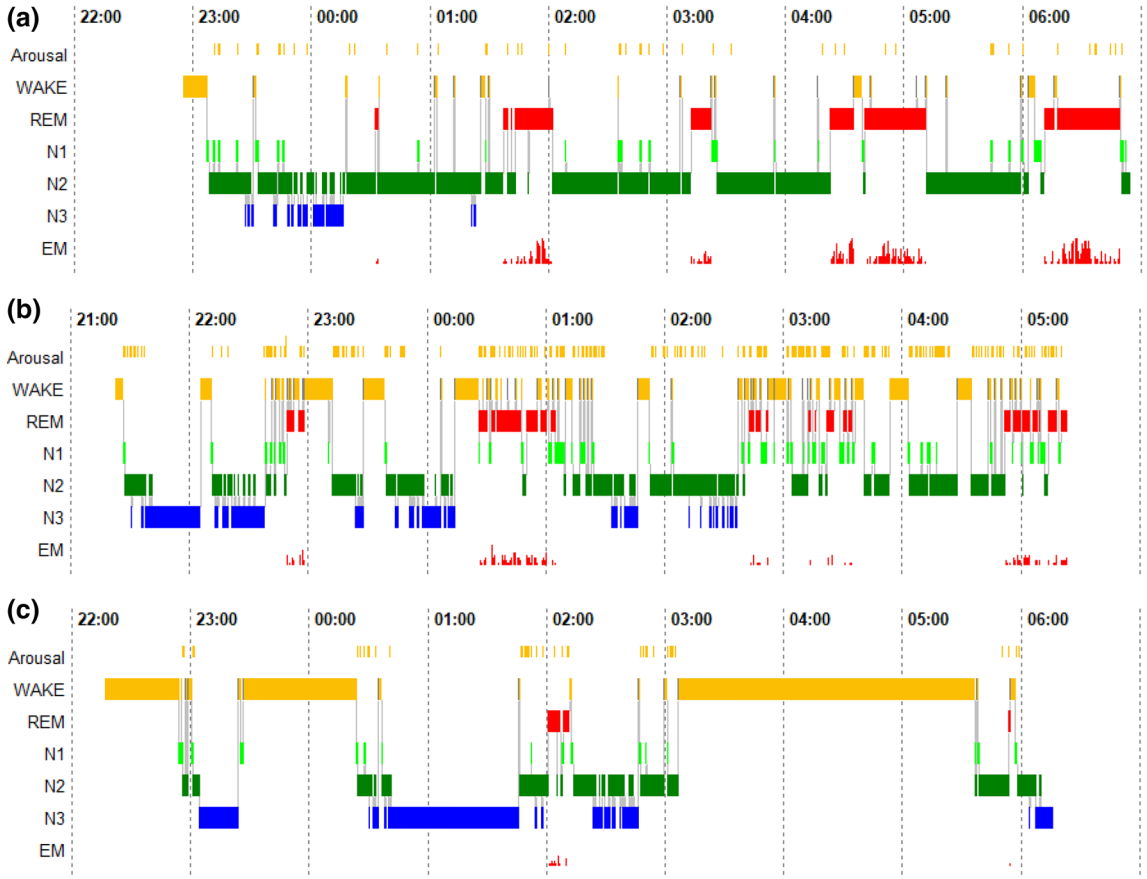

FIGURE 2 Polysomnographic (PSG) profiles of a good sleeper (upper panel; a) and patients with insomnia (lower panels; b,c). The *y*-axis displays arousal (micro-arousals), wake and sleep stages (rapid eye movement [REM], stage N1, N2 and N3) as well as eye movements. The *x*-axis is the time axis. (b) A patient with insomnia who has only a slightly reduced total sleep time, but a high number of arousals during sleep and a fragmented REM sleep. (c) A patient with insomnia who has an objectively shortened sleep duration

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et al., 2008; Sivertsen et al., 2009). Data from France indicated a sum of 2 billion USD in 1995 (Leger et al., 1999). Data from the USA resulted in a sum of 150 billion US dollars for direct and indirect costs of insomnia (Reynolds & Ebben, 2017). A Canadian study (Daley et al., 2009) reported total annual costs for ID alone to be about 6.5 billion Canadian dollars. Recent data indicate that treatment using digital CBT-I reduces healthcare expenditure, and Markov health economic modelling indicates that digital CBT-I may be highly cost-effective when offered at scale (Darden et al., 2021). Further details of the costs and risks of insomnia are given in the European Academy for Cognitive Behavioural Therapy for Insomnia Report (Baglioni et al., 2020). An important clinical and research question relates to the hypothesis that adequate insomnia treatment might not only effectively target insomnia symptoms but might reduce subclinical and clinical psychopathology, and also be of general preventive value for mental disorders and physical diseases.

3 | AETIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

Recent reviews synthesized current neurobiological, cognitive, behavioural and emotional models for insomnia and its relationship to psychopathology (Figure 3; Espie, 2022; Riemann et al., 2020; Van Someren, 2021).

Current theoretical approaches span from cognitive-behavioural to neurobiological models, and models taking into account both levels simultaneously.

The basic structure of the model depicted in Figure 3 is taken from the so-called 3P model of insomnia (Spielman et al., 1987). The 3Ps signify: predisposing, precipitating and perpetuating factors.

"Predisposing" factors come from the areas of (epi-)genetics and early life stress that contribute to individual differences at the level of brain function and personality. Genetic and epigenetic factors have been shown to be involved in the aetiology of insomnia by family and twin studies (for an overview, see Palagini et al., 2014). Genome-wide association studies point to an involvement of a very large number of genes, each with a very small contribution, and shared genetic factors for insomnia and restless legs, cardiometabolic, and especially psychiatric traits (Jansen et al., 2019; Lane et al., 2019). Interestingly, the brain tissues and cell types expressing sets of insomnia risk genes are not primarily part of the known circuitry regulating sleep but are rather part of circuitries involved in emotion regulation (Van Someren, 2021).

Still, for completeness, a discussion on the development and maintenance of insomnia should include the neurobiological mechanisms of sleep, notably homeostatic and biological time-keeping mechanisms (Borbély, 1982). The flip-flop switch model of sleep regulation (Saper et al., 2005) suggests a bistable switch mechanism between sleep and wake promoting centres of neuronal cell groups. Wakefulness is governed by a network of cell populations in the hypothalamus (including orexinergic neurons), basal forebrain and brain stem, activating thalamus and cortical structures. These structures include and extend beyond the cell groups in the reticular formation of the brainstem (originally described as ascending reticular activating system). The main sleep-inducing centres are located in the ventrolateral-preoptic nucleus (VLPO), which becomes active during sleep and inhibits all major wake-promoting centres in the hypothalamus and brain stem, with the neurotransmitters galanin and gamma-aminobutyric acid. The VLPO receives afferent input from each of the major monoaminergic systems, and is inhibited by noradrenaline and serotonin. A mutual inhibitory circuit between both systems, the wake and the sleep system, leads to a flip-flop switch with "sharp" transitions between sleeping and waking. Thus, insomnia on this level can be conceptualized as imbalance between sleep-inducing and wake (i.e. arousal)-inducing mechanisms. A hyperactivity of the arousal system or a hypoactivity of the sleep system or both simultaneously could thus "drive" the insomnia. Circadian and homeostatic mechanisms are also involved in this switch process, and it has been speculated that a dysfunctional "key switch" (see above) could play a role in the pathogenesis of insomnia. According to the two-process model of sleep regulation (Borbély, 1982), sleep–wake behaviour is governed by circadian time-keeping mechanisms and a homeostatically controlled process S, representing the sleep drive. Being out of synchrony with the internal body clock (e.g. due to shift work) or having a decreased sleep drive would logically result in sleep complaints. Indeed, the main effective component of CBT-I, sleep restriction, is hypothesized to act on the sleep drive (Maurer et al., 2018), and long-term effectiveness of CBT-I improves with the addition of circadian interventions (Dekker et al., 2020; Leerssen et al., 2021). Notwithstanding these effects, decades of research in insomnia have failed to reveal circadian and homeostatic mechanisms as primary factors involved the origin and pathophysiology of the majority of people suffering from ID (Van Someren, 2021). One might conclude that enhancement of homeostatic sleep pressure and support of circadian rhythm amplitude alleviates insomnia, but that we may have to look beyond hourglass and clock to find underlying causes predisposing to insomnia.

A third factor involved in sleep and predisposing to insomnia is emotion (Saper et al., 2005). This factor is frequently overlooked, in spite of the ubiquitous experience that sleep initiation is difficult under threatening conditions—no matter what our hourglass and clock suggest. Indeed, from an evolutionary perspective this would be extremely disadvantageous. An increasing number of observations suggests a key role of this third factor in the origin and pathophysiology of the predisposition to insomnia (for review, see Van Someren, 2021). For example, the trait to exhibit a pronounced disturbed sleep response to stressful events has been shown to be a major risk factor for insomnia (Drake et al., 2014). Also other personality traits related to emotion regulation have been linked to insomnia, including neuroticism, perfectionism, sensitivity to anxiety symptoms, and the tendency to internalize problems (Dekker et al., 2017; van de Laar et al., 2010). The major early developmental factors predisposing to insomnia involve emotion as well: risk genes seem to have a preference for brain circuitries involved in emotion regulation, and early childhood adversity likewise affects these circuitries (Van Someren, 2021).

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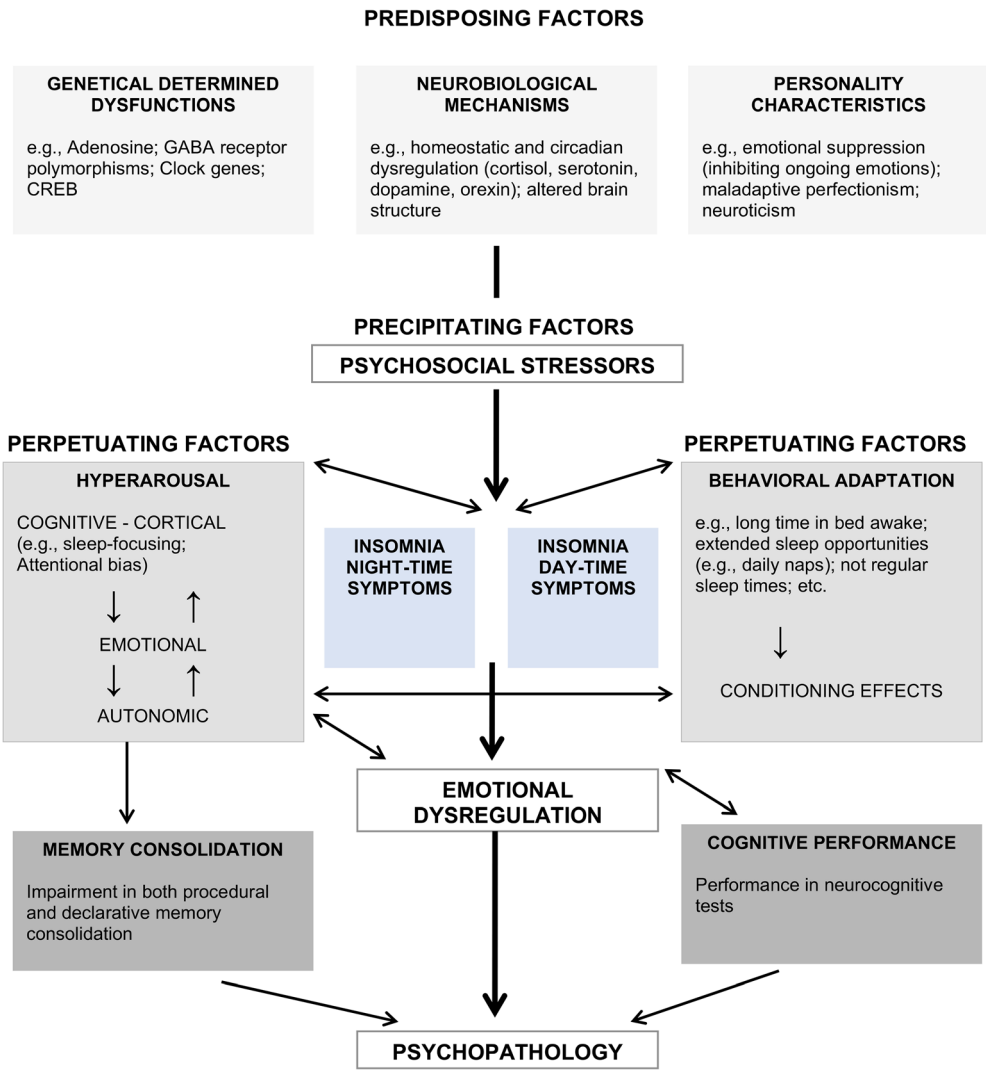

FIGURE 3 Comprehensive insomnia model (see text)

"Precipitating" factors can be readily identified in many cases. These are usually significant life events that facilitate the onset of acute episodes of insomnia. Most frequently, reported triggers of acute episodes of insomnia are stressful life events related to a threat of security to family, health and work–school living that are coupled with negative emotional valence. Fortunately, not everyone exposed to stress in adulthood develops insomnia, most likely only those that have a predisposing profile.

"Perpetuating" factors can be discussed with respect to hyperarousal, which can be conceptualized as overactivity of the arousal-promoting systems, out of balance with the activity in sleep-inducing systems. Hyperarousal includes physiological, cognitive and emotional components, and has been considered a stable characteristic of people with insomnia both during the night and during the day (Morin et al., 2015; Riemann et al., 2010, 2015). It has been demonstrated that patients with insomnia show increased levels of autonomic activity (though the issue is discussed critically with respect to heart rate variability; Dodds et al., 2017) and an overactivity of the HPA-axis, as documented by increased levels of cortisol output during day- and night-time (see meta-analysis by Dressle et al., 2022). Central nervous system (CNS) indicators of hyperarousal in people with insomnia are increased amounts of micro-arousals and increases in fast EEG frequencies (in the sigma and beta bands) during sleep (Christensen et al., 2019; Feige et al., 2013; Perlis et al., 1997, 2001; Spiegelhalder et al., 2012), and also wake EEG shows signatures of increased excitation (Colombo, Ramautar, et al., 2016; Colombo, Wei, et al., 2016) and somatic awareness and responsivity (Wei et al., 2016; Wei, Blanken, & Van Someren, 2018; Wei, Ramautar, et al., 2018). Although still too small for voxel-wise consistent findings (Tahmasian et al. 2018), the rapidly increasing number of neuroimaging studies on insomnia (Riemann et al., 2015) suggests an overactivity of cortico-limbic networks relative to sleep-promoting neuronal networks. Most interestingly, in recent years a special role of rapid eye movement (REM) sleep disturbance (REM sleep instability/restless REM sleep) has been postulated to be of utmost relevance for the experience of insomnia, and specifically their altered perception of sleep and inability to discard hyperarousal (Riemann et al., 2012; Van Someren, 2021). This lead was primarily based on the finding of increased micro-arousals during REM sleep in insomnia (Feige et al., 2008)—further studies revealed that upon awakening out of REM sleep, patients with insomnia

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more frequently stated having been awake compared with non-REM (NREM) sleep and good sleepers (Feige et al., 2018). Following up on these findings, Feige et al. (2021) used an event-related potentials paradigm to demonstrate that ID patients differed from good sleepers by showing reduced P2 amplitudes only in phasic REM sleep. These studies highlight a special role of REM sleep for insomnia.

The mechanisms underlying this special role of REM sleep in the predisposition, perpetuation and psychiatric consequences were addressed in a series of seminal studies (Wassing et al., 2016; Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). In brief, Wassing et al. showed that the restless REM sleep that is characteristic of people with insomnia interferes with overnight adaptation in limbic circuits of the brain. The consequential difficulties with dissolving of distress could be key to the development and perpetuation of hyperarousal as well to the risk of developing psychiatric disorders, as supported by other studies (Halonen et al., 2021; Pesonen et al., 2019). Restless sleep lacks the prolonged silencing of the locus coeruleus and consequential drop in cerebral noradrenaline that characterizes normal restful REM sleep (Kjearby et al., 2020). Because REM sleep is a period of pronounced limbic reactivation of emotional memory traces, it has been hypothesized that the increased level of noradrenaline during restless REM sleep interferes with the synaptic plasticity processes underlying adaptation of the neuronal engrams that represent distress, and could even result in sensitization, indicating maladaptive sleep (Van Someren, 2021). Others have proposed that the low level of noradrenaline during REM sleep is key to restore the noradrenergic tone, to enable a low tonic and high phasic locus coeruleus activity during wakefulness (Goldstein & Walker, 2014).

Restless REM sleep thus has a specific contribution to "emotional" perpetuating factors, and may explain why patients with insomnia are so prone to develop anxiety and depressive disorders in the long run. Indeed, sleep has been conceptualized as a basic psychophysiological process that is fundamental for stress, behaviour and emotion regulation (Hagger, 2010; Palmer & Alfano, 2017). Consistently, most mental disorders are associated with sleep impairment (Baglioni et al., 2016), and insomnia-related problems in children have been linked with difficulties in socio-emotional development (Sadeh et al., 2014; Vermeulen et al., 2021). In adults, insomnia has been found to be a predictor of years-long lingering of emotional distress (Wassing et al., 2016; Wassing, Lakbila-Kamal, et al., 2019), of depression, and of anxiety disorders (Baglioni et al., 2011; Hertenstein et al., 2019; Leerssen et al., 2021). Experimental studies have shown that patients with insomnia report more negative emotions than good sleepers (McCrae et al., 2008; Scott & Judge, 2006). Psychophysiological studies have also evidenced an emotional bias in people with insomnia to sleep-related stimuli with negative valence compared with good sleepers (Baglioni et al., 2010; Baglioni, Spiegelhalder, et al., 2014).

Perpetuating factors also include inadequate "behaviours", like prolonged bedtimes, irregular sleep–wake schedules, napping during the day and other maladaptive behaviours, such as using alcohol to combat insomnia. Usually, these strategies are attempted to compensate for lost sleep; however, in the end insomnia is maintained and exacerbated by decreasing sleep drive.

In addition, "cognitive perpetuating factors" have been identified, such as beliefs, worry and attentional bias (Espie, 2002; Harvey, 2002; Morin et al., 2007). These cognitions include unrealistic beliefs about sleep requirements and excessive worry for not meeting these standards. In recent years, the literature has emphasized the role of selective attention processes in people with insomnia. Specifically, it has been argued that the attentional system of patients with insomnia may be abnormally sensitive to sleep-related information (Harris et al., 2015). It has been hypothesized that such attention bias may exacerbate sleep-related rumination and lead to sleep effort (Espie et al., 2006; Harvey, 2002).

Summarizing, acute precipitating life events can "set the wheels in motion"—acute insomnia is triggered. The question of why most individuals who develop acute insomnia do not go on to develop the chronic condition has not yet been clarified (Ellis et al., 2012)—but likely involves genetic and early life stress-induced neurobiological vulnerability to keep "the train rolling." A complex network of associated symptoms including cognitive-, emotional- and cerebral hyperarousal, unstable REM sleep and maladaptive behaviours will keep the furnace burning. Sleep-preventing learned associations (conditioning effects) are strongly involved in this process as well, giving credit to Bootzin's assumption that in insomnia the original connection between the bed (stimulus) and the behaviour of sleep (response) has been lost or "unlearned" (Bootzin et al., 1991).

The CBT-I (see below) mainly targets the perpetuating factors, for example, relaxation techniques and mindfulness aim to address psychophysiological hyperarousal; sleep hygiene, stimulus control and sleep restriction try to correct maladaptive behaviours and enhance sleep drive; whereas cognitive strategies aim to alter "racing thoughts", dysfunctional beliefs and attitudes, and to reduce nocturnal worrying and ruminations.

4 | TREATMENT (S)—FOCUS ON PSYCHOLOGICAL APPROACHES: PRESENT GUIDELINES, WHAT IS CBT-I, STEPPED CARE AND DIGITAL CBT-I?

All insomnia-related guidelines published in the last 5 years agree that CBT-I should be the first-line treatment for insomnia, based on the accumulated scientific evidence from the literature. These guidelines include the American College of Physicians (Brasure et al., 2016; Kathol & Arnedt, 2016; Qaseem et al., 2016; Wilt et al., 2016), the American Academy of Sleep Medicine (AASM; Edinger et al., 2021a, b), the German and the European Sleep Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017), and the British Association for Psychopharmacology consensus statement (Wilson et al., 2019). Overall, these guidelines make a strong case for CBT-I as first-line treatment for insomnia, and hypnotics are recommended for short-term use and only if CBT-I is either not available or ineffective. As hypnotics in this context, melatonin agonists, benzodiazepines,

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benzodiazepine receptor antagonists, some sedating antidepressants and orexin receptor antagonists are recommended mainly for short-term use (less than 4 weeks) only. An overview of the present state of hypnotic treatment can be found in reviews (Herring et al., 2019; Riemann & Nissen, 2012; Roehrs & Roth, 2012).

The CBT-I comprises a family of interventions and is not "one" homogenous therapeutic strategy *per se* (Table 2).

The CBT-I is in essence a multicomponent approach, comprising cognitive and behavioural parts, within each of which domain there is a wide range of treatment options. The principal behavioural therapies are sleep restriction and stimulus control. Cognitive techniques include reappraisal, cognitive control and paradoxical intention. There is also a range of relaxation therapies, and sleep hygiene education, although not effective as a standalone treatment, is commonly part of the CBT-I toolkit. A brief description of these techniques is given in the table. For further details, the interested reader is referred to a new CBT-I textbook that will be published in 2022 (Baglioni et al., 2022). A new clinician handbook on insomnia will also be available shortly (Espie, 2022).

Logically therefore CBT-I is not "a treatment" but is "a system of cognitive and behavioural therapeutics", akin to pharmacotherapy (which is not a drug treatment but a "pharmaceutical approach" to clinical care; Espie, 2022). The history of evidence-based psychotherapy (in most disorders) reveals a period of time during which there was a tendency towards "lumping" of therapeutic elements, rather than the creation of precision techniques that "may" be used in combination. This is certainly true of the non-pharmacological management of insomnia, and the term CBT-I has for the past 20 years or more been used rather generically in the literature because the majority of studies have deployed a CBT-I package.

In earlier times there was a focus upon more specific interventions. For example, comparing the effectiveness of abbreviated progressive relaxation, stimulus control therapy and paradoxical intention (Espie et al., 1989), or even investigating components of a single therapy (Woolfolk & McNulty, 1983: compared progressive relaxation, progressive relaxation without tension release, imagery with tension release, and imagery without tension release). Interestingly, of late, there has been renewed interest in single-component therapies. We now find ourselves unpicking or deconstructing CBT to evaluate its active component treatments, and even its active treatment ingredients. The best example is sleep restriction therapy (SRT), widely regarded to be the most effective element of CBT (Edinger et al., 2021a; Maurer, Schneider et al., 2021). A series of laboratory-based experiments has recently explored the homeostatic, arousal and circadian mechanisms of sleep restriction (Maurer et al., 2020, 2022; Maurer, Ftouni et al., 2021).

In support of this is the fact that CBT protocols are effective even when they vary. The AASM practice parameters task force recently grappled with the question, what are the "minimal characteristics" of effective CBT (Edinger et al., 2021a). They concluded that "all studies included SRT, stimulus control and some form of cognitive therapy"; however, the cognitive component varied widely. Whether or not relaxation strategies or sleep hygiene were included in the CBT-I regimen varied across studies as well. It was beyond the scope of this (group) to recommend a specific CBT protocol, and "these variations did not appear to systematically impact the effectiveness of the treatment" (p. 261). This evidences the versatility and robustness of what is sometimes now referred to as CBTx (cognitive and behavioural therapeutics), that is, a "therapeutic formulary", where not everyone needs the same content, or the same order of content (Espie, 2022). Analysis of how SRT is configured suggests there is gross variability between studies and protocols (Kyle et al., 2015); it would be prudent to establish what is the most effective combination of SRT parameters, including tailoring to presenting insomnia phenotype. Indeed, the widespread development of "precision medicine" (Ginsburg & Willard, 2009; Jain, 2002) has spawned interest in how "personalized behavioural sleep medicine" for insomnia may evolve in the future (Kyle et al., 2014).

Despite the impressive evidence base for CBT-I, its recognition internationally as the treatment of first choice for the management of insomnia and the fact that the CBTx formulary of treatments is quite wide ranging, in practice the majority of insomnia patients seeking medical help continue to receive medication. The issue here is not so much overprescribing of drugs as it is under-provision of CBT-I. Two innovations have been developed to address this problem. The first, at the level of the treatment itself there has been growing interest in, and a rapidly accelerating evidence base for digital CBT-I, that is CBT-I delivered by fully automated web and mobile means. The second, at the level of the service, has been the development of the "stepped care" model of insomnia service delivery.

The effectiveness of digital CBT-I has been robustly and rigorously demonstrated against psychological placebo (Espie et al., 2012), attention control (Christensen et al., 2016; Kaldo et al., 2015), sleep hygiene (Espie et al., 2019; Ritterband et al., 2017; Vedaa et al., 2020), waitlist (Zachariae et al., 2018) and usual care (Freeman et al., 2017) in a range of clinical and co-morbid populations. Several meta-analyses report large between-group effects on insomnia severity, and medium effects on sleep diary outcomes (Seyffert et al., 2016; Soh et al., 2020; Zachariae et al., 2016), and benefits to sleep are durable, being maintained up to a year and beyond (Blom et al., 2017; Luik et al., 2020; Vedaa et al., 2019). Whereas meta-analyses report effect sizes in the range of face-to-face CBT-I thereby suggesting non-inferiority, head-to-head comparisons have shown mixed findings (Blom et al., 2015; De Bruin et al., 2016; Kallestad et al., 2021; Lancee et al., 2016). It seems likely, however, that the evolution of highly engaging clinically evidenced software will address engagement and treatment implementation challenges that are apparent for all forms of CBT-I delivery. It may also be the case that differences exist between different digital CBT-I formats (Hasan et al., 2022). These outstanding questions warrant further investigation.

Beyond improved sleep, digital CBT-I, like "traditional" CBT-I, yields benefits to additional clinical and functional outcomes of relevance to insomnia. Several studies have documented reductions in symptoms of anxiety and depression, including in individuals with clinically significant depressive symptoms (Blom et al., 2015, 2017; Cheng et al., 2019; Henry et al., 2021; Pillai et al., 2015; van der Zweerde

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TABLE 2 CBT-I ingredients (from Baglioni et al., 2020)

CBT-I strategy	Description
Sleep restriction	*Behavioural strategy*: A method that aims at strengthening homeostatic sleep pressure and stabilizing circadian control of sleep and wakefulness, by decreasing the opportunity to sleep over successive nights. Patients are instructed to restrict their time in bed to match their average (self-report in sleep diaries) total sleep duration. The time in bed is then gradually increased until reaching patients' optimal sleep need. An alternative method, called *sleep compression*, consists in gradual constriction of time in bed until reaching the optimal sleep need.
Stimulus control	*Behavioural strategy*: Several instructions aiming at strengthening the bed as a cue for sleep, weakening it as a cue for activities that might interfere with sleep, and helping the insomniac acquire a consistent sleep rhythm, based on operant conditioning model: (1) lie down to go to sleep only when you are sleepy; (2) do not use your bed for anything except your sleep and sexual activity; (3) if you find yourself unable to fall asleep, get up and go to another room. Stay up as long as you wish, and come back to bed when you feel sleepy; (4) If you still cannot fall asleep, repeat step (3). Do this as often as is necessary throughout the night; (5) Set your alarm and get up at the same time every morning irrespective of how much sleep you got during the night; (6) no napping during daytime.
Sleep hygiene education	Behavioural and educational strategy: General health instructions about internal and external factors that might influence sleep (e.g. sport, light, temperature, etc.).
Relaxation	Behavioural and cognitive strategy: A set of methods aiming at reducing somatic or cognitive hyperarousal (e.g. progressive muscle relaxation, autogenic training, imagery training, meditation).
Cognitive reappraisal	Cognitive strategy: Strategies directed to reduce dysfunctional beliefs, attitudes, concerns and false beliefs about the cause of insomnia and about the inability to sleep.
Cognitive control/ Worry time	Cognitive strategy: The patient is instructed to sit comfortably in an armchair, and write down a list of worries and list of what to do the next day. The rationale of this strategy is to prevent emotionally loaded intrusive thoughts during the sleep-onset period, as all worries have been "already" processed before going to bed.
Paradoxical intention	Cognitive strategy: Strategy aimed at reducing the anticipatory anxiety at the time of falling asleep. Patients are instructed to remain still in bed with the eyes closed and to try to keep awake as long as they can. This takes away the responsibility to try to fall asleep, which in turn often leads to falling asleep quicker.

Abbreviation: CBT-I, cognitive-behavioural treatment for insomnia.

et al., 2019). From a scientific perspective, digital CBT-I confers advantages such that it permits examination of potential mediators of treatment effects using a standardized therapeutic approach. Large randomized-controlled trials and secondary analyses show that insomnia symptom reduction mediates improvements in mental health symptoms (Freeman et al., 2017; Henry et al., 2021), and improvements in quality of life, health and wellbeing, and cognitive function (Espie et al., 2019; Kyle, Hurry, et al., 2020). This evidence therefore supports treating insomnia complaints whenever it presents. Emerging data also suggest that demographic variables including age, race, gender or socio-economic status do not moderate the effectiveness of digital CBT-I (Cheng et al., 2019).

Real-world evidence further underscores the value of digital CBT-I. Recent uncontrolled data evaluating digital CBT-I in existing healthcare settings in the UK show reductions in insomnia and augmentation of the effects of in-person therapy for anxiety and depression (Cliffe et al., 2020; Luik et al., 2017; Stott et al., 2021). Importantly, from a health economic perspective, analyses suggest that digital CBT-I is cost-effective, and may lead to cost savings if made available at scale (Darden et al., 2021; Sampson et al., 2021). This growing body of evidence behind digital CBT-I has led to increased recognition of it as a viable and effective treatment option. Indeed, in the USA, Somryst has been cleared by the FDA as a prescription digital therapeutic (Morin, 2020). Likewise, Sleepio (www.sleepio.com) is widely available in the USA, integrated into healthcare pathways and on the digital formulary, and is available in major parts of the UK National Health Service.

By overcoming the barriers preventing access to therapist-delivered CBT-I, digital CBT-I has the potential to provide access to clinically effective, evidenced-based and guideline-recommended insomnia treatment. These fundamental properties of effectiveness and scalability make digital CBT-I attractive as a first-line insomnia intervention, providing an accessible alternative to pharmacotherapy (Figure 4).

The stepped-care model is a population health service approach to providing people with insomnia with access to evidence-based care (Espie, 2009; Espie et al., 2013). Stepped care is often conceptualized as a pyramid consisting of different levels, with at the bottom the least specialized help applicable for those with less severe and more generic complaints and highly specialized help for those with more severe, complex and rare problems as the top. The level of intervention is naturally not arbitrary; treatment is tailored to and based on the needs of the patient and the nature of their complaints. The number of steps in any stepped care model would be determined by the levels of intervention that are proven and available, and by what within the healthcare system would be affordable. Stepped care models have been recommended for use in insomnia (Baglioni et al., 2020, 2022), and are sometimes adopted in healthcare systems (Vincent & Walsh, 2013).

With regard to insomnia, therefore, digital CBT might be particularly suitable to be one of the entry-level methods for the treatment

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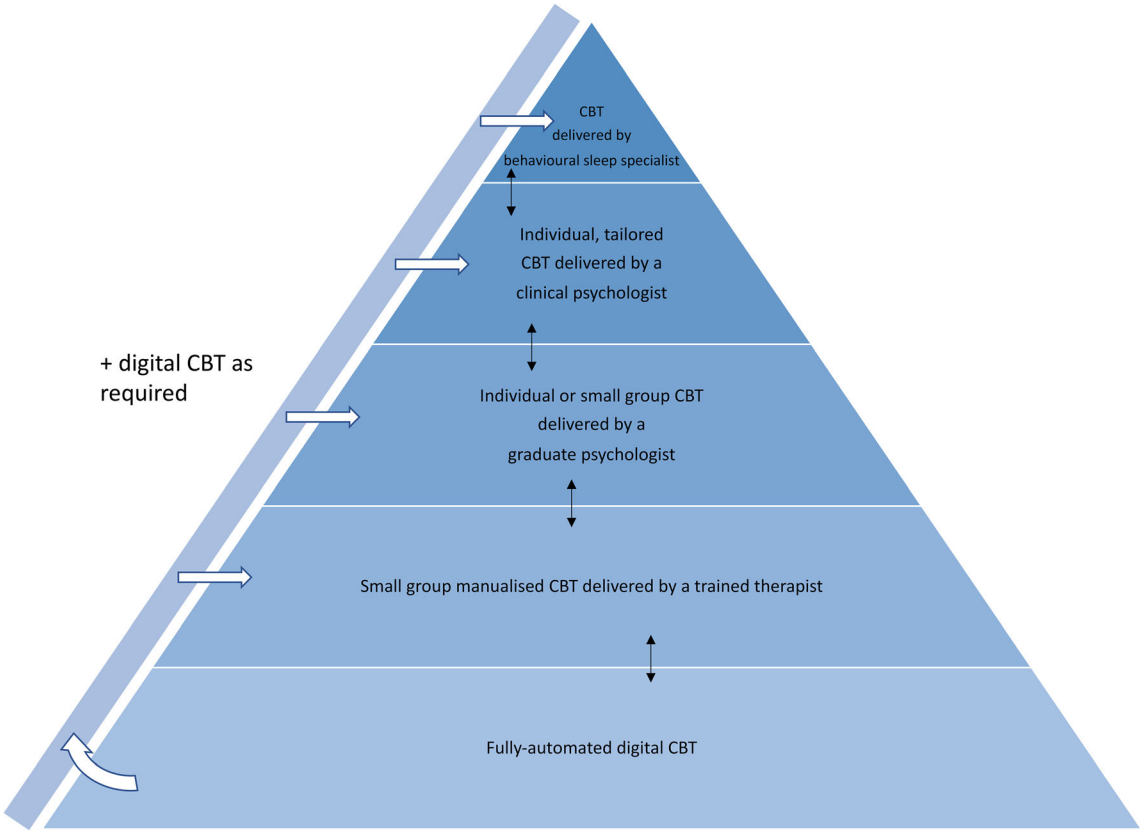

FIGURE 4 A proposed stepped care model for delivery of cognitive-behavioural therapy (CBT) as clinical guideline care. Digital CBT offers accessible treatment for all, but also may be integrated into the care pyramid supporting in-person therapy. The stepped care model conserves expert resources for more complex and treatment-resistant cases

of insomnia, as it has considerable "scalability", particularly when fully automated. Another approach at this level might be using self-help books of good standing, perhaps as part of a "books on prescription" scheme. Next in the hierarchy might be insomnia services that require some in-person support, but thought would be given to how such care could be provided with efficiency. Examples here might include telehealth rather than in a clinic, and the use of small group therapy rather than individual treatment. Other factors to be considered would be the nature of the treatment itself and the expertise of the therapist. For example, it could be possible to train healthcare workers in the provision of manualized CBT-I without them having to have a deep understanding of sleep medicine or mental health (training primary care nurses, for example). This approach is very protocol-driven and can be readily standardized (Kyle, Madigan, et al., 2020). As you then continue up the hierarchy there is greater need for insomnia-specific expertise and for the use of tailored therapy. At the peak of the pyramid the likelihood is that not only specialist expertise but also specialized facilities such as those available at a sleep centre may be required to address the needs of the most complex patients.

Stepped care systems require decision algorithms for two processes. First, to ensure that people are correctly allocated to the appropriate level of care in the first instance; and secondly, to ensure that people are able to step up to more advanced care depending on their treatment response.

5 | FUTURE PERSPECTIVES WITH RESPECT TO DIAGNOSIS, MEASUREMENT, AETIOLOGY AND PATHOPHYSIOLOGY; NEW TREATMENTS

Given the drastic changes we have been witnessing concerning insomnia and its diagnosis, pathophysiology/aetiology and treatment in the last 30 years, one might be tempted to answer the question "Can we rest yet?" (Harvey & Tang, 2003) with "Yes!." However, this would be premature and inadequate with respect to the many open questions still facing us in the insomnia field. Therefore, at this point, we would like to highlight some issues/avenues for future research and clinical practice we consider of utmost importance.

Given the fact that at present we have reached the unique situation that all major diagnostic systems (DSM-5, ICSD-3, ICD-11) have agreed upon ID (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013; World Health Organization, 2019), the situation seems ideal that all types of studies into ID use more or less the same diagnostic criteria, which would be ideal to make data coming from all over the world easily comparable. This would also entail homogenization of our diagnostic and research instruments (questionnaires, PSG, etc.). However, as mentioned before, there definitely are different insomnia phenotypes that should not be neglected. A data-driven approach to delineate and characterize these

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phenotypes seems warranted (Blanken, Benjamins, et al., 2019; Kao et al., 2021), possibly further refined by adding physiological data by means of PSG to questionnaire datasets.

In this regard, pooling data from different sleep labs could be beneficial in order to address the issues of small sample sizes and poor replicability in the insomnia field. This would require the use of standard methodology and paradigms across different labs. The UK Biobank (www.ukbiobank.ac.uk; see Allen et al., 2014 for a detailed description), a large biomedical database including a sample of about 500,000 adults, has already proven to be useful for insomnia research (Jansen et al., 2019; Kyle et al., 2017; Lane et al., 2019). Although the UK Biobank is not specifically optimized for insomnia research, cross-validation showed the available phenotype to very accurately match diagnosed insomnia patients (Hammerschlag et al., 2017).

Given the costs and artificiality of the traditional sleep laboratory, home-based easy to apply measures need to be developed, allowing repetitive CNS-based measurements in the natural environments of our patients, reaching beyond actigraphy (Debener et al., 2015; Mikkelsen et al., 2019). This would allow to study the dynamics of features reflecting the sleep drive and REM sleep characteristics longitudinally and in relation to different treatments and their outcomes in much more detail.

Given the prominence of the hyperarousal concept in almost all insomnia models, one should also start to think about developing a hyperarousal test, which at best could be applied during daytime or routine office/hospital hours. One could think about a stress/challenge paradigm, measuring autonomous nervous system activity (e.g. heart rate, galvanic skin response, etc.), cortisol as main marker of the stress response and EEG during baseline, rest and different stress conditions. One of the best accepted stress paradigms now is the Trier social stress test—its usefulness has already been tested (Chen et al., 2017). Alternatively, probably just the instruction "please try to sleep now" probably might offset a marked stress response in insomniacs. Such a psychophysiological paradigm administered during the day can also easily be coupled with neuroimaging methods, that is, functional magnetic resonance imaging. Needless to say, these data should be coupled with descriptive questionnaire data. Assuming that it will be possible to develop an easy to apply and valid hyperarousal test, this instrument could be used for phenotyping, relating the data to (epi-)genetic data, general diagnostics, differential-therapeutics and therapy outcomes. Given the emerging evidence of maladaptive sleep (Van Someren, 2021), essential insights could require repeated assessment of hyperarousal from evening to morning across recorded nights. Analyses can then address which sleep features determine the overnight fate of distress—which could range from full adaptation even to maladaptive sensitization (Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019). Nevertheless, deeper insights into the mechanisms of hyperarousal in insomnia, its causes and consequences for cognitive processes and brain health in general are needed. This will help to further increase the value of the hyperarousal concept for insomnia research and could also help to identify a valid hyperarousal test.

Interestingly, also with therapeutics at present we have reached a unique situation concerning treatment—all presently published relevant guidelines agree that CBT-I should be the first-line treatment for insomnia. A statement like this would have caused a lot of many raised eyebrows even just 10 years ago! This development is probably because on one hand, the CBT-I literature is blooming and has generated a solid and ever-increasing evidence base, but on the other hand maybe also due to a stagnation in the sector of hypnotic development and the withdrawal of many major players in psychopharmacology from CNS-oriented Research & Development. It has to be judged in the next few years whether the worldwide introduction of orexin receptor antagonists will markedly alter the hypnotic market. From a future perspective, we would like to suggest that research into the roles of histamine and noradrenaline and sleep regulation could lead to new discoveries (Thakkar, 2011; Van Someren, 2021). Maybe also approaches encompassing non-invasive brain stimulation might complement insomnia treatment strategies (Herrero Babiloni et al., 2021).

A better understanding of the psychoneurobiological mechanisms of insomnia is urgently needed to monitor and evaluate treatment effects of CBT-I beyond subjective measures, and further develop complementary treatment strategies. First, preliminary findings suggest that 1 night of experimental sleep restriction (delaying bedtime by 2 hr) may help to stabilize restless REM sleep (Kao et al., 2021). However, it remains to be seen whether this stabilization is observed in therapeutic SRT, and whether it translates into improvements in regulation of emotional distress, hyperarousal and the risk of developing mental disorders. Second, notwithstanding the established efficacy of CBT-I, it is important to acknowledge that two out of five patients do not show full remission, even after boosting CBT-I effects with subsequent pharmacological treatment (Morin et al., 2020). We still have very limited insight into who will respond and who will not. Novel graph theory-based analyses like network outcome analysis and network intervention analysis may reveal how non-responders differ in their initial symptom profiles and trajectories of change of symptoms during the intervention (Blanken, Benjamins, et al., 2019; Blanken et al., 2020; Blanken, van der Zweerde, et al., 2019). Pinpointing such differences could provide leads to novel strategies.

Also the gradual wearing off of initial benefits of CBT-I deserves attention (van der Zweerde et al., 2019). Two recent studies indicate that beneficial effects of CBT-I may be preserved longer if CBT-I is combined with interventions aimed at supporting circadian rhythms (Dekker et al., 2020; Leerssen et al., 2021).

What we consider probably the most important challenge for the future is the integration of CBT-I into the standard treatment of patients with mental disorders, especially anxiety and depression. It is known that almost all mental disorders are afflicted with disturbances of sleep continuity (Baglioni et al., 2016), and we also know that paying proper therapeutic respect to including insomnia-related components into the overall therapeutic concept will improve outcomes in general and speed up the therapeutic process (Gee et al., 2019; Hertenstein et al., 2022; Manber et al., 2008). Models how to do this have been suggested by several authors (Kraepelien et al., 2022; Schneider et al., 2020)—thus, the times seem right to postulate insomnia as a transdiagnostic mechanism for mental disorders (Harvey et al., 2011, 2021; Van Someren, 2021) and also insomnia treatment

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based on CBT-I as a basic mode in psychiatric/psychotherapeutic treatment.

One step further will address the primary prevention of mental disorders. There is a strong probability that adequate insomnia treatment will reduce the incidence and recurrence of depressive episodes and anxiety disorders (Benz et al., 2020; Cheng et al., 2019; Irwin et al., 2022; Leerssen et al., 2021). In a first step, one might address risk groups especially prone to mental illness and offer sleep treatment versus a control condition and compare longitudinal outcomes, as recently demonstrated by Leerssen et al. (2021). In a next step it might be tested whether educating and training of the general population to utilize the principles that underlie CBT-I could prevent insomnia. Such efforts may be especially relevant to prevent mental disorders that tend to surface during important transition periods, like in students moving from high school to university.

CONFLICT OF INTEREST

Dieter Riemann is a member of the Executive Board of FAVT (Freiburg Institute for Behavioural Therapy/non for profit), a salaried activity. He is Editor-in-Chief of the *Journal of Sleep Research*, which is owned by the European Sleep Research Society (non-profit body) and receives payments for this task. Dieter Riemann receives royalties from publishing and honoraria for lecturing (no pharmaceutical industry), and is funded by several grants from the German Federal state. Colin A. Espie reports research support from NIHR-HTA (UK), receiving payments from book publishing and lecture fees. He also reports being a cofounder and Chief Scientist of Big Health Ltd (the developer of Sleepio). He is a shareholder of and receiving salary from Big Health. Alasdair L. Henry is employed by, receives a salary from and is a shareholder of Big Health. All other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Dieter Riemann provided an outline of the article and did the final editing. All the other authors contributed equally.

DATA AVAILABILITY STATEMENT

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