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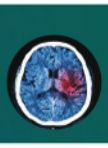

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POSITION PAPER

Insomnia disorder: clinical and research challenges for the 21st century

Luigi Ferini-Strambi[1,2] | Reto Auer[3] | Bjørn Bjorvatn[4,5] | Vincenza Castronovo[2] | Oscar Franco[6] | Luca Gabutti[7] | Andrea Galbiati[1,2] | Goeran Hajak[8] | Ramin Khatami[9] | Tsuyoshi Kitajima[10] | Doug McEvoy[11] | Christoph Nissen[12] | Michael Perlis[13] | Dirk A. Pevernagie[14] | Winfried Randerath[15] | Dieter Riemann[16] | Giovanni Rizzo[17] | Eus Van Someren[18,19] | Alexandros Vgontzas[20] | Fabrizio Barazzoni[21] | Claudio Bassetti[22,23] | the European Sleep Foundation

[1]"Vita-Salute" San Raffaele University, Milan, Italy

[2]Neurology – Sleep Disorders Center, IRCCS San Raffaele Scientific Institute, Milan, Italy

[3]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[4]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[5]Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

[6]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

[7]Institute of Biomedicine, University of Southern Switzerland, Lugano, Switzerland

[8]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Social Foundation Bamberg, Bamberg, Germany

[9]Center of Sleep Medicine, Sleep Research and Epilepsy, Klinik Barmelweid, Barmelweid Academy, Barmelweid, Switzerland

[10]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan

[11]Adelaide Institute for Sleep Health, College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia

[12]University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

[13]Department of Psychiatry, Behavioral Sleep Medicine Program, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[14]Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium

[15]Institute of Pneumology at the University of Cologne, Solingen, Germany

[16]Department of Psychiatry and Psychotherapy, Medical Centre—University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[17]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

[18]Department of Sleep and Cognition, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

[19]Departments of Integrative Neurophysiology and Psychiatry, Center for Neurogenomics and Cognitive Research, Amsterdam UMC, Amsterdam Neuroscience, VU University, Amsterdam, The Netherlands

[20]Sleep Research and Treatment Center, Department of Psychiatry, Penn State Hershey Medical Center, College of Medicine, Pennsylvania State University, Hershey, PA, USA

[21]Ente Ospedaliero Cantonale (EOC) Head Office, Bellinzona, Switzerland

[22]Department of Neurology, Inselspital University Hospital, University of Bern, Bern, Switzerland

[23]Department of Neurology, Sechenov University, Moscow, Russia

Correspondence
Luigi Ferini-Strambi, Department of Neurology OSR-Turro, Sleep Disorder Center, Vita-Salute San Raffaele University, Milan, Italy.
Email: ferinistrambi.luigi@hsr.it

Abstract

Background and purpose: Insomnia is a common and debilitating disorder that is frequently associated with important consequences for physical health and well-being.

Methods: An international expert group considered the current state of knowledge based on the most relevant publications in the previous 5 years, discussed the current challenges in the field of insomnia and identified future priorities.

Results: The association of trajectories of insomnia with subsequent quality of life, health and mortality should be investigated in large populations. Prospective health economics studies by separating the costs driven specifically by insomnia and costs attributable to its long-term effects are needed. Ignoring the heterogeneity of insomnia patients leads to inadequate diagnosis and inefficient treatment. Individualized interventions should be promoted. More data are needed on both the impact of sleep on overnight effects, such as emotion regulation, and the potential compensatory effort to counteract diurnal impairments. Another gap is the definition of neurocognitive deficits in insomnia patients compared to normal subjects after chronic sleep loss. There are also a number of key gaps related to insomnia treatment. Expert guidelines indicate cognitive–behavioural therapy for insomnia as first-line treatment. They neglect, however, the reality of major healthcare providers. The role of combined therapy, cognitive–behavioural therapy for insomnia plus pharmacological treatment, should be evaluated more extensively.

Conclusion: Whilst insomnia disorder might affect large proportions of the population, there are a number of significant gaps in the epidemiological/clinical/research studies carried out to date. In particular, the identification of different insomnia phenotypes could allow more cost-effective and efficient therapies.

KEYWORDS
cognitive-behavioral therapy for insomnia, insomnia, insomnia treatment, phenotypes, sleep

INTRODUCTION

Since Hippocratic times lifestyle has constituted a cornerstone of health and prevention. The three key pillars of lifestyle are diet, activity and sleep. Sleep, a key part of our life, has been challenged by the westernization of lifestyle and by a dramatic increase in the use of technology in daily life.

Insomnia disorder is the second most prevalent mental disorder[1] and is the most common sleep complaint[2] Insomnia is defined by difficulties initiating or maintaining sleep, subjectively experienced to have adverse consequences for daytime functioning and occurring despite appropriate circumstances and opportunity for sleep. If the complaints occur at least three times a week and last for at least 3 months, the diagnostic criteria for insomnia disorder are met. Importantly, according to both the International Classification of Sleep Disorder third edition (ICSD)[2] and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM)[3] the distinction between primary and secondary insomnia was removed in favour of an umbrella category for insomnia disorder which can be used also when insomnia is comorbid with other conditions. This modification reflects understanding that, although insomnia frequently accompanies other disorders, it can also precede the comorbid condition, persist despite effective treatment of the comorbid condition, or aggravate the symptoms of the comorbid condition[4] The prevalence of acute insomnia symptoms in the general population is estimated to be up to 37% per annum[5–8] The prevalence of chronic insomnia is about 10%–20% and is more prevalent in women, older adults and individuals of lower socioeconomic status[2,9,10] Although insomnia shows high prevalence, it is seldom adequately assessed. This probably reflects the fact that most medical school and internal and family medicine residency training programmes dedicate very little time to the assessment and treatment of sleep disorders (in general) and to the evaluation and management of insomnia (specifically)[11,12] The more recent diagnostic criteria[2,3] recommend that 'insomnia disorder' should be coded 'whenever diagnostic criteria are met whether or not there is a coexisting physical, mental or sleep disorder'. Insomnia is ubiquitous, so it is important that clinicians and, in particular, general practitioners have the ability to identify patients with insomnia. The identification of brief, reliable and valid screening tools to evaluate insomnia disorder in everyday clinical practice is undoubtedly needed.

Several neurological disorders are frequently complicated by comorbid insomnia. Insomnia may influence the severity of both epilepsy and headache, and its treatment may improve seizure and headache frequency[13] Insomnia may be a potentially modifiable risk factor for Alzheimer's disease[14] Insomnia symptoms have been reported in up to 80% of patients with Parkinson's disease (PD), but according to the diagnostic criteria of 'insomnia disorder' the prevalence rate is 43%[15] At least 40% of subjects affected by multiple sclerosis (MS) have chronic insomnia, and the prevalence could be higher in relation to underdiagnosis[16] Moreover, insomnia is frequently associated with sleep breathing disorder. Indeed, up to 58% of patients with sleep apnoea report symptoms indicative of comorbid insomnia[17]

An important aspect is to establish when the clinical assessment cannot be considered enough in the diagnostic approach. Polysomnography and actigraphy provide estimates of objective sleep and wake duration; however, a meta-analysis showed that polysomnography measures in patients suffering from insomnia may not deviate from normal values in many patients and do not capture the subjective experience of being awake[18]

Some studies in the last few years indicated precise insomnia phenotypes. For instance, insomnia with short sleep duration (ISSD) is recognized as the most severe phenotype[19] All-cause mortality, incident cardiovascular disease (CVD), hypertension and diabetes are higher in individuals with ISSD in comparison with other phenotypes[20] It should be clarified whether genetics or neuroimaging may offer a concrete contribution in the definition of different phenotypes of insomnia.

Lastly, insomnia is a treatable disorder. There is a very substantial level 1 evidence base evaluating pharmacological treatments and cognitive–behavioural therapy for insomnia (CBT-I). Expert guidelines recommend CBT-I as first-line treatment for insomnia, but it should be recognized that in-person CBT-I may be difficult to access. Accordingly, dissemination of information regarding assessment and access to referral information is critical.

The present overview results from a collaborative effort of a group of international experts in the fields of interest. It summarizes the most important recent research and medical findings in the field of insomnia and identifies the unsolved needs.

METHODS

This paper summarizes the results of a symposium (Think Tank 2019) organized by the European Sleep Foundation following a standardized approach used in three previous editions of Think Tank[21–23] The original idea of these meetings was conceived by some members of the Sleep-Wake Disorders Scientific Panel of the European Academy of Neurology. Thirty international experts were invited to Think Tank 2019 and 23 participated in the conference, held from 18 to 20 October 2019 in Baveno, Italy. Experts were from the domains of sleep research, sleep medicine, neurology, psychiatry, family medicine and public health. Ten countries from four continents, Europe, United States, Japan and Australia, were represented to reflect different healthcare systems. Five major topic areas were used to guide the definition of important clinical questions and challenges regarding insomnia including (1) epidemiology and public health, (2) the role of the family medicine and the sleep medicine centre in assessment and treatment, (3) phenotype heterogeneity, (4) neurocognitive performance and (5) non-pharmacological and pharmacological treatments.

The participating experts were divided into five subgroups. Each subgroup defined the most important clinical challenges and research priorities by discussing the most relevant papers published in the last 5 years for each of the five major topic areas. These groups drafted five documents that were then revised by the conference leaders.

RESULTS/CONSENSUS STATEMENTS

Session 1—Public health and insomnia

Currently, the prevalences of short sleep duration and acute insomnia symptoms in the general population are approximately 29% and 37%, respectively[5–8,24] Of these, approximately two-thirds can be considered poor sleepers whilst the remaining require clinical support and treatment and can be considered as suffering from chronic insomnia disorder. Persons with poor sleep have a higher chance of developing insomnia disorder[25] The prevalence of chronic insomnia is about 10%–20% and is more prevalent in women, older adults and individuals of lower socioeconomic status[2] Additional factors related to poor sleep and/or chronic insomnia include life event stress, physical illness and injury, response to sleeplessness and, to some extent, diet (caffeine, alcohol and energy drinks), iatrogenic effects from medications, substance use and abuse, electronic device use, socioeconomic status, occupational status and environmental noise pollution (including light and sound).

Over the last eight decades, there has been an exponential rise in the number of papers on insomnia, reflecting increased attention to the epidemiology of insomnia, the theory regarding the aetiology and pathophysiology of insomnia, assessment and classification, treatment development, and clinical trials of medical and behavioural therapeutics for insomnia (Figure 1).

One particularly productive strategy has been the evaluation of the consequences of one particular insomnia phenotype: ISSD. Recent studies show that ISSD has a differential response to treatment based on this phenotypic distinction[26] Besides the prognostic impact of phenotypes, the impact of insomnia severity has been analysed by the number of complaints and the associated risk. Longitudinal data support a dose-dependent association of baseline number of insomnia symptoms and the risk of heart failure[27] In addition, the presence of insomnia in patients with established heart failure is an independent predictor of cardiac events[28] Individual insomnia symptoms also have prognostic value. A meta-analysis of 23 cohorts estimated the risk of having difficulties falling asleep, having difficulties maintaining sleep, early morning awakening and non-restorative sleep. Difficulties both falling asleep and maintaining sleep were associated with an increased risk of CVD events[29,30]

On the other hand, sufficient sleep duration in addition to all four traditional healthy lifestyle factors (physical activity, nutrition, smoking and alcohol intake) was associated with 65% lower risk of CVD and 83% lower risk of fatal CVD in one large European cohort[31]

However, it is still unknown whether the association of insomnia with cardio-metabolic risk is causal due to reverse causation bias and residual confounding factors inherent to observational studies. Furthermore, how sleep is measured and the mechanisms explaining the association of sleep disorders with health issues and mortality remain unclear. Therefore, recent and ongoing research is addressing the need to integrate other lifestyle factors as possible mediators in the association of insomnia and CVD risk. Remarkably, individuals with high Mediterranean diet score are less likely to have ISSD compared with those with low Mediterranean diet score[32]

Future priorities and next steps include:

1. To further investigate in large populations with heterogeneous characteristics the association of trajectories of insomnia with subsequent health, quality of life and mortality.

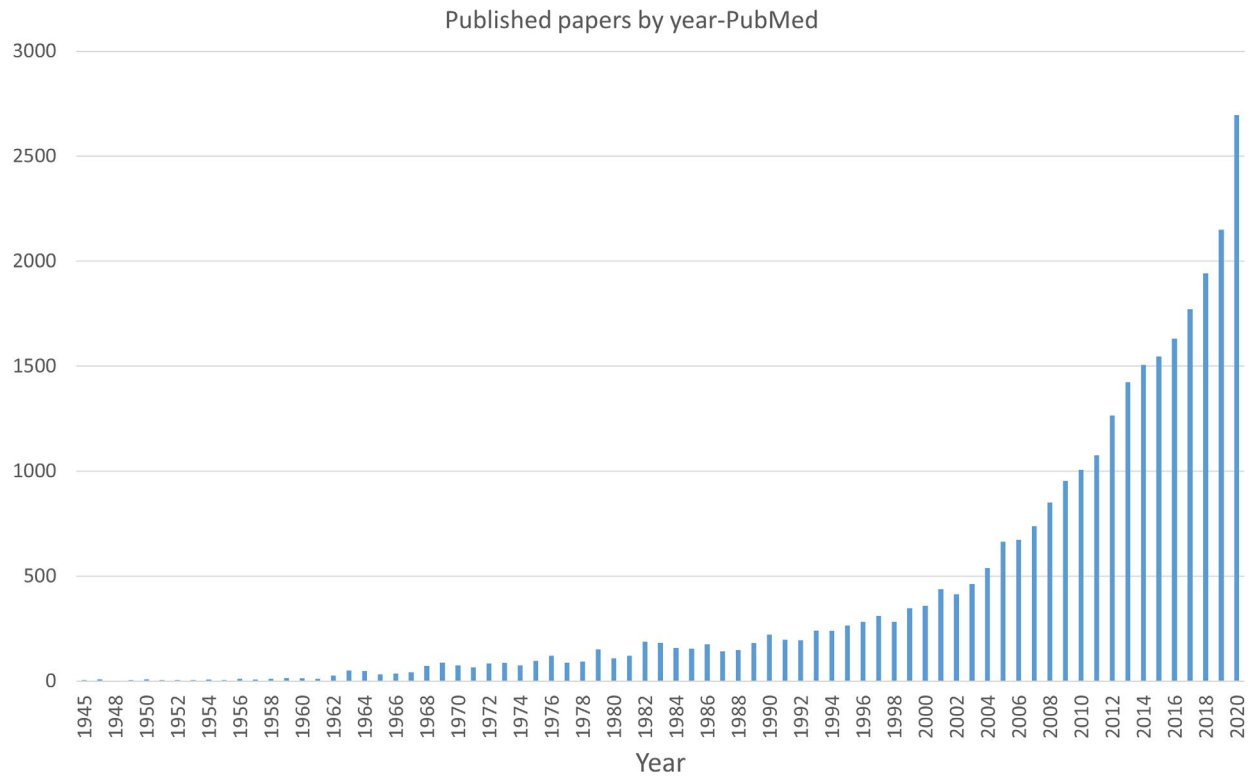

FIGURE 1 Number of published papers by year for insomnia as the major MeSH topic [Colour figure can be viewed at wileyonlinelibrary.com]

2. To perform prospective health economics studies separating the costs specifically from insomnia and costs attributable to its long-term effects.
3. To use large-scale datasets from consumer apps and wearables to better understand the associations of the continuum of physical activity, diet, stress and sleep, together with other lifestyle factors, with health, quality of life and mortality.
4. To assess the causal pathways between insomnia and sleep disorders and risk factors (e.g., hypertension, glucose metabolism), diseases (e.g., affective disorders, neurodegenerative conditions, CVD) and mortality. Analyses of prospective cohort studies applying rigorous statistical methods enabling causal inference, in particular Mendelian randomization, are promising approaches.
5. To design and implement public health policies and strategies aimed to improve sleep health in the population (e.g., noise reduction, flexible working conditions, improvements in physical activity) as a means to improve population and planetary health.

Session 2—Insomnia disorder diagnosis: the role of family medicine

Internal and family medicine practitioners, who are at the forefront of healthcare delivery in most European countries and many others worldwide, are ideally placed to diagnose and manage insomnia. There are few studies on insomnia amongst patients visiting their general practitioner (GP)[33] Sleep complaints often co-occur with other existing psychological and somatic conditions; thus the prevalence of insomnia is likely to be higher in patients visiting GPs in comparison to the prevalence found in the general population. In what is perhaps the first study of this issue, some 20 years ago, the prevalence of insomnia was reported to be over 50% in primary care patients[34] A more recent study in consecutive patients approached in the GP's waiting room in New Zealand showed a prevalence of insomnia of 41%[35] Another study in consecutive and unselected patients visiting their GPs in Norway found a prevalence of 53.6%[36] Are GPs aware of how common insomnia may be amongst the patients visiting their practice? Interestingly, in another Norwegian study, GPs estimated the prevalence of sleep problems amongst their patients to be 11%[37] The GP is usually the first point of contact, and a survey indicated that 79% of GPs see subjects with a sleep complaint at least once a week[38] Figure 2 highlights the importance of considering primary care practitioners in the diagnosis and treatment of chronic insomnia. 'The ecology of medical care'[39] has provided a framework for thinking about the organization of healthcare, medical education and research. If a population of 1000 adults is considered, of whom half would experience insomnia symptoms per year and 15% chronic insomnia symptoms, the majority will be seen in family medicine and community settings and a minority in specialized sleep centres. Population-level chronic insomnia treatment policies should integrate family medicine and foster interdisciplinary collaboration with specialized sleep centres.

However, the evidence points to a failure of family care practitioners to enquire about sleep difficulties and a reluctance for

insomnia sufferers to seek their advice. This 'don't ask, don't tell' phenomenon is not well understood but probably arises from a lack of knowledge on the part of both patients and GPs concerning the adverse health consequences of chronic insomnia. Despite GPs believing that a sleep assessment and the identification of insomnia are crucial, the time to devote to each patient is limited. Thus, a brief measure for insomnia screening is important. The two-item Sleep Condition Indicator may help GPs to rapidly screen insomnia in the clinical practice [40,41] (Table 1). An even shorter assessment can be made with the UK Biobank multiple choicequestion 'Do you have trouble falling asleep at night or do you wake up in the middle of the night?' The answer 'usually' distinguishes diagnosed people with insomnia from controls answering 'sometimes' or 'never/rarely', with an accuracy of 0.91[42]

Concerning the management of insomnia by GPs, there is limited evidence. Sleep hygiene education (SHE) is the most commonly used non-pharmacological treatment in general practice[43] A recent systematic review and meta-analysis showed that SHE is substantially less efficacious than other non-pharmacological treatments such as CBT-I[44] CBT-I is a multimodal treatment that includes SHE but has, as the putatively more active components, sleep restriction and stimulus control therapies. Some practitioners also augment standard CBT-I with one or more of the following: more rigorous forms of cognitive therapy, mindfulness training, behavioural experiments and/or bright light therapy. The data on the effectiveness and safety of CBT-I is strong and CBT-I is now considered the first-line therapy for chronic insomnia in major guidelines throughout the world[10,45] This said, of the few family medicine practitioners who have heard of CBT-I, they believe it to be outside their scope of practice and find it difficult to refer patients. Potential solutions to this problem are (1) to disseminate information about provider directories (e.g., https://cbti.directory/), (2) to consider access to CBT-I via specialists who provide telehealth care and (3) to consider prescribing accessing online CBT-I programmes (e.g.,https://sleepful.me/; https://www.somryst.com/; https://www.sleepio.com/). With respect to the last of these options, use of the online programmes may require that the individual healthcare system has a contract with the online provider and/or that the treatment be part of the system's formulary. Finally, the various online programmes may work best when a health provider concurrently monitors patient progress for treatment response or failure.

Finally, patients who fail to articulate their problem to their family physician self-medicate with ineffective or even harmful agents (e.g., alcohol); and the family physician who is made aware of the patient's problem prescribes hypnotic drugs or off-label sleep promoting medications, despite knowing their potential long-term risks.

Future priorities and next steps include:

1. To inform the general community and family health professionals of

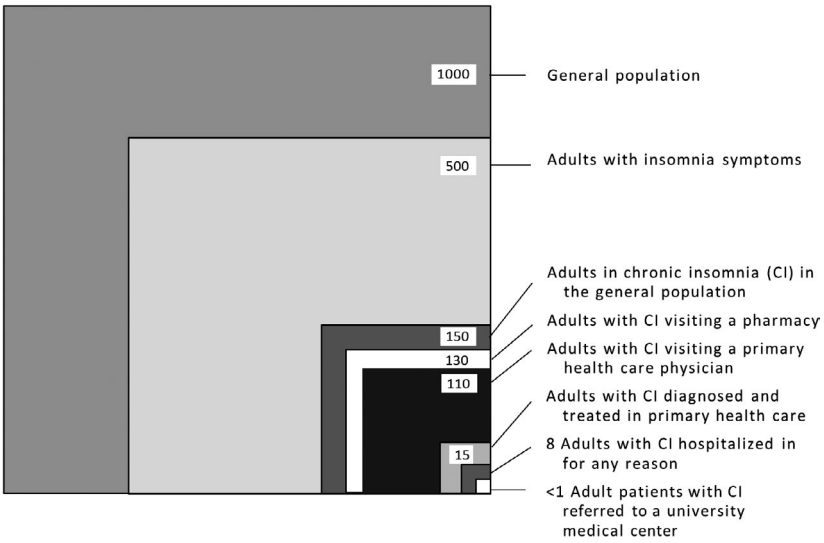

FIGURE 2 The ecology of healthcare revisited for chronic insomnia. Estimates of healthcare utilization per year of a population of 1000. Each box represents a subgroup of the largest box, which comprises 1000 persons. Data are for adult persons of all ages

	Score				
	4	3	2	1	0
Thinking about the past month, to what extent has poor sleep troubled you in general?					
	Not at all	A little	Somewhat	Much	Very much
Thinking about a typical night in the last month, how many nights a week do you have a problem with your sleep?					
	0–1	2	3	4	5–7

Note: A higher score means better sleep [33] Scores ≤2 indicate bad sleep quality.

TABLE 1 Scoring instructions: add the item scores to obtain the sleep condition indicator (SCI) total (minimum 0, maximum 8)

a. the serious personal, societal and medical costs of chronic insomnia, and that
b. effective non-pharmacological treatment such as CBT-I is available;
c. the potential harms and addictive potential of drug therapies such as benzodiazepines and z-drugs when used to treat chronic insomnia.

2. To provide to family medicine practitioners a chronic insomnia 'toolkit' enabling
   a. screening for chronic insomnia with simple questions to quickly identify the high risk patient; and then
   b. diagnosis of chronic insomnia and other sleep disorders with more detailed, yet brief, clinical sleep assessment;
   c. shared decision making between clinicians and patients with patient decision aids helping patients choose the treatment options that match their preferences and values (the decision aid would highlight the benefits, risks and treatment burdens of non-pharmacological and pharmacological therapies [CBT-I]);
   d. interdisciplinary care of chronic insomnia with algorithms presenting when to refer to specialized sleep healthcare.
3. To create interdisciplinary networks between family medicine practitioners and sleep centre specialists to
   a. provide the necessary CBT-I training;
   b. take referrals for complex or treatment-resistant cases.

Session 3—Insomnia and phenotype heterogeneity

In contrast to what the name suggests, insomnia differs strongly from curtailed sleep duration in otherwise good sleepers. Polysomnography recordings show that people with insomnia disorder do sleep, but in a fragmented and unstable way[18]

Insomnia complaints commonly co-occur with somatic, mental and other sleep disorders and usually worsen their severity. Clinicians should especially be aware of the common co-occurrence of insomnia with other sleep disorders[46–48] It is only very seldom appropriate or helpful to regard insomnia as 'secondary', as merely a symptom of another disorder. On the contrary, as for other disorders[49] in a better conceptualization insomnia is actionable and a successful intervention can ameliorate the severity of other symptoms.

A continuing question is whether insomnia is a single homogeneous disorder. Heterogeneity of complaints and treatment response suggested the existence of different types and/or 'subtypes' with different underlying mechanisms. In terms of presenting complaints, several subtypes are clearly apparent, classically referred to as initial, middle, late and mixed insomnia. Clinically, there are three to four presentations that have been classified in previous versions of the DSM and ICSD nosologies[2,3] including psychophysiological insomnia; paradoxical insomnia (i.e., sleep state misperception insomnia); idiopathic insomnia; and possibly physiological insomnia. Whilst these types are prototypic, the degree to which they are orthogonal and/or reliably diagnosed has led some to simply adopt the global classification of 'insomnia disorder'[50,51] This does not mean that insomnia is a homogeneous disorder. On the contrary, it means that a top-down subtype definition may not necessarily result in robust subtyping.

Converging support suggests a separate subtype of people with insomnia who sleep <6 h, as assessed either during the first night of polysomnography or on average across multiple nights[19] The ISSD subtype is in addition characterized by a longer history of insomnia, more deviant biomarkers, increased health risks and treatment resistance[26,52] All mentioned subtypes have a limited consistency over time[51] for example, of the people diagnosed with ISSD after one night, two-thirds may not fulfil the criterion anymore on a second night[52] More recently, big data and data-driven methods have revealed other robust and replicable subtypes based on multivariate profiles of traits and personal history and linked to biological features[53]

It is expected that these novel subtyping efforts will increase the chances of revealing distinguishable underlying mechanisms leading to seemingly similar sleep complaints, but possibly requiring different treatments. An unmet current need for big data subtyping is to assess individual differences in responses to different treatments. Doing this will ultimately allow us to predict which treatment works best for whom.

Genome-wide association studies (GWAS) have recently addressed insomnia risk genes. In fact, across all disorders, the largest GWAS to date (N = 1.3 million) for any trait or disorder specifically addressed insomnia[54] Findings indicate that insomnia is a highly polygenic complex trait. As commonly found in GWAS, there is considerable pleiotropy and overlap of risk genes for insomnia and other phenotypes and disorders. Interestingly, the overlap is stronger with mood and anxiety phenotypes than with sleep-related phenotypes. Also clock-related genes are not particularly represented. The use of GWAS goes beyond just finding genes that each explain very little variance. The availability of gene expression databases has made it possible to suggest particular brain areas and cell types most likely to convey the genetic risk that multiple gene variants convey. Concertedly, identified brain areas, cell types and phenotypic and genotypic associations provide little support for insomnia being a disorder of sleep regulation and rather suggest it concerns problematic regulation of stress and emotion.

Future priorities and next steps

To move forward in understanding insomnia, ideally existing large cohort studies with extensive multivariate biomarkers would be exploited. If cohorts have not assessed insomnia yet, the inclusion of at least a single question indicator variable of the diagnosis of insomnia is advocated. The UK Biobank question on insomnia, for example, shows good accuracy compared to a diagnosis based on a structured interview[42]

The next steps include:

1. To use data-driven approaches in existing databases to find novel sleep electroencephalogram and actigraphy features of relevance for insomnia.
2. To monitor the release of new wearables (e.g., oxygen desaturation + actigraphy) and evaluate their use to find features of relevance for insomnia.
3. To use advanced multivariate methods like symptom network analysis to disentangle the risk of morbidity and mortality insomnia conveys relative to common comorbidity and symptoms.
4. To commence a collaborative intervention trials registry for assessment of individual profile treatment outcomes and use data-driven (e.g., machine learning) approaches to ultimately predict who responds best to which treatment.

Session 4—Neurocognitive performances in insomnia disorder

Although insomnia is commonly conceived of as a night-time disorder, its complaints and consequences extend well beyond the nocturnal period. Indeed, its pathophysiology has been predominantly framed on the hyperarousal model[55] According to this view, which is based on both clinical observation and scientific evidence, insomnia is characterized by an augmented state of arousal that is expressed on an autonomous nervous system, behavioural, cognitive emotional and cortical level throughout the entire day. Despite this hyperactivation, patients frequently report impaired quality of life and a variety of adverse health conditions, such as depression, and there is also evidence that insomnia represents a risk factor for several other psychopathologies such as anxiety, alcohol abuse and psychosis[56] Insomnia is also associated with increased absenteeism at work and loss of productivity probably due to an impaired diurnal functioning. Accordingly, patients complain of decreased cognitive functioning that frequently involves memory, executive functions, decision making and, more in general, work-related mistakes. Notably, these impairments are not always corroborated by objective investigations. A meta-analysis reported that insomnia had mild to moderate impairments on specific cognitive domains. Specifically, patients performed poorly on tasks assessing working memory, episodic memory and problem solving and they exhibited only mild to moderate impairment for several attentional processes. However, their performances did not differ in comparison to good sleepers for psychomotor processes, verbal functions, procedural memory and global cognitive functioning[57] Some have argued that the observed lack of objective findings with respect to daytime impairment belies the actual or core complaint of those with insomnia; it is not so much a matter of successful output/performance, it is the effort required to reach these ends that seems affected by poor sleep continuity and/or reduced sleep duration[58]

Another relevant issue is represented by the discrepancies between subjective and objective sleep assessment. Large dataset analysis reported only minor polysomnographic alterations. In particular, results showed that patients with insomnia have a sleep continuity disruption and a reduction of slow wave sleep and rapid eye movement sleep compared to good sleepers[18] However, it is recognized in the scientific community that insomnia patients are prone to underestimate their total sleep time and overestimate their sleep onset latency and wakefulness after sleep onset. This implies that sleep misperception might be a core feature and an essential aspect to understand the disorder but unveil also a chicken-and-egg problem: sleep state misperception is the cause or effect of insomnia? Interestingly, there is also evidence that local aspects of both sleep and wakefulness might help in understanding and solving the problem[59,60]

Future priorities and next steps include:

1. To investigate brain mechanisms of poor subjective sleep quality by
   a. challenging the hyperarousal concept;
   b. cycling alternating pattern;
   c. slow wave sleep and homeostasis;
   d. concepts of local wakefulness and sleep;
   e. concepts of orchestration of brain oscillations (e.g., spindle activity phase-locked to sleep slow oscillations);
   f. provocation tests (e.g., homeostatic response to sleep restriction, probe individual sleep need).
2. To investigate the mechanisms of subjective daytime impairments and neurocognitive performance deficits by
   a. further assessment of sleep impact on overnight effects, such as emotion regulation;
   b. the assessment of potential compensatory effort to counteract diurnal impairments;
   c. the assessment of neurocognitive deficits in insomnia patients vs. the effect of chronic sleep restriction in normal subjects.
3. To investigate the potential causality of the links between insomnia and adverse health conditions, such as dementia.

Session 5—Treatment of insomnia disorder

In recent years, evidence has emerged that patients with insomnia face a tremendous chance to be effectively treated in the short and in the long term[61] In general, pharmacological agents have been tested in short-term studies and there is little evidence for their effectiveness or safety beyond 3–4 months' treatment[62] The robust efficacy of CBT-I has been unequivocally proven in the short and long term[63,64] Respective expert guidelines which provide CBT-I as first-line treatment can rely on a valid database[10,45] However, they neglect the reality of major healthcare providers. The de facto insomnia treatment is provided by GPs. GPs claim that CBT-I transfer into wide clinical use requires more detailed data on the way and quality of its application in primary care settings before being recommended for broad use[65] Patients as well as doctors' education and awareness programmes promise a better use of CBT-I and its

implementation. However, this requires a scientific approach to validate their quality and efficiency. The significant mismatch between expert recommendations and availability of CBT-I treatment calls for, as noted above, a broader conceptualization about how to inform primary care practitioners regarding how to access/refer for CBT-I.

A recent study showed that CBT-I is feasible in patients with MS and produces significant improvements in insomnia severity, sleep quality, as well as in fatigue and depression symptoms[16] Moreover, small studies showed that CBT-I is a safe and efficacious treatment also in PD, but strategies to enhance therapy adherence are needed[15] Strikingly, CBT-I is also effective in improving insomnia symptoms in patients with untreated obstructive sleep apnoea and in increasing subsequent continuous positive airway pressure therapy outcomes[66]

Concerning pharmacological treatment, an increasing number of field studies as well as data from controlled studies have revealed a positive correlation of the use of benzodiazepine receptor agonistic hypnotics (BRZA) with medication abuse and dependence, infection rates, falls, accidents and mortality[67,68] The criticism arising about sleeping pills has reduced prescription rates of BRZA worldwide. This reaction has taken place even though most long-term field studies lack reliable proof that hypnotic intake is causing harm rather than an epiphenomenon of a genuine sick population with comorbid or coincident insomnia. On the other hand, it has been observed recently that one in five new users of sedative–hypnotics will become a long-term user, but only 0.5% will become excessive users[69] A switch to the prescription of sleep promoting drugs of other pharmacological classes is observed in most industrialized countries. Sedating antidepressants, some herbal drugs, orexin receptor antagonists and antipsychotics have short-term efficacy in insomnia patients[10,61,70] The scientific community, however, is asked to assess their benefit/risk ratio especially in the long term. In particular, serious cardiac and metabolic effects of some agents challenge their off label use in chronic insomnia. Moreover, a recent systematic review on drug treatments for insomnia people with dementia showed that there was evidence of some beneficial effects from trazodone and orexin antagonists but larger long-term trials are needed also for the assessment of adverse effects[71] These authors found no evidence for beneficial effects of melatonin (up to 10 mg) or ramelteon, a melatonin receptor agonist. However, in another recent review on the management of insomnia in PD, the authors suggested the use of prolonged release melatonin or doxepine for patients aged >65 years, and prolonged release melatonin or doxepine or eszopiclone or zolpidem for patients aged <65 years[15] Moreover, the authors reported that there are few safety data concerning the long-term use of sedative–hypnotic drugs also in PD[15]

Currently, and in the future, it will be insufficient for pharmaceutical companies to convince consumers that a particular drug provides significant sleep improvement. Rather, they must provide unequivocal evidence that its benefit in health improvement outweighs its potential risk and harm. It also appears to be a serious demand to further investigate the mechanisms of action in order to better understand the heterogeneity of these drug classes.

Clinical experience in daily practice has created the wording that 'getting to sleep with drugs is just a question of dosing'. Limitations of this approach arise mainly from unwanted side effects such as dose- and drug-dependent hangover effects and lack of improvement of daytime well-being and functioning with increasing treatment dose. It rarely drives doctors to a general critical position towards the use of sleeping pills. Unfortunately, the current debate on the benefit–risk ratio of hypnotics is rather emotional and mainly driven by the concern for abuse and dependence. No issue of hypnotic use has gained more attention during the last decades. It is true that some long-term studies with medication intake on a nightly basis over up to 1 year have failed to show a cure of the disease after end of treatment. It is also true, however, that dose escalation has rarely been found. Furthermore, withdrawal of modern hypnotic agents such as selective benzodiazepine receptor agonists, melatonin agonists, sleep promoting antidepressants or orexin receptor antagonists do not exhibit similar withdrawal symptoms to older types of hypnotics or rebound insomnia even after abrupt cessation of treatment. This does not rule out psychological dependence to stimulate patients regaining treatment to restore their former satisfaction with the drug-related sleep benefit.

Following the widely accepted and evidence based hypothesis that a chronic neuronal hyperarousal accounts for chronic insomnia, a continuous arousal-suppressing medication could be seen as an appropriate drug class to be evaluated for treatment. Physicians in general have accepted that patients with diabetes or arterial hypertension take their medication on a regular basis. Moreover, patients with these diagnoses have undoubtedly been shown to profit from behavioural treatments such as diet or physical activity. To prevent them from receiving a medication, however, would be understood as medical misconduct. Instead of arguing on the best treatment modality for patients between healthcare providers, our time and energy as healthcare professionals should go to informing patients on the menu of treatment options available, both behavioural and pharmacological—to highlight their benefits, risks and treatment burdens. Shared decision making with patient decision aids enabling healthcare providers to diagnose patients' preferences and values for various treatment modalities could be a method to achieve this goal.

This is even more the case when taking into account epidemiological data showing that the majority of patients suffer from acute and transient insomnia and, even amongst patients with chronic insomnia, sleep problems often occur only during some nights of the week. This suggests that appropriate treatment regimens rather than a fundamental pro and con debate should lead clinical decisions. The combination of cognitive–behavioural therapy and intermittent, as needed, hypnotic use has been shown to improve sleep significantly whilst drug intake remained low or even declined over time[72]

Future priorities and next steps include the following.

1. Observational studies are required to prove CBT-I in real life settings.
2. Strategies are required to enhance CBT-I adherence in patients with PD and MS.
3. The implementation of CBT-I in neuropsychiatric disorder and in patients with comorbid obstructive sleep apnoea is needed.
4. Stepped care approaches should consider the use of single CBT-I components reaching to complex programmes and those with a combination with pharmacological treatment.
5. Should CBT-I or hypnotic drugs be used in acute/short-term insomnia to prevent chronicity of the disorder (such as in pain treatment)?
6. Clinical studies with non-nightly drug intake with or without behavioural treatment components could clarify the efficiency of these treatment schedules in patients with transient insomnia or chronic insomniacs with not-every-night sleep complaint.
7. There is an urgent need for studies of widely used drugs without scientific evidence (e.g., sedating antidepressants, antipsychotics, antiepileptics).
8. Long-term clinical trials for insomnia especially in neurological patients, with the assessment of adverse effects, are needed.
9. Patient decision aids presenting the treatment options available to patients need to be developed in order to enable healthcare professionals to diagnose patients' preferences and values and move towards shared decision making.
10. Research in the future will have to question the validity of standard electrophysiological measurements in their value to assess the effect of treatments. Functional magnetic resonance imaging or positron emission tomography, near infrared spectroscopy or electroencephalographic fine structure analysis could provide a better understanding of sleep-related states of consciousness, as well as of treatment effects.

CONCLUSION

Insomnia is a common and debilitating disorder that is frequently associated with important consequences for physical health and well-being. There are a number of significant gaps in the epidemiological/clinical/research studies carried out to date. From the epidemiological point of view, the association of trajectories of insomnia with subsequent health, quality of life and mortality should be investigated in large populations with heterogeneous characteristics. How sleep is measured and the mechanisms explaining the association of sleep disorders with health issues and mortality remain unclear. Moreover, prospective health economics studies by separating the costs driven specifically from insomnia and costs attributable to its long-term effects are needed.

Despite the high prevalence of insomnia in the primary care setting, only a small proportion of patients report sleep problems to their physician. GPs believe that a sleep assessment and the identification of insomnia are crucial, but the time to devote to each patient is limited. Thus, a brief measure for insomnia screening is important for possible referral to a sleep specialist.

Whilst insomnia disorders might affect large proportions of the population, these tend to present differently and respond differently to treatment, highlighting heterogeneous phenotypes within the insomnia spectrum. Ignoring the heterogeneity leads to inadequate diagnosis and inefficient treatment with subsequent challenges in the understanding of the causative physio-pathological mechanisms. At the same time, introducing too many phenotypes could also jeopardize diagnosis, treatment and ethological research efforts. Is there a single insomnia phenotype or multiple phenotypes, how many and how should they be defined remain fundamental issues in sleep research. However, individualized interventions should be promoted: individual recommendations of sleep duration should be based on individual sleep need (the popular notion of '8 h for everybody' should be abandoned).

More data are needed on both the impact of sleep on overnight effects, such as emotion regulation, and the potential compensatory effort to counteract diurnal impairments. Another gap is the definition of neurocognitive deficits in insomnia patients compared to normal subjects after chronic sleep restriction. There are also a number of key gaps related to insomnia treatment. Expert guidelines which provide CBT-I as first-line treatment can rely on a valid database. They neglect, however, the reality of major healthcare providers. The de facto treatment is provided by general care physicians, not by scientific or clinical experts in either sleep or psychotherapy. In acute short-term insomnia there is a conflict whether CBT-I or pharmacological treatment should be used, both promising to prevent chronicity of the disorder. Combined therapy might be a solution for sub-chronic insomnia, but has not been proven.

AUTHOR CONTRIBUTIONS

Luigi Ferini Strambi: Conceptualization (lead); writing original draft (lead). Reto Auer: Conceptualization (supporting); writing original draft (supporting). Bjørn Bjorvatn: Conceptualization (equal); writing original draft (supporting). Vincenza Castronovo: Conceptualization (supporting); writing original draft (supporting). Oscar Franco: Conceptualization (supporting); writing original draft (supporting). Luca Gabutti: Conceptualization (supporting); writing original draft (supporting). Andrea Galbiati: Conceptualization (supporting); writing original draft (supporting). Goeran Hajak: Conceptualization (supporting); writing original draft (supporting). Ramin Khatami: Conceptualization (supporting); writing original draft (supporting). Tsuyoshi Kitajima: Conceptualization (supporting); writing original draft (supporting). Doug McEvoy: Conceptualization (supporting); writing original draft (supporting). Christoph Nissen: Conceptualization (supporting); writing original draft (supporting). Micheal Perlis: Conceptualization (supporting); writing original draft (supporting). Dirk A.A. Pevernagie: Conceptualization (supporting); writing original draft (supporting). Winfried Randerath: Conceptualization (supporting); writing original draft (supporting). Dieter Riemann: Conceptualization (supporting); writing

original draft (supporting). Giovanni Rizzo: Conceptualization (supporting); writing original draft (supporting). Eus J.W. Van Someren: Conceptualization (supporting); writing original draft (supporting). Alexandros Vgontzas: Conceptualization (supporting); writing original draft (supporting). Fabrizio Barazzoni: Conceptualization (supporting); writing original draft (supporting). Claudio L Bassetti: Conceptualization (supporting); writing original draft (supporting).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Luigi Ferini-Strambi https://orcid.org/0000-0003-2867-5424
Giovanni Rizzo https://orcid.org/0000-0002-9718-2044
Claudio Bassetti https://orcid.org/0000-0002-4535-0245

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