

# Chronic Insomnia: Clinical and Research Challenges – An Agenda

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## Abstract

Chronic insomnia afflicts up to 10% of the population in Western industrialized countries. It is characterized by delayed sleep onset, problems in maintaining sleep, early morning awakening or the feeling of non-restorative sleep coupled with significant daytime impairments on an emotional, social or professional level. It can occur as a co-morbid condition in any other medical or mental disorder, but also as a primary condition. Within the last decade new diagnostic and differential diagnostic approaches have been suggested that enhance diagnostic precision. Epidemiological data and data relating to the health care and cost situation of chronic insomnia suggest a huge burden for society. Chronic insomnia leads to a clear-cut increased risk for psychopathology (i.e., affective disorders) and probably also for cardiovascular and metabolic dysfunction. The pathophysiology of

the condition is still poorly understood and will profit from integrating modern neuroscientific approaches (animal studies, molecular biology, neuroimaging, neurophysiology, etc.). Current treatment strategies are mainly based on cognitive behavioural interventions (CBT-I) and hypnotic treatment with benzodiazepine receptor agonists and sedating antidepressants. Although the effectiveness of these treatments has been clearly demonstrated, a substantial proportion of patients proves to be treatment-resistant or profits only poorly. The question of long-term pharmaceutical treatment of chronic insomnia, at least in Europe, is unresolved and urgently needs answers. Novel rational treatment avenues require clues on causes and mechanisms from integrated neuroscientific approaches. The important issues concerning insomnia treatment in the future especially in Europe will be reviewed and discussed critically.

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## Insomnia: A Brief Historical Perspective

It would be beyond the scope of this article to cover entirely what is known about the 'history' of insomnia over the last 2 or 3 thousand years. We will restrict this introduction to a few selected impressions which are of relevance for today's views and attitudes towards insomnia.

It is reasonable to assume that insomnia as a complaint, syndrome or disorder has accompanied mankind forever. Early testimonies indicate that ancient Greeks worshipped Hypnos (the twin brother of Thanatos=death) who was responsible for bringing sleep to humans and animals alike. He lived in a valley watered by Lethe, the river of oblivion. Around the entrance of his hut, plants were growing which were used for inducing sleep, thus the term hypnotics for sleep-inducing pills [1]. One can also find fre-

quent references to insomnia in ancient sagas, for example, in the epic of Gilgamesh, in the Odyssey or in the Indian Gitagovinda [2].

Anthropological studies in nowadays primitive cultures suggest that nocturnal wakefulness of a part of the population may have been quite normal and even profitable; awake individuals may have safeguarded their fellows by "keeping the fire on" and staying alert for large carnivores [3]. Thus insomniacs may once have been honourable members of their tribes with an important and respected role in survival of all members. The possible value for survival may even be hypothesized to be the reason that population genetics still cause ~10% of the people to suffer from insomnia. If indeed 'insomniacs' once were important for survival, then it is likely that insomnia should be a robust heterogeneous trait, solidly anchored in many different polymorphism

profiles. May the people who stayed awake once have been very honorably group members that safeguarded survival, the situation is much different to date, with little respect (or even stigma) in general for people who complain of “broken” nights.

Others have suggested insomnia rather to be related to the requirements and habits of modern society. Summers-Bremner [2] comments on the introduction of coffee and tobacco to Europe as a possible cause for an increase in insomniac complaints in the 17<sup>th</sup> and later centuries. The same author offers an intriguing hypothesis related to the prevailing puritanism and economical liberalism dominating in the 17<sup>th</sup> and 18<sup>th</sup> century in the British Empire and the Netherlands. Both countries, that were dominating the world trade followed the ideal that a God-fearing individual is permanently striving for sanctification by ‘restless work’. This would, in turn, be awarded with wealth, and vice versa, wealth would reflect a subject’s exemplary life. Given the economic situation of the times and the complex dynamics of world trade already at that time, with successful trading being based on ‘continuous chains of credit’, it becomes clear that being wealthy must also have been associated with high levels of anxiety to lose everything, in consequence leading to nocturnal insomnia. According to this model anxiety/threat and guilt as a sociological function of a certain age coupled with ‘restless’ work and the intake of sleep-disturbing substances (coffee, tobacco) may have paved the way for the epidemic of insomnia that we face nowadays. This may also reflect the paradoxical situation of many insomniacs: in conscious life during daytime, increased effort will lead to better achievement – if you place the same effort on your sleep, it will have the opposite effect.

That insomnia may have severe repercussions on mental health is not a discovery of the last 20 years but was already mentioned in 1914 in *The Lancet*. Ernest Pronger in a letter titled ‘Insomnia and Suicide’ noted ‘For a long time past newspaper reports of suicides, associated with insomnia, have attracted my attention. Probably if all the cases in all the papers were collected we should find that annually a very great wastage of human life from this cause alone goes on which might be prevented.’ This sounds astonishingly modern when considering the paragraph on sleep and psychopathology in this article.

Probably the first neurobiological approach to insomnia was pursued by von Economo [4]. Through his neuropathological study of Encephalitis Lethargica he discovered that not all cases of the disease are linked with fatigue/hypersomnia, but he noted that some of the afflicted individuals suffered from choreatic movements coupled with severe insomnia. He was able to demonstrate specific central nervous lesions, especially in the mid-brain, which initiated his theory of a localizable ‘sleep center’ in the brain.

As can be seen from this short historical excursion many of our modern scientific views towards insomnia bear the imprint of past modes of thinking, although we now have the advantage of more sophisticated measures and technologies to explore sleep in all its facets.

## Insomnia: Definition, Diagnostic Criteria, the Role of Polysomnography and Related Methods

### Diagnostic systems

The major current diagnostic systems ICD-10 (*International Classification of Diseases*, 10<sup>th</sup> edition) and DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, APA) include sections

**Table 1** Research on diagnostic criteria for insomnia disorder.

<b>A) The individual reports one or more of the following sleep-related complaints:</b>
1. difficulty initiating sleep
2. difficulty maintaining sleep
3. waking up too early
4. sleep is chronically non-restorative or poor in quality
<b>B) The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.</b>
<b>C) At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the individual:</b>
1. fatigue/malaise
2. attention, concentration, or memory impairment
3. social/vocational dysfunction or poor school performance
4. mood disturbance/irritability
5. daytime sleepiness
6. motivation/energy/initiative reduction
7. proneness for errors/accidents at work or while driving
8. tension headaches, and/or GI symptoms in response to sleep loss
9. concerns or worries about sleep

on sleep disorders and insomnia. DSM-IV criteria are exclusively based on the subjective experience of the afflicted individual and do not include criteria that quantify the frequency or the dimension of the complaint. In DSM-IV, insomnia disorders are differentiated into primary insomnia (PI), insomnia related to a mental or medical condition and insomnia related to substance abuse. A much more detailed taxonomy is suggested by the ICDSD-2 (*International Classification of Sleep Disorders*, 2<sup>nd</sup> edition, AASM [5]) encompassing 11 insomnia subtypes. For insomnia researchers and specialists, research diagnostic criteria for insomnia (RDC-I) were published by Edinger and colleagues [6]. Basic insomnia criteria from RCD are presented in [Table 1](#). Both ICD-10 and DSM-IV are currently under review. Presumably, DSM-V will be published in 2012 and will include a thorough revision of insomnia criteria. It is under discussion whether the category ‘primary insomnia’ should be replaced by the term ‘insomnia disorder’. This would emphasize the independence of the category by giving up the notion of primary/secondary insomnia in favor of the comorbidity concept, as suggested by the State of the Science conference on insomnia [7]. Considering the development of diagnostic systems and insomnia criteria over the past 20 years, the definition of insomnia has certainly become more refined and differential diagnosis has become easier.

Summarizing, insomnia as reflected by modern diagnostic systems is primarily viewed as a subjective experience without any objective means to document its presence. This leads to the question why polysomnography (PSG), as an objective sleep measure, is not an acknowledged diagnostic tool for insomnia, in striking contrast to its important role for the diagnosis of sleep-related breathing disorders.

### Polysomnography

As a large number of PSG studies on patients with chronic insomnia, especially PI, have been published, it is beyond the scope of this report to review all of these investigations. Instead, we will rely on several overviews on this topic [8–11]. PSG derived investigations showed that PIs have a prolonged sleep-onset latency (SOL), an increased wake time after sleep onset (WASO) and reduced sleep efficiency. With respect to sleep architecture, only a few studies reported either SWS (slow wave sleep) or REM (rapid eye movement) sleep reductions in insom-

nia samples. Concerning total sleep time, absolute differences to good sleeper controls (GSC) are not huge (ca. 30–60 min), but statistically significant when sample sizes are large enough. One of the most consistent findings is that PSG-derived differences between PIs and GSCs are of much lesser magnitude than differences between subjectively reported sleep variables. This observation led to the terms sleep 'state misperception' and 'paradoxical insomnia'. This difference between subjectively reported severely disturbed sleep and PSG measured minor sleep loss is probably the main reason for PSG not being considered an adequate diagnostic method for insomnia. However, up to now, PSG has never been tested empirically with respect to the question whether it may serve as a differential-diagnostic or differential-therapeutic tool, for example for the decision whether to treat a patient with hypnotics or *cognitive behavioural treatment for insomnia* (CBT-I).

### Multiple sleep latency test

Studies using the *multiple sleep latency test* (MSLT) in insomnia patients [12–15] revealed prolonged sleep latencies, contrary to expectations derived from studies on the impact of sleep loss on MSLT sleep latencies. Bonnet and Arand [16–18] have thoroughly investigated this effect confirming increased sleep latencies during the day in chronic insomnia patients. These findings are in line with a 24-h hyperarousal in insomnia (see the Section on the Hyperarousal Concept). Unfortunately, these results discredited insomniac patients' complaints about daytime impairments and increased daytime fatigue and further contributed to the wide-spread assumption that 'nothing is wrong' with insomnia patients except marked **subjective** complaints about daytime performance and nighttime sleep without objectively measurable signs.

Recent years have seen the application of more sophisticated EEG-based methods like spectral analysis, the registration of event-related potentials (ERP) and the analysis of the cyclic alternating pattern (CAP) to find objective correlates of the subjectively experienced complaints.

### Spectral analysis of the sleep EEG

Using spectral analysis, Freedman [19] found increased spectral power in the EEG beta band in insomnia patients during wake, stage 1 and REM sleep compared to GSCs. However, no difference was found in this study in NREM stages 2, 3 and 4. Merica et al. [20] reported an increased beta power across all sleep stages in their chronic insomnia sample, and a reduction of slow EEG frequencies. In a study by Perlis et al. [21], spectral power in the beta and gamma bands of both the REM and NREM sleep were specifically increased in PIs when compared with GSCs and secondary insomnia patients. Krystal et al. [22] examined 2 groups of insomnia patients: those with objectively determined sleep loss and those without (paradoxical insomnia). The paradoxical insomnia group revealed an increased alpha, sigma and beta power during NREM sleep and a decreased delta power. Those insomnia patients with objectively determined sleep loss, however, showed no major differences to GSCs. Buysse et al. [23], in the largest study so far, found no overall difference in their spectral analysis between PIs and GSCs, but an increased absolute delta and beta power specifically in the female patients. Summarizing these findings, an increased spectral power in the high frequencies of the sleep EEG is likely to be evident in insomnia patients, at least in subgroups of those with chronic insomnia. Since high-frequency cortical EEG signals in the beta and

gamma bands are presumed to reflect cortical activation, an increase in this frequency range during sleep can be interpreted as a sign of hyperarousal. This might be evident in insomnia patients even when their sleep is non-pathological according to conventional sleep stage scoring.

### Event-related potentials

Markers of insomnia do not necessarily have to be confined to nocturnal measurements. A sophisticated method to investigate hyperarousal in insomnia patients is the analysis of *event-related potentials* (ERP) in response to stimulus presentations. Devoto et al. [24, 25] used an oddball paradigm in insomnia patients and found that a 'bad' night of sleep was associated with a high P300 amplitude, and vice versa, a good night of sleep with a low P300 amplitude. In these 2 studies, the increased P300 amplitude was interpreted as a state marker of hyperarousal. Sforza and Habarubio [26], also applied an oddball task to insomnia patients and GSCs and could not find any significant between-group differences, either in the morning or evening. Bastien et al. [27] studied ERPs in the morning, evening and during sleep onset in a sample of PI patients and GSCs. The insomnia patients had an increased N100 amplitude during the morning and evening. During sleep onset, the patients group had an increased P220 amplitude and a decreased N350 amplitude. According to the authors, these results are more in line with an 'inhibition deficit' (to disengage from waking processes) in the insomnia group than with hyperarousal. Yang and Lo [28] used an interesting approach applying an auditory oddball task during sleep. In this study, insomnia patients had an increased N100 amplitude as well as a decreased P220 amplitude during the first 5 min of stage 2 sleep. However, when analyzing ERPs across the whole night, no differences to GSCs were found.

In summary, the existing studies on ERPs in insomnia patients suggest an increased sensitivity to auditory stimulation during wakefulness and sleep-onset.

### Cyclic alternating pattern

The *cyclic alternating pattern* (CAP) [29] is an NREM sleep phenomenon that is characterized by sequences of electrocortical events, that are distinct from background EEG, and recur with a periodicity of 20–40 s. CAP is an indicator of arousal fluctuations, and more generally unstable in poor sleep. Terzano et al. [30] investigated CAP in PI patients and GSCs and found an increased CAP rate in the patients groups, accompanied by a disturbed sleep according to classical sleep staging. More specifically, in a group of patients with paradoxical insomnia, the same group of authors just recently found similar results [31].

In summary, several quantitative electrophysiological methods (spectral analysis, ERP, CAP) have the potential to elucidate the states of different brain subsystems, while classical sleep staging is based on the assumption that the whole brain is in one of few well-defined states in every single moment. To that effect, these studies hold promise for explaining why classical sleep staging often fails to fully reflect the subjective complaints of disturbed sleep in insomnia patients. A major breakthrough with respect to the discrepancy in objectively determined and subjectively reported sleep was made by the first PET (positron emission tomography) study in PI published by Nofzinger et al. [32] In short, this study showed an increased metabolism in several brain areas of insomnia patients despite them being asleep in well-defined 'normal' stage 2 non-REM sleep.

In conclusion, a caveat of most of the electrophysiological and PSG investigations referred to above are small sample sizes, the inhomogeneity in insomnia definitions, and sometimes inadequate control of concomitant medication intake. There is, however, a common trend towards signs of increased arousal or cortical excitability in insomnia patients. It is suggested to improve the statistical power of any kind of electrophysiological study by enhancing sample sizes ( $n \geq 100$ ) in prospective investigations with well-phenotyped samples including insomnia subtype differentiation (i.e., psychophysiological, idiopathic, paradoxical, etc). Insomnia subtype differentiation has recently become the topic of a large-scale population-based internet research project in the Netherlands (The Netherlands Sleep Registry) that may be ported to the EU level. Pooling of archival data sets from different research centers may serve as an interim strategy to overcome the problem of small sample sizes. Prospective studies should simultaneously include other neurobiological measures, i.e., blood samples for molecular genetic analysis, cortisol saliva measurements to measure the activity of the HPA (hypothalamic-pituitary-adrenal) axis and neuroimaging techniques like PET or fMRI to attain insight into the patients' brain activity during wakefulness and sleep. Furthermore, more thought should be given to the proper psychometric determination of sleep quality and sleep duration. Interestingly, in our study on 100 PI patients and 100 GSCs [33], we showed that a considerable number of PI patients subjectively underestimated their sleep time, however, more than the majority of patients (57%) overestimated their PSG-derived total sleep time, like most of the healthy controls (77%).

## Epidemiology, Health Care and Costs of Insomnia

### Prevalence

Ohayon [34] has summarized the available epidemiological literature on insomnia according to different definitions and found that according to DSM-IV criteria, the prevalence of primary insomnia in the general population is 3%. Women suffer more frequently than men from insomnia and the prevalence increases with age. More recently, Ohayon and Reynolds [35] analyzed the prevalence of insomnia in more than 25000 participants representative for the general population in France, UK, Germany, Italy, Portugal, Spain and Finland. In this sample, 9.8% fulfilled the diagnostic criteria (DSM-IV) for insomnia. Half of these insomnia patients also had another mental disorder, mainly anxiety and mood disorders. Primary insomnia alone had a prevalence rate of 3%. 44% of the patients with insomnia diagnoses reported that insomnia affected their health due to physical fatigue or weariness. Around one third of insomniacs described negative effects of their sleep disorder on work performance, daily activities and/or family relationships, and to a somewhat lower extent on social relationships.

### Psychosocial factors

There are few studies trying to support the link between occupational categories, perceived job stress and the prevalence of insomnia. Nakata et al. [36] found an overall prevalence rate of insomnia of 23.6% in 1161 male white-collar employees of a Japanese electric equipment company. Workers with high intra-group conflict (odds ratio=OR 1.6), high job dissatisfaction (OR 1.5) had a significantly increased risk of insomnia after adjusting for multiple confounding factors. In the French population, the

prevalence of insomnia was the highest in the white-collar group (20.8%) [37]. Doi et al. [38], in a cross-sectional study including 4868 day time white-collar workers, similarly showed that poor sleep was significantly more prevalent in white collars (30–45%) than in the Japanese general working population. Gellis et al. [39] have investigated the likelihood of insomnia and insomnia-related health consequences among a sample of at least 50 men and 50 women in each age decade from 20 to 80+ years of age. Results indicated that individuals of lower individual and household education were significantly more likely to experience insomnia, even after controlling for ethnicity, gender, and age. Insomnia seems to be associated with an increased health-care use. Several studies have shown that insomniacs make more medical visits, are twice more frequently hospitalized and have twice more absenteeism than good sleepers [40,41].

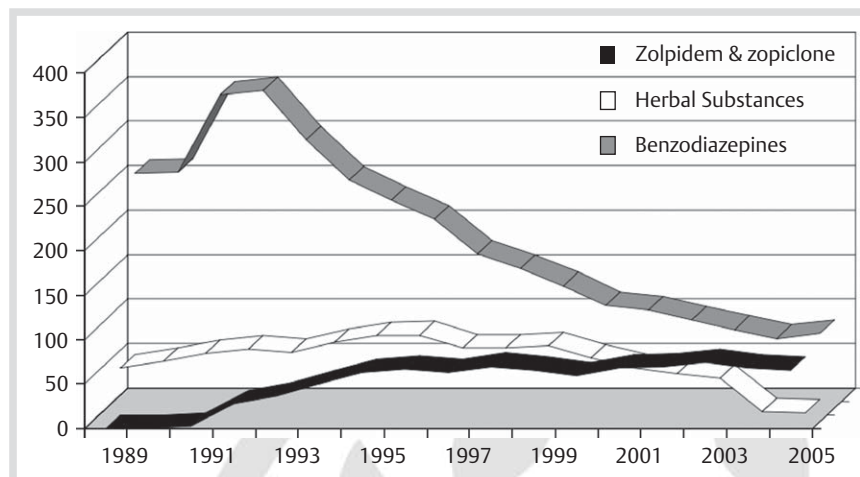
### Costs

Direct and indirect costs of insomnia have been assessed by several studies. Direct costs of insomnia are charges for medical care or self-treatment that are borne by patients, government, organized health-care providers, or insurance companies. Indirect costs refer to patient- and employer-borne costs that result from insomnia-related morbidity and mortality. Daley et al. [42] have recently analyzed the economic costs of insomnia for participants in the province of Quebec (Canada) differentiating insomnia syndrome (meeting DSM-IV criteria for insomnia diagnosis), insomnia symptoms and good sleepers. Individuals with insomnia syndrome produced significantly enhanced costs due to utilization of the health care system. With respect to absenteeism and work productivity, time taken for sick leave was 3 times higher in insomnia syndrome than in good sleepers. Furthermore, loss of productivity over the last 3 months was almost 5 times higher in insomnia syndrome than in good sleepers. Daley et al. [42] calculated the total direct and indirect annual costs of insomnia for the province of Quebec at 6.6 billion Cdn \$, which is impressively high.

### Pharmacoepidemiology of hypnotics

As there has been concern about use and abuse/dependence from hypnotics [43], pharmacoepidemiology is very important. Léger and colleagues [44] provided an estimate of direct costs and particularly those due to hypnotic prescriptions in the USA and France. According to this analysis, annual costs for prescription of hypnotic substances were 1.97 billion US dollars in the USA and 310 Mio US dollars in France. Walsh and colleagues [45,46] showed that there has been a considerable shift of prescribing patterns for US physicians. An analysis of the last 20 years indicated that there was a drastic decrease in the prescription of benzodiazepines (BZ) and benzodiazepine receptor agonists (BZRA), which was, however, compensated by an increasing rate of prescriptions of sedating antidepressants and antipsychotics for insomnia patients. According to an analysis for 2002 [46], the so-called 'off-label' use of sedating antidepressants for insomnia was more frequent than the use of substances that are primarily approved for insomnia (e.g., benzodiazepines).

For Germany, yearly data for prescription drugs are published in the drug report ('Arzneimittelreport' [47]). The prescription of hypnotics over the last 15 years according to the drug report is presented in **Fig. 1**. It can be seen that the prescription of benzodiazepines has strongly declined while Z-substances (zolpidem and zopiclone) maintain a considerable stable share of prescriptions in Germany.



**Fig. 1** Hypnotic prescription data from Germany from 1989–2005 (Schwabe und Paffrath [47]). Daily defined drug dosages in mio. From 1991 including former Eastern Germany.

This picture suggests a strong tendency for an overall decline in hypnotic prescriptions over the last 15 years in Germany. However, these data only reflect prescriptions at the expense of the major health insurance providers. A more sophisticated analysis published recently gave evidence that prescriptions at the cost of the patients did increase substantially over the last 15 years, especially for benzodiazepine receptor agonists [48]. With the increased off-label use of antidepressants and sedating antipsychotics for insomnia it seems unlikely that, at least for Germany, drug treatment of insomnia has decreased over the last 10–15 years, perhaps even on the contrary.

A crucial question is how many patients with chronic insomnia are treated with a specific class of hypnotics. Mendelson et al. [49] reported that the most common insomnia treatments are over-the-counter sleep aids and alcohol, whereas prescription hypnotics are taken regularly by only 6% of chronic insomniacs. About 40% of those took their hypnotic for longer than 4 weeks. Females consumed hypnotics more frequently than males and their use increased with age. Our data from epidemiological studies in Germany indicated that approximately 10–20% of patients with chronic insomnia regularly (at least 3 nights per week) use hypnotics from the BZ/BZRA type [50,51].

Summarizing in conclusion, insomnia as a distinct disorder is frequent and afflicts approximately 10% of the European population. One third of the cases falls into the category of primary insomnia, the remaining ones are comorbid with mental or medical disorders. Not more than a quarter of insomnia patients seek help for their sleep problem; all others are unrecognized and medically untreated. There are few or no data on the natural history of insomnia and on cohorts of insomniacs followed on a long-term prospective. Direct and indirect costs are very high also with respect to absenteeism and loss of work productivity. An estimated 10% of patients with chronic insomniac takes prescription medication on an almost daily basis. The pharmacoepidemiological situation is difficult to grasp due to widespread 'off-label' use of other sedating drugs (especially sedating antidepressants) which are primarily not indicated for insomnia and because of prescriptions at the cost of the patients, circumventing reimbursement by health insurance companies (at least in Germany). No valid data exist giving a picture of how many patients switch from short to long-term medication and whether chronic medication intake is more harmful than of benefit for the patient. This type of data would be of utmost importance to settle the controversy around the issue of long-term hypnotic treatment with respect to risks of abuse/dependency.

### Insomnia – A Risk Factor for Other Disorders/ Diseases?

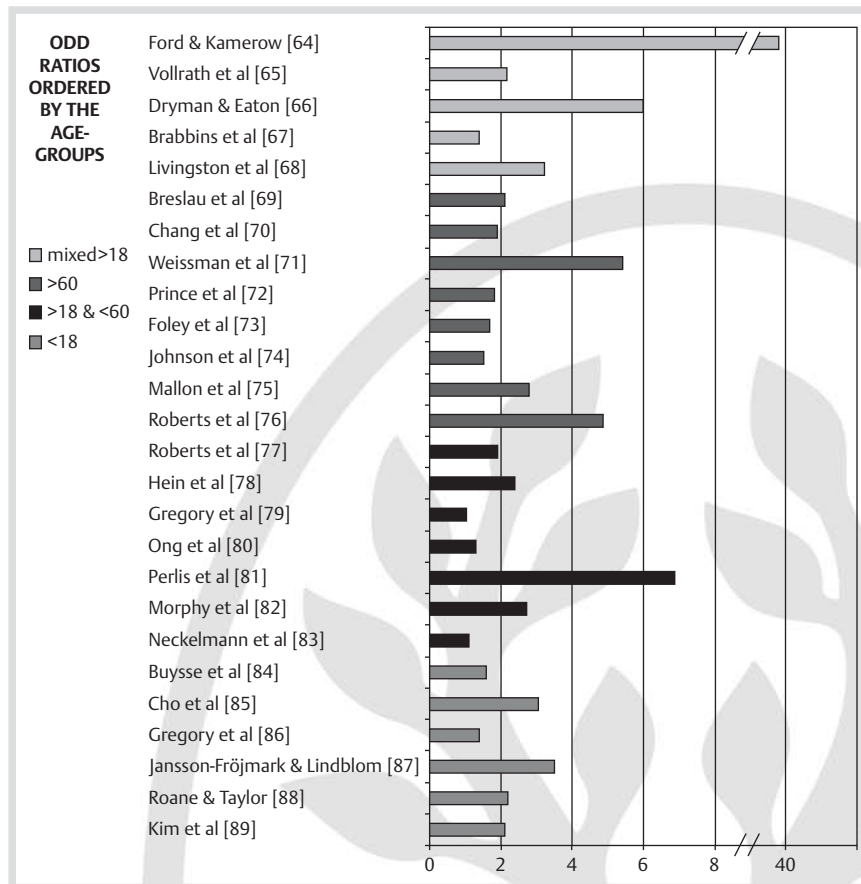
One of the most important questions for research and clinical practice is whether 'pure' primary insomnia is just a mere nuisance, or, instead, has negative short- and long-term effects on daytime performance as well as on mental and physical health.

#### Cognitive performance

In light of overwhelming evidence that short-term or chronic (experimental) sleep loss negatively affects daytime functioning (see, for example [52]), it has been hypothesized that patients with chronic insomnia have daytime impairments, especially in cognitive functioning. This is in line with subjective reports of insomnia patients, who typically report deficits in neuropsychological domains, most notably alertness and memory functioning. Daytime impairments are also the most frequent reason for insomnia patients to seek medical help [53]. However, neuropsychological studies often failed to detect clear-cut deficits in the daytime performance of insomnia patients when using standardized tests. A recent investigation reported that insomnia patients had no impairments at all in objectively determined measures of cognitive performance despite subjectively reported deficits [54]. 2 review articles on this topic [55,56] came to the conclusion that insomnia patients have only minor deficits in daytime performance with significant group differences to GSCs in only 20–25% of all comparisons in the literature. However, using more challenging and naturalistic tests in large sample sizes might reveal deficits in insomnia patients [57]. Also, the use of computerized reaction time assessment on a task that systematically varied a complexity parameter successfully identified deviations from normality in a sample of insomniacs [58].

#### Neuropsychology and neuroimaging

In light of the inconsistent results and the strong discrepancy between subjective reports and objectively documented findings, further research is needed to determine whether daytime functioning is really impaired in primary insomnia. The combination with neuroimaging techniques seems promising. Altena and colleagues [59] used fMRI (functional magnetic resonance imaging) to investigate neuropsychological performance during a category and a letter fluency task. According to the results, PI patients had a hypoactivation of medial and inferior prefrontal cortical areas. This finding occurred in the absence of any behavioral differences during the 2 tasks. After successful cognitive



**Fig. 2** Relationship between insomnia and depression (odds ratios) in longitudinal epidemiological studies (data taken from Baglioni et al. [90]).

behavioral therapy, the hypoactivation pattern recovered. Thus, while net performance on many tasks may not be compromised, hypoactivation of task-related areas may be compensated by increased activation in other areas. It is not unlikely that such shifts from optimally suited to alternative ways of brain activation may underlie the subjective complaints about difficulties with cognitive performance.

### Nocturnal memory consolidation

Another fruitful line of research has focused on sleep-related memory consolidation [60]. In patients with primary insomnia, 2 studies have been published so far suggesting impairments in procedural [61] and declarative [62] nocturnal memory consolidation. In both studies, memory tasks were used in insomnia patients and healthy controls before and after a night of sleep in the sleep laboratory. Performance deficits in insomnia patients were found specifically in the morning suggesting a disturbed sleep-related memory consolidation.

In conclusion, in light of the literature, we are strongly endorsing a shift of paradigm from classical neuropsychological testing to the investigation of everyday long-lasting neuropsychological challenges, sleep-related memory function and reaction time tasks with systematic variation of, e.g., a task complexity parameter. Additionally, future studies should combine these paradigms with neuroimaging methods to teach us new insights about neurocognitive functioning in insomnia.

### Psychopathology

Insomnia is independently associated with psychopathological conditions, most notably depressive disorders (e.g., [63]). An overview of longitudinal epidemiological studies investigating

the association between insomnia and depression is given in **Fig. 2**.

In this figure, odds ratios for depression at follow-up (usually 1–3 years after baseline measurement) are presented for those patients having insomnia at baseline in comparison to patients with no insomnia at baseline. It can be seen that most of the studies described significantly increased odds ratios indicating that subjects with insomnia are more likely to develop depression one or several years later than subjects without insomnia. This overwhelming evidence clearly indicates that insomnia is a predictor for depression. Following this line of reasoning, Ford and Kamerow suggested in 1989 that ‘treatment of insomnia may prevent psychiatric consequences’ [64]. However, this assumption has not yet been put to test empirically and needs to be addressed in large-scale longitudinal investigations. This seems mandatory and very important for public health, as a recent longitudinal study demonstrated that disturbances of sleep onset/maintenance are associated with an increased risk for suicidal ideation/behavior even in the absence of other psychopathology [91].

Depressed patients frequently suffer from disturbances of sleep continuity including an increased latency to fall asleep, an increased frequency of nocturnal awakenings and early morning awakenings. Furthermore, specific sleep architecture alterations are evident in depression, namely a reduction of slow wave sleep, a shortened REM latency and an increased REM density [92]. Insomnia patients usually do not have these REM sleep alterations supporting the assumption that insomnia is an independent disorder and not merely an early symptom of depression.

In conclusion, given the high prevalence and economic burden of affective disorders, it is of significant importance to investi-

gate the role of insomnia for psychopathology more extensively. Primary Insomnia, as the 'pure' form of insomnia is the ideal model for investigating this relationship as the results are not affected by other medical or psychiatric conditions. Future studies should try to identify specifically those people with insomnia who are at future risk to develop depression. The reason behind the association between insomnia and depression should be further investigated. A biological link between the 2 disorders might be hypercortisolism, which is present in both depressive disorder [93] and at least in some PI patients [94]. Future work on the relationship between insomnia and depression should thus focus on the HPA (hypothalamic-pituitary-adrenal) axis, including 'real life' measurements by using salivary cortisol measurements at home (which are easy to perform and non-invasive). The inclusion of challenge tests (like the dexamethasone suppression test or the combined dexamethasone/CRH test) is strongly suggested as these tests are very sensitive to detect subtle changes in the HPA system.

### Cardiovascular events

There is emerging evidence both from epidemiological and experimental studies supporting the hypothesis that insomnia increases the likelihood for cardiovascular disease and mortality independently of classic coronary risk factors.

### Cardiovascular mortality

3 large-scale longitudinal studies of population-based samples revealed an association between sleep complaints and cardiovascular mortality [95–97]; for a meta-analysis see also [98]). Schwartz et al. [95] investigated 2960 older adults at baseline and after 3 years at follow-up. Subjective sleep complaints at baseline were a significant predictor of myocardial infarction. Using a longer follow-up period in over 30 000 participants, Nilsson et al. [96] reported similarly that sleep disturbance is a predictor of cardiovascular mortality. Mallon et al. [97] found an association between sleep initiation difficulties at baseline and coronary artery disease mortality at a 12-year follow-up in 906 male subjects. However, these findings are still under debate as more recent investigations failed to find this association [99, 100]. These studies included very large sample sizes (over 1.1 million and over 13 000), however, follow-up measurements were conducted much earlier than in the studies of Nilsson et al. [96] and Mallon et al. [97].

### Hypertension

Another line of research has focused on the association between insomnia and known risk factors for cardiovascular diseases, most notably hypertension [101–106]. In the study of Gangwisch et al. [102], the association between short sleep duration and hypertension was investigated prospectively in 4810 subjects. Even after controlling for potential confounding variables, the analysis revealed a significant predictive value of short sleep duration for hypertension. Similarly, Suka et al. [101] investigated 4794 subjects and found insomnia to be a significant predictor of hypertension. However, Phillips and Mannino [103] and Phillips et al. [104] could not replicate this finding, while Vgontzas et al. [105] found the insomnia-hypertension association only in a subgroup of those insomniac subjects with objective short sleep duration. Using an experimental approach, Lanfranchi et al. [106] reported an elevated blood pressure in a small group of well-described normotensive chronic insomnia patients that was evident specifically during the night.

### Heart rate and heart rate variability

Elevated resting heart rate (HR) and alterations in heart rate variability (HRV) are also subclinical predictors of cardiovascular mortality [107, 108]. In patients with chronic insomnia, resting HR has been reported to be elevated [109, 110]. However, an increased resting HR in insomnia has not been reported consistently [111–113]. In the largest study so far, Nilsson et al. [96] reported that the sleep complaints 'difficulties falling asleep' and 'early awakening in the morning' were associated with a significant but marginal elevation in resting heart rate of 0.8 and 0.6 bpm, respectively. HRV has been investigated in insomnia patients using polysomnographic recordings [110]. In this study, insomnia patients had an increase in sympathetic and a decrease in parasympathetic activity during sleep and nighttime wakefulness supporting the hyperarousal model of primary insomnia. However, this finding could not be replicated in a recent nocturnal investigation [114]. During daytime, no study has reported HRV changes in insomnia up to now [113, 115]. Generally, it should be noted that those studies that investigated HRV in insomnia included only small sample sizes.

In a concluding summary, there is growing evidence that insomnia is associated with cardiovascular disease and cardiovascular risk factors. However, most findings have not been replicated unequivocally. Based upon previous work, further large-scale longitudinal studies are needed to determine the risk potential of insomnia for cardiovascular health. Ideally, initial PSG measures should be taken to determine to what extent the objective, albeit minor, sleep loss inherent in insomnia plays a role for cardiovascular risk.

### Body weight/diabetes

There is now a huge body of evidence linking short sleep duration to increases in body weight and to the development of the metabolic syndrome in cross-sectional and longitudinal studies [116]. Work in children confirmed these results at least for the cross-sectional approach [117]. The association between short sleep duration/poor sleep quality and increased BMI has been explained on the basis of knowledge about interrelationships between sleep regulation, glucose metabolism and other hormones involved in hunger/satiety as leptin and ghrelin [118, 119].

Short sleep duration is not necessarily identical with insomnia as a disorder, because insomnia has to be coupled with subjective suffering and daytime sequelae to be considered as such. Vgontzas et al. [120] studied more than 1 000 subjects by means of PSG and subjective sleep questionnaires cross-sectionally and were able to show that obese individuals had a higher rate of subjective insomnia complaints than non-obese individuals. Furthermore, several longitudinal studies [121–123] reported a statistically significant relationship between poor sleep quality/sleep disturbances and an increased risk to develop diabetes at follow-up.

In conclusion, seemingly short sleep duration and maybe poor sleep quality are related to weight gain and the development of diabetes. This cannot be directly translated to insomnia as a disorder, because none of the relevant studies so far included specifically patients with insomnia diagnoses. Referring to this, future studies are mandatory. This avenue is especially interesting, because the neuropeptide orexin has been postulated to be involved in both arousal/sleep regulation and food intake/obesity [124]. As outlined later, the orexin system is suggested to play an important role for insomnia and orexin antagonists for the treatment of insomnia are currently being developed.

## Mortality

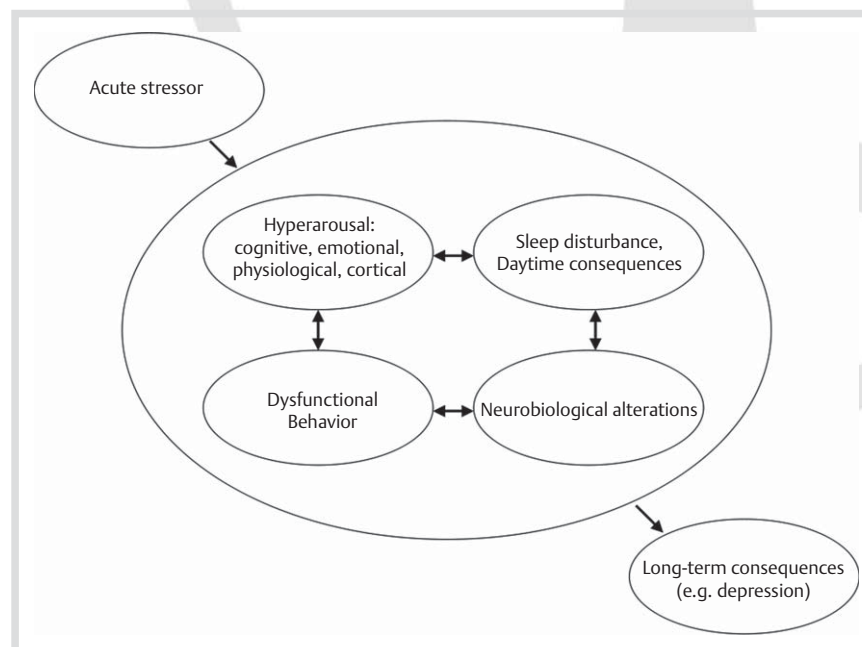
Several studies have addressed the question whether sleep duration or poor sleep quality are linked to mortality (for overview, see [125]). One of the first studies in this field was based on the hypothesis that shortened sleep duration and/or the complaint of insomnia might be a risk factor for increased mortality [126]. The results of this study, however, showed that both sleep durations shorter than 7 h or in excess of 7.9 h were correlated with increased mortality. Furthermore, chronic use of sleeping pills was also associated with increased mortality. The same group investigated 1.1 million Americans and reported that insomnia and short sleep duration (between 5 and 7 h) without comorbidities (e.g., depression) bore little risk for increased mortality. Surprisingly, sleep durations equal or longer than 8 h and the use of sleeping pills significantly increased the mortality risk [99]. These results were confirmed by a Japanese study in more than 100 000 representatively sampled Japanese citizens [127]. Gallicchio and Kalesan [128] conducted a meta-analysis over 16 studies that were relevant to the question whether sleep duration is associated with mortality. According to this, both short (<7 h) and long sleep duration (>9 h) are related to an increased all-cause mortality, suggesting a U-shaped relationship between both variables.

Again, caution is necessary in translating these findings to insomnia. Althuis et al. [129], for example, showed with a longitudinal design that older women with insomnia did not display increased rates of mortality during a 2-year follow-up. The picture is further complicated by the fact that the intake of hypnotics itself has been linked with increased mortality. Kripke and colleagues [99, 126, 130] were able to confirm a statistical relationship between hypnotic intake (mostly classical benzodiazepines) and a slightly elevated mortality in several data analyses of huge databases. The authors themselves urge caution about conclusions with respect to causality [99]. In a recent publication of longitudinal data with a 20-year follow-up interval, hypnotic usage was a risk factor for significantly increased mortality in men and women after adjusting for other known risk factors [131]. In this study, hypnotic usage was associated with sleep disturbances and, among several health problems, depression.

In conclusion, there is little evidence to suggest that there is a direct link of chronic insomnia to increased mortality. Evidence relating chronic hypnotic usage to increased mortality should be taken extremely seriously and more work in this area is needed to understand what is at the core of this finding. Further studies are urgently needed to test for today's most frequently prescribed substances, also for those prescribed 'off-label'. As we have seen that insomnia is a risk factor for significant psychopathology and maybe also for cardiovascular disease as well as for obesity and the metabolic syndrome, the relationship between insomnia and mortality might disappear when partialling out these variables statistically (as is done in most of the relevant work).

## Hyperarousal Concept

According to current etiological models of insomnia, a cognitive, emotional and physiological hyperarousal plays an important role in the development and maintenance of the disorder (see [94]). Perlis and colleagues [132, 133] combined the hyperarousal perspective with neurobiological variables to a theory which they termed the 'neurocognitive' model of insomnia (modified version see **Fig. 3**). The model is based on the classical theory by Spielman et al. [134], according to which insomnia develops due to predisposing and precipitating factors (e.g., psychosocial stressors), and becomes chronic due to perpetuating factors. According to the neurocognitive model of insomnia, somatic, cognitive and cortical arousal may act as perpetuating factors for the disorder. It is hypothesized that cortical arousal occurs as a result of classical conditioning and is measurable by an increased amount of fast frequencies in the sleep EEG. These are, in turn, associated with enhanced information processing or abnormal long-term memory formation which lead to disturbances in sleep continuity and/or paradoxical insomnia. Espie et al. [135] published a cognitive-psychological theory for chronic psychophysiological insomnia called the attention-intention-effort (A-I-E) pathway. In this theory, cognitive mechanisms potentially underlying the hyperarousal in insomnia patients are described. Basing on a perspective of sleep normalcy,



**Fig. 3** Simplified neurocognitive model of insomnia (modified according to Perlis et al. [132, 133]).



increased attention on sleep-related internal and external stimuli, explicit intention to sleep and effort to fall asleep are assumed to be psychological factors that are crucial for the development and maintenance of psychophysiological insomnia.

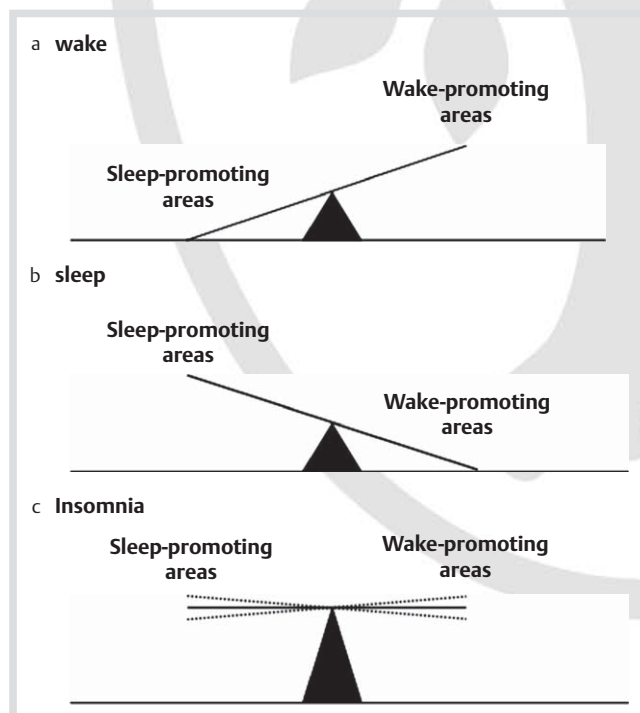
The empirical evidence that supports the hyperarousal concept has just recently been summarized in 2 review articles [94, 136]. Given the somewhat inconsistent findings, it is important point to note that 2 effects are, at least to some extent, opposing in chronic insomnia: on the one hand, sleep deficits or chronic minor sleep loss affects neurobiological processes and neuropsychological performance; on the other hand, there is the elevated arousal level which can be measured in several physiological systems. These opposing processes might be a major reason for the conflicting results. Subtyping insomnia patients according to signs of hyperarousal and sleep loss might offer a way to disentangle both phenomena.

We and others [94, 133] have tried to connect the hyperarousal concept with up to date knowledge about the neurobiology and neurochemistry of sleep-wake regulation. In short, according to the 'flip-flop' switch model [137, 138] (see ◉ Fig. 4), wakefulness is maintained by a network of cells in the hypothalamus (including orexin neurons) that activate the thalamus and cerebral cortex. The most important input to these hypothalamic neurons stems from the upper pons (cholinergic cells). In addition to the hypothalamic cells, other areas like the dorsal and median raphe nuclei and the locus coeruleus are involved in activating the cortex. The central idea of the flip-flop model is, that a 'key switch' in the hypothalamus is able to shut off the complete arousal system during sleep. If the switch is destabilized (for example, after a loss of orexin neurons), behavioral states can change inappropriately, as it happens in narcolepsy patients with sudden sleep attacks and cataplexy. In primary insomnia, it can also be speculated that a dysfunction of the 'key switch' is involved. This might be associated with a dysbalance

between sleep-promoting brain areas (i.e., the ventrolateral preoptic nucleus, VLPO; neurotransmitter: GABA) and arousal-promoting areas (for example, hypothalamic orexin neurons) with a hypofunction of the VLPO and/ or an overactivity of the orexin system. A recent study with proton magnetic resonance spectroscopy [139] which demonstrated a global reduction of GABA in the brains of insomniac patients supports these assumptions.

Using a sophisticated and promising methodology, Cano et al. [140] placed rats in a dirty cage that was previously occupied by another rat, which is a potential psychological stressor for the animals. This resulted in an acute stress response and in sleep disturbances in the long-term. Those rats that were exposed to the cage exchange condition revealed a pattern of Fos expression demonstrating a simultaneous activation of sleep-promoting and arousal-promoting brain regions. Accordingly, it is hypothesized that insomnia is due to a simultaneous activation of the VLPO and the arousal system. The results of this animal study are also in line with the phenomenology of human insomnia. Indeed, many patients report that they simultaneously experience daytime fatigue/exhaustion and the inability to 'de-arouse' when intending to sleep.

In conclusion, animal models of insomnia as well as current neurobiological knowledge about normal and disturbed sleep-wake regulation might open the perspective to a neurobiological insight into the hitherto mainly descriptive concept of hyperarousal in insomnia. It has to be noted that animal studies cannot simulate insomnia as a subjective experience which is accessible from introspective self-reports. However, the theoretical and empirical synthesis of insomnia concepts with basic neuroscience is nevertheless important to foster the development of new treatment strategies targeting for example orexinergic neurotransmission (see for example [141]) or serotonergic or histaminergic mechanisms.



**Fig. 4** Flip-flop switch model of sleep-wake regulation (modified from Saper et al. [137]). Note: in chronic insomnia there is an instable switch position especially during the night.

### Current Treatments and their Limitations

Current widely utilized treatments for chronic insomnia include pharmacological and non-pharmacological strategies, i.e., cognitive-behavioural treatment of Insomnia (CBT-I). The empirical evidence for both types of treatment has been reviewed in detail elsewhere [142].

### Pharmacological treatment

Short-term treatment (maximum study duration 4 weeks) with BZ (benzodiazepines) and BZRA (benzodiazepine receptor agonists) produces stable gains with respect to sleep continuity, but no evidence is available suggesting any positive effects on sleep beyond the actual treatment periods. An important issue is the question of tolerance and rebound phenomena occurring during or after discontinuation of BZ/BZRA. Both phenomena are thought to be involved in the development of drug dependence because of dose escalation possibly due to tolerance or the inability to stop medication intake due to rebound insomnia. It is largely unknown which individual characteristics predispose an individual to develop tolerance and rebound to BZ/BZRA, but it is obvious that these disadvantages have led to prescription guidelines in Europe restricting the intake of BZ/BZRA to 3/4 weeks. This in itself creates a somewhat paradoxical situation, keeping in mind that these treatments are only symptomatic and that insomnia is chronic. Insofar, patients might be better off

if not treated at all with this type of medication, unless there is evidence that long-term treatment is effective and safe for the patients. Pharmacoepidemiological research indicates that many physicians go beyond the limit of 3/4 weeks and do prescribe BZ/BZRA or other hypnotic treatments 'off-label' for much longer periods due to the patient's needs [48]. This is seen very critically by many stakeholders in the health-care system. In other areas of medicine, for example, hypertension, diabetes or in rheumatic conditions, no one questions chronic pharmacological treatment even if life style changes might be equally or better effective (see, for example, the situation for type II diabetes). Chronic insomnia thus still seems to be misunderstood as a condition which responds to short-term pharmacological intervention with long-lasting effects, which is not the case. Unfortunately, only a very few long-term studies (treatment duration of 6 months) have been published so far and exclusively so in the USA but not in Europe [143–146]. For the pharmacological treatment of chronic insomnia, it is mandatory that all substances will be investigated not only in terms of short-term effectiveness but also in terms of long-term effectiveness, tolerance, rebound and dependence symptoms in longitudinal designs (at least for a period of 3 or 6 months). This can, however, only be achieved when governmental bodies and physicians acknowledge the chronicity of many forms of insomnia and therefore also the need for long-term treatment (under the precondition that the suggested substances are free from serious side-effects and long-term risks). This also applies for medications presently considered as "off-label" treatments for insomnia, like sedating antidepressants and neuroleptic agents, which are now prescribed rather frequently by physicians for insomnia, in spite of a rather thin database with respect to randomized controlled trials.

### Psychological treatment

At first glance the situation of CBT-I for insomnia gives a much more positive impression. As reviewed elsewhere [142], CBT-I has been subjected to several meta-analyses and thorough narrative literature reviews which clearly showed that these interventions are safe and effective. And, most importantly, these treatments do exert stable long-term effects as evidenced by longitudinal follow-ups. Having a closer look at some of the studies, it needs to be mentioned that therapeutic effects are significant or even highly significant, but there is a substantial proportion of subjects who do not respond or remit during treatment. This can be illustrated by a very recent and excellent study [147]. In this study CBT-I was administered alone or in combination with zolpidem and patients were followed up longitudinally. CBT-I alone produced significant gains in the short-term, during the maintenance phase and at 6 months follow-ups. Positive treatment response could be confirmed in 60% of subjects at all 3 measurement points. Looking more strictly at the remission criterion, approximately 40% of patients fell into this category during the 3 measurements, meaning that 60% of patients did not achieve remission.

It needs to be mentioned critically that most of the work on CBT-I comes from academic research settings and not from standard health-care environments, apart from a few exceptions [148]. We do not know much about effectiveness and compliance rates outside a research setting – it can be assumed that in routine clinical populations non-compliance with stimulus control/sleep restriction might be much higher than in a research setting due to the strenuous nature of these approaches. Another problem is the routine availability of these interventions for

help-seeking individuals. There are no data in Europe or the USA about how many state of the art CBT-I treatments are administered per year, but we estimate that currently not more than 1% of chronic insomniacs world-wide receive CBT-I. This is maybe due to the fact that a translation of knowledge about CBT-I from academia to general health-care has not happened yet. As CBT-I in its standard form has been known for 2 decades, one may wonder why this is the case.

In a summarizing conclusion, the treatment situation of patients with chronic insomnia in specifically in Europe, the picture is far from being ideal, as it already has been demonstrated by testimony from the patient's side for the USA [149]. Hypnotic drugs are available in routine medical care prescribed by GPs or medical specialists. Guidelines suggest to restrict prescriptions to limited periods of time, i.e., 3–4 weeks due to the risks inherent in these drugs. However, as outlined several times in this review, insomnia is typically a chronic disorder and not self-limiting. Additionally, drug treatment is only symptomatic and upon discontinuation it is highly likely that the full-blown symptomatology will return. CBT-I looks 'better on paper', especially concerning long-term effectiveness, but is probably only available to a tiny minority of afflicted individuals. Insofar the present situation reflects a very dreary outlook for chronic insomniacs and we have to think about powerful strategies to overcome this situation.

### Clinical and Research Agenda

As said before, chronic Insomnia is a very common disorder afflicting up to 10% of the general population in most western industrialized countries. It is associated with considerable suffering, causes high costs for the health-care system and there is clear-cut evidence that chronic insomnia serves as an independent predictor for depressive disorders, and, additionally, it may also be a risk factor for cardiovascular diseases.

An overview of suggested strategies to better understand and treat insomnia is given in **Table 2**.

**Table 2** Clinical and research agenda.

#### A) Epidemiological area

- long-term studies in children, adolescents and adults
- intervention studies: prevention of psychiatric/somatic sequelae
- inclusion of molecular genetic and other neurobiological measures

#### B) Neurobiological area

- animal studies
- subtype insomnia by neurobiological means (i.e., PSG, spectral analysis, imaging, etc.)
- investigate psychological concepts (for example, attentional bias) with neuroimaging methods
- hyperarousal model: longitudinal studies of biological measures (PSG, HPA-axis, neuroimaging etc.) in relation to natural course and therapeutic interventions

#### C) Treatment area

- current drug treatments: better characterize short-/long-term benefits & risks
- development of new drug mechanisms: i.e., orexinergic, serotonergic, histaminergic and other pathways
- future drug development: include long-term perspective (3–6 months studies) with long-term follow-ups
- CBT-I: improve translation into general health care: test self-help, internet-based and stepped care approaches
- CBT-I: devise new strategies, i.e., neuropsychotherapy etc.

Long-term prospective studies are needed to better understand the natural history of insomnia. Epidemiological studies evaluating insomnia and the impact of therapeutic interventions in children, adolescents and adults have to be developed in order to better prevent the development of mental diseases associated to insomnia. This type of study, when combined with neurobiological measurements may also clarify which aspects of insomnia are responsible for its negative influences on mood and physical health.

The study of insomnia by means of animal studies, molecular genetics and neuroimaging methods has been largely neglected up to now. This may be due to the wide-spread attitude to perceive insomnia as a merely psychological problem without any somatic involvement. Recent investigations with sophisticated methodologies have clearly shown that this is a misconception, and have moreover shown new directions for possible causes, mechanisms and consequences of insomnia. Functional imaging studies suggest that normal performance in insomniacs may in fact be the net result of dysfunctional cortical areas and compensation by others [59]. Structural imaging studies have suggested reductions in hippocampal volume [150] and orbitofrontal gray matter [151]. The involvement of the latter area in comfort recognition, in combination with a recently observed deficiency in comfort evaluation in insomniacs [152] opens up a whole new research direction; the investigation of whether the insomniac brain may have a compromised capacity to read out input from the periphery signalling that it is safe to fall asleep, e.g., with respect to body position and thermal environment.

Although there are empirically effective pharmacological and non-pharmacological treatment protocols for chronic insomnia, the situation is frustrating: concerning pharmacotherapy, the discontinuation of any effective substance leads to a relapse in most of the cases; moreover, sometimes rebound effects occur. Additionally, there is still the open question of the efficacy and safety of long-term pharmacological treatment of insomnia. Therefore we need independently funded studies that investigate the impact of long-term medication on insomnia and related health outcomes. Also, new modes of action need to be introduced. Admittedly, it is still the GABA pathway which dominates: substances influencing the orexinergic system or having an impact on histamine or serotonin receptors are urgently awaited.

With respect to CBT-I, short- and long-term effectiveness have been clearly shown. Nevertheless, the question of non-responders has not been addressed adequately yet as outlined before. Another problem with CBT-I is the fact that it is not largely available and mainly offered in specialized research settings. A translation from the university setting to general outpatient care has not been established so far. With respect to this, the development of self-help treatment strategies [153] and internet-based interventions [154] might help to provide adequate treatment for more patients. Huge efforts have to be undertaken to translate our knowledge of CBT-I into general health care. Espie [155] has suggested a 'stepped care' approach to solve this problem. It also needs to be noted that standard CBT-I methods have now been known for 20 years without any kind of new development. This is in striking contrast to other fields of psychotherapy, for example, depressive disorders. It seems that CBT-I is uncoupled from the realm of scientific and clinical psychotherapy development. Therefore, we suggest a closer connection and interaction between CBT-I specialists on the one hand and GPs and psychotherapists on the other hand.

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