

Comorbid Sleep Disorders in Neuropsychiatric Disorders Across the Life Cycle

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Abstract The association between psychopathology and poor sleep has long been recognized. The current review focuses on the association between the most prevalent sleep disorders (insomnia, sleep-related breathing disorders and restless legs syndrome) and four major psychiatric disorders: alcohol dependence, schizophrenia, depression and anxiety disorders. Decreased total sleep time and increased sleep onset latency as measured by polysomnography as well an increase of the prevalence of insomnia has been reported in all of these psychiatric disorders. Furthermore, sleep disturbance is a risk factor for their development. Cognitive-behavioral therapy for insomnia has been shown to have a positive impact on both sleep and symptoms of depression and anxiety. Whether adequate treatment of sleep disorders can prevent the incidence of psychiatric disorders, remains to be investigated.

Keywords Sleep disorders · Insomnia · Psychiatric disorders · Schizophrenia · Depression · Affective disorders · Anxiety disorders · Alcohol dependence · Life cycle

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Introduction

The association between psychopathology and poor sleep has long been recognized. Consequently, in the Diagnostic and Statistical Manual of Mental Disorders-IV (DMS-IV) and International Classification of Diseases (ICD-10), disturbed sleep is a key symptom of many psychiatric disorders [1]. Beyond that, Harvey et al. suggested that sleep disturbance is not only a symptom of psychopathology but a mechanistically transdiagnostic process [2•], which means that there is a causal relationship between sleep disturbance and psychiatric disorders. Suggested causal links include the association between sleep disturbance and 1) emotion regulation, 2) genes that have also been linked to psychiatric disorders, and 3) dopaminergic and serotonergic dysfunction [2•].

The most commonly encountered sleep disorder in patients with psychiatric disorders is insomnia, a condition that is defined by difficulties initiating/ maintaining sleep or non-restorative sleep accompanied by at least one form of related daytime impairment [3]. Chronic insomnia is associated with a severely reduced quality of life [4], cognitive impairments [5, 6], physical complaints [7] and poor social functioning [8, 9]. The treatment of choice is cognitive-behavioral therapy for insomnia (CBT-I) which is safe and effective, and, most importantly, exerts stable long-term effects [10–13]. Other prevalent sleep disorders include sleep-related breathing disorders [14] and the restless legs syndrome (RLS) [15].

The current review focuses on the association between these sleep disorders and four major psychiatric disorders: alcohol dependence, schizophrenia, depression and anxiety disorders. For each of these psychiatric disorders, we will summarize a) polysomnographic findings, b) epidemiological studies on the association with insomnia, c) CBT-I studies that have been conducted in patients in which insomnia co-occurs with the psychiatric disorder, d) studies on sleep-related breathing disorders and RLS. Of note, the

importance of sleep disorders for the prevention and course of neuropsychiatric disorders of aging has been reviewed elsewhere [16, 17].

Alcohol Dependence

Benca et al. [18] performed a meta-analysis on polysomnographic findings in different psychiatric disorders. The results revealed a decreased total sleep time and an increased sleep onset latency in patients with alcohol dependence. With respect to sleep stages, a decreased percentage of slow wave sleep (SWS %) and an increased percentage of rapid eye movement sleep (REM %) was reported.

In line with these results on sleep onset and sleep duration, the prevalence of insomnia symptoms is markedly higher in alcohol dependent patients than in healthy individuals [19–22]. During acute withdrawal, almost 50 % of alcohol dependent patients suffer from insomnia [23]. Furthermore, even in abstinent patients, insomnia often persists [20]. Longitudinal epidemiological studies suggest that insomnia is not only prevalent in patients with alcohol dependence but also a risk factor for the development of the disorder [24] and for relapses after withdrawal [22]. Of note, after withdrawal, the sleep EEG of relapsers is characterized by increased REM sleep pressure [25, 26] and increased spectral power in the beta range [27]. In addition to this, insomnia is also associated with a higher rate of suicidal thinking in patients with alcohol dependence [28].

With respect to insomnia treatment, Currie et al. [29] investigated 60 recovering patients with alcohol dependence using individual CBT-I, a self-help manual and a wait-list control condition (n=20 each). The active treatment conditions improved sleep efficiency, sleep onset latency and sleep quality, however, no effect on the prevention of relapses was observed. Later, Arnedt et al. [30] performed an uncontrolled pilot study in which they found that CBT-I was effective in improving sleep efficiency and sleep onset latency in a small group of seven abstinent patients. A second study of this research group used a randomized controlled design and reported that CBT-I improved sleep efficiency in comparison with a behavioral placebo treatment [31]. However, like in the investigation of Currie et al. [29], CBT-I had little impact on alcohol consumption.

Alcohol consumption is also associated with an increased prevalence of sleep-related breathing disorders in the general population [32], and, consequently, sleep apnea syndrome is prevalent in patients with alcohol dependence [33]. Furthermore, the PLMS arousal index is significantly increased in patients with alcohol dependence [34, 35] and has been reported to be a predictor for relapses [34].

Schizophrenia

In the meta-analysis of Benca et al. [18], unmedicated patients with schizophrenia showed decreased total sleep time, decreased sleep efficiency and increased sleep onset latency while no alterations were observed for SWS % and REM %. A more recently published meta-analysis that was based on a considerably broader data base replicated these findings [36].

In terms of diagnosis, one study reported that 77 of 175 (44 %) outpatients with schizophrenia or schizoaffective disorder met clinical diagnosis for insomnia [37], which was, in turn, independently associated with lower quality of life in these patients. Importantly, sleep disturbances seem to be a risk factor for the development of schizophrenia. This has been shown in a prospective multicenter study of 245 potentially prodromal patients who were investigated with a follow-up time of 18 months [38••]. Moreover, insomnia seems to be a predictor of worsening of positive symptoms following antipsychotic withdrawal [39].

In a promising pilot trial, CBT-I had an effect on both sleep and persistent persecutory delusions in patients with schizophreniform disorders [40]. However, despite of the clinical importance of insomnia in schizophrenia, up to now, the efficacy of CBT-I has not been widely investigated in this group.

In addition to the findings of prolonged sleep onset and disturbed sleep continuity, circadian rhythms are severely disturbed in patients with schizophrenia. A recent investigation showed that 50 % of schizophrenia patients on stable medication show circadian misalignment with a markedly delayed sleep phase in approximately 25 % of the afflicted individuals [41]. These abnormalities seem to be related to impaired cognitive functioning [42] underlining the clinical importance of monitoring circadian parameters in the management of patients with schizophrenia. Furthermore, obstructive sleep apnea may be a common condition in patients with schizophrenia treated with atypical antipsychotics [43, 44] and some antipsychotics may induce RLS [45–47].

A reduced number of sleep spindles has also been found in patients with schizophrenia [48, 49]. This finding may explain the observed impairment in sleep-related memory consolidation in this disorder [50], which, in turn, may be partially reversible by transcranial direct current stimulation [51].

Depression

Benca et al. [18] reported decreased total sleep time, decreased sleep efficiency and increased sleep onset latency in patients with affective disorders. Furthermore, SWS % was

found to be decreased, and, one of the most widely discussed biological findings in depression, REM latency was found to be decreased with an increase in REM %. These findings were replicated in a more recently published meta-analysis [52]. In line with the findings concerning sleep onset and sleep continuity, insomnia is a key criterion for the diagnosis of depression in DSM-IV and ICD-10.

According to epidemiological studies, up to 90 % of patients with depression suffer from insomnia [53, 54]. In addition to this, insomnia has been clearly shown to be a risk factor for the development of depression with an overall odds ratio of 2.1 (95 percent confidence interval: 1.9 – 2.4) [55••]. Furthermore, insomnia seems to be a prodromal symptom in recurrent depression [56] and a major factor that increases the duration of depressive episodes [57]. Insomnia is also associated with suicidal thinking [58] and completed suicides [59, 60].

In light of these findings, it appears to be very important to study the preventive effect of insomnia treatment on the development of depression, however, this has not been done up to now. With respect to the treatment of comorbid insomnia and depression, CBT-I has been shown to improve both sleep and depressive symptoms in a number of recent investigations [61••, 62–64]. In one of these studies, 73 outpatients with depression were randomly assigned to treatment as usual or treatment as usual plus 4 weekly 1-hour individual CBT-I sessions. After treatment, the CBT-I group had significantly lower insomnia and depression scores as well as higher remission rates for both insomnia and depression [61••].

Obstructive sleep apnea seems to be a risk factor for the development of depression [65], however, there is no evidence for the reverse causal relationship [66]. Furthermore, RLS is a prevalent condition in patients with depression [67] and antidepressant pharmacological treatment may induce RLS with severe disruptions of sleep onset and sleep continuity [68]. Vice versa, RLS seems to be also a risk factor for the development of depression [69].

Anxiety Disorders

The meta-analysis of Benca et al. [18] reported that patients with anxiety disorders show a decrease in total sleep time and sleep efficiency and an increase in sleep latency. With respect to sleep architecture, no gross alterations to healthy controls were reported. Both in DSM-IV and ICD-10, sleep-related symptoms are included in the criteria for the diagnosis of generalized anxiety disorder and posttraumatic stress disorder.

In line with the polysomnographic findings on sleep onset and sleep continuity, the prevalence of insomnia is increased in anxiety disorders [70, 71]. Conversely, anxiety

levels were found to be increased in insomnia patients [72, 73]. Of possible importance for prevention is the fact that insomnia is a risk factor for the development of anxiety [74–76]. Vice versa, there are also studies reporting that anxiety is a risk factor for the development of insomnia [77, 78].

As recently summarized by Sánchez-Ortuno & Edinger [79], some studies investigated the effect of CBT-I components in patients with posttraumatic stress disorder. However, all of these studies combined the CBT-I components with imagery rehearsal therapy making it impossible to separate the effects of these two treatments. The impact of CBT-I on anxiety levels in insomnia patients has been investigated in a recent meta-analysis [80••]. The overall effect size was 0.41 indicating a small to moderate effect.

In a large cohort study, the prevalence of post traumatic stress disorder and other anxiety disorders was about twice as high among individuals with sleep apnea syndrome than among those without [81]. However, the association between anxiety and sleep-related breathing disturbances was not found in all investigations [82]. In RLS patients, the prevalence of generalized anxiety disorder, panic disorder and posttraumatic stress disorder are considerably increased [83, 84]. In line with this, subclinical anxiety levels appear also to be increased in patients with RLS [85].

Conclusions

Sleep disturbances are associated with psychopathology and occur in alcohol dependence, schizophrenia, depression and anxiety disorders. With respect to polysomnographic parameters, decreased total sleep time and increased sleep onset latency has been found in all of the above mentioned psychiatric disorders. Sleep architecture (the composition of sleep stages across the night) is altered only in some of them. All four psychiatric disorders are characterized by an increased prevalence of insomnia defined by subjective sleep complaints.

For each psychiatric disorder, at least one longitudinal study suggests that sleep disturbance is a risk factor for the development of psychopathology. Furthermore, insomnia plays an important role in recurrent psychiatric disorders. More specifically, insomnia is a risk factor for relapses in alcohol dependence and seems to be a risk factor for schizophrenia after antipsychotic withdrawal and for depressive episodes in recurrent depression.

Regrettably, the treatment of choice for insomnia, CBT-I, has not been investigated as a preventive treatment for the development of psychiatric disorders. However, CBT-I improves sleep when insomnia occurs comorbid with alcohol dependence, schizophrenia or depression (see also [86]). The impact of CBT-I on major psychopathologies is mixed:

while depression and anxiety scores improve, alcohol consumption is only little affected and the evidence for an impact on schizophrenia symptoms is limited.

With respect to sleep-related breathing disorders and RLS, there is a close relationship between these sleep disorders and alcohol dependence, schizophrenia, depression and anxiety disorders. However, in analogy to the situation described for insomnia, little has been done with respect to trials that investigated the preventive impact of standard treatment protocols on the development of psychiatric disorders.

In summary, disturbed sleep is not only a key symptom of many psychiatric disorders but also a risk factor for their development (see also [16, 17] for the importance of sleep disorders for neuropsychiatric disorders of aging). CBT-I has been shown to have a positive impact not only on insomnia symptoms, but also on symptoms of depression and anxiety. Whether adequate treatment of sleep disorders can prevent the incidence of other psychiatric disorders, remains to be investigated.

Conflict of Interest Kai Spiegelhalter declares that he has no conflict of interest.

Wolfram Regen declares that he has no conflict of interest.

Svetoslava Nanovska declares that she has no conflict of interest.

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- Of importance
- Of major importance

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