Sleep Deprivation and Psychiatric Disorders

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Introduction

Adequate quantity and quality of sleep is fundamental to psychological and psychiatric stability. Sleep loss has been associated with psychological status in healthy subjects undergoing experimental sleep deprivation [1]. Negative impact on mood scales has been reported with both sleep deprivation and sleep fragmentation protocols in healthy adults [2]. Interestingly, acute sleep deprivation may have differential impact on healthy individuals compared to patients with depression, wherein mood may transiently improve. Symptoms of sleep disturbance and/or non-refreshing sleep are common components of many psychiatric disorders. The term sleep disturbance most typically refers to insomnia, and thus we begin with an overview of insomnia, emphasizing the challenges in characterizing this complex constellation of symptoms and presentations. Insomnia may be reported as a subjective complaint involving difficulty with initiation of sleep, maintaining sleep throughout the night, and/or awakening earlier than intended. Objective data is not required for either the psychiatric or sleep medicine diagnostic criteria for insomnia or its subtypes, and indeed laboratory polysomnography (PSG) is not routinely indicated in the evaluation of patients with insomnia [3, 4]. Instead, the diagnosis is made by the subjective clinical history, including the diagnostic subtype varieties such as primary, psychophysiological, or secondary to other causes. Despite this reliance on self-report for the diagnosis of insomnia, it is important to be aware of a particular phenomenon in some patients called paradoxical, misperception, or subjective insomnia [5]. This is defined by a mismatch between objective measures and the subjective reporting of the insomnia sleep complaint: when PSG and subjective data are available, the sleep latency can be overestimated, and the total sleep time (TST) can be underestimated, compared to objective measures. While there is increasing evidence that this mismatch occurs along a spectrum of severity [6–10], the strict diagnostic criteria used for paradoxical insomnia require extreme underestimation of TST in otherwise normal sleep, and thus its prevalence is estimated at only 5 % in the diagnostic manual of sleep disorders [11]. However, the occurrence of some degree of mismatch may be much more common.

Although objective measures are not routinely indicated for insomnia [3], performing PSG allows one to describe the degree of misperception between the objective and subjective aspects of a patient's sleep disturbance. Treatment response, whether via pharmacological or behavioral

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interventions, is also based on subjective clinical report, and thus the issue of mismatch (subjective perception of sleep improvement relative to objective measures) arises in the management/treatment phase, as well as the diagnostic phase for patients with insomnia. Understanding the degree of mismatch via objective sleep measurement might assist in management of insomnia among those with misperception. For example, among patients choosing pharmacotherapy for insomnia, the risk–benefit discussion should include, among other things, some estimate of the medical severity of the insomnia, which is most recently linked to objective sleep duration [12]. In addition, and perhaps most interestingly, feedback provided to reassure patients that they are sleeping more than they perceive may be of clinical benefit [13, 14]. If further trials confirm that feedback using objective home sleep monitoring is effective, such non-pharmacological strategies may enjoy important benefits over pharmacotherapy, which has been increasingly linked to adverse outcomes [15–20]. However, these epidemiological association studies have their own limitations [21, 22]. Structured risk–benefit balance is challenging in the domain of pharmacotherapy – a motivating factor to actively pursue non-pharmacological interventions to expand the already proven options of cognitive behavioral therapy [23, 24].

The majority of epidemiological reports of insomnia prevalence and links to other medical and psychiatric problems are primarily based on subjective reports (with some exceptions [25, 26]). As there is a growing literature describing the prevalence of mismatch between objective and subjective metrics of sleep, some caution is required when interpreting epidemiological links with self-reported insomnia symptoms and/or sleep durations. In other words, within a group of individuals felt to be "similar" in that they all report 5 h of sleep per night due to insomnia, there may be a spectrum of objective sleep durations on objective testing. Because of the potential for misperception, this apparently homogenous group may differ in objective measures of sleep duration, thus introducing "noise" into the epidemiological literature. Thus, epidemiological studies run the risk of diminished or falsely negative associations of insomnia and clinically relevant morbidity. For example, subjective–objective mismatch may occur across the spectrum of insomnia diagnostic subtypes, thus decreasing the power to identify associations that have objective underlying mechanisms that can be identified through physiological, serologic, or other forms of testing. These underlying mechanisms may have important implications for guiding appropriate interventions for insomnia.

There is additional potential for inconsistency in self-reported sleep depending on when an individual is asked to report the duration of sleep. For example, comparing the self-reported sleep durations obtained in the morning (referring to the prior night), with a retrospective self-reported summary of the previous week of sleep, individuals who underestimated their sleep duration on the morning diary entries showed a greater underestimation in their 1-week-later retrospective self-report [27]. In other words, patient self-report appears to become increasingly discordant with objective measures over time. This has important implications for the clinical evaluation of insomnia patients, who may report on even longer durations of weeks or months, with the possibility of what may be considered a meta-misperception of their sleep–wake patterns. Clinical practice often involves having patients record a daily diary of their sleep, which may mitigate some of this exaggeration effect.

The altered perception of sleep–wake times among those with insomnia may actually have a biological basis, which may be distinct from the biology of objective sleep disturbance. For review of this intriguing phenomenon, the reader is directed to the excellent summary by Harvey and Tang [5]. Several groups have proposed contributing factors associated with subjective–objective mismatch in insomnia. Altered time perception has been proposed as a mechanism, meaning that there is a primary issue of altered perception of time, and this time misperception may not be specific for only wakefulness and may extend to sleep time perception as well. However, some studies do not support a primary time perception issue [27, 28]. Psychological

factors have been investigated, including personality types and mood symptoms [9, 29–31]. Objective physiological correlates include hyperarousal mechanisms [32], alpha–delta pattern of NREM sleep EEG [33], and the cyclic alternating pattern [34]. Our recent efforts to link sleep stages, arousal index, or sleep fragmentation showed no clear relationship with the degree of mismatch in a clinical cohort [10]. This included a machine learning approach (Naïve Bayes Classifier) to use a collection of demographic and PSG characteristics to predict mismatch, emphasizing the complexity of this problem. We also reported that subjective–objective mismatch was distinct for sleep latency (overestimated in insomnia) and for wake after sleep onset (WASO; underestimated in insomnia), an additional reminder of the complexity of a process that patients and providers alike may implicitly assume to be straightforward. Thus, the mismatch that may occur between subjective and objective sleep–wake times can differentially impact wake time depending on context (sleep onset versus within-sleep-period awakenings), in addition to overall sleep duration.

It should also be noted that occult sleep disorders may be comorbid with insomnia, such as obstructive sleep apnea (OSA) [35, 36], which cannot be reliably excluded with screening inventories [37]. This is an important topic of clinical relevance, given that the literature has been interpreted to conclude that PSG is not indicated for evaluation of mood disorders; this is based in part on the question of whether sleep physiology (such as REM latency) might be considered supportive data for making the psychiatric diagnosis. Instead, one could consider PSG evaluation for occult OSA as a potential treatable contributor to sleep and/or mood symptoms. Thus, it is arguable that some patients with insomnia should undergo objective testing for the dual purpose of gaining insight into the degree of mismatch and identifying potentially treatable comorbid conditions. An additional consideration is that certain more commonly used pharmacological treatments for insomnia among patients with mood disorders (such as benzodiazepines) carry a potential risk of worsening breathing in sleep, and thus one would not want to overlook the possibility of occult sleep apnea.

Anxiety and Depression

It is perhaps not surprising that epidemiological associations have been reported between insomnia and mood symptoms or disorders [38–42]. Sleep complaints, especially disturbed or nonrefreshing sleep, are part of the diagnostic criteria for mood disorders, and thus correlation is expected based on the clinical definitions alone. However, the question of causality between sleep disturbance and mood disorders/symptoms is difficult to answer for several reasons, as has been discussed previously [43–45]. There is likely to be shared pathophysiology between insomnia and mood disorders, such that each can impact the other; there may also be shared risk factors or common biological pathways that contribute to both. Also, the temporal order of symptom appearance has been shown in both directions, namely that insomnia may precede mood complaints, or may appear after or with the onset of a mood disorder. It is likely that several mechanistic links are possible, and teasing them apart, especially within the context of the mainly subjective measures of sleep, remains challenging due to the mismatch between objective and subjective sleep reports. When both insomnia and a mood disorder or symptoms are present, it is not always the case that insomnia is secondary to the mood disorder, and thus treatment should not simply focus on the psychiatric arena in hopes of indirectly resolving the insomnia [46–48]. Despite the overlap between sleep disturbance (such as insomnia or OSA) and psychiatric disorders, it may be that one or the other aspect of the clinical presentation may dominate the diagnostic and treatment strategies. It is thus important to explore sleep and psychiatric symptoms in concert when evaluating a patient with either one of these complaints.

Studies in Which Insomnia Precedes Mood Symptoms

Several studies have shown that sleep complaints are associated with increased future risk of psychiatric disorders. A meta-analysis of risk factors for incident depression in older adults reported that over 50 % of the risk for future development of depression was associated with insomnia complaints [49]. Perlis has reported an increased risk of incident depression among older adults with baseline insomnia [50]. In a 1-year study of over 10,000 adults, baseline insomnia in those without psychiatric diagnoses predicted incident depression [42]. In a 20-year study of young adults, Buysse reported that 17–50 % of individuals with insomnia episodes of at least 2 weeks in duration later developed major depression [51].

In a large survey study of adults assessed at baseline and at 10-year follow-up, Neckelmann et al. reported that baseline insomnia increased risk of incident anxiety disorder (OR 1.6), but the association was even stronger for those reporting insomnia only at the 10-year time point (OR 3.4) or at both the entry and the 10-year time points (OR 4.9) [52]. Intervening time courses were not assessed, but the presence of insomnia at both time points suggests that chronic or recurrent insomnia has a greater association than transient insomnia for incident anxiety. This study also investigated associations with depression, but found it was only associated with insomnia at the 10-year follow-up point (OR 1.8), though not with prior insomnia or persistent (both time points) insomnia.

Breslau et al. showed in a longitudinal study that individuals reporting insomnia had a higher prevalence of depression—and those with both insomnia and sleepiness had even further comorbid depression [53]. Baseline insomnia also predicted a variety of incident psychiatric diagnoses at follow-up, including anxiety and substance abuse. Yokoyama et al. showed greater incident depression with sleep onset difficulties, but not other sub-categories of insomnia—i.e., sleep maintenance or early morning awakening [54]. Further research into insomnia phenotyping [55–57] may be useful to establish epidemiological associations; however, it may prove challenging to gather large enough sample sizes to achieve adequate statistical power to test multiple insomnia sub-categories.

Studies in Which Mood Symptoms Precede Insomnia

Other studies have shown that baseline psychiatric symptoms or disorders are associated with incident insomnia. LeBlanc reported that insomnia was associated with concurrent symptoms of anxiety and depression, whereas incident insomnia was associated with prior reports of pain, poor self-rated health, positive insomnia family history, and previous insomnia [58]. Singareddy reported that incident insomnia was predicted by mental health (including depression) [59]. Salo also showed increased incidence of insomnia in patients with depression—and also, interestingly, with sleep medication which predicted subsequent depression independent of insomnia symptoms [60]. Similarly, Kripke has reported an association between hypnotic use and depression [61]. Bi-directional influences (in terms of the temporal order of insomnia and mood symptoms) have been noted in another epidemiological prospective study [62], and in a 1-year longitudinal study of nearly 5,000 adults, bi-directional associations between sleep and psychiatric symptoms were reported [63]. Baseline anxiety, depression, and pain symptoms predicted incident insomnia at follow-up, and baseline insomnia was associated with incident anxiety, depression, and pain symptoms at follow-up. In that study, persistent insomnia (evident at both time points) was associated with advanced age. Insomnia may be a perpetuating factor in cases of persistent or relapsing depression [64, 65]. Depression has also been associated with persistent insomnia [26].

Treatment of Concomitant Insomnia and Depression

There is great interest in multimodal treatment strategies for patients in whom depression and

insomnia coexist. For example, it has been reported that sleep complaints are among the most common in patients under remission from depression using an SSRI [66], although in that study relapse was not predicted by this finding. Establishing a causal relationship by clinical history may or may not be critical for treatment planning in the patient with both diagnoses. Alternatively, if the history suggests a clear temporal order of insomnia after mood symptoms, one might opt for a trial of mood treatment (medication or behavioral) to determine if the insomnia would resolve with mood improvement. Choice of antidepressant agent may consider the sleep complaints, with more activating agents possibly chosen in the patient with hypersomnia (after ruling out primary causes), while sedating antidepressants might hold dual benefit for a patient with concurrent insomnia.

Recent randomized controlled studies suggest the utility of concomitant treatment of sleep and depression, whether pharmacologically [47, 48, 67–70] or with behavioral therapy [71]. Importantly, it was shown that elective hypnotic use was not prevalent in follow-up of a combined drug therapy trial, and that subjective sleep benefits persisted after hypnotic discontinuation [68].

In summary, the collection of epidemiological studies cited above suggests a complex interplay between sleep disorders, especially insomnia, and depression and anxiety. It is likely that bidirectional mechanisms exist, such that in patients presenting with either a sleep disorder or a mood disorder, treatment of one may reduce future risk of development of the other, or improve the symptoms of the other if concomitantly present. Much work remains to test this exciting hypothesis more broadly.

Other Sleep Disorders Linked to Mood Symptoms

Fatigue and/or sleepiness is weakly associated with sleep apnea presence or severity, and when present in the psychiatric population they are arguably even less specific [72], making the clinical screening for sleep apnea even more challenging than it already is [37]. For example, the Epworth Sleepiness scale, despite its wide use, shows minimal relation to the presence or severity of OSA [73, 74]. Depression has also been associated with sleep apnea in clinical populations, with depression rates between 7 % to over 60 % of OSA patients, and the relationship may be stronger in women than in men [72, 75, 76]. Depressed mood could indirectly increase OSA risk, perhaps through weight gain. In a study of patients with major depression and comorbid insomnia, more than a third had an AHI >15 on PSG testing [36]. In a large-scale study of over one million medical records, Sharafkhaneh showed increased prevalence of anxiety, depression, and PTSD in the United States Veterans with OSA, although in this study the prevalence of OSA was somewhat low at 2.9 % [77]. Although the literature is inconsistent in cross-sectional studies of OSA and depression [72], in a prospective study, the risk of incident depression was linked to the severity of OSA at baseline [78].

Treatment of OSA may have positive mood impact on patients with comorbid depression, in addition the improvements in quality of life and sleepiness reported in general [79], although the placebo potential in this setting should not be overlooked [80]. Although some recent work showed no improvement in mood after CPAP treatment, important limitations exist, including that the outcome mood measures were only after 2 or 3 weeks of follow-up [81, 82]. It is possible, on the converse perspective, that treating depression could indirectly improve OSA by increasing motivation, since interventions such as weight loss and adherence to CPAP require ongoing patient effort [83].

It is also worth noting that insomnia and OSA are frequently comorbid [35], thus potentially further increasing the risk of mood symptoms. There is less data linking other sleep disorders with mood symptoms. In a large 6-year follow-up study of the Nurses Health Study (over 50,000 women), Li showed that baseline self-report of physician-diagnosed restless legs syndrome (RLS) was associated with incident diagnoses of depression (relative risk of 1.5) [84].

Role of Sleep Testing for Patients with Mood Disorders

As mentioned earlier, in general, isolated mood symptoms are not considered to be an independent indication for PSG. However, there are several arguments to be made for objective investigation of sleep in patients with mood disorders. For example, comorbid insomnia is common, and understanding potential contributors to insomnia such as periodic limb movements of sleep, occult OSA, and misperception all require formal testing to evaluate. Even in the psychiatric patient without significant sleep complaints, occult OSA may be present, as it can be asymptomatic by objective and subjective evaluations of sleepiness [73, 85, 86]. As emphasized above, predicting OSA is not straightforward based on the clinical history and symptoms alone. Discovering occult OSA in a patient with psychiatric symptoms may however be an important therapeutic opportunity, and thus it is important to consider this possibility. The relationship of "classic" OSA features (e.g., obesity, snoring) with the presence and severity of OSA is only modest, so the practitioner should not be falsely reassured by the absence of common markers of OSA—e.g., normal BMI and absence of snoring or sleepiness—when considering whether to evaluate for OSA.

Sleep and Bipolar Disorder

Sleep complaints are also common in patients with bipolar disorder, during manic as well as depressed phases [87]. Insomnia is associated with mania, and while this may be described as decreased sleep need, the experience can be distressing. In some patients, increasing insomnia symptoms may be an antecedent stimulus for switching to a manic phase [88], and therapeutic sleep deprivation has been associated with increased probability of manic symptoms [89]. However, more recent data suggests that acute deprivation coupled with bright light and phase advance chronotherapy yielded longer duration (7 weeks) improvements in mood [90]. There is only sparse data regarding OSA and bipolar disorder, consisting mainly of case reports and preliminary studies of clinical screening [91, 92].

Posttraumatic Stress Disorder

Patients with posttraumatic stress disorder (PTSD) have been shown to have objective impairments of sleep architecture, for example, by actigraphy [93] and by PSG [94–97]. This population may also show discrepancies between subjective sleep reports and objective measures, as is commonly seen with patients reporting insomnia. However, at least one study showed accurate match between subjective and actigraphic TST reporting in PTSD [98]. However, in that study, sleep latency and WASO were misestimated in all subjects, with or without PTSD, while controls overestimated TST compared to actigraphy. OSA has also been observed at higher prevalence in PTSD [95, 99], emphasizing the importance of objective evaluation of sleep in this population.

A 2007 meta-analysis of studies using PSG to evaluate PTSD patients suggested that the disorder is associated with increased amounts of stage N1 sleep, and decreased amounts of stage N3 sleep. In addition, age, sex, and comorbid depression were suggested to modulate PTSD-related sleep physiology. REM density (eye movement frequency during REM sleep) was also found to be increased in PTSD. These results are important because such factors may differ among studies and thus contribute to heterogeneity in the literature of PTSD and sleep [97]. van Liempt showed that PTSD patients had twice as many night-time awakenings in the early portion of PSG recording, and decreased GH levels despite similar amounts of slow wave sleep by absolute minutes and percentage of TST [100]. Using a bed sensor over multiple nights, Woodward and colleagues showed autonomic dysfunction among those with PTSD, as well as increased time in bed and increased TST (as estimated by the bed monitor, not PSG) [101]. Ulmer and colleagues similarly showed autonomic dysfunction

in the form of altered blood pressure regulation (baroreceptor sensitivity) linked to sleep fragmentation in women with PTSD [102].

Comorbidity between PTSD and substance use, as well as prescription medication use, makes the evaluation of sleep physiology a challenge since illicit drugs, alcohol, over-the-counter, and prescription medications may all have effects on sleep as measured by PSG. Nevertheless, deciphering sleep changes is central to the development, natural history, and treatment response of PTSD. In addition, it is possible that preexisting sleep abnormalities or sleep disorders may make certain individuals who experience trauma more vulnerable to the development of PTSD. Finally, further research is needed to establish whether treatment to optimize sleep will also improve PTSD symptomatology. Despite these uncertainties, it is worth emphasizing that insomnia and OSA warrant treatment independent of PTSD, and thus it would seem reasonable to pursue evaluation and management of such sleep disorders in the PTSD population.

Schizophrenia and Sleep

Sleep disorders are common in those with schizophrenia and sleep disturbance is among the most common symptoms of the disorder. It is reported that between 30 and 80 % of patients with schizophrenia have some form of sleep and circadian rhythm disruption (SCRD) [103]. In fact, in a community sample of older adults with schizophrenia, sleep improvements were ranked among the highest needs of treatment [104]. Objectively measured sleep disturbances in schizophrenia include reductions in TST, increased sleep latency, reduced REM sleep density and REM sleep latency, decreased sleep efficiency, and reduced slow wave sleep [105]. The most significant subjective sleep impairments are reported to be insomnia, as characterized by difficulty initiating and maintaining sleep [106].

It is possible that side effects of antipsychotic medications play a role in sleep disturbance in this population. However, this seems unlikely as sleep disturbance commonly precedes the onset of Schizophrenia and the disturbance of SCRD is observed in both medicated and un-medicated patients with Schizophrenia. Furthermore, patients with schizophrenia treated with antipsychotics demonstrate improvements in sleep physiology—i.e., atypical antipsychotics have been associated with improved sleep efficiency and increased TST and slow wave sleep [103, 107].

Suicidality and Sleep

Sleep disorders and/or disturbed sleep have been linked to suicidality—with studies investigating suicidal ideation, suicide attempts, and completed suicides. Of note, sleep disturbance is a common and disruptive class of symptoms across psychiatric disorders, often listed in the actual diagnostic criteria. Understanding sleep complaints among psychiatric patients at risk for suicide may increase the potential to intervene against suicidality in vulnerable individuals. Most of the evidence reports associations of suicidality with sleep disturbance, but much less is known regarding whether the sleep disturbance is a reliable predictor of future suicidality [108].

Sleep complaints appear to be common in epidemiological studies of attempted suicide. In a study of 100 emergency room patients who had survived a serious suicide attempt, although the presence of a specific plan was not predictive of the suicide attempt, insomnia symptoms were among several predictive symptoms. Specifically, 92 % reported at least one insomnia symptom (onset or maintenance problems) while 46 % reported "global" insomnia (onset and maintenance) [109]. In another study of 165 suicide attempters, sleep disturbance was common: onset insomnia (73 %), maintenance insomnia (69 %), and early morning awakening (58 %) [110].

The National Comorbidity Survey Replication (a large representative sample) found that sleep problems (i.e., difficulty initiating sleep, maintaining sleep, early morning awakening) were associated with increased risk of suicidality—that is, suicidal ideation and plans or attempts (OR = 4.2–9.1) [111]. Most notably, this relationship remained even after controlling for mental health

diagnoses, such as depression, anxiety disorders, and substance abuse. This study also found that different aspects of sleep disturbance were associated with different forms of suicidal behavior. For example, difficulty initiating sleep predicted suicidal ideation and planning, while problems maintaining sleep predicted suicidal ideation and suicide attempt. Total insomnia scores and early morning awakening were predicting for suicidal ideation, planning, and suicide attempt—all three forms of measured suicidal dimensions. The association of insomnia symptoms and suicidality has also been described in other countries: a large-scale Korean survey reported an association between decreased sleep time and increased suicidal ideation in women [112].

With regard to treatment, identification and intervention of sleep disturbance and/or disorders may be useful for the prevention and treatment of suicidality in psychiatric disorders, but much work is required to further explore this area.

Conclusion

Sleep disturbance clearly plays a fundamental role in psychiatric disorders. Although the mechanistic links are complex and incompletely understood, sleep problems represent a potential point of intervention in this population. Whether addressing concomitant insomnia with behavioral or pharmacological strategies, or screening for treatable primary disorders such as sleep apnea, the opportunity for intervention is within reach during routine clinical care. With recent technological advances for measuring sleep, there will be increasing opportunity to monitor sleep on a longitudinal basis, providing important objective data to complement the largely symptom-driven clinical practice. For example, novel autonomic metrics have recently been shown useful in characterizing sleep disturbance in depression [113]. From diagnostic phenotyping to treatment monitoring to relapse prediction, sleep physiology continues to offer important windows into psychopathology.

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