Insomnia and Depression: A Multifaceted Interplay

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Historically, insomnia has been viewed as a symptom of depressive illness that is expected to resolve with adequate treatment of the depressive disorder. This article reviews the evidence that increasingly challenges this simplistic view and summarizes research demonstrating the multifaceted interplay between insomnia and depression. It discusses the prevalence, clinical significance, and time course of insomnia, distinguishing between poor sleep and an insomnia disorder. The article also discusses abnormalities in sleep architecture in major depressive disorder and theories about the pathways connecting sleep and depression. It concludes with a discussion of issues related to treatment, including the effects of antidepressants on sleep and new evidence of the utility of adding an insomnia-specific therapy for improved management of depressed patients with comorbid insomnia.

Introduction

Historically, insomnia has been viewed as a symptom of depressive illness. Evidence increasingly challenges this simplistic view and instead supports the view that insomnia and depression are often separate disorders with an entwined relationship [1]. Insomnia and poor sleep incur risks for the onset, relapse, and reoccurrence of an episode of depression and do not fully resolve in remitted individuals. Recent clinical trials suggest that the management of depression can be improved by treating both depression and insomnia. The aim of this article is to summarize the current findings about the multifaceted interplay of insomnia and depression.

Prevalence of Disturbed Sleep and Insomnia in Depression

Preferred nomenclature

Older literature used the term *insomnia* in reference to symptoms of difficulties initiating and maintaining sleep. In recent years, sleep researchers have emphasized an important distinction between an insomnia disorder and its nocturnal symptoms, reserving the term insomnia for a diagnosable sleep disorder whose symptoms include difficulties falling or staying asleep as well as daytime symptoms of impairment and distress [2]. We reserve the phrase *disturbed sleep* for describing sleeping difficulties without confirmation of the presence of daytime disturbance. According to the *DSM-IV*, an insomnia disorder is diagnosed when the nocturnal symptoms, most commonly difficulties initiating or maintaining sleep, last at least 1 month and cause clinically significant distress or impairment in functioning during the day. Whereas 33% of the population experience sleep disturbances at a given time, only 6% meet criteria for an insomnia disorder [3]. Insomnia disorder unrelated to a medical condition, mental disorder, or another sleep disorder (primary insomnia) is estimated to affect 1.3% to 2.4% of the adult population [3,4], with similar rates for adolescents (ages 15–18 years) and young adults (ages 19–24 years) [5].

Insomnia disorder is often comorbid with other mental disorders

A large European study estimated that one quarter to one third of individuals who meet the *DSM-IV* criteria for an insomnia disorder have a comorbid mental disorder [4]. Another population-based study found that depression and anxiety are the most frequent comorbid diagnoses among individuals with insomnia [3]. Patients with multiple psychiatric disorders seem to experience greater sleep disturbances than those with a single diagnosis. Insomnia patients with comorbid psychiatric disorders have greater sleep-related mental arousal, more maladaptive beliefs and attitudes about sleep, and poorer sleep hygiene than those without psychiatric comorbidities [6,7].

Sleep Symptoms in Depressive Disorder

Disturbed sleep

Disturbed sleep is a defining symptom in all depressive disorders and is one of nine diagnostic criteria for major depressive disorder. Just as depression is highly prevalent among patients with insomnia, disturbed sleep is present in most depressed patients. In one study, 65% of 361

depressed patients reported severe sleep difficulties (highest score on the Hamilton Depression Rating Scale) [8]. It has been hypothesized that poor sleep constitutes a homeostatic compensatory response intended to increase serotonergic tone and exert an antidepressant effect [9]. This hypothesis is consistent with reported transient improvement in mood following total sleep deprivation [9].

Hypersomnia

Hypersomnia, defined in the *DSM-IV* as increased sleep duration, is much less common than sleep difficulties among depressed patients. Hypersomnia is lumped in the *DSM-IV* with difficulties initiating or maintaining sleep as one of the nine defining symptoms of major depressive disorder. *DSM-IV*–defined hypersomnia is not equivalent to daytime sleepiness. Multiple sleep latency tests (which yield an average of the time needed to fall asleep on several 20-minute daytime nap opportunities), used as an objective measure of daytime sleepiness, have not documented clinically significant excessive daytime sleepiness in patients with depression [10]. Moreover, the correlations between objective measures of sleepiness and objective measures of sleep quality and quantity among depressed patients are negative, which is the opposite of what is observed among patients with sleep apnea [11]. That is, in depressed individuals, paradoxically more disturbed sleep is associated with greater daytime alertness. These results suggest that self-reported hypersomnia in depression may not reflect a greater propensity to sleep, but rather self-reported hypersomnia may reflect related constructs such as low energy level, fatigue, or avoidance [10].

Clinical Significance

Poor sleep contributes to depression severity

The severity of subjectively reported sleep disturbance correlates with overall depression severity and poorer quality of life [12]. The greater depression severity may be related to the daytime malaise, negative mood, irritability, decreased motivation, and difficulty with attention and concentration that result from insomnia, even in the absence of a depressive episode. The negative sequelae of poor sleep may contribute to negative affect, anhedonia, lethargy, and poor concentration in patients who suffer from depressive illness. In other words, depressed patients who experience insomnia may have more severe depression not only because of their insomnia per se, but also because insomnia exacerbates other symptoms of depression. For example, poor sleep incurs risk of suicidal ideation and specific plans for suicide [13]. The presence of nightmares also has been associated with increased risk of suicidal ideation [14].

Possible mechanisms by which insomnia may amplify depression were recently outlined by Walker [15•]. He proposed a "sleep to forget and sleep to remember" hypothesis to explain how sleep—in particular rapid eye movement (REM) sleep—strengthens emotional memories. He summarizes the evidence that emotional memories are better recalled than neutral memories. Over time, however, the individual retains the content of the memory, yet does not re-experience the same level of autonomic arousal that was experienced when the event occurred. Walker [15•] posits that the "decoupling" of affect and the memory occurs during REM sleep, when there is increased activation in the limbic and paralimbic structures (structures involved in emotion and memory), greater theta electroencephalogram (EEG) activity possibly allowing for the integration of new memories with old memories, and a lack of aminergic activity. Across numerous sleep episodes, the content of the memory is presumed to be repeatedly consolidated and integrated, whereas the emotional tone fades over time. Walker [15•] hypothesizes that during depression, the increase in REM sleep allows for greater time to consolidate the disproportionately greater number of negative memories in comparison with positive memories related to greater negative bias that is present during depression. Indeed, Nofzinger et al. [16] found greater REM activity at night associated with greater emotional intensity during the day. This relationship was observed in depressed men, but not in nondepressed controls. Sbarra and Allen [17] examined the dynamic interplay between disturbed sleep and mood over the course of 5 months in the context of an acupuncture treatment study for major depressive disorder. Using sophisticated latent difference score structural equation modeling, they found that the greatest improvements in mood occurred after a reduction in high levels of sleep disturbance [17].

Disturbed sleep is associated with poor response to depression treatment

Both subjective sleep disturbance and objectively determined abnormal sleep architecture, most notably in REM sleep, predict poor response to psychotherapy and pharmacologic treatment of depression [18,19,20•]. Response to cognitive therapy among 90 depressed patients was 70% for those with a normal sleep profile but only 30% for those with an abnormal sleep profile [19]. REM sleep parameters also distinguished between nonresponders and those with rapid and sustained response to a combination of nortriptyline and interpersonal psychotherapy [18]. A recent study found that the presence of insomnia predicted a more protracted course of depression among older adults in primary care [20•], an effect that was more pronounced among patients receiving usual care than those whose care was enhanced by the availability of consultations with a depression specialist.

Disturbed sleep is a common residual symptom following depression treatment

A substantial percentage (30% to 50%) of depressed patients continue to have residual symptoms even when treated to remission, with sleep disturbance being one of the most common [21]. For example, in a study in which fluoxetine was used as antidepressant treatment, disturbed sleep was present as a residual symptom in 44% of patients who remitted [22]. In another study of patients who remitted after cognitive therapy or pharmacotherapy (various medications), 53% reported residual insomnia symptoms [23]. The distribution

of residual symptoms in this study was 22% with difficulty falling asleep, 26% with middle-of-the-night awakening, and 17% with early-morning awakening [23]. Insomnia symptoms in those who remitted from depression may in some cases indicate that an insomnia disorder has developed and become comorbid with major depressive disorder. However, to date, there are no available estimates of the prevalence of an insomnia disorder among those who remit following depression treatment.

Residual insomnia predicts relapse and recurrence

Persistent disturbed sleep after successful treatment of depression increases the risk of reoccurrence of a depressive episode [24–26]. This relationship has been observed following a variety of treatments and in different samples, including older adults [26], non–older adult women [24], and pregnant women [25]. The last of these studies examined this relationship in a sample of pregnant women ($n = 65$) whose depression remitted following treatments provided in a randomized controlled trial of acupuncture for depression during pregnancy and who no longer met criteria for depression during the third trimester of pregnancy. The women who continued to have difficulties falling or staying asleep during the third trimester of pregnancy were more likely to have a re-emergence of a core symptom of depression about 10 weeks after the birth of the child than those who did not [25]. Dombrovski and colleagues [24] suggested that residual insomnia symptoms may be related to hyperarousal. Among participants who achieved remission only after a selective serotonin reuptake inhibitor (SSRI) was added to interpersonal psychotherapy, 65% of those with persistent poor sleep (at least twice a week) experienced recurrence of depression within 2 years, compared with only 13% of those without persistent insomnia [24].

Polysomnogram Findings in Depression

Sleep architecture is altered in depressed patients. Almost two dozen studies document that the distribution of sleep stages is altered in individuals with major depressive disorder compared with nonpsychiatric controls [27]. The most robust findings pertain to alterations in REM sleep, slow-wave sleep (present mostly in men [28]), and percentage of time spent awake [29]. Alterations in REM sleep include shortened latency to the first REM episode, longer duration of the first REM episode, and greater density of eye movements during REM sleep, all reflecting disinhibition of REM sleep. Although it was previously hypothesized to be the case, it is not clear that REM suppression plays a causal role in or is necessary for successful therapeutic outcome, because not all effective therapies suppress REM (eg, mirtazapine, nefazodone, bupropion, or cognitive-behavioral therapy and interpersonal therapy). Abnormal sleep EEG profiles in major depressive disorder do not have strong clinical utility, in part because the EEG profiles cannot consistently differentiate subtypes of depression (eg, endogenous vs exogenous), unipolar from bipolar depression, manic from depressive episodes, or even depression from other psychiatric illnesses. It is also not yet clear which aspects of sleep EEG abnormalities, if any, are truly state dependent, because the extant literature is not consistent. For an in-depth review of this literature, the interested reader is directed to a recent review by Krystal and colleagues [27] and to Riemann and colleagues [29].

Time Course of Insomnia and Depression

Insomnia may predate the depressive episode or emerge as one of its symptoms or as a side effect of antidepressant medications. The relationship between the onset of insomnia symptoms and the onset of mood and anxiety disorders was examined in a large retrospective study ($n = 14{,}915$) in four European countries. Among those with a first depressive episode and insomnia, insomnia symptoms emerged before major depressive disorder in 41%, at the same time as major depressive disorder in 29%, and after the depressive episode in 29% [4]. Furthermore, when individuals with a history of major depressive disorder relapsed into a new major depressive episode, insomnia symptoms predated the depressive episode in more than 50% of the cases. This is also true for adolescents, with 69% of patients experiencing disturbed sleep before the onset of depression [30]. Given the high comorbidity between anxiety and depression, it is important to note the contrast in the timing of insomnia symptoms in the context of anxiety disorders, as in the vast majority of cases, disturbed sleep appeared at the same time as or after the onset of an anxiety disorder [4]. More recently, a prospective study found that anxiety was strongly predictive of future insomnia, whereas insomnia strongly predicted future depression [31]. These data suggest that disturbed sleep may play a different role in depression than it does in anxiety.

Disturbed sleep and insomnia increase the risk of a future episode of major depressive disorder by twofold to 40-fold in most epidemiologic studies, with differing methodologies using varying definitions of insomnia. Most of these relatively large studies defined depression and insomnia based on symptom severity rather than diagnostic interviews. Nonetheless, the picture that emerges is consistent: insomnia/disturbed sleep at time 1 predicts depressive disorder/symptoms 1 to 3 years later. For a review, see Riemann and Voderholzer [32]. The conclusion holds true in the absence of a psychiatric disorder at time 1 [33], across various age groups [34,35], and among pregnant women [36]. Disturbed sleep also seems to emerge as one of the first symptoms of recurrence in previously remitted depressed patients [37].

The mechanism by which disturbed sleep/insomnia contributes to the emergence of a future depressive episode is not well understood. It is possible that this relationship is mediated by stress response. That is, individuals whose stress response includes disturbed sleep may be more vulnerable to depression. Consistent with this assertion is the finding from the Johns Hopkins Precursors Study, in which 1053 medical students were observed annually for a median of 34 years. This study found that after adjusting for age at graduation,

class year, parental history of clinical depression, coffee drinking, and measures of temperament, the RR of a depressive episode was greater in those with difficulty sleeping under stress in medical school (RR, 1.8; 95% CI, 1.2–2.7) compared with those who did not report difficulty sleeping [38]. One cross-sectional study supports the idea that sleep in depressed individuals may be more easily perturbed by life events that are stressful or disrupt social rhythms than the sleep of healthy controls [39]. It also has been proposed that "learned helplessness" stemming from "fruitless efforts to combat sleeplessness" may be the link between insomnia and future depression [29]. A recent study documented that experimentally induced sleep deprivation alters processing of and reaction to negative emotions [40]. If replicated in a naturalistic context, with chronic sleep deprivation that results from the inability to experience sufficient sleep, this may also explain the mechanism by which poor sleep contributes to the development of insomnia.

One recent study explored the contributions of genes and environment to the longitudinal course of sleep disturbance and depression symptoms in 300 twin pairs at 8 and 10 years of age [41]. Consistent with past findings, sleep disturbance at age 8 years predicted symptoms of depression at age 10 years, but depression did not predict future sleep disturbance. Although the genetic and environmental contributions to the association between sleep disturbance at age 8 and depression at age 10 years was not statistically significant, genetic cross-lagged modeling revealed a strong stability in depression and sleep disturbance across time. The stability in depression was primarily due to nonshared environmental influences in contrast to a strong genetic influence on sleep disturbance. Researchers are also examining the shared neurobiological pathways to understand the bidirectional association of insomnia and depression. Proposed pathways include the glutamate system, monoaminergic neurotransmitters, clock genes, and the hypothalamic-pituitary-adrenal axis. Although several neurobiological theories have been proposed (ie, two-process model, reciprocal interaction model, cholinergic supersensitivity), each theory has been met with mixed evidence [42].

Treatment-emergent Sleep Disturbance

SSRIs are common first-line pharmacologic approaches for depression, but a sizable minority of patients report disturbed sleep and somnolence as side effects. In one meta-analysis, SSRIs led to disturbed sleep in 16% of treated depressed patients [43]—similar to rates reported by patients taking bupropion, moclobemide, duloxetine, and venlafaxine [44]. Mirtazapine, trazodone, and nefazodone result in nearly half the rate of disturbed sleep compared with SSRIs [45,46], whereas those taking reboxetine report twice the rate of sleep disturbance [47]. The impact of antidepressant medications on hypersomnia is seldom reported [47]. Research instead has focused on somnolence as a side effect of antidepressant medications. A meta-analysis found that somnolence was reported by 12% of participants treated with SSRIs [43], and other studies found comparable rates among those treated with venlafaxine and duloxetine [44]. Somnolence is less frequently reported as a side effect of bupropion [43] and reboxetine [47] and more frequently reported with use of mirtazapine and trazodone [45]. Restless leg syndrome has been reported as a side effect of antidepressant medications, but this report is based on a handful of case reports, and the data have not been replicated in more recent research [48].

Treating Disturbed Sleep in Depression

The ideal treatment of insomnia in depressed patients should have long-lasting effects and alleviate insomnia without a negative interaction with the prescribed antidepressant or adverse effects. The two most common strategies used in the clinical management of disturbed sleep in depressed patients are the selection of an antidepressant that is sedating and/or improves sleep continuity and the augmentation of antidepressant therapy with a sedative such as a benzodiazepine [49], zolpidem [50], or other sedating medications (eg, H_1 antihistamines [51] or trazodone [52]). The first approach includes the use of antidepressant medications that block postsynaptic serotonin (5-HT_2) receptors and those that have pronounced antihistaminic effects (eg, amitriptyline, trazodone, nefazodone, mirtazapine, doxepin, and trimipramine) [53]. Although this is a commonly used treatment strategy, we know of no data on the comparative efficacy of sedating and nonsedating antidepressant medications on depression outcome in individuals with comorbid insomnia.

Coadministration of a sedative hypnotic seems to improve the sleep of depressed patients without hindering short-term antidepressant response [49,50]. Emerging evidence suggests that an insomnia disorder that coexists with a depressive disorder can be treated successfully. Most importantly, two recent randomized controlled studies of patients with major depressive disorder and *DSM-IV*–defined insomnia found that the concomitant treatment of insomnia and depression enhances depression outcome compared with treatment of only the depressive disorder. The first of these studies, which enrolled 545 patients, found higher rates of remission from depression (42%) in those patients receiving combined fluoxetine and eszopiclone than in those receiving fluoxetine plus placebo, of which only 33% remitted [54•]. Furthermore, 50% of patients receiving combined fluoxetine and eszopiclone had no clinically meaningful insomnia at the end of treatment, compared with 33% of the fluoxetine plus placebo group. A second, much smaller (n = 30) randomized controlled study found that adding cognitive-behavioral therapy for insomnia to the antidepressant escitalopram resulted in higher rates of remission of depression than a control therapy (62% vs 33%) and higher rates of remission of insomnia (50% vs 7%) [55•].

Cognitive-behavioral therapy for insomnia is a skill-based, nonpharmacologic intervention with many attributes that make it appealing for addressing insomnia in the context of major depressive disorder. Extensive research summarized in several meta-analyses (eg, [56]) has shown that cognitive-

behavioral therapy for insomnia produces improvements in primary insomnia equivalent to those achieved during acute treatment with hypnotic medications and has more durable effects after treatment is discontinued [57•]. If this advantage of cognitive-behavioral therapy generalizes to insomnia comorbid with major depressive disorder, it is likely to improve the long-term outcome of antidepressant therapy, as treated depressed patients who remain insomnia free are likely to remain depression free for longer periods of time than those in whom insomnia recurs [37]. Cognitive-behavioral therapy for insomnia is generally viewed as safe and devoid of the treatment-confounding side effects that occur with hypnotic therapy, with the exception of transient daytime sleepiness at the initial stages of sleep restriction [58], a component of cognitive-behavioral therapy for insomnia. It is also well accepted by patients, many of whom have concerns about developing hypnotic dependence [59].

Conclusions

Recent advances in science have broadened our understanding of the bidirectional association of depression and insomnia/disturbed sleep and suggest that insomnia may merit focused attention as part of the overall management of depression. Future directions for research on insomnia in depression include understanding the shared and distinct neurobiology of depression and insomnia, further elucidation of the unique heritable and environmental contributions to insomnia and depression, investigation of insomnia as a modifiable risk for first onset and recurrence of major depressive disorder, and identification of the best strategies for managing insomnia in depression.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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