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Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications

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Abstract

The majority of individuals with depression experience sleep disturbances. Depression is also over-represented among populations with a variety of sleep disorders. Although sleep disturbances are typical features of depression, such symptoms sometimes appear prior to an episode of depression. The bidirectional associations between sleep disturbance (especially insomnia) and depression increase the difficulty of differentiating cause-and-effect relationships between them. Longitudinal studies have consistently identified insomnia as a risk factor for the development of a new-onset or recurrent depression, and this association has been identified in young, middle-aged, and older adults. Studies have also observed that the combination of insomnia and depression influences the trajectory of depression, increasing episode severity and duration as well as relapse rates. Fortunately, recent studies have demonstrated that both pharmacological and nonpharmacological interventions for insomnia may favorably reduce and possibly prevent depression. Together, these findings suggest that sleep-related symptoms that are present before, during, and/or after a depressive episode are potentially modifiable factors that may play an important role in achieving and maintaining depression remission.

Keywords

depression; insomnia; sleep; behavioral treatment; hypnotic; antide-pressant

Sleep disturbances are nearly universal in psychiatric disorders, especially mood disorders. Research investigating associations between sleep and affective illness has largely focused on depression and major depressive disorder (MDD). This paper will review cross-sectional associations between sleep disturbance and MDD, longitudinal risk relationships between insomnia and the subsequent development of depression, the implications of insomnia for clinical course, treatment response, and relapse in MDD, and lastly the effectiveness of targeted sleep interventions in improving sleep and depression outcomes. Although not the primary focus, findings in bipolar disorder will be briefly covered.

Sleep complaints and depression are bidirectionally related

As many as 90% of patients with depression will have sleep quality complaints.[1] About two thirds of patients undergoing a major depressive episode will experience insomnia, with about 40% of patients complaining of problems initiating sleep (sleep onset difficulties), maintaining sleep (frequent awakenings), and/or early-morning awakenings (delayed or terminal insomnia), and many patients reporting all three.[2,3] Hypersomnia occurs in about 15% of patients. Sleep problems sometimes emerge as a symptom of depression or as a side

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effect of treatment. Insomnia occurring within major depressive disorder (MDD) has traditionally been assumed to be a secondary symptom of depression. Depression is identified as the most frequent cause of chronic insomnia in both clinical and epidemiological samples.[4,5] However, sleep problems often appear prior to the onset of a new or recurrent episode of major depression. Patients with mood disorders commonly report that insomnia appeared either before (40%) or at the same time (22%) as other depression symptoms.[6] Evidence that insomnia can be a prodromal symptom in MDD[7] suggests that sleep may be involved in the pathogenesis of depression. Chronic insomnia can also exist months or years before an episode of depression, and shares consistent clinical features, course, and response to treatment as insomnia during MDD. Thus, a recent National Institutes of Health conference suggested that "comorbid" insomnia may be a more appropriate term than "secondary."[8]

Depression is also overrepresented in individuals with sleep disorders.[9] As many as 24% to 58% of individuals with sleep disordered breathing (eg, obstructive sleep apnea) meet the criteria for depression.[10–12] One general population survey of 18 980 adults reported that 0.8% of the sample had both sleep disordered breathing and MDD.[13] As many as 18% of individuals diagnosed with MDD also had sleep disordered breathing, and 17.6% of individuals with sleep disordered breathing were diagnosed with MDD. Patients with narcolepsy, a disorder characterized by excessive daytime sleepiness, similarly have elevated rates of depression; as many as 28% to 57% have elevated depression symptoms,[14,15] and in one sample, 20% met current or past criteria for depression.[16] As many as three quarters of individuals with delayed sleep phase syndrome, a circadian rhythm disorder that leads to secondary insomnia and negatively impacts daytime functioning, have a past or current history of depression,[17] and such individuals report poorer sleep quality and more depression.[18] Restless legs syndrome also has an increased association with depression[19]; as many as 53% of clinic patients with restless legs syndrome or periodic limb movements have elevated depression ratings.[14,20]

Insomnia is a risk factor for developing depression

A number of longitudinal studies support the notion that insomnia is a risk factor for developing both first-onset and recurrent MDD. In the National Institute of Mental Health Epidemiologic Catchment Area study sample (n=7954), individuals with persistent insomnia (present at both baseline and 1-year follow-up) were much more likely to develop a new depressive episode at follow-up compared with individuals whose insomnia resolved by follow-up (odds ratio (OR)=39.8, 95% confidence interval (CI)=19.8–80.0 vs OR=1.6, 95% CI=0.5–5.3).[21] Subsequent analyses[22] revealed that of all the symptoms of depression, sleep problems were the most prevalent (13.6%), and those with sleep problems had the highest relative odds (7.6 times) of developing a new-onset major depressive episode during the next year compared with those without sleep problems. Sleep problems also identified 47% of individuals who develop depression in the following year, more than any other depression symptom. Thus, sleep problems had the strongest predictive value of who would develop MDD. In a different subsequent analysis,[23] individuals with insomnia but without any psychiatric disorders were also more likely to develop a new-onset MDD in the subsequent year (OR=5.4, 95% CI=2.6–11.3) compared with individuals with neither insomnia or psychiatric disorders. The authors suggested that the early diagnosis and treatment of insomnia may prevent subsequent depression.

In a longitudinal study of 979 young adults,[24] insomnia increased the relative risk for depression fourfold (95% CI=2.2–7.0) over a 3-year period, even after controlling for baseline depression symptoms. In another longitudinal study in 591 young adults, depression and insomnia symptoms were assessed six times over 21 years.[25] The presence of insomnia

either with or without comorbid depression tended to be highly stable over time. Between 17% and 50% of cases without depression but with 2 weeks or more of insomnia in the past 6 months developed a major depressive episode at a subsequent time point. The presence of insomnia (without depression) and depression (without insomnia) were not longitudinally related to each other. Insomnia comorbid with depression, however, was longitudinally related to having both.

Two other studies have similarly identified insomnia as a risk factor for depression over long follow-up periods. One study[26] followed over 1000 male medical students for a median of 34 years (range 1–45). Both insomnia and difficulty sleeping under stress in medical school increased the risk for subsequent depression (relative risk and 95% CI, respectively, 1.9, 1.2–3.2 and 1.7, 1.1–2.5). Another study followed 1244 middle-aged adults for 12 years.[27] Chronic insomnia was reported in a third of women and a quarter of men; three quarters of those with insomnia at baseline also had insomnia at the 12-year follow-up. Only women who reported insomnia at baseline were significantly more likely to report feeling depressed at follow-up (OR=4.1, 95% CI=2.1–7.2), whereas the relationship in men was not significant (OR=1.3, 95% CI=0.8–2.3).

Similar risk relationships have been identified in older adults. In a study[28] involving 147 older adults without a prior history of mental illness, the presence of insomnia (scoring 1 or higher on any of the Hamilton Rating Scale for Depression sleep items) was assessed at two time points separated by 1 year. Participants with insomnia that persisted at both time points were more likely to develop a first episode of depression during the 1-year follow-up period (OR=6.9, 95% CI=1.3–36.1) compared with participants who scored 0 on the three sleep items at both time points. In a larger longitudinal study of 524 older adults,[29] sleep disturbances at baseline predicted depression 2 to 3 years later (odds ratio=3.2, 95% CI=1.5–6.8), after adjusting for other risk factors. Individuals with persistent sleep disturbances were more likely to be depressed than individuals whose insomnia had resolved at follow-up or individuals who developed insomnia during follow-up.

Insomnia does not precede depression in all cases, and nor do the above findings prove causal relationships between insomnia and depression. Further, ample evidence suggests that both depression and its treatment can induce sleep disturbances. Thus, although there are bidirectional influences between insomnia and depression, the consistency of these longitudinal observations strongly suggests that insomnia poses significant risk for depression. Insomnia may simply be a proxy for other causal factors, or insomnia may mediate the development and severity of depression. If the latter is the case, this may have important implications for preventing the onset or recurrence of depression. Further research will be necessary to determine whether such prophylactic treatments can reduce the incidence of depression in individuals with sleep problems.

Insomnia is a risk factor for poor depression outcomes

Acute depression remission

Insomnia impacts the trajectory of MDD, increasing the severity and duration of an episode of depression. Poor subjective sleep quality before starting treatment may predict reduced treatment response. For example, pre-treatment sleep quality ratings were higher in women who had significant improvements in mood while undergoing interpersonal therapy compared with women whose depression did not remit.[30] Similarly, poor sleep quality was associated with a poorer response to combined pharmacological and psychological treatments of depression.[31] Studies have also associated sleep disturbances with suicide. Suicidal individuals have higher rates of poor sleep quality,[32] insomnia, and hypersomnia.[33,34] In one study, insomnia severity was one of several clinical features that

prospectively predicted suicide within 1 year.[35] Analogous findings associating sleep with depression severity and suicide have been reported adolescence. In a sample of 553 adolescents with MDD,[36] 73% had sleep disturbance: 54% had insomnia, 9% had hypersomnia, and 10% had both. Adolescents with both insomnia and hypersomnia were the most severely depressed, and those with either insomnia or hypersomnia were more depressed compared with those without sleep disturbance. Sleep disturbance was also associated with having more depressive symptoms and comorbid anxiety disorders. Sleep disturbances are also associated with elevated risk for suicide in children and adolescence.[37] In a sample of 135 children and adolescents with MDD,[38] patients who reported current or past suicidal ideation with a plan were significantly more likely to have insomnia (72%) compared with nonsuicidal youth (46%).

Pigeon and colleagues[39] examined the impact of persistent insomnia on response to treatment in older adults with MDD. Mean scores across the baseline and 3-month time points on the three sleep items of the Hopkins Symptom Check List-20 (HCSL) were used to categorize patients into persistent insomnia (n=207), intermediate insomnia (n=1301), and no insomnia (n=293) groups. There was a dose-response relationship between the level of insomnia and presence MDD at 6 months, with 44% of “persistent insomnia,” 29% of “intermediate insomnia,” and 14% of “no insomnia” groups meeting DSM-IV criteria for MDD. Those with persistent insomnia were more likely to remain depressed and/or achieve less than 50% clinical improvement (HCSL) at 6 and 12 months. In another study,[40] insomnia persisted in patients who remained depressed during 4 weeks of antidepressant treatment (imipramine or amitriptyline). These results suggest that insomnia, particularly when persistent, may perpetuate depression and/or impair treatment response.

Depression recurrence

Patients who are treated successfully for MDD report improved sleep quality.[41] Improvements in subjective sleep quality also appear to be related to lower recurrence rates of depression.[42] The recovery of poor subjective sleep quality in older adults with remitted depression predicted which patients remained well during 1 year of follow-up with maintenance interpersonal psychotherapy after switching to pill placebo[43]; 90% of the patients with improved sleep quality remained well, compared with 33% of patients with persistent insomnia who remained well.

Unfortunately, sleep problems frequently do not spontaneously resolve with typical treatments for depression. In fact, insomnia is the most common residual symptom following remission from depression, occurring in 44% to 51% of treatment responders following cognitive-behavioral therapy or pharmacotherapy for depression.[44,45] Patients with residual symptoms are 3 to 6 times more likely to relapse than patients in full remission,[46] and relapse may occur more quickly in the presence of residual symptoms.[47] Left untreated, insomnia increases the risk for relapse of MDD. In one small study of patients with recurrent MDD who were currently in remission for at least 4 weeks,[7] progressively greater levels of subjective sleep disturbance preceded the recurrence of a depressive episode. Thus, residual symptoms generally, and those related to insomnia specifically, confer significant risk for relapse of MDD.

Given the high degree of residual insomnia following antidepressant treatments, targeted insomnia interventions may be more effective in improving insomnia, and therefore resulting in better depression outcomes. Insomnia-specific interventions may therefore lead to remission that is more stable, extending the time between depressive episodes and possibly lowering relapse rates.

Treating sleep favorably impacts the trajectory of depression

Insomnia

Insomnia and other sleep disturbances often go unrecognized; however, treating insomnia may lessen depression severity and hasten recovery. The strongest evidence comes from a recent placebo-controlled, double-blind study in which 545 patients meeting criteria for both MDD and insomnia received fluoxetine (a selective serotonin reuptake inhibitor, SSRI) in the morning and were randomly assigned to placebo or eszopiclone (a benzodiazepine receptor agonist) in the evening. Across the 8-week treatment trial, self-reported measures of sleep and depression showed significantly greater progressive improvement in those assigned to coadministration of fluoxetine and eszopiclone. Notably, by the end of the trial, there were significantly more responders (59% vs 48%) and remitters (42% vs 33%) in the fluoxetine/eszopiclone group, suggesting that improving sleep may enhance the antidepressant response. After the 8-week treatment trial, patients received 2 weeks of continued SSRI and placebo. Hypnotic discontinuation over this 2-week period was not associated with a rebound in either insomnia or depression.[48] A smaller double-blind trial of 50 patients with MDD treated with fluoxetine and either hypnotic (the benzodiazepine clonazepam) or placebo, however, failed to find sustained improvements in depression over a 3-month period in the hypnotically-treated group.[49] In another placebo-controlled trial,[50] 190 depressed adult patients who had persistent insomnia in the presence of at least 2 weeks of effective treatment with SSRIs were assigned to placebo or the hypnotic zolpidem (a benzodiazepine receptor agonist). Compared with the placebo group, patients assigned to the hypnotic had improved self-reported sleep, daytime function, and well-being. Thus, pharmacotherapy for insomnia did not impair the antidepressant response in patients who had already responded to pharmacotherapy for depression. Studies in which benzodiazepines such as clonazepam, lorazepam, and lormetazepam were used as an adjunctive treatment also showed that depressed patients had improved sleep without worsening of depression.[49,51,52] Rather, each of these studies suggested that adjunctive benzodiazepines may be associated with improved response, more rapid response, greater compliance, or a greater percentage of responders.

There are fewer studies investigating nonpharmacological interventions for insomnia in depression. Behavioral interventions include stimulus control instructions[53] and sleep restriction.[54] Cognitive-behavioral therapy for insomnia (CBT-I) usually includes an additional cognitive component such as correcting dysfunctional beliefs about sleep (eg, “I must get 8 hours of sleep to be able to function the following day.”). These nonpharmacological interventions have been consistently demonstrated to be effective in improving sleep in primary insomnia,[55–57] as well as for treating insomnia comorbid with medical or psychiatric conditions (see ref 58 for review). The effects of CBT-I have been demonstrated to last up to 2 years in primary insomnia.[59] This has particular relevance for treating insomnia in MDD, as individuals who remain in insomnia remission are more likely to remain in depression remission.[7,28]

One randomized control trial of CBT-I in patients with MDD has been reported.[60] Individuals with comorbid insomnia and MDD (n=30) received 12 weeks of open-label SSRI (up to 20 mg of escitalopram), while concurrently receiving 5 weekly and 2 biweekly sessions of either CBT-I or a control therapy (quasi-desensitization). Compared with the control group, those assigned to SSRI and CBT-I coadministration had higher rates of both depression remission (62% to 33%) and insomnia remission (50% to 8%). Although the difference in rates of depression remission did not reach statistical significance, likely a function of the small sample size, these findings suggest that insomnia and possibly depression can be successfully improved using nonpharmacological interventions.

Several studies have reported improvements in depression severity following CBT-I. One small pilot study[61] evaluated CBT-I for comorbid mild depression and insomnia, finding that all 8 participants who completed the CBT-I intervention no longer met criteria for insomnia, and all but one participant reported normal post-treatment depression scores (Beck Depression Inventory scores <9). Two other reports that examined individuals with and without depression documented equivalent improvements in sleep following CBT-I[62] or a self-help intervention that consisted of stimulus control, relaxation, and cognitive components[63]; improvements in sleep were also associated with significant reductions in self-reported depression severity.

Further controlled trials are needed to replicate these findings, to examine whether the resolution of insomnia following CBT-I and/or pharmacotherapy leads to longer periods of depression remission, and whether targeted insomnia interventions favorably impact sleep and depression in individuals whose insomnia emerges during treatment or remains a residual symptom following an adequate antidepressant trial. These initial findings, however, suggest that both hypnotics and CBT-I may lead to improvements in depression and insomnia symptoms, and therefore such interventions may lead to depression remission that is more stable.

Hypersomnia and fatigue

Less research has examined the impact of hypersomnia on depression and its treatment. Although the symptom of hypersomnia is reported less often in patients with MDD, daytime sleepiness and fatigue are common symptoms of depression, and are also prevalent in the prodromal and residual phases of MDD. Such symptoms can occur independently, or they may occur secondarily to sleep continuity difficulties or insomnia comorbidity, as well as short- or long-term side effects of antidepressant medications. Fatigue is the second most common residual symptom in depression.[45] Like insomnia, treating daytime sleepiness and fatigue within the context of depression may favorably impact remission.

Modafinil is a novel psychostimulant approved to treat excessive daytime sleepiness in narcolepsy, sleep apnea, and shift work sleep disorder. Modafinil has several properties that make it a potential candidate to treat residual sleepiness and fatigue in MDD; it is relatively well-tolerated, and unlike classic stimulants, modafinil has less euphoric effects and is thought to have lower abuse potential. Several uncontrolled, open-label trials in depression have reported improvements in sleepiness and fatigue following modafinil (see ref 64 for review). Two placebo-controlled trials[65,66] of modafinil in partial responders to SSRI therapy for MDD failed to find persistent improvements in fatigue, sleepiness, or depressive symptom severity. In a retrospective analysis,[67] the data were pooled across these two studies. Only individuals with sleepiness, fatigue, and depression scores in the moderate and higher range were included (n=348, 77% of the original samples). Compared with the placebo group, the modafinil group had statistically significant improvements in overall clinical condition, depressive symptoms, and fatigue at week 1 and at the end of treatment 6 to 8 weeks later, but not during any of the intermediary time points. Although efficacy and longitudinal data are currently lacking, modafinil may provide some benefits in reducing fatigue and sleepiness in depression.

Sleep disturbance and bipolar depression

Although less studied, sleep disturbances are characteristic features in bipolar depression (BD) with decreased need for sleep symptomatic in episodes of mania, and either insomnia or hypersomnia symptomatic in episodes of depression. Sleep also appears to be significantly impaired during euthymic periods, with elevated levels of sleep disturbance and reduced daily sleep-wake rhythm stability.[68] Such sleep disturbances may also be

related to the pathogenesis of depression and especially mania, with increases in sleep problems just prior to an episode that continue to worsen within an episode. According to a systematic review of prodomal symptoms among patients with BD,[69] sleep disturbance was the most common prodome for mania (reported by a median of 77% of individuals), and the sixth most common prodrome for depression (reported by a median of 24%). Targeting sleep during mania may shorten episode duration. Although these findings suggest that treating sleep disturbance may prolong remission and prevent relapse, no prospective data yet exist supporting this notion. However, treatments that target sleep/wake regularity may help reduce relapse in BD. Stabilizing social rhythms with interpersonal and social rhythm therapy is effective in reducing relapse in bipolar disorder.[70] For further information on sleep and circadian rhythm disturbances in BD, see the following recent reviews.[68,71,72]

Treatment implications

In depressed patients with sleep complaints, referral to a sleep disorders specialist may help determine whether there is an underlying comorbid sleep disorder such as sleep apnea or restless legs syndrome that may cause or contribute to the symptoms of depression. Although insomnia is the sleep disorder with the strongest association with depression, other prevalent sleep disorders (ie, sleep apnea and restless legs syndrome) can lead to symptoms of insomnia, and they are overly represented in patients with depression and vice versa.

Based on the findings reviewed above, it is important for clinicians to carefully evaluate sleep symptoms in patients with depression. The emerging view that insomnia is commonly comorbid with depression, rather than simply secondary to depression, suggests that both insomnia and depression may warrant specific treatment in many cases. Although there have been few randomized, controlled treatment trials on insomnia comorbid with depression, the available evidence suggests the efficacy of several treatment approaches.

Antidepressant pharmacotherapy alone

In most patients treated successfully with antidepressants, sleep symptoms improve in parallel with other depressive symptoms. This is true even with relatively “alerting” drugs such as SSRIs. However, a substantial minority of patients experience increased sleep disturbance with SSRIs and bupropion, either in the form of insomnia or restless legs symptoms. Direct comparisons confirm that more “sedating” antidepressant drugs such as nefazodone and amitriptyline improve sleep symptoms and polysomnographic findings to a greater degree than SSRIs.[7,73,74] Nefazodone also showed greater sleep improvement than depression-specific psychotherapy in one study.[75] Thus, among patients who present with significant insomnia at the time of depression, selection of a more sedating antidepressant drug, such as mirtazapine, may be reasonable. If the risks of a tricyclic antidepressant or full-dose trazodone are reasonable in a specific patient, these might also be considered.

Antidepressant plus hypnotic

For most patients, the favorable risk-benefit profile of SSRI and SNRI drugs warrant their use as first-line agents. Among patients with comorbid insomnia, benzodiazepine receptor agonist hypnotics can be an efficacious adjunctive treatment. For instance, the combination of eszopiclone plus fluoxetine has been shown to be associated with greater sleep improvement, and strong trends toward an increased rate of depression response, compared with treatment with fluoxetine alone.[48,76] Older studies also suggest that depression outcomes are not adversely impacted by the addition of a benzodiazepine to other antidepressant treatment, and that this strategy may improve compliance.[49,51]

Antidepressant plus low-dose trazodone or doxepin

Although no large randomized clinical trials have been conducted, smaller studies suggest that the addition of low-dose (50 to 100 mg) trazodone to an SSRI or monoamine oxidase inhibitor can improve insomnia comorbid with depression.[77] In one placebo-controlled study[77] of adjunctive trazodone, a good hypnotic response was observed in 67% with trazodone and only 13% with placebo. Excessive sedation is sometimes observed because of the relatively long duration of action of trazodone. In a case series of patients with insomnia associated with fluoxetine,[78] adjunctive trazodone was stopped for excessive sedation in 5 of 21 patients (24%). There is also a potential for "serotonin syndrome"[79] in patients treated with both an SSRI and low-dose trazodone, although such cases are apparently rare.

One potential advantage of prescribing adjunctive medications (either a sedating antidepressant or a benzodiazepine receptor agonist), in contrast to a sedating anti-depressant alone, is that the adjunctive medication can be adjusted or discontinued if a patient's sleep disturbance improves while the other antidepressant agent is maintained.

Depression treatment plus behavioral treatment for insomnia

A number of studies have suggested that sleep-focused psychotherapies and behavioral therapies are efficacious in patients with comorbid insomnia and depression,[80] although some of these studies have suggested that the response rate for cognitive-behavioral treatment of insomnia may be lower in insomnia patients with comorbid depression. However, recent results from a small controlled clinical trial of depression pharmacotherapy combined with cognitive-behavioral therapy for insomnia showed improved sleep and depression outcomes compared with pharmacotherapy combined with an inactive therapy control.[60]

Conclusions

Symptoms of insomnia and depression share bidirectional relationships. Cross-sectional studies show a strong relationship between symptoms of depression and insomnia, and insomnia is longitudinally associated with the development of depression and poor treatment outcomes. Evidence that sleep strongly influences both the development and trajectory of depression, impacting episode frequency, severity and duration, suggests that sleep-related symptoms may be important and modifiable risk factors to prevent depression and/or achieve and maintain depression remission. Patients with mood disorders who have sleep disturbances should be carefully evaluated. Other sleep disorders, comorbidity with another medical or psychiatric disorder, and medication side effects should be considered in patients with insomnia or hypersomnia symptoms. Recent evidence suggests that interventions for insomnia, which include both behavioral and psychological treatments and pharmacotherapy, may be helpful in depression, but further controlled trials are needed.

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