Recent advances in sleep and depression

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Purpose of review
There is increasing interest in the connection between sleep disturbances and mood disorders. The purpose of this review is to summarize and evaluate current research on the role of sleep disturbance in the development of depression, as well as to describe recent advances in treatments that improve both sleep and depression symptoms.

Recent findings
Relevant publications included in this review cover a wide range of topics related to sleep and depression. Data from large longitudinal studies suggest that insomnia and evening circadian preference are unique risk factors for depression. Depression treatment studies indicate poorer outcomes for those with comorbid sleep disturbances. A few recent trials of cognitive behavioral therapy for insomnia and triple chronotherapy in unipolar depression have shown promising results.

Summary
Sleep disturbance is a modifiable risk factor in the development and maintenance of depression. In the context of current depression, although the data is mixed, some evidence suggests treating sleep disturbance can improve overall outcomes. Recent evidence also suggests that treating sleep disturbance may prevent the future depressive episodes.

Keywords
chronotherapy, cognitive behavioral therapy for insomnia, depression, sleep

INTRODUCTION

Major depression, characterized primarily by depressed mood and/or loss of interest or pleasure in daily activities for 2 weeks or more, is a common and often debilitating mental disorder [1]. Recent epidemiological survey data suggest that approximately 8.4% of adults and 17% of adolescents in the United States experienced at least one major depressive episode (MDE) in 2020 [2], with rates increasing during the coronavirus disease 2019 (COVID-19) pandemic [3]. Sleep disturbance is common in depression; symptoms of insomnia (i.e. difficulty initiating or maintaining sleep) exceed 80% in those who are concurrently depressed [4], and hypersomnolence is also frequently reported, alone or in combination with insomnia [5,6]. Recent research has also considered the role of features such as circadian preference (specifically, evening circadian preference) in the development and maintenance of depression [7,8]. Among adults with depression, sleep disturbance is associated with greater depressive symptom severity [9,10], lower rates of remission from depression [11], higher risk of depression relapse [12], and increased risk for suicidal thoughts and behaviors and nonsuicidal self-injury [13–17], and is the symptom most likely to persist following treatment remission [18,19].

Pharmacotherapy, specifically selective serotonin reuptake inhibitors (SSRIs), is a first-line recommended treatment for depression [20]. Although half of adults with major depression receive pharmacotherapy, an estimated 30% of those adults do not experience remission even after multiple medication trials [21]; pharmacotherapy is also associated with unpleasant side effects (including increased sleep disturbance in approximately 25% of patients taking SSRIs) and discontinuation symptoms [22]. As reviewed above, given that sleep disturbance is frequent and portends poorer illness course and relapse in depression, recent research

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KEY POINTS

- Sleep disturbance is very common in depression, is often neglected in standard treatment, and is associated with greater depressive symptom severity, worse treatment outcomes, and greater risk of relapse.
- Sleep disturbance in depression most commonly presents as insomnia (i.e. difficulty initiating or maintaining sleep), but rates of hypersomnia and evening circadian preference are also notable.
- Nonpharmacological treatments for sleep disturbance, such as cognitive behavioral therapy for insomnia and triple chronotherapy, are safe and promising treatment options for patients with co-occurring depression and sleep disturbance.
- Pharmacological treatments, while effective, are not preferred treatments for sleep disturbance.

has turned to nonpharmacological sleep treatments, such as cognitive–behavioral therapy for insomnia (CBT-I) or chronotherapy, as alternatives and/or complements to antidepressant pharmacotherapy [23,24].

The present review focuses on sleep as an important pathway in the progression of major depressive disorder (MDD) and an important target warranting independent treatment. Several excellent reviews have recently summarized the bidirectional association between sleep and depression [25–27], and the efficacy of sleep treatments in improving depression symptoms [23,24,28]. This article will focus on an update of recent evidence supporting the importance of sleep disturbance in depression (with a particular focus on insomnia and evening circadian preference), its contribution to illness course, and recent advances in treatments of various sleep disturbances.

THE ROLE OF SLEEP DISTURBANCE IN DEPRESSION

Sleep disturbance is common in depression

Sleep disturbance is a diagnostic feature of depression. Per the DSM-5, insomnia or hypersomnia are clinical symptoms of a MDE [1]. Sleep disturbance is one of the most commonly reported symptoms of depression, with more than 80% of patients with MDD reporting sleep disturbances [4,29]. Sleep in depression is typically measured either by retrospective self-report, collecting prospective data via a sleep diary [30] or inferred from rest and activity patterns via actigraphy. Actigraphy is increasingly used to estimate sleep-and-wake patterns as it is low burden and provides motor activity data across a 24 h period [31–33]. Although polysomnography is considered the gold standard for measuring objective sleep, it is also costly and time-intensive and, as such, is not recommended as the standard of practice in routine evaluation of sleep disorders like insomnia [34].

Although insomnia is the most common profile of sleep disturbance during an MDE, insomnia and hypersomnia symptoms co-occur in about a quarter of patients with an MDE, and hypersomnia alone is not uncommon [5,6]. Co-occurring insomnia and hypersomnia appears to be a unique risk factor for greater functional impairment and use of treatment [5,35].

In addition to sleep disorders such as insomnia or hypersomnia, there has been increasing recognition of the importance of circadian rhythm features in depression. Specifically, depressed patients with evening circadian preference (i.e. a diurnal preference for activity and alertness in the evening) experience more severe depressive symptoms, greater functional impairment, and higher rates of suicidal ideation compared with patients without evening preference [11,36]. Although circadian preference is often measured by self-report (e.g. Morning-Eveningness Preferences Scale), the onset of melatonin release in dim light conditions in the evening (DLMO) is the gold standard objective measurement of biological circadian rhythm timing [37,38]. Multiple studies have shown that adversely timed DLMO in relation to sleep/wake behavior (i.e. bedtime, waketime, midsleep, etc.) – often referred to as 'circadian misalignment', and measured using the phase-angle difference between DLMO and sleep/wake behavior – is associated with greater severity of depressive symptoms [39–41].

Sleep disturbance precedes and predicts development of depression

There is evidence for a bidirectional association between sleep disturbance and MDD. Among those with and without MDD, sleep disturbance is one of the more important predictors of a future depressive episode; likewise, depressive symptoms appear to increase risk for future insomnia [12,42,43]. In a network analysis, Blanken *et al.* [44] recently documented that individual insomnia complaints (specifically, difficulty initiating sleep) prospectively predicted first-onset MDD at 6-year follow-up, with sleep-onset insomnia conferring a two-to-three-fold greater risk of subsequent new-onset depression. Among children, as part of the Norwegian Mother, Father and Child Cohort Study, Sivertsen *et al.* [45▪] recently showed that short sleep duration and

frequent nightly awakenings at 1.5 years predicted the development of depressive symptoms at 8 years of age. Taken together, these studies underscore the importance of insomnia across the lifespan in relation to future depressive episodes.

Similarly, there is evidence to suggest a bidirectional association between evening circadian preference, which typically develops during adolescence, and MDD [8]. More recently, in the IDEA-RiSCo study, 96 adolescents were stratified into either low-risk for depression, high-risk for depression, or experiencing current MDD; the high-risk adolescents shared sleep and rhythm alterations (i.e. higher social jetlag, lower relative amplitude of activity, and higher exposure to artificial light) with the MDD group, presenting identifiable and modifiable risk factors for depression [46]. Analyzing genetic and phenotypic data from a large sample of adults ($n = 451\,025$), O'Loughlin *et al.* [47▪▪] found robust support for morning circadian preference as a protective factor against depression, as well as support for the role of circadian misalignment in the development of depression.

Sleep disturbance mediates and moderates response to depression treatment

An existing body of research suggests that sleep disturbance affects response to depression treatment [48–50]. More recently, it appears that improvements in sleep disturbance early on in treatment increase likelihood of depression remission [51]. In a trial conducted by Boland *et al.* in 2020, 523 adults with recurrent MDD underwent cognitive therapy for 12–14 weeks. In this sample, greater baseline sleep disturbance predicted worse response to treatment, but patients whose sleep disturbance improved (as opposed to persisted) over time had significantly higher rates of treatment response and depression remission [52]. Similar findings have also been reported using digital CBT-I (dCBT-I): Henry *et al.* [53▪] in 2021 analyzed results from two large RCTs of dCBT-I among participants with insomnia and clinically significant depressive symptoms, finding that improvements in insomnia symptoms at mid-intervention mediated 87% of the effects on depressive symptoms at postintervention. Hence, it appears as though reductions in sleep disturbance made relatively early in treatment portend better outcomes for the treatment of concurrent depression.

Evening circadian preference has also been shown to impact treatment across trials of CBT-I, pharmacotherapy, and bright light therapy [54, 55,56▪▪]. Further analysis of the TRIAD Study by Asarnow *et al.* [55] in 2020 revealed that greater evening preference at baseline predicted smaller reductions in depressive symptom severity at post-treatment across both groups. Similarly, in a 2019 RCT augmenting SSRIs with zolpidem among 108 patients with comorbid MDD and insomnia, Rumble *et al.* found that eveningness was independently associated with greater suicidal ideation over the course of treatment, regardless of depression severity, insomnia severity, or treatment assignment [57,58▪]. Chan *et al.* [56▪▪] in 2022 conducted a RCT of bright light therapy for adults with unipolar depression and evening preference; participants who experienced a change in eveningness by week 5 of treatment were twice as likely to experience remission of depression at follow-up than those who did not experience a change in eveningness.

TREATING SLEEP DISTURBANCE IN DEPRESSION

A summary of treatments for sleep disturbance in depression along with recent supportive evidence can be found in Table 1.

Pharmacological treatment

Antidepressant pharmacotherapy is the standard of care for treating MDD [20]; however, evidence about the impact of antidepressants on sleep is mixed [61]. Several studies suggest that antidepressant pharmacotherapy occasionally causes an increase in insomnia, somnolence, and nightmares [22,69]. However, as noted by a recent review, there are few, mostly small studies with short-term follow-up and design limitations examining the effects of antidepressants on sleep [70].

Nonetheless, there are a few promising studies of pharmacological treatments for sleep disturbance in depression. For example, in the REST-IT study, participants with insomnia, MDD, and suicidal ideation were randomized to either zolpidem-CR hypnotic therapy or a placebo, in conjunction with a selective serotonin reuptake inhibitor [57]. Results showed robust antiinsomnia effects of zolpidem-CR, but no significant effects on depression; however, among those with more severe insomnia, significant posttreatment decreases in suicidal ideation were observed in the zolpidem group compared with the placebo [57]. Although an important benefit of pharmacological treatments for insomnia is a shorter time-to-onset-of-effect, sedative-hypnotics are associated with discontinuation because of side effects, adverse events, and withdrawal symptoms, compared with nonpharmacological treatments [71]. Although not focused on depressed samples,

Table 1. Available treatments for various sleep disturbances in depression

Sleep disturbance type	Nonpharmacological treatments	Pharmacological treatments
Insomnia	Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as the first-line treatment for insomnia comorbid with depression and is preferred over pharmacological management of sleep disturbance [73]. Multiple meta-analyses confirm CBT-I is efficacious in the context of comorbid insomnia and depression [59,60].	Using GRADE criteria, the American Academy of Sleep medicine finds weak supportive evidence for multiple benzodiazepine, nonbenzodiazepine receptor agonists, orexin receptor antagonists and other classes of medication for the treatment of insomnia [61].
Hypersomnolence	An empirically supported treatment for sleep and circadian challenges (including hypersomnolence) comorbid with serious mental illnesses has been developed [62]. Cognitive Behavioral Therapy for Hypersomnolence (CBT-H) in central disorders of hypersomnolence and comorbid depressive symptoms has been described and preliminarily evaluated [63]. Other approaches to treating hypersomnolence in co-occurring mood disorders have been described [64].	Algorithms for pharmacological management of hypersomnolence in the context of mood disorders have been described [65].
Evening circadian preference	Morning bright light has been used to advance sleep schedules and modify evening preference in depressed samples [56▪▪]. A behavioral intervention to modify evening circadian preference in adolescents (some of whom had elevated depressive symptomatology) showed mixed results [66].	Exogenous low-dose melatonin or melatonin receptor agonists have been used to shift circadian timing in individuals with delayed circadian phase [67], and are supported by clinical practice guidelines outlined by the American Academy of Sleep Medicine [68]. Melatonin administration to modify evening preference has received less empirical attention.

a recent meta-analysis of pharmacological treatments for insomnia compared the efficacy, acceptability, and tolerability of benzodiazepines, Z-drugs (such as zolpidem), and other sedative-hypnotics. Benzodiazepines were found to be the most efficacious for acute treatment, and lemborexant and eszopiclone for long-term treatment; however, all drugs that outperformed placebo in terms of efficacy had either poor or inconclusive safety profiles [71].

Cognitive behavioral therapy

Cognitive behavioral therapy for insomnia is considered an efficacious treatment for sleep disturbances [72]; it is recommended over pharmacotherapy as the first-line treatment by the American College of Physicians [61,73]. Drawing directly from basic science on sleep and circadian rhythms, CBT-I combines multiple treatment elements including sleep education, stimulus control techniques, sleep restriction techniques, and cognitive therapy [74,75]. CBT-I has multiple benefits – it can be delivered effectively one-on-one, in groups, or even digitally (dCBT-I), it has few side effects, and the length of treatment is designed to be short. There is some evidence to suggest that among patients with MDD and insomnia, CBT-I is equally effective in reducing depressive symptoms and superior in reducing insomnia severity, compared with depression treatment alone [76–78]. However, in two recent RCTs that assess augmenting depression treatment with CBT-I, the addition of CBT-I did not significantly improve treatment outcomes; some suggest that these findings indicate there may be a 'ceiling' effect [51,76].

Given that sleep disturbance often precedes and predicts the onset of MDD, there has also been increased interest in the possibility of CBT-I as a preventive measure for individuals with at risk for future depression [79]. A recent RCT of dCBT-I by Cheng *et al.* [80] in 2019 in a sample of 1358 adults with insomnia and minimal-to-no depression resulted in a 50% reduction of depression incidence 1 year after treatment, compared with a sleep education control condition; in further follow-up 3–4 years later, these researchers documented that participation in dCBT-I continued to offer protective benefit from MDD into the COVID-19 pandemic [81▪]. In a sample of older adults, Irwin *et al.* [82▪▪] documented that, compared with a sleep education control condition, CBT-I resulted in decreased incident and recurrent MDD over a 3-year follow-up period, with results most pronounced among those in sustained remission from insomnia. Felder *et al.* [83▪▪] conducted an RCT of dCBT-I vs. standard care for pregnant people with insomnia; follow-up data at 3 and 6 months postpartum revealed significantly higher rates of probable major depression (18 vs. 4%) in the standard care group compared with the dCBT-I group. Taken together, these studies raise the

exciting possibility that treatment of insomnia may have a protective benefit for incident depression that persists years after treatment.

Triple chronotherapy

Given the association between circadian dysfunction and depression, there has been increased interest in chronotherapy – specifically, triple chronotherapy, a nonpharmacological treatment that combines sleep deprivation, sleep phase shifting, and bright light therapy – for the treatment of depression. Although primarily used as a treatment for bipolar depression, chronotherapy has also been evaluated in unipolar depression given its minimal side effects and rapid treatment effects (typically by 2 weeks) [24]. Humpston *et al.* [24] completed a meta-analysis of chronotherapy for unipolar and bipolar depression across 16 studies, finding treatment to be similarly effective for both conditions and superior to other types of therapy. Two RCTs have since been published, which further assessed the efficacy of triple chronotherapy for unipolar depression [84,85]. Yuen *et al.* [84] conducted a small trial of triple chronotherapy in a sample of 44 outpatient adults with unipolar depression, finding remission rates 1 week out to be higher (25 vs. 7%) in those who received chronotherapy vs. an alternate protocol; however, results were not statistically significant possibly because of limited power. In a slightly larger trial ($N = 82$) of outpatient adults with depression, Veale *et al.* [85] showed those randomized to triple chronotherapy showed a significant reduction in depression symptoms by 1 week after randomization – treatment effects which persisted through 26 weeks. In summary, accruing data for chronotherapy among patients with unipolar depression are promising, but larger RCTs are needed.

CONCLUSION

Sleep disturbance is an important factor in the development and maintenance of major depression. Treating specific sleep disturbances in the context of existing depression has the potential to improve outcomes for both conditions, although evidence is mixed. Accruing evidence suggests that treating sleep disturbance reduces the likelihood of incident and recurrent MDD for years following treatment – suggesting sleep treatment may be an important tool in the prevention of depression and reducing the global burden of the disease. Data suggests that when compared with depression treatments, CBT-I may have similar antidepressant effects. Furthermore, given that CBT-I is a relatively low-stigma treatment compared with antidepressants or depression-focused psychotherapy, CBT-I may be an acceptable alternative for patient populations where mental healthcare stigma is high. Although augmenting depression treatment with sleep treatment among patients with comorbid insomnia and depression does not significantly improve depression outcomes, early insomnia improvement appears to predict improved depression response across samples. This underscores the importance of weekly monitoring in treatment and raises the possibility that an adaptive, flexible intervention with the capability of being tailored during treatment to nonresponders may show greater benefit to subsequent depression reduction. Research is underway evaluating so-called 'just in time adaptive interventions' [86] and/or stepped-care approaches with flexible delivery of CBT-I treatment [87,88] to evaluate this possibility.

In conclusion, recent research has generated a more nuanced picture of the relationship between sleep and depression. The relationship between sleep and depression is far more complex and complicated to treat than was once imagined. These data suggest the need for a precision medicine approach to the treatment of concurrent depression and sleep disturbance. More research on specific sleep and circadian moderators and mediators of depression outcomes is needed.

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Conflicts of interest

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- ■ of special interest
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