Clinical Relevance of Disturbances of Sleep and Vigilance in Major Depressive Disorder: A Review

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Objective: The primary objective of this article is to provide a concise review of the clinical relevance of sleep and vigilance in major depressive disorder.

Data Sources: PubMed was reviewed (1990–2009) and English-language articles were identified using the key words *sleep and depression* and *sleep and antidepressants*. Secondary searches included articles cited in sources identified by the primary search.

Study Selection: The narrative review provides brief descriptions of the normal physiology of sleep and changes associated with depression, as well as the impact of various treatments on these processes.

Data Synthesis: Although it has long been known that sleep disturbances are an important characteristic of depression, relatively few studies have been conducted with the newer-generation antidepressants. Neither of the most widely used classes of antidepressants, the selective serotonin reuptake inhibitors and the serotonin-norepinephrine reuptake inhibitors, have particularly beneficial effects on sleep and, among the medications that reliably improve sleep efficiency, including mirtazapine and the tricyclic antidepressants, problems with daytime sedation can offset therapeutic benefit. Despite relatively widespread use, trazodone has not been demonstrated to be an effective and safe hypnotic in patients taking other antidepressants. For many patients, ongoing concomitant treatment with benzodiazepines and related drugs is the preferred option, again without convincing empirical support of longer-term efficacy. Among newer and investigational antidepressants, agomelatine shows promise with respect to both overall safety and effects on insomnia, although possible negative effects on liver function warrant further study.

Conclusions: Sleep disturbances are a significant aspect of depressive syndromes, and relief of insomnia remains an important unmet need in antidepressant therapeutics. Development of a well-tolerated antidepressant medication that rapidly improves sleep maintenance without daytime sedation is a priority for drug development.

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Disturbances of sleep and daytime vigilance (alertness) are becoming increasingly common. This trend may result in part from reduced sleep duration and/or voluntary sleep restriction, a consequence of the demands of modern life.[1,2] A study comparing sleep trends in the 1930s and 1980s demonstrated an increase in the reporting of factors related to daytime fatigue, including feeling unrested, inability to get going, and lack of overall stamina.[3] Disturbances in sleep onset (also called initial or early insomnia) may be a consequence of the pressures of everyday life and may be exacerbated by a variety of commonly used agents such as caffeine and decongestants. However, insomnia can also be a symptom of an underlying psychiatric disorder or other significant medical illnesses. A wide range of conditions are associated with insomnia, including depression and bipolar affective disorder, anxiety disorders, restless leg syndrome, chronic pain syndromes, and cardiopulmonary disorders.[4]

Sleep disturbance and daytime fatigue complaints are highly prevalent in primary care populations. A study of 1,934 respondents from 5 family practice centers found that more than half the patients reported excessive daytime sleepiness at least once weekly and one-third reported insomnia.[5] Insomnia and daytime sleepiness were reported more often by those patients who rated their health as fair or poor, those who smoked cigarettes, and those with pain syndromes, cardiovascular disease, hypertension, or lung disease.[5] In light of the increasing prevalence of sleep complaints in primary care practices, it is important to recognize and understand the relationship of sleep disturbances with depression, a highly prevalent and often undertreated condition in the primary care setting.[6]

Sleep disturbance is 1 of the 9 diagnostic criterion for major depressive disorder (MDD) in the *DSM-IV*.[7] Up to 70% of people seeking treatment for MDD suffer from insomnia and experience difficulties falling asleep, difficulties staying asleep, or early morning awakenings. Hypersomnia (ie, sleeping too much),

Clinical Points

- Sleep disturbances have been recognized as an important aspect of depression since antiquity.
- Although the most widely prescribed antidepressants, the selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, may lessen patients' complaints of insomnia, they do not have beneficial effects on sleep physiology, and many patients must take concomitant medications to manage persistent sleep disturbances.
- As the longer-term utility of the most widely used concomitant medications, including sedative hypnotics and the lower doses of more sedating antidepressants such as trazodone or mirtazapine, have not been demonstrated convincingly, identification of a safe, effective antidepressant that treats insomnia and does not cause daytime sedation continues to be an important unmet need in the pharmacotherapy of depression.

although less common than insomnia, plagues the lives of another 10%–20% of depressed people.

Depression is common in people who suffer from insomnia. Approximately 20% of patients reporting insomnia have been classified as depressed.[8] Data from a study of older patients from a general practice setting suggested that subjects reporting sleep difficulties were almost 4 times more likely to be depressed than those who had no sleep problems.[9] Results of a nationwide Japanese general population survey revealed that those individuals getting too much sleep (> 8 hours) or too little sleep (< 6 hours) had higher depression ratings than those getting about 6–8 hours of sleep.[10] This association was observed for all age groups and highlights the importance of adequate (but not excessive) sleep in relation to subjective well-being.[10]

Patients with MDD can experience a range of sleep disturbances, including early insomnia (difficulty falling asleep), intermittent awakenings (sleep continuity disturbance), or terminal insomnia (early morning wakefulness). The probability of clinically significant insomnia increases with advancing age and greater symptom severity.[4,11] Recognition of sleep disturbance as a core symptom of depression is essential for prompt diagnosis, and characterization of these sleep disturbances is crucial for proper classification (which may in turn assist in subsequent treatment decisions).

Although sleep disturbances usually resolve with remission of the depressive episode, the improvement of these symptoms may take time depending on the type of treatment. Furthermore, sleep disturbances can persist as residual symptoms with important prognostic implications. The persistence of residual symptoms such as insomnia and poor sleep in remitted patients may increase the risk for a relapse of depressive illness and has been implicated in the risk of subsequent suicidality.[12–15] Some antidepressant medications can actually worsen sleep, and, in this regard, it is sometimes difficult to determine if persistent insomnia is an unresolved feature of the illness or a side effect of the treatment.

For example, in a study of depressed patients with significant insomnia that compared 2 distinctly different antidepressants, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and nefazodone, a phenylpiperazine compound that primarily antagonizes serotonin-2 (5-HT_2) receptors, patients treated with fluoxetine experienced significant worsening of a number of relevant sleep parameters, whereas those treated with nefazodone did not.[12,16] Consistent with this observation, more than one-third of outpatients successfully treated with fluoxetine reported persistent subjective complaints of insomnia and fatigue.[17]

The objectives of this article are to review the relationship of sleep disturbances with depression, the impact of antidepressant therapies on sleep parameters, and the treatment options to address sleep abnormalities in patients with depression. PubMed was reviewed (1990–2009) and English-language articles were identified with the key words *sleep and depression* and *sleep and antidepressants*. Secondary searches included articles cited in sources identified by the primary search.

NORMAL SLEEP PATTERNS: AN OVERVIEW OF SLEEP ARCHITECTURE

Sleep is divided into physiologically distinct stages that alternate throughout the night and can be monitored by polysomnography.[18–20] These stages are subcategorized into non–rapid eye movement (NREM) and rapid eye movement (REM) periods. NREM sleep can be further subdivided into 4 sleep stages: stage 1, the transition between drowsiness and light sleep, which is characterized by slowing of electroencephalographic (EEG) activity; stage 2, a deeper sleep, which is characterized by the appearance of sleep spindles and K complexes in the EEG; and stages 3 and 4, the deepest NREM sleep stages, which are characterized by the appearance of

desynchronized, slow delta waves. Conceptually, the 2 latter "deeper" stages are often grouped together and referred to as delta or slow-wave sleep (SWS). Each period of NREM sleep typically ends with the onset of a period of REM sleep. REM latency refers to the interval between sleep onset and the first REM period. Across the night, REM periods occur at approximately 90-minute intervals, so a typical night of 7 hours of sleep would include 4 or 5 REM episodes. NREM and REM sleep show reciprocal temporal trends across a normal night of sleep—SWS is the greatest during the first few hours of sleep, whereas REM periods tend to become longer and more intense during the last few hours of sleep.[18–20]

The propensity for SWS is heavily age dependent, with a steady reduction in the amount of deep sleep across decades in adult life. Sleep patterns are further influenced by sex and, for females, the menstrual cycle and menopausal status. Compared with males, for example, females spend less time awake ($P < .05$) and in stage 1 sleep ($P < .05$) and significantly more time in SWS ($P < .05$).[21] Hormonal status may further affect sleep variables, as REM sleep typically intensifies during the late luteal phase of the menstrual cycle and SWS decreases and time awake increases following menopause.[22] The age-dependent decline in SWS is more precipitous in men across age groups, and they are more likely to report early morning awakening than women.[23] These age-dependent and sex-dependent changes in normal sleep also help to shape the characteristic sleep disturbances associated with several subforms of depression, including atypical depression (ie, hypersomnia in younger women) and melancholia (ie, sleep continuity disturbances and early morning awakening in postmenopausal women).

There are 3 interrelated processes that affect sleep patterns.[18,20] The first governs the daily or circadian rhythm that also regulates core body temperature and secretion of key hormones including cortisol; this circadian process helps to regulate the propensity for REM sleep, referred to as process C in the classic 2-process model of sleep regulation.[24] This circadian component of sleep regulation is governed by a hypothalamic clock located in the suprachiasmatic nucleus. In humans and other higher primates, sleep is most likely to occur between sundown and sunrise. Melatonin, which is typically secreted after dusk from the pineal gland, helps to biologically prime the brain for sleep onset. Melatonin production, which is suppressed during daylight, mediates the rhythm of the suprachiasmatic nucleus, ie, it entrains the biologic rhythm to the light-dark cycle.

The second process serves a homeostatic function, which regulates sleep propensity in the aforementioned model.[24] A putative sleep factor (process S) accumulates during wakefulness and is depleted during sleep. The strength of this process is reflected by the intensity of SWS during the following sleep period. Thus, the longer the period of wakefulness, the greater the physiologic drive for sleep and the duration and intensity of SWS. Because of the interaction of process S and process C, sleep is most stable when initiated some hours before the body temperature and cortisol minimum. It also explains sleep disturbances due to jet lag or shift work.

The third process, which is associated with sleep pattern regulation and interacts with the other 2 processes, controls the infradian cycle reflected by the alternation between NREM and REM sleep periods. This process is controlled through a complex interaction between cholinergic neuronal projections in the dorsolateral tegmentum and in the pedunculopontine nuclei, located in the pontine brain area. These cholinergic neurons are active during REM sleep and are suppressed during NREM sleep. Serotonergic and noradrenergic neurons originating from the dorsal raphe and locus ceruleus, respectively, have a suppressive effect on these cholinergic neurons.[25] Due to this fact, all drugs that inhibit 5-HT and norepinephrine reuptake suppress REM sleep. During SWS, neurons of all 3 nuclei have a very low activity. With this knowledge, it is possible to understand the action of antidepressants on the sleep pattern.

SLEEP PATTERN DISRUPTION IN DEPRESSION

Distinguishing different types of sleep disturbances experienced by people with depression can enhance appropriate treatment planning. In a cluster analysis, 65% of outpatients with major depression of moderate severity reported at least 1 severe sleep complaint: 38% presented initial insomnia; 39%, middle insomnia; and 41%, delayed insomnia, ie, early morning awakening.[26] Sleep disturbances appear to be more pronounced in severe types of depression. Initial or early insomnia, which is defined by a delay in sleep onset of over 1 hour, occurred in a study focusing on melancholic depression in about 3 quarters of patients.[27] In addition, up to 65% of these patients experienced frequent awakenings and fragmented sleep (middle insomnia), and 70% experienced early morning awakening (2–3 hours prior to the usual time).[27]

Both age and sex influence sleep patterns in depression. For example, early morning awakening, which is one of the defining symptoms of melancholic depression, is relatively uncommon among younger, less severely ill patients.[28,29] With regard to gender, it is important to note that hypersomnia is more frequent in women compared with men.[30] In accordance, atypical depression, for which hypersomnia is one of the defining criterion,[7] occurs more frequently in younger women.[31] Therefore, hypersomnia should be regarded as an important warning signal for this population. We will describe research on predictive markers for the development of a depressive disorder in more detail below.

Although these subjective symptoms have been objectively confirmed by polysomnography, the correlation between subjective and objective assessments of insomnia is relatively low. Objective sleep parameters, however, may give a better understanding of the underlying biology and may help to differentiate different patient groups. Sleep EEG profiles of people with depression document several characteristic alterations, including reduced REM latency, increased REM density (ie, an increased frequency of rapid eye movements per unit of REM sleep), and decreased sleep efficiency.[32] Although some depressed patients also report an increase in dreaming, for the most part, the alterations in REM sleep associated with depression do not have subjective correlation. Other studies have found a reduced duration of NREM sleep; however, the duration of SWS, which was regarded as a major component of the sleep disturbances according to the 2-process model of sleep regulation, has not been demonstrated to be consistently reduced across studies and different patient populations.[33,34]

Patients with atypical depression seem to share a shortened latency to REM sleep with other depressive subtypes but do not seem to present the sleep continuity problems.[35] It is important to note that the characteristic sleep disturbances of depression are associated with many other relevant biologic correlates, which reinforces the notion that disturbed sleep is just 1 element of broader patterns of pathophysiologic alterations. For example, there is a strong correlation between the overactivity of the stress hormone system and the extent of sleep disturbances, in particular, regarding nocturnal awakenings and the reduction of SWS.[36] Similarly, patients who have suffered a number of recurrent depressive episodes are more likely to have sleep disturbances than those experiencing a first lifetime episode even after controlling for age.[37,38]

There is also the related notion of a "scar" in the sleep pattern of patients with previous episodes of depression, or alternatively, the hypothesis that patients with certain sleep patterns may be at risk for developing a major depressive episode. This issue was studied in depth by investigators of the Munich Vulnerability Study on Affective Disorders.[39,40] The results of this study generally supported the vulnerability hypothesis, since healthy individuals with no personal history or diagnosis, but with a family history of affective disorders, had reduced SWS and increased REM density compared to individuals with no affected family members.[39,40] These findings were stable over a follow-up period of 3.5 years, suggesting that selected alterations in polysomnographic parameters may serve as "vulnerability markers" for depression even in patients who never experienced the disorder.[40] In this context, the issue arises if there is a difference between patients with unipolar versus bipolar affective disorder. Preliminary data suggest that there is no difference in polysomnographic markers of subjects related to families with bipolar disorder versus those with unipolar disorder.[41] However, in a longitudinal prospective study of adolescents with MDD, the sleep profiles of those who subsequently experienced hypomanic or manic episodes differed from those who continued to meet criteria for a "unipolar" depressive disorder. Specifically, those who developed bipolar disorder typically did not manifest the characteristic disturbances of REM sleep during the index depressive episode.[42]

Subjective reports of sleep disturbance may also be predictive of a depressive episode. A review of 8 epidemiologic studies concluded that insomnia, lasting for a period of 2 weeks at a given time point, was predictive for the development of depression in the subsequent 1 to 3 years.[43] In particular, insomnia at baseline and 1 year postbaseline was strongly predictive of major depression (adjusted odds ratio (OR) = 39.8; $P < .01$ for patients with insomnia at both interviews compared with those with no sleep complaints).[43] These sleep disturbances seem to have some specificity for depression. In comparison, the predictive values for anxiety or another psychiatric disorder were far lower.[44] Interestingly, this study also found a similar association for the symptom of hypersomnia persisting for 2 or more weeks, wherein the greatest association was linked to major depression (adjusted OR = 48.9; $P < .001$).[44]

A recent study examining 116 patients aged ≥ 70 with unipolar depression who successfully remitted following pharmacotherapy and interpersonal psychotherapy demonstrated that residual sleep disturbance (early, middle, or late insomnia) predicted a shorter time to recurrence while on maintenance therapy (hazard ratio = 1.11; CI, 1.03–1.20; $P = .01$).[13] In an earlier study of elderly patients with depression treated with maintenance nortriptyline with or without interpersonal therapy, better subjective sleep quality was associated with a lower risk for recurrence regardless of treatment.[12]

The durations of SWS and REM density may also be important predictors of depression recurrence; the results of 1 small study in patients with recurring (n = 8) or nonrecurring depression (n = 7) indicated that reduced SWS, especially in the first third of the sleep period, and increased REM density at the end of treatment were related to an increased risk for recurrence.[15] In a study of children and adolescents with MDD, those with recurrences within 1 year had significantly lower sleep efficiency ($P = .003$) and tended to have longer sleep latency ($P = .051$) than those who did not suffer a recurrence, while no differences in REM or NREM sleep were observed.[14] In particular, it has been shown that sleep disturbances commonly occur as residual symptoms in patients with depression who have responded acutely to SSRIs such as fluoxetine, with rates as high as 44% of patients in 1 study.[17] In some patients, these persistent

disturbances in sleep could be indicative of an impending recurrence or incomplete remission. Prospective studies targeting such persistent insomnia for treatment are now needed to determine if this is a modifiable risk factor.

EFFECT OF ANTIDEPRESSANT MEDICATIONS ON SLEEP EEG

The sleep disturbances associated with depression are substantially affected by the use of antidepressant medications, which can affect both REM and NREM sleep parameters, depending on the class of the drug. Further, some antidepressants increase awakenings during sleep to such an extent that it may provoke insomnia. With regard to the most widely prescribed antidepressants, venlafaxine may have the most pronounced effects in terms of increased sleep disturbances at the beginning of therapy,[45] whereas bupropion causes a moderate increase in the number of awakenings but not the time awake.[46] In fact, only a few of the newer antidepressants reliably improve sleep disruptions associated with major depressive episodes.

Effects on sleep parameters differ according to the class of antidepressant used. Monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine[47] are often associated with decreased sleep continuity and are potent suppressors of REM sleep.[48] Although prolonged pharmacologic suppression of REM sleep may not be overtly harmful, abrupt withdrawal of a medication that has strong suppressant effects can cause REM rebound. Clinical experience suggests that moclobemide, a reversible inhibitor of the A isoenzyme of MAO, has less impact on REM sleep.[49] Although the impact of the transdermally delivered formulation of selegiline, the newest type of MAOI therapy, on sleep EEG has not been systematically studied, an incidence of insomnia of 12% versus 7% in placebo during acute phase therapy is reported in the manufacturer's prescribing information.[50]

All of the tricyclic antidepressants (TCAs) suppress REM sleep, with clomipramine probably having the most pronounced effects and trimipramine having the smallest effect.[51] The more antihistaminic members of the TCA class, such as doxepin, amitriptyline, and trimipramine, have rapid sedative effects that can be initially beneficial in patients with depression who are experiencing severe insomnia.[52] Trimipramine, for example, reduces awake time and increases SWS, total sleep time, and sleep efficiency measures in patients with depression.[53,54] However, sedating TCAs can have problematic adverse event profiles, including daytime grogginess and fatigue,[55] and may not promote a durable improvement in sleep patterns over time.[52]

The selective norepinephrine reuptake inhibitors reboxetine and atomoxetine (the former widely approved outside the United States for antidepressant therapy and the latter approved in the United States only for treatment of attention-deficit/hyperactivity disorder) are associated with changes in sleep EEG parameters similar to those caused by the SSRIs, specifically with regard to their effects on REM sleep and awakenings. In patients with MDD, a 2-week course of reboxetine treatment resulted in decreased total sleep time, increased stage 2 sleep, increased time awake, decreased REM time, and increased REM latency.[56]

The selective serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, have also been found to increase REM latency and decrease REM sleep in studies of depression. Although no study has directly compared the effects of these medications on sleep, looking across studies, venlafaxine therapy appears to be associated with greater effects on sleep continuity (decreased total sleep time and increased wake time) than duloxetine.[45,57]

The SSRIs and SNRIs generally replaced the TCAs and MAOIs as first-line and second-line therapies by the mid-1990s largely because of improved safety and, on average, better tolerability.[58] Although the relatively low incidence of daytime sedation and the virtual lack of anticholinergic side effects were welcomed changes for treatment of less severely depressed patients, the SSRIs and SNRIs have their own characteristic problematic effects on sleep-wake profiles. Some patients experience sleep disruptions that commonly warrant use of sedative hypnotic medications. However, these effects often diminish over time. For example, whereas 22% of patients taking fluoxetine reported insomnia in the early treatment period (weeks 1–4), only 9% reported this symptom during continuation phase therapy (weeks 22–26 of treatment, $P < .001$).[58] Thus, the decision to coprescribe a hypnotic substance early in the course of therapy should not necessarily be viewed as a need for longer-term therapy with sedative hypnotic medications.

The SSRIs and SNRIs also have suppressive effects on REM sleep. In healthy volunteers, fluoxetine treatment resulted in increased REM latency and sleep-onset latency, with no significant change in nocturnal awakenings.[59] Fluoxetine reduced the proportion of REM sleep and lengthened REM latency in patients with depression.[54,60] In a study by Armitage et al,[60] fluoxetine actually increased the number of awakenings during the course of the trial. Sertraline prolonged REM latency, decreased the average number of REM periods, and prolonged sleep latency in a placebo-controlled study of 47 patients with MDD.[61] A study of patients with depression receiving fluvoxamine showed increased REM latency, reduced REM sleep, and increased sleep-onset latency, whereas the subjective sleep parameters showed an improvement over time, especially in the responders.[62] Acute administration of paroxetine in healthy volunteers also decreased REM sleep and increased REM latency

but increased awakenings and reduced overall sleep time and efficiency.[63] Therefore, it appears that, as a class, the SSRIs demonstrate the potential for sleep disruption.

Interestingly, on the basis of early studies that correlated clinical response with the degree of REM suppression during therapy with the TCAs and MAOIs, it was once widely believed that REM suppression was an integral aspect of antidepressant activity. This hypothesis has been rejected,[8,48] as the antidepressant activity of several medications that do not suppress REM sleep, including bupropion, nefazodone, and tianeptine (an antidepressant approved for use in France), has been established.

For example, although equivalent antidepressive efficacy was observed for nefazodone and fluoxetine in an 8-week comparative study of depressed patients with sleep disturbance, fluoxetine decreased REM sleep and prolonged REM latency, whereas nefazodone increased REM sleep and reduced REM latency.[60] Further, findings of a 6-week study comparing the effects of paroxetine with tianeptine in patients with MDD indicated that tianeptine had essentially no effects on REM sleep in contrast to paroxetine, the active comparator in the study.[34] A lower REM density after the first week of treatment (ie, a marker of early REM suppression) was associated with beneficial clinical outcome in paroxetine-treated patients but not in tianeptine-treated patients.[34] Differing effects on sleep architecture and subjective sleep quality have also been observed in comparative studies of fluoxetine and mirtazapine. Although treatment of patients with MDD and insomnia with mirtazapine or fluoxetine resulted in similar improvements in mood and subjective sleep disturbance over the course of an 8-week study, there was a significantly greater improvement in sleep latency and total sleep time in the patients treated with mirtazapine.[64]

Taken together, these findings illustrate that various types of antidepressants have differing effects on both sleep architecture, as measured by polysomnography, and subjective reports of sleep quality in patients with depression and sleep disturbances. It is important to consider the potential impact of these treatments on sleep when attempting to resolve residual sleep symptoms in remitted patients, especially in view of the association between residual sleep disturbance and relapse risk described earlier.[12,13,15]

CURRENT OPTIONS FOR THE MANAGEMENT OF SLEEP DISTURBANCES ASSOCIATED WITH DEPRESSION

In addition to pharmacotherapy, there are nonpharmacologic options for addressing new or persistent sleep disturbances in patients with depression; the first is a psychoeducational intervention that focuses on helping patients to implement proper "sleep hygiene."[19,65] These simple strategies include adopting a regular and consistent sleep-wake cycle, avoiding naps, eating a light snack prior to bedtime, restricting caffeine intake (eg, no coffee after lunchtime), and maintaining a sleep area that is cool, quiet, and dark.[19,65] However, a recent report on practice parameters for the treatment of insomnia highlights insufficient evidence to recommend sleep hygiene education as a single therapy.[66] Another nonpharmacologic approach is cognitive-behavioral therapy for insomnia (CBT-I), which has shown to be effective in the treatment of chronic insomnia.[66] This therapy includes both cognitive (changing patient's beliefs and attitudes about insomnia) and behavioral (stimulus control, sleep restriction, relaxation training) components. In studies of primary insomnia, CBT-I has an average benefit that is comparable to that of standard sedative-hypnotic drugs. The therapeutic effects of CBT-I tend to be slower in onset than those of sleeping medications, though benefits tend to be more durable after completion of time-limited therapy. CBT-I may also be effective in reducing depressive symptoms. A pilot study of patients with insomnia and mild depression (N = 10) demonstrated that all patients who completed 6 sessions of CBT-I (n = 8) experienced a normalization of sleep pattern and demonstrated improved depression scores.[67] Significant improvements in sleep latency, wakefulness after sleep onset, total sleep time, sleep efficiency, sleep quality, and depression scores were maintained after 3 months of follow-up.[67]

Current pharmacologic options for the effective treatment of sleep disturbances associated with depression are limited. Evidence from a 1995 drug utilization review suggested that one common practice used to address sleep disturbance associated with SSRIs was to augment with benzodiazepines and other sedatives.[68] In 1 study, the coadministration of clonazepam to the antidepressant treatment with fluoxetine increased the onset of improvement as measured by the 17-item Hamilton Depression Rating Scale (HDRS-17) in a short-term study (3 weeks)[69] as well as during the first week of treatment in a long-term study.[70] In the latter report, clonazepam, however, did not change the outcome in the long run.[70] Also, the improvement during the first week was attributed to an improvement of the sleep items only, not the core symptoms of depression.[70] Although the safety of combining a benzodiazepine with an antidepressant is generally favorable, there are some clinically relevant drug-drug interactions.[71] Moreover, the impact of benzodiazepine therapy on cognitive function and risk of falling should not be overlooked in the elderly population.

More recently, nonbenzodiazepine hypnotics such as eszopiclone have been used in combination with SSRIs.[72] In a large, double-blind, placebo-controlled study of patients with a new episode of both insomnia and MDD,[72] patients were randomly assigned to treatment with

fluoxetine and either adjunctive eszopiclone or placebo for 8 weeks, followed by a 2-week, single-blind, placebo washout period. Results of the study demonstrated that patients who were prescribed adjunctive eszopiclone had significantly greater reductions in sleep latency and wakefulness after sleep onset and increased total sleep time compared with those taking fluoxetine plus placebo.[72] The improvements began on the first treatment night and were sustained throughout the double-blind treatment period. In addition, the antidepressant response in the adjunctive eszopiclone group was significantly more rapid than in the placebo group, and significantly more patients in the adjunctive eszopiclone group were responders (59% vs 48%; $P = .009$) and remitters (42% vs 33%; $P = .03$) at week 8. These findings emphasize the importance of treating insomnia associated with SSRI use and the potential benefit of improving depressive symptoms further.[72] As the study was only 8 weeks long, however, the findings do not help to inform clinicians about the optimal duration of adjunctive eszopiclone therapy.[72] Additional research comparing γ-aminobutyric acid type A receptor ($GABA_A$) selective agents such as eszopiclone with commonly prescribed benzodiazepines such as lorazepam or clonazepam would be worthwhile.

Although the risk of development of dependence with a benzodiazepine or a $GABA_A$ selective compound is small, for a common condition like depression, for which up to one-third of patients receive adjunctive anxiolytics or sedative hypnotics, the number of people at risk is not negligible. For this reason alone, the search continues for novel pharmacologic strategies that effectively relieve both depression and insomnia without any risk of dependence. With respect to older antidepressants, low-dose therapy with trazodone has been used "off-label" for several decades as a non–habit-forming sedative hypnotic medication. Although trazodone has clinical efficacy similar to the TCAs and SSRIs at higher doses (ie, 300–600 mg/d), in current practice, it is almost exclusively prescribed in doses that are unlikely to exert antidepressant effects (ie, 50–150 mg/d)[73] and is effective as an adjunctive therapy to SSRIs to reduce sleep disturbances.[74] With regard to objective sleep characteristics, this compound increased the total sleep time, the percentage of stages 3 and 4, the sleep efficiency index, and the sleep continuity index and decreased the percentage of stage 1 and the number of awakenings.[74]

As noted earlier, few current antidepressant treatments specifically address the sleep disruptions of depression. Among the newer antidepressants, only nefazodone and mirtazapine reliably improve measures of sleep continuity disturbance. Although structurally unrelated, these 2 drugs as well as trazodone share 2 common pharmacologic properties: they are potent antagonists of the 5-HT_2 receptor and do not potently inhibit reuptake of monoamines. Unlike nefazodone, mirtazapine has strong antihistaminergic properties.

Following 8 weeks of mirtazapine treatment in patients with depression and insomnia, significant improvements from baseline were observed in sleep latency ($P = .0015$), total sleep time ($P = .044$), sleep efficiency ($P = .0004$), and wakefulness after sleep onset ($P = .0008$).[64] However, the pharmacologic profile of mirtazapine is also directly linked to several tolerability concerns. Sedation in some patients and increased appetite and weight gain are common and undesirable for many less severely depressed patients.[20,75] Nefazodone was withdrawn from the market in several countries because of hepatic side effects.

The augmentation of antidepressants with atypical antipsychotics such as olanzapine may also be beneficial for the treatment of sleep disturbances in patients with MDD.[20,76] In a small, open-label study of 12 patients with MDD who previously had an unsatisfactory response to SSRI treatment, the addition of olanzapine improved depressive symptoms and increased sleep continuity and SWS. These effects were maintained over the 3-week treatment period,[76] but no significant correlations were observed between changes in sleep parameters and changes in efficacy as assessed by HDRS total and depressed mood scores. Unfortunately, the risk of olanzapine-associated adverse events such as weight gain and metabolic disturbances may limit the utility of this approach.[20]

FUTURE PHARMACOLOGIC OPTIONS AND THEIR EFFECTS ON THE SLEEP EEG

New pharmacologic agents in development may offer effective treatment for the core symptoms of depression. However, specific data on the effect of sleep, as measured by polysomnography, are not currently available for many compounds. However, sleep data have been collected for several compounds in various stages of clinical development for treatment of MDD, including mifepristone, agomelatine, and vilazodone.

Mifepristone (RU-486) is an antagonist of one of the receptors involved in the action of the stress hormone cortisol, ie, it acts as a glucocorticoid receptor antagonist, but also has an effect at progesterone receptors. Due to this mechanism of action, it is approved for use in chemical abortion. As an increase in the stress hormone system has been implicated in the pathophysiology of severe forms of depression, efficacy in this particular type of depression, accompanied by severe sleep disturbances, was expected. A short-term study in healthy volunteers, however, demonstrated a delay of sleep onset and of getting into SWS after the initiation of sleep,[77] which does not fit with the assumption of a beneficial effect in the targeted population.

A new antidepressant compound, agomelatine, acts as both a 5-HT_{2C} receptor antagonist and a melatonin type 1 and type 2 receptor agonist.[78–81] The principal usefulness of 5-HT_2 antagonist compounds was discussed before.[82] In addition to this, the efficacy of the melatoninergic mechanisms for the improvement of sleep disturbances in depression has been demonstrated in patients with MDD in clinical trials[78,81] and is approved for use in some countries in Europe. Agomelatine has demonstrated antidepressant efficacy in patients with MDD in clinical trials in Europe.[82] In a small study, patients with depression underwent polysomnography several times over a 4-week period. More specifically, there was an increase in SWS, particularly in the early hours of sleep.[83] This typically occurs in patients who show an improvement in their depressive symptoms. More specifically, however, there was an increase in SWS, in particular in the beginning of the night, which appears like a normalization of the SWS distribution. No change in REM sleep parameters occurred.[83] These findings suggest that agomelatine may have the potential to effectively treat depression and sleep disturbance without the disruptive effects on REM sleep or the need for sedative comedication. Although actual cases of liver injury have, to date, been rarely reported, some patients experience elevations in transaminase levels during agomelatine therapy, and, as a precautionary measure, monitoring of liver function studies has been recommended.

Vilazodone is a compound that combines SSRI and 5-HT_{1A} partial agonistic properties in 1 molecule. Positive results for a late-stage clinical trial have been reported.[84] In this clinical trial, biomarkers that may predict the response have been assessed. In a small trial of healthy subjects, this compound induced an extreme suppression of REM sleep and an increase in intermittent wakefulness; however, it also induced an increase in SWS, particularly at the beginning of the night.[85]

CONCLUSION

Sleep disturbances are a core symptom of MDD, have the potential to worsen depressive symptoms, and are linked to relapse. No current antidepressant treatment addresses the specific sleep disruptions of depression, and current pharmacologic options are limited. Although clinically effective in the short term, augmenting an antidepressant with a sleep aid may be suboptimal over long-term use. Relief of insomnia associated with depression remains an important unmet need in the current therapeutic landscape, and, accordingly, development of well-tolerated antidepressant medications that improve sleep without causing excessive daytime sedation or other untoward adverse effects continues to be an important topic for drug discovery.

Drug names: atomoxetine (Strattera), bupropion (Aplenzin, Wellbutrin, and others), casopitant (Rezonic and others), clomipramine, clonazepam (Klonopin and others), doxepin (Zonalon and others), duloxetine (Cymbalta), eszopiclone (Lunesta), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lorazepam (Ativan and others), mifepristone (Mifeprex), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), selegiline (EMSAM, Eldepryl, and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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