Processes governing the initiation and maintenance of sleep originate in the central nervous system, and all major regions of the brain play key roles in this process. These processes orchestrate a complex array of changes that are reflected throughout the body, including the respiratory, endocrine, musculoskeletal, and digestive systems. The sleep process involves a “demand” component that is directly related to an individual’s prior amounts of rest and work, as well as a circadian component that regulates various physiologic and behavioral functions on a 24-hour basis. Sleepiness is a manifestation of a normal biological need to sleep.

Disturbances in sleep and wakefulness, such as insomnia, excessive sleepiness, and fatigue, are common symptoms in depressed patients. Insomnia, excessive sleepiness, and fatigue are experienced by most individuals suffering from depression. It is not surprising, therefore, that sleep disturbances are hallmark criteria for depressive disorders in all nosologies employed in current psychiatry. Results of a pan-European survey of approximately 1900 subjects in the community who had consulted a health care professional about depression showed that 76% suffered low mood, 73% complained of reduced energy and fatigue, and 63% suffered from sleep problems. The inability to initiate or maintain sleep, insomnia, is common in patients with depression and primarily comprises problems with sleep span (i.e., difficulty falling asleep, frequent awakenings during the night, and early morning wakefulness). Excessive sleepiness, or somnolence—the unavoidable consequence of an unsatisfied need to sleep—is common in depression. Reduced alertness caused by somnolence manifests itself as a tendency to fall asleep during usual daytime hours and diminished reaction time, memory, psychomotor coordination, information processing, and decision-making ability. Although daytime sleepiness may be caused by a curtailment of nocturnal sleep, results of a cross-sectional questionnaire survey of 11,354 Finnish twin adults (aged 33–60 years) demonstrated that it is also associated with depression, sleep-disordered breathing, and insomnia. Of this total population, 1026 adults (9%) reported daytime sleepiness occurring every or almost every day. Beck Depression Inventory scores indicated depression in about half of this sleepy cohort (of which 25% scored in the moderate-to-severe range). About 40% attributed daytime sleepiness to insomnia. Fatigue differs from somnolence in that it is more a feeling of weakness and lack of energy than a feeling of sleepiness. As described by Fava elsewhere in this supplement, many patients with depression experience fatigue.

In addition to these subjective sleep complaints, patients with depression who experience sleep disturbances exhibit some electroencephalogram (EEG) sleep disturbances: poor sleep efficiency, decreased slow-wave delta sleep (sleep stages 3 and 4), reduced rapid eye movement (REM) latency (time from sleep onset until the beginning of the first REM period), and increased REM activity. Changes in the temporal distribution of REM sleep segments (i.e., the first REM period is the longest and the last one is the shortest, which is the reverse of normal) are also evident in patients with depression.
These changes have diagnostic implications as well as implications in possible outcome and course of depression. The persistence of some of these sleep abnormalities has been shown to predict recurrences of depression in addition to family risk for depressive disorders.\(^6\)

**IMPACT OF SLEEP DISTURBANCE**

Sleepiness itself can affect daytime functioning in a number of areas including attention span and reaction time.\(^4\) It can also highly predict impairments in social and occupational daytime functioning, which has a negative effect on quality of life. Individuals who are sleepy and fatigued do not show up to work on time and are at increased risk for accidents.\(^5\) According to a 1998 report from the American Medical Association, driver sleepiness is a factor in up to 3% of all motor vehicle crashes in the United States.\(^1\)

The clinical consequences of diminution in deep, or delta, sleep are uncertain, but various disturbances of deep sleep are associated with daytime impairment. In addition, studies that have artificially reduced deep sleep levels in animals have found tremendous physiologic aberrations in these animals that at times led to death.\(^6\) Delta sleep production is related to growth hormone secretion, and these sleep disruptions in patients with depression could pose problems in immune function and other physiologic functioning.

Symptoms of sleep disturbance frequently occur in the acute phase of depression and often precede the depressive episode. Changes in sleep occur not only as acute symptoms of depression but also as both prodromal and residual symptoms.\(^7\)

Individuals who have achieved remission of depression also have a high propensity for the persistence of sleep abnormalities.\(^7\) Nierenberg and colleagues\(^8\) have shown that even when patients have responded to antidepressant therapy, residual symptoms that affect energy and sleep may persist. In their study, 48 (44%) of 108 patients with DSM-III-R/major depressive disorder (MDD) whose depression had remitted with fluoxetine treatment Hamilton Rating Scale for Depression [HAM-D] score ≤ 7 considered themselves to be not sleeping well, and 41 (38%) considered themselves to be highly fatigued. These residual symptoms were the most commonly reported residual symptoms after 8 weeks of treatment.

**TREATMENT STRATEGIES**

Effective treatment for sleep problems is dependent on a clear diagnosis of the problem. For example, is the sleep problem an integral symptom of the depression? If it is, the treatment strategies outlined in this section may be beneficial, and choosing an antidepressant that manages depression as well as counteracts the sleep and/or fatigue problems may be the most effective treatment strategy. However, if the sleep problem is due to another disorder, such as sleep apnea or narcolepsy, the patient may need to be referred to a sleep specialist. Sleep problems may also be a side effect of treatment for other health issues. Regardless of the sleep/wake issues associated with the depression, depression should be the primary target of treatment. Several options for treating patients with sleep problems in depression are available and are summarized in Table 1.

Although the treatment strategies discussed in this section focus on treating specific sleep disturbances associated with depression, controlled trials focusing on relapse rates, duration of remission, quality of life, and other issues are needed to further support a symptomatic approach to treating depression.\(^7\)

**Sedating Agents**

Certain antidepressants have been shown to be beneficial for sleep disturbances in the acute phases of treatment for patients with depression with marked insomnia.\(^19\)–\(^30\) Some of the most sedating of these agents are mirtazapine, nefazodone, and trazodone, and possibly some of the tricyclic antidepressants (TCAs; e.g., amitriptyline, imipramine, doxepin, and trimipramine).

Mirtazapine has been effective at alleviating insomnia and improving sleep architecture. In a small, open-label study,\(^24\) mirtazapine, 15 mg/day, was administered to 6 outpatients who scored ≥ 4 on the 3 sleep items of the

<table>
<thead>
<tr>
<th>Table 1. Strategies to Manage Sleep Disturbance in Patients With Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Problem Is</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Soresne or fatigue</td>
</tr>
<tr>
<td>Persistence of sleep disturbances</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
HAM-D. Using polysomnography at baseline and at weeks 1 and 2 to record and measure changes in sleep architecture, Winokur et al. found that mirtazapine monotherapy significantly decreased sleep latency and increased total sleep time and sleep efficiency. REM sleep parameters did not change, and improved HAM-D scores indicated that mirtazapine was effective in alleviating the depression.

In an open-label trial of another second-generation antidepressant, nefazodone improved sleep latency and efficiency. These findings were confirmed in 2 double-blind, 8-week trials of similar design. In these studies, outpatients with nonpsychotic MDD with insomnia were randomly assigned to nefazodone or fluoxetine. At endpoint, both antidepressants had been effective against depression; however, nefazodone progressively increased sleep efficiency and reduced the number of awakenings over the course of the 8 weeks, while fluoxetine had the opposite effect. Patients on nefazodone monotherapy experienced improved sleep quality.

The results of studies of nefazodone monotherapy or in combination with cognitive behavioral therapy (Cognitive Behavioral Analysis System of Psychotherapy [CBASP]) indicated significantly more rapid and greater improvement in insomnia ratings for the nefazodone groups when compared with CBASP treatment alone. Nearly 600 outpatients with chronic DSM-III-R depression and at least 1 insomnia symptom were randomly assigned to nefazodone, 16 CBASP sessions, or the combination. Although patients receiving combination therapy did not score markedly better on insomnia measures than patients receiving nefazodone monotherapy, they were significantly more likely to achieve at least a 50% decrease on the sleep quality measures of the 24-item HAM-D (p < .001) than patients treated with nefazodone monotherapy. Nefazodone, either in combination with CBASP or as monotherapy, was effective in treating insomnia symptoms in depressed patients. Results of a more recent study of similar design confirmed these findings. Nefazodone monotherapy improved early morning awakening and total sleep time. In combination with CBASP, nefazodone improved sleep quality, sleep latency, and sleep efficiency.

Few studies of the effects of trazodone on sleep quality in depression have been reported to date, and it appears to be used more widely as a hypnotic rather than an antidepressant. In a recent 2-part study, polysomnographic data collected on 11 patients with depression with insomnia and 11 age- and sex-matched nondepressed healthy controls further supported the sleep-promoting effects of trazodone. At baseline, polysomnographic data of patients with depression with insomnia indicated decreased sleep efficiency, reduced total sleep time and total sleep period, early morning awakening, and sleep latency. In a subsequent acute, placebo-controlled crossover study, trazodone, 100 mg/day, was administered to these patients with depression and polysomnographic data were collected again. All measures improved in the trazodone group, including subjective reporting of quality of sleep, affectivity, numerical memory, and somatic complaints.

Patients with DSM-IV MDD who have been successfully treated with selective serotonin reuptake inhibitors (SSRIs) but continue to have persistent insomnia may also benefit from adjunctive therapy with a nonbenzodiazepine hypnotic, such as zolpidem or zaleplon. Used in combination with SSRIs (fluoxetine, sertraline, or paroxetine), zolpidem, 10 mg/day, has demonstrated improved sleep, greater sleep quality, and reduced number of awakenings and less daytime sleepiness compared with placebo.

One of the risks posed by targeting the antidepressant in such a way that its side effect is helpful is that the side effect may persist even after it is no longer helpful. Additionally, despite the data presented above, the sleep-promoting effects of antidepressants have not been clearly established, especially at different doses. For this reason, selecting a hypnotic with clearly established dose-response effects to treat the sleep problem specifically in a short-term time frame may be the preferable strategy.

Wake-Promoting Agents

Antidepressants that appear to enhance wakefulness include several TCAs (clomipramine, desipramine, and protriptyline), the monoamine oxidase inhibitors (MAOIs) including moclobemide, and escitalopram and some of the other SSRIs. The exact effect of these agents on sleep and wakefulness has not been well quantified in studies of sleep and depression. Again, using antidepressants that have a side-effect profile that promotes the desired sleep outcome may pose the risk of reversing the sleep problem during continuing treatment.

Responders to a single dose of bupropion SR, 150 mg/day, in one study showed an increase in REM sleep latency, whereas nonresponders showed a decrease in REM sleep latency. In this randomized, crossover, double-blind study, 20 patients with unipolar MDD were monitored by EEG at baseline and then during two 2-night sessions a week apart. Patients then received 8 weeks of open-label treatment with bupropion SR. Changes in REM latency were correlated with depression ratings, indicating a possible link via dopamine receptor-mediated effects or by noradrenergic mechanisms.

Although escitalopram has shown robust efficacy in the treatment of depression compared with placebo, insomnia has been reported to occur at a greater rate than with placebo. The wake-promoting effects of escitalopram, then, may be an appropriate treatment option for patients suffering from depression with somnolence.

Studies have explored the possibility of adding the older stimulants such as the amphetamines or methylphenidate to antidepressant treatment. These studies have
generally not looked carefully at the role of these stimulants in enhancing alertness and executive function; instead, they more closely examined these agents in achieving enhanced efficacy in patients with refractory depression on antidepressant treatment. Although some adjunctive effects were noted when these agents were used as add-on agents, these studies unfortunately suffer from various methodological pitfalls. In addition, these older agents have been associated with various side effects including blood pressure abnormalities and the precipitation of mania.

A more recent study has explored the utility of modafinil, a nonstimulant wake-promoting agent, as an augmenting treatment for fatigue and sleepiness in depression. In this double-blind, placebo-controlled trial by DeBattista and colleagues, modafinil, 100–400 mg/day, was administered as an adjunct treatment for fatigue and sleepiness in 136 patients with DSM-IV MDD who responded inadequately to antidepressant therapy. Results showed a rapid reduction in sleepiness scores at week 1 (p < .01) and fatigue scores at week 2 (p < .05) in the modafinil group compared with the placebo group. At week 6, however, the differences were not statistically significant. Modafinil, which has been approved by the U.S. Food and Drug Administration for the treatment of excessive daytime sleepiness associated with narcolepsy, was well tolerated in these patients taking a variety of antidepressants, but there was no impact on overall depression scale scores.

Additionally, in a retrospective case series, 7 patients with treatment-resistant depression (4 with DSM-IV MDD and 3 with DSM-IV bipolar depression) and fatigue and excessive daytime sleepiness had low doses of modafinil, 100–200 mg/day, added to their antidepressant treatment. All 7 patients achieved rapid (within 1 to 2 weeks) and full or partial remission of the depressive symptoms (5 of 7 achieved a 50% reduction in HAM-D score) as well as decreased fatigue and sleepiness. Controlled trials with larger cohorts are warranted to better define the role of modafinil in sleepiness associated with depression.

Other Strategies

In addition to pharmacologic agents, behavioral strategies can also be effective in diminishing sleep disturbances. Many patients with depression engage in behaviors that ultimately disturb nighttime sleep, such as napping during the day and consuming large quantities of alcohol at bedtime and caffeine during the day. Sleep hygiene education, i.e., discussing the conditions and practices that promote continuous and effective sleep, may be useful in a depressed population (Table 2).

Bright light therapy may also be of assistance in restoring proper sleep-wake cycling. Currently, light therapy is primarily administered as first-line treatment for depression associated with seasonal affective disorder. Light therapy is thought to regulate the circadian system and, when used in conjunction with antidepressant treatment, has been more effective than placebo in treating depression.

If some of these sleep manipulations and pharmacologic strategies prove to be unhelpful, then clinicians may want to consider expanding the scope by asking questions regarding other primary sleep disorders, including sleep apnea syndrome, periodic limb movements, and other disorders for which a polysomnographic study may be helpful.

**EFFECTS OF ANTIDEPRESSANTS**

Studies of the effects of antidepressants on the sleep of healthy individuals help document the incidence of sleep disturbances that occur as a result of the medication. One of the best-documented effects of antidepressants on sleep is the suppression of REM sleep, as measured by prolongation of REM latency and a reduction of REM time and percentage. Even though REM sleep time may be decreased, the density of REM periods may increase during antidepressant therapy. In addition, REM sleep time is redistributed into the later hours of the night, which leads to some patients reporting increased dreaming or nightmares. TCAs, MAOIs, and SSRIs all suppress REM sleep. Because there is a high prevalence of REM sleep disturbances in severe depression, REM sleep suppression is viewed as a critical factor in antidepressant action.

**SUMMARY**

The sleep process is complicated and the consequences of nonrestorative sleep are many. Reduced alertness, diminished reaction time, and reduced energy affect quality of life and frequently lead to impairments in social and occupational daytime functioning. Because sleep disturbances are a common symptom of depression, it is important for clinicians to recognize and treat sleep problems along with the depression.

Ensuring proper diagnosis is a logical first step to treating patients with depression and sleep problems. Sleep hygiene education and administration of antidepressant agents that address both the depression and the sleep problem are effective treatment strategies. Stimulating or activating agents or nonstimulant wake-promoting agents have
been the most effective treatment for somnolence and fatigue in depression. While modafinil, a wake-promoting agent, has shown some promise in treating fatigue in patients with depression, more controlled trials are needed to better define its role. Antidepressants that have a sedating effect, and which may be useful in depressions complicated by insomnia, include mirtazapine, nefazodone, trazodone, and some TCAs. Short-acting nonbenzodiazepine hypnotics (i.e., zolpidem and zaleplon) have been effective as adjunct therapy to antidepressants in the treatment of insomnia associated with depression. Bright light therapy may also be an effective adjunctive treatment for patients with depression who have concomitant circadian sleep problems.

**Drug names:** amitriptyline (Endep, Elavil, and others), bupropion (Wellbutrin and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan, Zonalon, and others), esctalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), methylenephedine (Ritalin, Concerta, and others), mirtazapine (Remeron), modafinil (Provigil), nefazodone (Serzone), paroxetine (Paxil), protriptyline (Vivactil), sertraline (Zoloft), trazodone (Deseryl and others), trimipramine (Surmontil), zaleplon (Sonata), zolpidem (Ambien).

**Disclosure of off-label usage:** The author of this article has determined that, to the best of his knowledge, amitriptyline, doxepin, mirtazapine, nefazodone, trazodone, trimipramine, zaleplon, and zolpidem are not approved by the U.S. Food and Drug Administration for the treatment of sleep disturbance in major depressive disorder; bupropion, clomipramine, desipramine, methylphenidate, and moclobemide are not approved for the treatment of sedation in major depressive disorder; and modafinil is not approved for the treatment of fatigue and sleepiness in major depressive disorder.

**REFERENCES**

1. Lyznicki JM, Doege TC, Davis RM, et al. Sleepiness, driving, and motor vehicle crashes. JAMA 1998;279:1908–1913
45. Loving RT, Kripke DF, Shuchter SR. Bright light augments antidepressant effects of medication and wake therapy. Depress Anxiety 2002;16:1–3