Treatment Issues Related to Sleep and Depression

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In the management of depression, the role of sleep and sleep disturbances is important for several reasons. The same neurotransmitter systems that regulate mood, interest, energy, and other functions that may be disturbed in depression also regulate sleep. Sleep disturbances may be responsive to treatment with some antidepressants and may be worsened during treatment with other antidepressants. Serotonergic neurons play a critical role in modulating the onset and maintenance of sleep, and it is thought that insomnia in depression is caused by dysfunction of serotonergic systems. For a significant minority, SSRIs can have negative effects on sleep patterns resulting in insomnia that requires concomitant sedatives or anxiolytics. By contrast, agents that block the serotonin type 2 (5-HT_2) receptor have beneficial effects on depressive insomnia. For example, a recent 8-week study comparing the effects of nefazodone and fluoxetine on sleep disturbances in outpatients with nonpsychotic depression and insomnia found that fluoxetine was associated with approximately a 30% increase in the number of nocturnal awakenings whereas nefazodone was associated with about a 15% decrease, a net difference of 45%. Long-term studies must be conducted to determine whether sleep benefits provided by the newer antidepressants will continue past the acute treatment phase.

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The role of sleep and sleep disturbances in the management of depression is important at several levels. At the simplest level, we spend almost one third of our lives asleep. At another level, the same neurotransmitter systems that regulate mood, interest, energy, and other functions that may be disturbed in depression also regulate sleep. The possibility of a sleep debt resulting from persistent insomnia causing impairment in attention and concentration and/or a lowering of mood is a credible hypothesis. Sleep disturbances may be responsive to treatment with some antidepressants and be iatrogenic side effects of other antidepressants. Epidemiologic and neurophysiologic consequences of sleep disturbances are also important. Sleep abnormalities may predict an ensuing onset of depression and be the presenting symptom in depressive episodes; 80% of patients with major depressive disorder have sleep problems.[1] In a prospective study of nondepressed subjects from the general population,[2] complaints of persistent sleep disturbances were risk factors for the onset of depression within 1 year. In patients with major depressive disorder, a complaint of insomnia is one predictor of suicide during the coming year.[3] Thus, sleep disturbances are not trivial; they can disrupt the timing of neurotransmitter and neuroendocrine release, exacerbate a negative mood, bring about a poor performance, and disrupt social schedules that keep biological rhythms entrained. Accordingly, the clinical relevance of sleep disturbances and the effects of antidepressants on sleep are important considerations in the treatment of depression.

POLYSOMNOGRAMS IN HEALTH AND DEPRESSION

The best way to study sleep scientifically is by recording EEG activity (polysomnograms). These recordings document transitions from waking to the deepest stages of slow-wave, non–rapid eye movement (NREM) sleep and the periodic shifts into more active rapid eye movement (REM) sleep. NREM is divided into 4 sleep stages on the basis of visually scored EEG patterns.[4] Major characteristics of healthy sleep architecture include the generalized slowing of EEG activity that distinguishes the transition from drowsiness to light stage 1 sleep, the emergence of sleep spindles and K-complex waves that accompany the onset of deeper stage 2 sleep, and the loping, desynchronized slow delta waves that define sleep stages 3 and 4. Physical functions are markedly reduced in NREM sleep, particularly in stages 3 and 4, and the decrease in physical activity is presumed to have a restorative function. Stage 1 is a brief transitional state between wakefulness and sleep and is the lightest stage of sleep. Most sleep time is spent in stage 2, in which the muscle tone is somewhat lower

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than in stage 1. Stages 3 and 4 (delta sleep or slow-wave sleep) are the deepest levels of NREM sleep. The greatest amount of slow wave sleep occurs during the first NREM interval. After 2 or 3 REM-NREM cycles, there is little deep sleep and lighter stages predominate.

REM sleep periods typically follow the orderly transition from light to deep sleep and occur at 90-minute intervals across the night. Thus, a healthy night's sleep usually includes 4 or 5 REM periods. The time interval between the onset of sleep and the first REM period is called the REM latency. This construct is of interest because it simultaneously measures the propensity toward deep sleep (which typically precedes the first REM period) and the "pressure" toward the onset of REM sleep. REM sleep tends to be more intense during the last third of the night and is associated with dreaming and physiologic arousal, yet paralysis of skeletal muscle. During REM sleep, the activated EEG patterns are close to aroused waking patterns. REM sleep disturbances are important because they are associated not only with physiologic arousal but also with an increased intensity of waking dysphoria, as seen in depression and posttraumatic stress disorder.[4,5]

The sleep patterns of a depressed person can be markedly different from those of a nondepressed person and may involve disturbances of any stage of the sleep cycle. A glossary of terms used to describe polysomnographic disturbances associated with depressive disorders are summarized in Table 1. Sleep patterns of depressed persons include difficulty in falling and/or staying asleep, decreased deep sleep, and increased amount or intensity of REM sleep. A large majority of severely depressed patients manifest at least several of the following EEG disturbances: poor sleep efficiency, decreased slow-wave sleep, reduced REM latency, and increased REM activity.[1,6] REM sleep disturbances are most pronounced during the first third of the night. However, these features are not specific to depression and may occur as isolated false positives in healthy individuals as well as in patients with schizophrenia, obsessive-compulsive disorder, alcoholism, and other dysphoric states.

Longitudinal studies of EEG sleep profiles in patients with depression suggest that some disturbances—notably REM density and poor sleep efficiency—are reversible or state-dependent abnormalities; other features, such as decreased slow-wave sleep, seem to be persistent or traitlike.[6] As will be discussed subsequently in more detail, a number of antidepressants distort sleep architecture by suppressing REM sleep and delaying the onset of the first REM period by 60 or 90 minutes or even longer. To eliminate the potential confounds of medications and identify traitlike or state-independent (type 1) subgroups and those predicted to be reversible or state-dependent (type 2) subgroups, the sleep profiles of depressed patients before and after 16 weeks of cognitive-behavioral therapy (CBT) were examined.[7] Type 1 sleep disturbances (reduced REM latency, decreased delta sleep ratio, and decreased slow wave) were stable, as predicted, across time. A composite measure of type 2 disturbances, based on REM latency, sleep efficiency, and REM density, improved significantly, although nearly 50% of patients in remission had persistent abnormalities. It was concluded that EEG sleep correlates of depression can be disaggregated into state-independent and partially reversible subgroups, and that modern forms of psychotherapy likely have significant neurobiological effects.

Table 1. Glossary of Terms Used to Describe Polysomnographic Disturbances Associated With Depressive Disorders[a]

Term	Definition
Delta sleep ratio	The ratio of computer-scored delta wave counts in the first and second NREM periods. Normally, values exceed 1.1. Lower values have been associated with an increased risk of recurrent depression
Hypersomnia	Sleeping more than 1 hour longer each night than what is considered normal by the individual
Phase delay disorder	A significant delay of the sleep-wake cycle in relation to the other circadian rhythms
REM activity	The phasic activity of visually scored REM sleep (as measured minute by minute using a scale of 0 to 8)
REM density	The average phasic activity within each minute of visually scored REM sleep. Abnormal elevations are typically > 1.5 units
REM latency	The number of minutes from the onset of stage 2 sleep to the onset of the first period of visually scored REM sleep. Reduced values are typically below 65 minutes in younger patients and 50 minutes among elders
Sleep efficiency	The percentage of time spent asleep during the all-night recording period. Ideally, values should exceed 90% (older) to 95% (younger age groups)
Sleep latency	The number of minutes it takes from "lights out" to reach stage 2 sleep
Sleep maintenance	Sleep efficiency recalculated after excluding sleep latency
Slow-wave sleep	Visually scored sleep stages 3 and 4. Ideally, greater than 10% (younger) or 5% (older age groups)

[a]From Thase,[5] reprinted with permission. Abbreviations: NREM = non–rapid eye movement, REM = rapid eye movement.

ANTIDEPRESSANT EFFECTS ON SLEEP

Serotonergic tracts emanating from the dorsal raphe nucleus mediate neurobehavioral response systems that are involved in both consummatory (appetitive) and inhibitory (quieting or calming) behaviors. The greatest density of slow waves during deep sleep is observed in serotonergically innervated areas of the prefrontal cortex. It is thought that insomnia in depression is caused by a deficiency of inhibitory serotoninergic tone, although deficits of other neurotransmitters (e.g., gamma aminobutyric acid) and excesses of yet others (e.g., corticotropin-

releasing hormone) may be implicated. There are differences among the various subtypes of serotonin receptors, however, and stimulation of serotonin-2 (5-HT_2) receptors also can increase nocturnal awakenings.[4] Serotonergic neurons also play a critical role in modulating the onset and maintenance of REM sleep.[3,5] Serotonergic neurons projecting to the pons tonically inhibit the cholinergic neurons from firing. This effect may block, inhibit, or delay the onset of REM sleep. Thus, a deficit of 5-HT, either inherited or acquired, may cause both a disinhibition of REM sleep and a diminution of slow-wave sleep. Depressed individuals and those at high risk for depression, for example first-degree relatives of affected patients, also appear to have hypersensitivity to cholinergic agonists.[7,8]

Antidepressants with varying modes of pharmacologic activity may produce different effects on sleep patterns. To date, there are more than 2 dozen antidepressant agents that are thought to work by 7 different pharmacologic mechanisms.[9] The 7 mechanisms include 2 that may be termed classic and 5 that are new. The 2 classic mechanisms of action are those of TCAs (tricyclic antidepressants), e.g., amitriptyline, and MAOIs (monoamine oxidase inhibitors), e.g., phenelzine. The TCAs primarily inhibit reuptake of norepinephrine and—to a relatively lesser extent—norepinephrine, although they also have potent effects on histaminic, cholinergic, and α-adrenergic receptors. The MAOIs are relatively devoid of receptor effect but increase serotoninergic, noradrenergic, and dopaminergic neurotransmission by inhibiting the metabolism of these neurotransmitters. The 5 newer categories include (1) SSRIs (selective serotonin reuptake inhibitors), e.g., fluoxetine; (2) selective SNRIs (dual serotonin and norepinephrine reuptake inhibitors), e.g., venlafaxine in medium-to-high doses; (3) SARIs (serotonin-2 antagonist/reuptake inhibitors), e.g., nefazodone; (4) NDRIs (norepinephrine and dopamine reuptake inhibitors), e.g., bupropion; and (5) NaSSAs (noradrenergic and specific serotonergic antidepressants), e.g., mirtazapine, which also has α_2-antagonist properties.

Most antidepressants, including TCAs, MAOIs, SSRIs, and venlafaxine, suppress REM sleep.[10] It was initially thought that antidepressants had to have REM-suppressing qualities to be clinically effective, although this hypothesis has now been rejected.[6] The first generation of antidepressants—the TCAs and MAOIs—have potent effects in suppressing REM sleep, variable effects in restoring sleep efficiency disturbances, and typically little or no effect in restoring slow-wave sleep. Some of the newer antidepressants have comparable efficacy yet have little or no REM-suppressing effects, which indicates that there are likely multiple pharmacologic pathways for the treatment of depression.

The SSRIs, now the most commonly prescribed class of antidepressants throughout most of the world, have variable effects on subjective reports of sedation and insomnia. Although there are modest differences between the 5 members of this class, approximately 10% to 15% of patients treated with an SSRI are likely to complain initially of sedation or insomnia. Objective effects of SSRIs on sleep patterns include increased sleep latency, increased wakefulness, decreased sleep efficiency, increased arousals, increased REM latency, and decreased total REM time.[11–13] To counteract the effects of SSRIs on sleep, a significant minority of patients receiving SSRIs are prescribed concomitant sedatives or anxiolytics. Data from a 1993 retrospective drug utilization review[14] using Texas Medicaid data found that 35% of 30,000 patients receiving SSRIs also received a sedative or anxiolytic agent. Although symptomatically beneficial, the use of adjunctive therapy may reduce compliance with antidepressant medications by increasing the complexity of the medication regimen. Moreover, once a regular pattern of sedative-hypnotic use is established, it may be difficult to discontinue.

Two small studies of the effects of venlafaxine on sleep patterns have been reported in normal volunteers[15] and in depressed patients.[16] Both studies suggest that venlafaxine has sleep effects similar to the SSRIs. Since norepinephrine reuptake inhibitors such as nortriptyline or desipramine also may fractionate or lighten sleep at clinically significant doses, the likely possibility is that when venlafaxine dosage is increased, the norepinephrine effects may further lighten sleep.

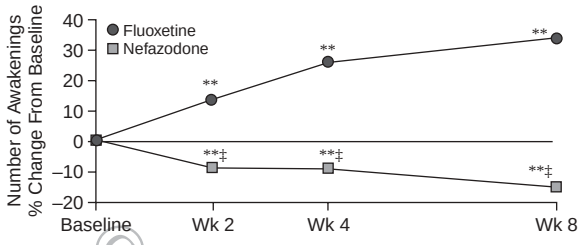
Mirtazapine appears to have significantly different effects on EEG sleep when compared with SSRIs or venlafaxine.[5] At lower doses (e.g., 15 mg/day), the prominent antihistaminic effects of mirtazapine may result in nonspecific sedative effects. In a study of a single dose of mirtazapine given to 6 subjects,[17] mirtazapine significantly shortened the time to onset of sleep, and stage 1 sleep was reduced while the amount of deep sleep was significantly increased. In addition, mirtazapine significantly increased the latency of REM sleep and reduced nighttime wakening. It is possible that, at higher doses, additional effects resulting from potentiation of noradrenergic or serotoninergic neurotransmission may result in REM suppression.[5]

Bupropion also appears to have unique effects on polysomnographic profiles.[6] A study comparing the effects of bupropion, fluoxetine, and CBT in remitted depressed men[18] revealed that REM latency was reduced while percentage of REM sleep and amount of time in REM sleep increased in 7 bupropion-treated patients. These effects contrasted with the effects of fluoxetine, CBT, and other antidepressants that cause REM suppression and prolongation of REM latency. It is speculated that a paired effect on norepinephrine and dopamine may result in a REM enhancing effect.

TREATMENT OF THE PATIENT WITH INSOMNIA

Disparity in the number of nocturnal awakenings that occur with various antidepressant treatments can have profound implications and serves as a dramatic example of the

Figure 1. Effects of Nefazodone and Fluoxetine on Objective Sleep Measures: Number of Awakenings[a]



[a]From Rush et al,[19] with permission. Nefazodone baseline (mean = 25.8), N = 59; fluoxetine baseline (mean = 22.1), N = 57.
**p ≤ .01 compared with baseline.
‡p ≤ .01 compared with fluoxetine.

functional significance of physiologic differences between various types of antidepressants. These differences are illustrated by a large comparative study examining the effects of nefazodone and fluoxetine on sleep disturbances in outpatients with unipolar nonpsychotic major depressive disorder and insomnia.[19] Three identical, multisite, randomized, double-blind trials compared sleep patterns of 62 nefazodone-treated patients (mean dose = 424 mg/day) with 60 fluoxetine-treated patients (mean dose = 32 mg/day). Polysomnograms and clinical ratings of the effects of nefazodone and fluoxetine on sleep were evaluated, as well as the timing of those effects over an 8-week, acute-phase treatment period. Overall, the 2 antidepressants were equally effective, and subjective complaints of insomnia, as a treatment-emergent adverse event, did not differ significantly between nefazodone and fluoxetine. However, fluoxetine was associated with approximately a 30% increase in the number of nocturnal awakenings compared with about a 15% decrease in nefazodone-treated patients, making a net difference of 45% between the 2 drugs (Figure 1). Similar statistically significant differences were observed on other measures of sleep continuity, such as sleep efficiency. A difference in total sleep time of nearly 30 minutes per night was observed, even though fluoxetine and nefazodone had similar effects on sleep latency (i.e., the time it takes to fall asleep).

Polysomnograms also revealed that fluoxetine suppressed REM sleep, prolonged REM latency, decreased the percentage of REM sleep, and increased the amount of light stage 1 sleep when compared with nefazodone. Clinician- and patient-rated assessments of sleep symptoms similarly revealed significant differences favoring nefazodone. Overall, the differential effects of nefazodone versus fluoxetine on both objective and clinician- and patient-rated assessments of sleep were consistent with the notion that those antidepressants may have different modes of action.

The nefazodone versus fluoxetine sleep comparison ended after the eighth week of treatment, and, as a result, it is not clear if the differences were sustained. This is important because a chronic sleep debt associated with decreased total sleep time or increased nocturnal awakenings might eventually result in complaints of fatigue, daytime sleepiness, or cognitive decrements. A longer-term comparison of the effect of these drugs on sleep is needed. Also, it is not certain that these results would directly apply to comparisons of other SSRIs, including citalopram, paroxetine, and sertraline.

TREATMENT OF THE PATIENT WITH HYPERSOMNOLENCE

Oversleeping, or hypersomnolence, is relatively more common among young patients, particularly women, and patients of both sexes with bipolar disorder.[20,21] Like the clinical response to antidepressants, the polysomnograms of patients with hypersomnolence are different compared with those of classically melancholic patients. Patients with atypical depression sometimes have completely normal profiles in the sleep laboratory, possibly because they are awakened relatively early in the morning. If allowed to sleep to the point of satiety, there are clear indications of long total sleep time. Slow wave sleep is relatively spared, and, across a long night of sleep, these patients may have more REM sleep than normal individuals because their longer sleep time results in 1 or 2 more REM sleep periods. Elsewhere, I have suggested that hypersomnolence may be a homeostatic response to compensate for a diminution of the restorative effects of sleep.[6]

There have been no comparative studies of SSRIs, bupropion, or MAOIs (i.e., antidepressants most commonly prescribed for such patients) on hypersomnolence. One would predict that effective treatment would result in a decrease in total sleep time, but no major change in sleep architecture. Clinical experience would suggest that more sedating TCAs and mirtazapine are not preferred treatments for hypersomnolent patients. It is not clear if nefazodone should be grouped with these less preferred agents or if its effects on polysomnograms would have a more normalizing effect for hypersomnolent patients.

BEHAVIORAL STRATEGIES TO MANAGE SLEEP DISTURBANCES

Sleep disturbances in patients with depression also can be managed by behavioral strategies.[22] General guidelines to improve sleep include maintaining regular sleep/wake habits, avoiding naps, having a light snack before bedtime, refraining from exercise or heavy meals within 1 hour of bedtime, restricting caffeine, avoiding late night or shift work, and maintaining a cool, dark, and quiet sleeping area (Table 2).[3] Additionally, using deep muscle relaxation and other forms of progressive relaxation may help individuals to fall asleep more quickly. Although these meth-

Table 2. Strategies for Alleviating Sleep Disturbances[a]

Maintain regular sleep/wake habits
Avoid naps
Eat a light snack before bedtime
Refrain from exercise or heavy meals within 1 hour of bedtime
Restrict caffeine
Avoid late night or shift work
Maintain a cool, dark, quiet sleep area

[a]Adapted from Gillin et al.[3]

ods are not widely known to physicians, controlled studies suggest effects as strong as, and with greater durability than, those observed with sedative hypnotics.

CONCLUSION

Sleep disturbances are common in patients with depression; they are intimately related with the pathophysiology of depression, are divisible into traitlike and state-dependent subgroups, and respond differentially to various antidepressants. Sleep patterns of depressed persons are markedly different from those of nondepressed persons and may involve disturbances to any stage of the sleep cycle. In the past, it was thought that antidepressants had to have REM-suppressing qualities to be clinically effective. However, some of the newer antidepressants have little or no REM-suppressing effects, which indicates that there are likely multiple pharmacologic pathways for the treatment of depression. In an 8-week study of 122 nonpsychotic depressed patients with insomnia, nefazodone improved many sleep parameters that were worsened by treatment with fluoxetine. Long-term studies are needed to determine if antidepressants that improve sleep efficiency during the acute treatment phase will continue to exert beneficial sleep effects over time.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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