Antidepressant Treatment of the Depressed Patient With Insomnia

Michael E. Thase, M.D.

Sleep disturbances are an integral part of depressive disorder. As such, they are a part of all contemporary sets of diagnostic criteria for major depression and of all major symptom-based rating scales for depression. Insomnia is a particularly frequent complaint, and it is reported by more than 90% of depressed patients. Although the "kindling" or "illness transduction" model of depression remains hypothetical, there is evidence that people with recurrent depression have more pronounced abnormalities of sleep neurophysiology than those experiencing a single or initial episode. Therefore, early relief of insomnia in a depressed patient, in addition to alleviating other symptoms, may increase adherence to treatment and increase daytime performance and overall functioning, while complete relief of insomnia may improve prognosis. Stimulation of serotonin-2 (5-HT_2) receptors is thought to underlie insomnia and changes in sleep architecture seen with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). This is the reason why hypnotics or low-dose trazodone are commonly coprescribed at the initiation of the treatment with either the SSRIs or SNRIs. On the other hand, antidepressant drugs with 5-HT_2 blocking properties, such as mirtazapine or nefazodone, alleviate insomnia and improve sleep architecture. In depressed patients, mirtazapine produces a significant shortening of sleep-onset latency, increases a total sleep time, and leads to a marked improvement in sleep efficiency. Antidepressants with preferential 5-HT_2 blocking properties are therefore a good treatment option for depressed patients with marked insomnia.

(J Clin Psychiatry 1999;60[suppl 17]:28–31)

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Sleep disturbances are a common feature of depressive disorders. They are also a key diagnostic criteria for major depression and feature in all the commonly used symptom-based rating scales for depression. It is therefore important when prescribing an antidepressant agent to consider the possible effects of therapy on sleep patterns and disorders.

Insomnia is the sleep disturbance that is frequently reported in depression, occurring in over 90% of depressed patients.[1] Persistent insomnia is difficult for the depressed patient to cope with and can impair daytime functioning. Relief of insomnia can increase daytime performance and greatly improve the depressed patient's general functioning and quality of life. Early relief of insomnia may also improve compliance with the treatment regimen, thereby improving the overall efficacy of treatment, and complete relief from insomnia may improve the patient's prognosis. However, it is thought that the use of adjunctive therapy for insomnia with sedative-hypnotics may reduce the patient's compliance with the regimen. Thus, a single antidepressant agent that alleviates both depression and sleep disorders may prove to be a more useful treatment option than an antidepressant that requires concomitant sedative therapy.

PATTERNS OF SLEEP IN NORMAL AND DEPRESSED PATIENTS

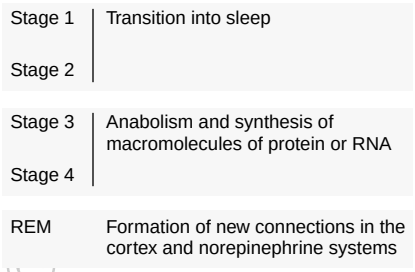
A normal sleep cycle consists of initial stages during which the subject makes the transition from wakefulness to sleep, deeper stages of sleep during which anabolism and synthesis of macromolecules take place, and a stage during which rapid eye movement (REM) takes place and new connections are made in the brain cortex (Figure 1). The sleep architecture observed by an electroencephalographic (EEG) recording made during normal sleep is shown in Figure 2. Normal sleep architecture is characterized by a progression from the generalized slowing of brain activity during stage 1 (light) sleep, spindles and complex waves during stage 2 (deeper) sleep, to slow delta waves during deep sleep (stages 3 and 4). Each sleep cycle terminates with a period of REM sleep during which brain activity increases and dreams occur. Several sleep cycles may occur during the night, and sleep usually becomes lighter as the night progresses.

From the Department of Psychiatry, University of Pittsburgh School of Medicine, and the Western Psychiatric Institute and Clinic, Pittsburgh, Pa.

Presented at the Scientific Expert Meeting, held in Monte Carlo, Monaco, February 26–27, 1999, and sponsored by NV Organon.

Reprint requests to: Michael E. Thase, M.D., Department of Psychiatry, University of Pittsburgh School of Medicine, and the Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

Figure 1. A Normal Sleep Cycle[a]



[a]Abbreviation: REM = rapid eye movement.

The sleep patterns of a patient who is depressed are markedly different from those of a nondepressed subject and may involve disturbances to any of the stages of the sleep cycle. Virtually all depressed patients exhibit poor sleep efficiency, reduced slow-wave sleep, decreased REM latency, and increased REM activity.[2] Typical sleep architecture occurring in depression is shown in Figure 2. It is thought that insomnia in depression is caused by the stimulation of serotonin-2 (5-HT_2) receptors and hence might respond to treatment by 5-HT_2 blockade.

EFFECTS OF ANTIDEPRESSANTS ON SLEEP

The effects of antidepressant therapy on sleep patterns can be marked, and these drug-induced changes have been subject to thorough investigation.

Selective Serotonin Reuptake Inhibitors

The use of selective serotonin reuptake inhibitors (SSRIs) can have a profound effect on sleep patterns. These agents act by selectively inhibiting the reuptake of serotonin (5-HT), and insomnia and agitation are common side effects. The sleep architecture associated with SSRI use is shown in Figure 2. In a study in which the effects of the SSRI paroxetine on sleep were compared with those of placebo,[3] there were significant differences in sleep parameters between the 2 groups. After 6 days' treatment with paroxetine, both the actual sleep time and the efficiency of sleep were significantly reduced ($p < .01$). In another study, 61 patients with major depression and insomnia received the SSRI fluoxetine for 8 weeks.[4] Fluoxetine recipients experienced significantly more awakenings, greater time spent awake and moving, and decreased sleep efficiency compared with baseline.

To counteract the effects of SSRIs on sleep architecture, patients receiving SSRIs are frequently prescribed concomitant sedatives or anxiolytic agents. A retrospective drug utilization review carried out using Medicaid data for Texas in 1993[5] found that 35% of 30,000 patients receiving SSRIs also received a sedative or anxiolytic agent. In all, 41.7% of paroxetine recipients, 35.8% of sertraline recipients, and 33.1% of fluoxetine recipients were prescribed concomitant sedatives or anxiolytics. However, it is thought that the use of adjunctive therapy can reduce compliance with an antidepressant regimen and may therefore reduce the overall efficacy of an SSRI regimen.

Venlafaxine

The antidepressant venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has a dual mode of action. It inhibits the reuptake of both serotonin and norepinephrine. The effects of venlafaxine on sleep were investigated by observing the sleep patterns of 8 normal subjects who received venlafaxine for 4 consecutive nights.[6] Venlafaxine significantly increased both the wake time (Figure 3) and stage 1 sleep ($p < .001$) compared with baseline. Sleep stages 2 and 3 were significantly reduced during treatment. Furthermore, REM sleep was significantly reduced to such an extent that it was completely suppressed in all volunteers by the fourth night of treatment (Figure 4). Thus, the SNRI venlafaxine was found to have a marked effect on sleep architecture.

Nefazodone

Nefazodone is an antidepressant that has potent 5-HT_2 receptor blocking activity and also inhibits 5-HT reuptake. The effects of nefazodone on sleep were compared with those of the SSRI fluoxetine in an 8-week, randomized study conducted in outpatients with major depression and insomnia.[4]

Nefazodone progressively improved both the number of awakenings and sleep efficiency, whereas both of these measures worsened during fluoxetine treatment (Figures 5 and 6). Furthermore, nefazodone significantly increased the total REM sleep time, whereas fluoxetine suppressed REM sleep. Nefazodone was found to have similar antidepressant efficacy to that of fluoxetine but, unlike fluoxetine, generally improved sleep architecture. It is thought that nefazodone's ability to block 5-HT_2 receptors is responsible for its beneficial effects on sleep patterns.

Mirtazapine

Mirtazapine is a novel antidepressant, known as a noradrenergic and specific serotonergic antidepressant (NaSSA). It is an antagonist of presynaptic α_2-autoreceptors and α_2-heteroreceptors, resulting in an increased release of both norepinephrine and serotonin, and it also enhances noradrenergic and serotonergic neurotransmission. In addition, mirtazapine potently blocks 5-HT_2 and 5-HT_3 receptors. The effects of a single dose of mirtazapine on sleep has been studied in 6 human volunteers with normal sleep patterns (Table 1).[7] Compared with placebo, mirtazapine promoted sleep. It significantly shortened the time to onset of sleep, and stage 1 sleep was reduced while the amount of deep sleep significantly increased (Table 1). In addition, mirtazapine significantly increased the latency of REM

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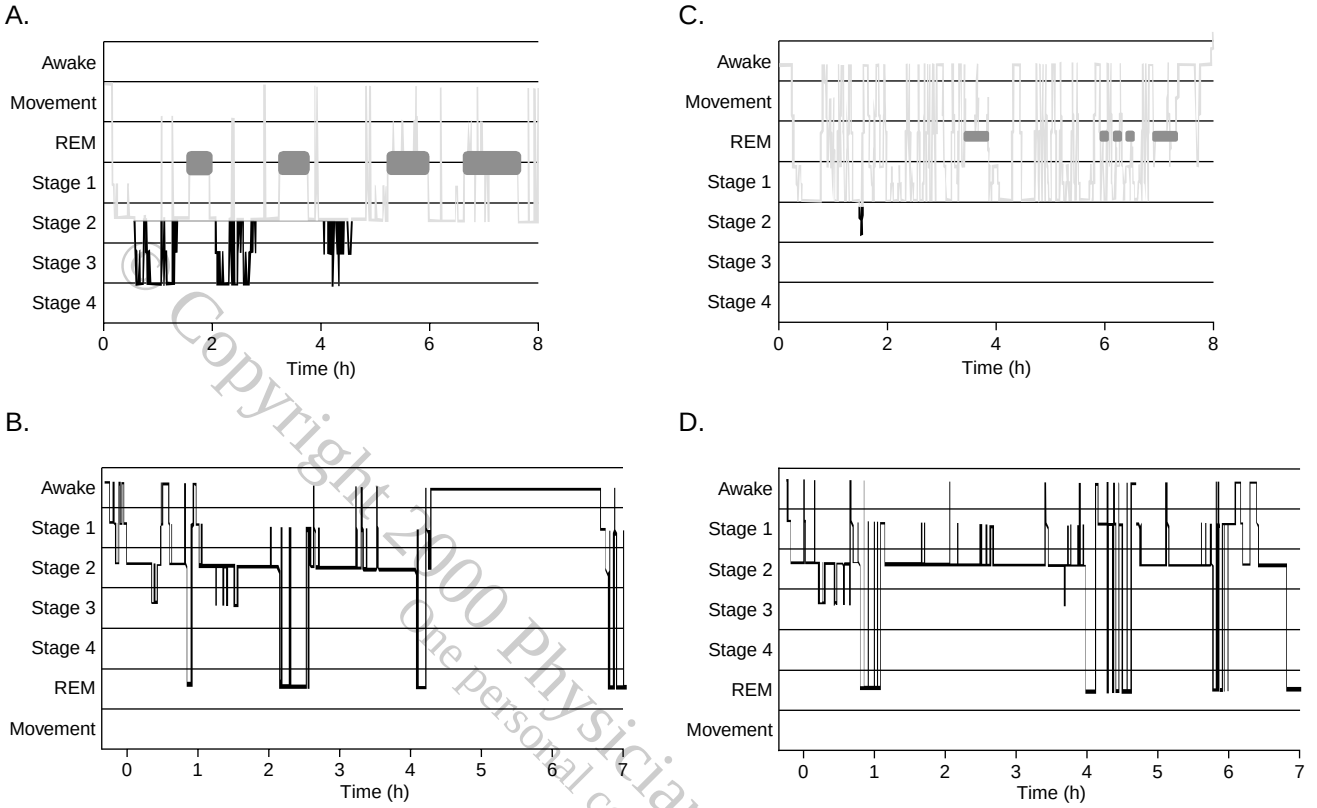
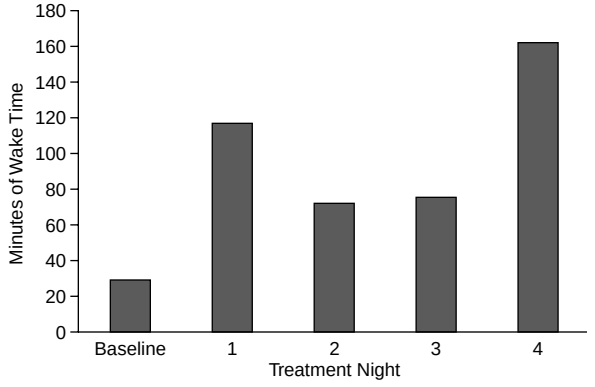
Figure 2. Sleep Architecture in (A) Normal Sleep and (B) Untreated Depression and During Treatment With (C) an SSRI or (D) Mirtazapine[a]



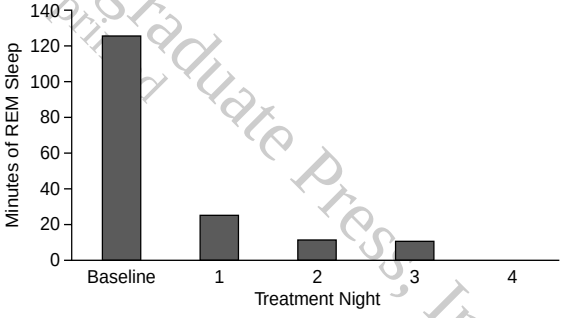
[a]Data for 2C are from reference 4, and data for 2D are from reference 8. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 3. Effect of Venlafaxine on Wake Time[a]



[a]Data from reference 6.

Figure 4. Effect of Venlafaxine on REM Sleep[a]



[a]Data from reference 6.

stage 2 sleep and reduced nighttime wakening. It is thought that mirtazapine's ability to increase deep sleep is also related to its 5-HT_2 receptor antagonism.[7]

Thus, mirtazapine should be able to counteract the detrimental effects of depression on sleep patterns, which include reductions in deep sleep, increases in nighttime wakening, and shortening of REM sleep latency. A recent pilot study was conducted to investigate the effects of mirtazapine on sleep in depressed patients.[8] Five adult patients with major depression and a score of at least 4 for sleep items on the HAM-D received mirtazapine, 15 mg/day, for 1 week, followed by mirtazapine, 30 mg/day, for 1 week. Sleep latency was significantly reduced, and total sleep time and sleep efficiency were significantly increased from baseline ($p < .05$; Table 2). Furthermore, REM sleep parameters were unaltered by mirtazapine treatment.

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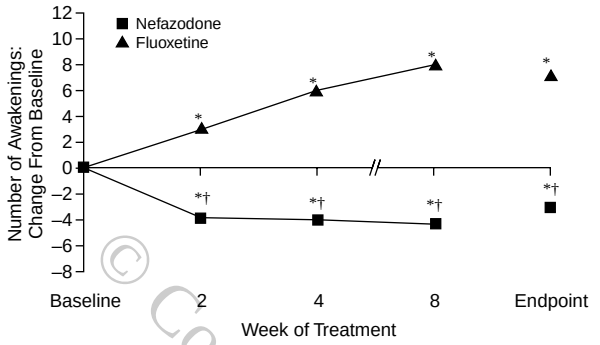
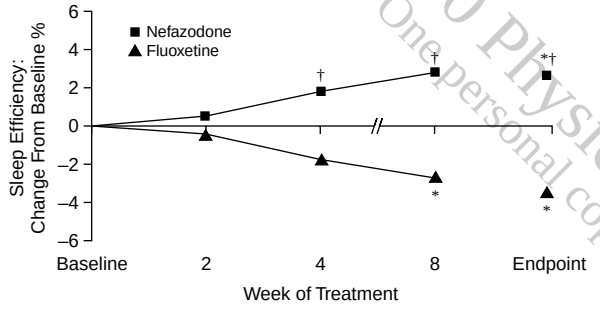
Figure 5. Effect of Nefazodone or Fluoxetine on Awakening[a]



[a]Data from reference 4.
*p < .01 vs. baseline.
†p < .01 vs. fluoxetine.

Figure 6. Effect of Nefazodone or Fluoxetine on Sleep Efficiency[a]



[a]Adapted from reference 4, with permission.
Sleep efficiency (%) = (total sleep time/time in bed) × 100.
*p < .05 vs. baseline.
†p < .01 vs. fluoxetine.

As a result, sleep parameters in depressed patients were improved by mirtazapine treatment, and sleep architecture was preserved (Table 2). Overall, it can be seen that sleep continuity is enhanced by mirtazapine due to a significant shortening of the latency of onset of sleep and a marked increase in total sleep time and sleep efficiency. Further study of larger groups of depressed patients is clearly needed.

CONCLUSIONS

Because sleep disturbances, particularly insomnia, are an integral feature of depression, it is important to consider the effects of antidepressant therapy on sleep architecture. It has been shown, both by subjective and objective measures, that 5-HT_2 blockade improves sleep. Clinical studies have confirmed that antidepressant agents such as mirtazapine and nefazodone, which possess 5-HT_2 blocking properties as part of their pharmacologic profile, are useful treatment options for depressed patients with insomnia.

Table 1. Mean Sleep Parameters With Mirtazapine and Placebo in Normal Volunteers (30-second epoch counts)[a]

Sleep Parameter	Mirtazapine	Placebo
Wakening	18*	124
Stage 1	51*	94
Stage 2	482	419
Stage 3	167*	99
Stage 4	69	62
REM	174	153
Total sleep	942*	836
Latencies		
Stage 1	2*	50
Stage 2	16*	89
REM 0	225	243
REM 1	225	193
REM 2	210*	154

[a]Adapted from reference 7.
*p < .05 vs. placebo.

Table 2. Effect of Mirtazapine on Sleep Parameters in Depressed Patients[a]

		Mirtazapine	
Sleep Parameter	Baseline	15 mg/d	30 mg/d
Sleep latency, min	4.3	4.6*	6.8
Total sleep time, min	356.5	417.8*	409.5*
Sleep efficiency, %	82.0	91.9*	91.2*

[a]Data from reference 8.
*p < .05 vs. baseline.

Drug names: fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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