# Comparative Effects of Mirtazapine and Fluoxetine on Sleep Physiology Measures in Patients With Major Depression and Insomnia

Andrew Winokur, M.D., Ph.D.;
Nicholas A. DeMartinis III, M.D.; Daniel P. McNally, M.D.;
Ellen M. Gary, B.S.N.; Jennifer L. Cormier, M.S.; and Keith A. Gary, Ph.D.

***Background:*** Sleep complaints are common in patients with major depressive disorder (MDD). Both MDD and antidepressant drugs characteristically alter objective sleep measures. This study compares the effects of mirtazapine and fluoxetine on sleep continuity measures in DSM-IV MDD patients with insomnia.

***Method:*** Patients (N = 19) received initial baseline polysomnography evaluations over 2 consecutive nights. Subjects were randomly assigned to either fluoxetine (20–40 mg/day) or mirtazapine (15–45 mg/day) treatment for an 8-week, double-blind, double-dummy treatment trial. Single-night polysomnograms were conducted at weeks 1, 2, and 8, with depression ratings assessed at baseline and weeks 1, 2, 3, 4, 6, and 8. Statistical analysis was performed by repeated-measures analysis of variance followed by Dunnet's post hoc analyses.

***Results:*** Patients receiving mirtazapine (N = 8) had significant improvement in objective sleep physiology measures at 8 weeks. Improvements in sleep latency, sleep efficiency, and wake after sleep onset were significant after only 2 weeks of mirtazapine treatment. No significant changes in sleep continuity measures were observed in the fluoxetine group (N = 11). Both groups improved clinically in mood and subjective sleep measures from baseline, with no differences between groups.

***Conclusion:*** These data demonstrate the differential effects of mirtazapine and fluoxetine, with significant improvement in favor of mirtazapine, on objective sleep parameters in MDD patients with insomnia.

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*Corresponding author and reprints: Andrew Winokur, M.D., Ph.D., Department of Psychiatry, University of Connecticut Health Center, Talcott Notch Road, Farmington, CT 06030-6415 (e-mail: winokur@psychiatry.uchc.edu).*

Sleep complaints are reported in a large percentage of patients with major depressive disorder (MDD).[1] While subjective complaints of insomnia (problems falling asleep, frequent awakenings during the night, early morning awakening, or nonrestorative sleep) represent the most common form of sleep disorder, a subset of depressed patients report hypersomnia, typically associated with anergy, lethargy, and fatigue. The common co-occurrence of mood and sleep disorders has prompted suggestions of a shared diathesis.[2] While alterations in sleep patterns are often conceptualized to represent a biological concomitant of clinical depression, the presence of sleep disturbance has also been proposed to represent a risk factor for the development of depression.[3,4]

During the past 40 years, studies employing the technique of polysomnography have consistently demonstrated alterations in sleep physiology in depressed patients.[4] The most commonly reported alterations in the sleep of depressed patients have included (1) disruption of sleep efficiency measures, (2) diminished slow-wave sleep during the first non–rapid eye movement (NREM) period, and (3) alterations in the timing of rapid eye movement (REM) sleep (most often characterized as shortened latency from sleep onset to the first REM period). Since neurobiological mechanisms regulating REM

have been proposed to include cholinergic, noradrenergic, and serotonergic systems, several investigators have speculated that changes in REM sleep observed in depressed patients may relate to alterations in cholinergic and/or monoaminergic systems.[5–7]

Clinical trials involving antidepressant drugs have demonstrated a range of effects on sleep latency and sleep efficiency as well as on daytime somnolence associated with various antidepressant compounds.[8] From a clinical perspective, agents with a more sedating profile are often preferentially selected for depressed patients reporting complaints of insomnia, whereas more activating antidepressants are typically selected for patients with a presentation of hypersomnia and daytime fatigue.[8] In recent years, studies employing polysomnographic techniques have demonstrated that some antidepressant drugs may produce disruption of sleep physiology measures (manifest by a reduction in sleep efficiency and increases in stage 1 sleep, number of awakenings, and wake time after sleep onset [WASO]). For example, some studies employing the selective serotonin reuptake inhibitor fluoxetine in the treatment of depressed patients have demonstrated this constellation of sleep-disruptive effects.[9–14]

The antidepressant drug mirtazapine has been reported to improve subjective complaints of sleep disturbance in placebo-controlled studies of depressed patients.[15–18] Conversely, 8% to 48% of depressed patients receiving mirtazapine therapy reported daytime somnolence, as compared with 18% of patients randomly assigned to placebo. These clinical trial findings with mirtazapine underscore the importance of polysomnographic studies to delineate its effects on objective measures of sleep physiology. To date, only 1 study has provided such data for mirtazapine based on observations in depressed patients. Winokur et al.[19] studied 6 patients with MDD plus subjective sleep complaints. Polysomnograms were carried out at baseline and at week 1 while patients were receiving open-label mirtazapine, 15 mg/day, and at week 2 while they were receiving mirtazapine, 30 mg/day. Compared with baseline values, mirtazapine administration was associated with a significant decrease in sleep latency and significant increases in total sleep time and sleep efficiency at both week 1 and week 2 of treatment. This study provided the first objective data supporting beneficial effects of mirtazapine on sleep physiology measures in patients with MDD associated with insomnia.

The present report extends the previous observations of Winokur et al.[19] by comparing effects of mirtazapine with effects produced by fluoxetine in an 8-week, double-blind, double-dummy treatment trial in a similar patient population. Polysomnographic evaluations were conducted at baseline and at weeks 1, 2, and 8 of treatment in patients randomly assigned to treatment with fluoxetine titrated up to a dose of 40 mg daily or to mirtazapine titrated to 45 mg daily. Data characterizing clinical response and polysomnographic variables during the course of treatment are presented.

## METHOD

### Patients

Twenty-two patients provided informed consent after detailed review with a research assistant and an investigator of logistical expectations and potential risks associated with study participation in a protocol reviewed and approved by the Institutional Review Board of the University of Connecticut Health Center. Three patients subsequently had to be dropped from inclusion in study participation or data analysis. One patient receiving fluoxetine demonstrated acute exacerbation of depressive symptoms with development of suicidal ideation during week 4 of the treatment protocol and had to be hospitalized for more intensive treatment. A second patient had laboratory findings consistent with obstructive sleep apnea syndrome during the initial baseline screening polysomnogram. This patient was terminated from study participation prior to randomization and referred for evaluation and treatment by means of continuous positive airway pressure. A third patient had technical problems occur during polysomnographic studies that made it impossible to include this subject's data in analysis of the study results. Thus, the findings in this report are based on data obtained from the 19 patients who met entrance criteria as described below and were enrolled and able to complete the entire polysomnographic testing and treatment protocol.

Enrolled patients were required to meet the following criteria: 18 to 75 years of age with a DSM-IV diagnosis of MDD based on a semistructured clinical interview; a score of ≥ 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[20]; and a score of ≥ 4 on the 3 HAM-D sleep items. Patients with a history of primary sleep disorder, significant medical problems, current alcohol or substance abuse or dependence, psychosis, or suicidal ideation and those performing shift work were excluded from the study. Subjects were required to maintain normal sleep/wake schedules with typical bed times of no earlier than 10:00 p.m. and typical rise times no earlier than 6:00 a.m. Similar schedules were maintained in the sleep laboratory. The first baseline night polysomnogram was also used as a screen for gross sleep abnormalities and/or sleep apnea, with subjects excluded from further participation if problems were detected. Psychotropic drugs were discontinued at least 1 week before study initiation, and no subject received any prolonged-acting central nervous system agent during the previous month.

### Treatment

Patients randomly assigned to the mirtazapine group received 15 mg daily of drug for the initial 3 days. The dose was increased to 30 mg daily through the end of week

2 and stabilized at 45 mg daily for the remainder of the study period. All mirtazapine doses were administered at bedtime. Study patients in the fluoxetine group received 20 mg daily for the first 4 weeks and had their dose increased to 40 mg daily during the final 4 weeks of the study. All fluoxetine doses were administered in the morning. During the screening phase from week 1 through week 4, patients were evaluated by means of a semistructured interview using a Structured Clinical Interview for DSM-IV format[21] and severity assessments were determined by means of the 21-item HAM-D and the Clinical Global Impressions scale (CGI).[22] A physical examination including vital signs and electrocardiogram was carried out, and blood and urine samples were obtained for laboratory tests to evaluate the presence of significant medical problems. At baseline, subjects were evaluated by means of 2 consecutive nights of polysomnography. The first night served as an accommodation to the sleep laboratory setting and also was used to screen for the presence of primary sleep disorders such as obstructive sleep apnea or period limb movements of sleep. Subjects who demonstrated the presence of a significant primary sleep disorder were excluded from further study participation. The second baseline polysomnogram served as the baseline assessment for analysis of subsequent treatment effects. All subjects who passed the baseline screening phase were studied with single-night polysomnograms at weeks 1, 2, and 8 of treatment. The baseline HAM-D and CGI ratings were obtained following the second baseline polysomnogram, prior to randomization to treatment. HAM-D and CGI ratings were also obtained at weeks 1, 2, 3, 4, 6, and 8. Patients also participated in multiple sleep latency testing (MSLT) as well as performance vigilance testing (PVT) and subjective assessments of daytime sleepiness by means of the Epworth Sleepiness Scale (ESS).[23] These procedures were carried out at the end of the baseline period after the second polysomnogram and again at weeks 2 and 8. Results for MSLT, PVT, and ESS testing from the present subject group will be combined with results from additional subjects currently being enrolled in this protocol to allow adequate power for data analysis on these measures and will be reported at a later date.

Following the 2 nights of baseline polysomnography and the day of additional laboratory assessments, patients were randomly assigned to a double-blind, double-dummy treatment paradigm with fluoxetine or placebo capsules for fluoxetine administered in the morning and mirtazapine or placebo capsules for mirtazapine administered at bedtime. The decision to administer fluoxetine in the morning and mirtazapine at bedtime was based on standard clinical practice and also followed a similar design employed by Rush et al.[24] in a study comparing effects of fluoxetine and nefazodone on sleep physiology in a similar patient population.

### Data Analysis

Polysomnographic data included total sleep time, sleep efficiency (the ratio of total sleep time to time in bed), and sleep latency (onset to first stage 1) as a priori primary variables and total sleep time, percentage of total sleep time for stages 1, 2, 3, and 4 and REM sleep, and REM latency as a priori secondary variables. Total sleep time measures for stages 1 through 4 were recorded to assess potential sleep stage–specific alterations induced by mirtazapine. Mean, standard deviation, and standard error of the mean were calculated for each parameter across subjects. The means were then compared using InStat statistical software (version 3.01, GraphPad Software, Inc., San Diego, Calif.) by 1-way repeated-measures analysis of variance (ANOVA) at baseline, week 1, week 2, and week 8. The Dunnet test was used for post hoc analysis of parameters achieving statistical significance at $p < .05$.

## RESULTS

### Subjects

Patients in each treatment group demonstrated no significant differences at baseline in depression severity or subjective reports of insomnia symptoms (Table 1). The mirtazapine group differed significantly from the fluoxetine group in the lower proportion of women.

### Mirtazapine Treatment

Patients randomly assigned to the mirtazapine treatment group had mean (SD) baseline HAM-D scores and 3-item sleep scores of 25.6 (7.6) and 4.8 (0.7), respectively. Significant improvement in both measures was reported at 2 weeks (HAM-D: 16.1 [5.7]; sleep items: 2.3 [0.7], and improvement continued through week 8 (HAM-D: 7.1 [3.7]; sleep items: 1.3 [1.8]).

Repeated-measures ANOVA analysis of polysomnographic sleep measures in patients receiving mirtazapine treatment revealed significant improvement in sleep latency ($F = 7.32$, $df = 3,31$; $p = .0015$), total sleep time ($F = 3.22$, $df = 3,31$; $p = .044$), sleep efficiency ($F = 9.49$, $df = 3,31$; $p = .0004$; Figure 1), and WASO ($F = 8.36$, $df = 3,31$; $p = .0008$) after 8 weeks of treatment (Table 2). Measures of sleep latency, sleep efficiency, and WASO indicated significant improvements by week 2 of mirtazapine treatment, and continued improvement in those parameters was observed throughout the remaining study period. No significant changes were observed in individual sleep stages or REM latency.

### Fluoxetine Treatment

Patients randomly assigned to the fluoxetine treatment group had mean (SD) baseline HAM-D scores and 3-item sleep scores of 26.7 (5.3) and 5.2 (0.9), respectively. Significant improvement in both measures was reported at 2 weeks (HAM-D: 18.0 [9.6]; sleep items: 3.5 [2.2], and

Table 1. Patient Characteristics at Baseline

| Variable | Mirtazapine (N = 9) | Fluoxetine (N = 13) |
|---|---|---|
| Gender, N (%) | | |
| Male | 6 (66.7) | 7 (53.8) |
| Female | 3 (33.3) | 6 (46.2) |
| Age, mean, y | 40.9 | 43.5 |
| HAM-D score, mean (SD) | | |
| Total | 25.6 (7.6) | 26.7 (5.3) |
| Sleep items | 4.8 (0.7) | 5.2 (0.9) |

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

improvement continued through week 8 (HAM-D: 12.2 [9.2]; sleep items: 2.9 [2.2]).

Polysomnographic sleep measures in patients receiving fluoxetine treatment indicated no significant changes in sleep latency, total sleep time, sleep efficiency, or WASO throughout the 8-week treatment period (Table 2). Significant alterations in sleep staging ($F = 5.16$, $df = 3,31$; $p = .0054$), however, were observed in this treatment group. Time in stage 1 sleep increased from 38.7 (11.9) minutes at baseline to 67.9 (28.6) minutes at week 8. Similarly, REM latency was significantly prolonged ($F = 3.33$, $df = 3,31$; $p = .033$) by week 2 and remained prolonged at week 8. Although failing to reach statistical significance, total slow wave sleep (stages 3 and 4 combined) trended toward a decrease by the end of the 8-week study period. No significant changes were observed in other individual sleep stages.

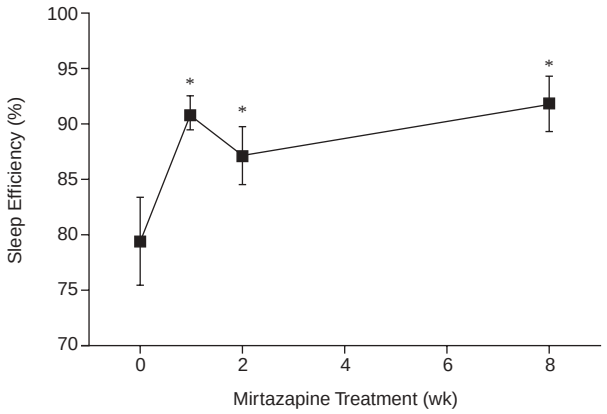
### Mirtazapine vs. Fluoxetine

Improvement in mood and subjective sleep during the course of the 8-week study, as measured by the HAM-D and sleep item scales, did not differ significantly between the 2 groups. Comparison of sleep physiology measures between the mirtazapine and fluoxetine treatment groups revealed a significantly greater improvement in sleep latency (Figure 2) and total sleep time (Figure 3) following mirtazapine treatment. Changes in sleep efficiency tended toward greater improvement in the mirtazapine group; however, results failed to achieve statistical significance. Evaluation of sleep staging variables indicated a significant increase in stage 1 sleep time for fluoxetine-treated patients by the end of the study period. Although failing to reach statistical significance, fluoxetine treatment tended toward reduced slow wave sleep, increased WASO, and increased REM latency.

## DISCUSSION

The present study findings confirm and extend a previous report characterizing effects of mirtazapine on sleep physiology measures in patients with MDD[19] and provide new information contrasting effects of mirtazapine and fluoxetine on sleep architecture. Compared with baseline

Figure 1. Sleep Efficiency During 8 Weeks of Mirtazapine Treatment as Compared With Baseline in Patients With Major Depressive Disorder and Complaints of Insomnia[a]




[a]Individual data points represent the mean ± SE for each treatment week.
*$p < .05$.

assessments, the mirtazapine-treated group demonstrated significant reductions in sleep latency and WASO and significant increases in sleep efficiency and total sleep time. The magnitude of the alterations in sleep latency and sleep efficiency produced by mirtazapine administration was comparable to changes in the same measures produced by hypnotic compounds such as zolpidem and zaleplon in efficacy studies of these compounds for the treatment of insomnia.[25,26] The present findings demonstrating beneficial effects of mirtazapine on sleep physiology parameters in MDD patients with subjective complaints of insomnia support its suitability for this patient population. Clinical ratings of depression symptoms based on the 21-item HAM-D demonstrated a 72% improvement from baseline to week 8 of treatment, associated with a comparable degree of improvement in subjective sleep complaints as assessed by means of the 3 sleep items included in the 21-item HAM-D. With respect to effects of mirtazapine on sleep architecture, the most notable finding was the lack of REM sleep suppression (as manifest by determination of total REM time and REM latency). The majority of antidepressant drugs currently available in the United States have been demonstrated to exert prominent REM-suppressant effects.[8] Previously identified exceptions to this profile include trimipramine, bupropion, and nefazodone. Based on the present findings, mirtazapine would be added to the short list of clinically effective antidepressant compounds that spare REM sleep.

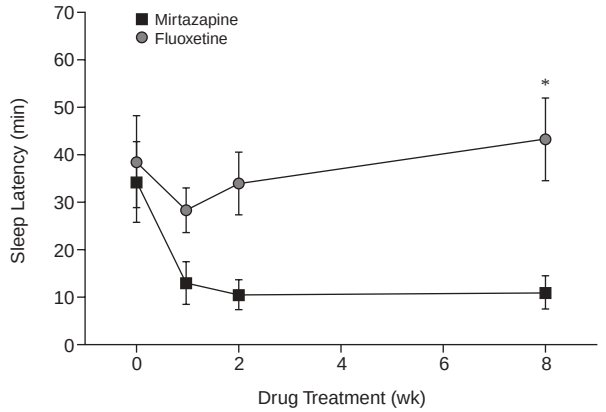
Alterations in sleep parameters associated with fluoxetine treatment included a significant increase in stage 1 sleep and prolongation of REM latency. Increased time in stage 1 sleep is generally interpreted as a disruption of sleep continuity. This finding is consistent with previous studies examining sleep measures with fluoxetine admin-

**Table 2. Polysomnographic Measures of Sleep[a]**

| | Mirtazapine | | | | Fluoxetine | | | |
|---|---|---|---|---|---|---|---|---|
| Measure | Baseline | Week 1 | Week 2 | Week 8 | Baseline | Week 1 | Week 2 | Week 8 |
| Sleep latency | 34.3 (24.0) | 13.1 (12.7)* | 21.8 (33.6)* | 10.9 (9.6)* | 38.6 (32.2) | 28.3 (15.6) | 34.0 (21.6) | 43.3 (28.4) |
| Total sleep time | 327.9 (81.8) | 359.2 (93.0) | 326.1 (110.8) | 428.1 (73.6)* | 317.4 (68.8) | 307.9 (90.4) | 352.3 (82.8) | 325.1 (116.4) |
| Sleep efficiency, % | 79.3 (11.3) | 90.9 (4.5)* | 87.1 (7.5)* | 91.7 (6.9)* | 83.5 (11.6) | 84.1 (11.6) | 86.9 (9.1) | 82.3 (14.0) |
| WASO | 81.0 (40.4) | 34.8 (20.0)* | 51.4 (32.4)* | 38.9 (30.1)* | 58.7 (26.1) | 58.7 (46.9) | 51.3 (31.6) | 69.1 (60.0) |
| Total stage 1 | 66.2 (43.7) | 80.9 (53.9) | 69.6 (33.3) | 111.2 (46.4) | 38.7 (11.9) | 47.4 (24.2) | 45.4 (17.6) | 67.9 (28.6)* |
| Total stage 2 | 157.2 (43.2) | 194.2 (68.8) | 170.0 (65.1) | 202.6 (43.0) | 186.5 (60.4) | 204.4 (64.9) | 235.4 (61.4) | 178.0 (66.0) |
| Total stage 3 + 4 | 40.7 (25.0) | 36.0 (26.0) | 36.9 (21.9) | 42.8 (21.4) | 34.1 (26.2) | 30.9 (34.4) | 28.7 (25.1) | 19.1 (13.3) |
| Total REM | 60.4 (33.8) | 48.1 (24.5) | 50.5 (26.0) | 71.5 (28.8) | 59.5 (33.0) | 25.1 (24.6) | 42.8 (27.3) | 60.2 (55.2) |
| REM latency | 122.0 (68.7) | 134.3 (76.3) | 156.4 (39.9) | 140.9 (57.1) | 127.0 (52.4) | 189.9 (94.8) | 211.9 (82.4)* | 201.2 (101.5)* |

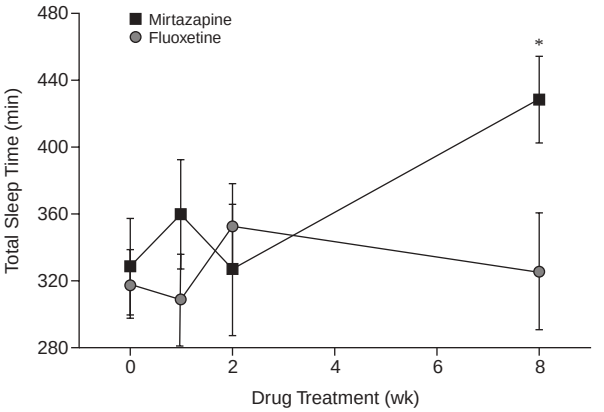
[a]Values shown as mean (SD) minutes unless otherwise noted.
*p < .05 vs. baseline.
Abbreviations: REM = rapid eye movement, WASO = wake time after sleep onset.

**Figure 2. Sleep Latency During 8 Weeks of Treatment With Either Fluoxetine or Mirtazapine in Patients With Major Depressive Disorder and Complaints of Insomnia[a]**




[a]Individual data points represent the mean ± SE for each treatment group.
*p < .05.

**Figure 3. Total Sleep Time During 8 Weeks of Treatment With Either Fluoxetine or Mirtazapine in Patients With Major Depressive Disorder and Complaints of Insomnia[a]**




[a]Individual data points represent the mean ± SE for each treatment group.
*p < .05.

istration.[9–14] Unlike a subset of other fluoxetine studies that also reported an increase in WASO and a decrease in total sleep time, the present study did not find that these parameters were significantly altered by fluoxetine. Additionally, while a significant increase in REM latency was demonstrated in the fluoxetine group, total REM time was not significantly reduced.

Several significant differences were noted when comparing effects of mirtazapine and fluoxetine on sleep physiology in this study population. Mirtazapine therapy was associated with a significantly greater decrease in sleep latency and a significantly greater increase in total sleep time. These alterations in sleep physiology are indicative of improvement in sleep quality. Fluoxetine treatment, in contrast, was associated with a significant increase in light stage 1 sleep and a trend for reduced slow wave sleep. Both the mirtazapine- and the fluoxetine-treated patients demonstrated robust antidepressant responses as reflected by large decreases in ratings on the HAM-D. Moreover, both groups had substantial reductions in the total scores for the 3 HAM-D sleep items. Patients receiving mirtazapine demonstrated a numerically larger decrease in sleep disturbance scores than was observed for the fluoxetine group, although this difference did not reach statistical significance.

The observed differential effects of mirtazapine and fluoxetine on sleep physiology may relate to differences in pharmacologic properties characterizing these antidepressant drugs. Sleep-disruptive effects produced by fluoxetine have been speculated to result from enhanced serotonergic actions at the serotonin-2 (5-$HT_2$) receptor site.[27] Mirtazapine increases both noradrenergic and serotonergic neurotransmission by blocking central presynaptic $\alpha_2$-adrenergic autoreceptors and heteroreceptors while also selectively blocking postsynaptic 5-$HT_2$ and 5-$HT_3$ receptors.[28] Effects of mirtazapine at the 5-$HT_2$ receptor have been speculated to underlie its profile of enhancing sleep.[27]

Several limitations of the present study should be noted. Although this report substantially extends the number of patients with depression who have been evaluated by means of polysomnogram during the course of mirtazapine therapy, the numbers of subjects in both the mirtazapine and fluoxetine treatment groups were still quite small and, therefore, the findings should be viewed as preliminary. Additionally, while assignment to drug treatment group was randomized, the absence of a placebo control group makes it impossible to ascertain the extent of improvement in depression scores that represents a true antidepressant response. However, the primary goal of the present study was to assess effects of mirtazapine and fluoxetine on parameters of sleep architecture rather than to verify their well-documented antidepressant efficacy. While administration of fluoxetine in the morning and mirtazapine at bedtime might contribute to the lack of comparable sleep effects between these 2 antidepressant compounds, these administration times represent the most commonly employed schedules in standard clinical practice. Finally, sleep studies at weeks 1, 2, and 8 involved only a single-night polysomnographic laboratory assessment. The use of single-night assessments during the treatment period increases the possibility of enhanced variability of sleep data. Despite this methodological limitation, substantial and statistically significant differences were observed in sleep parameters between the mirtazapine and fluoxetine treatment groups.

The current findings indicate prominent differences in effects of mirtazapine and fluoxetine on sleep physiology in depressed patients with subjective complaints of insomnia. These findings extend previous observations of differential effects of antidepressant drugs on sleep architecture. In particular, the prominent effects of mirtazapine in shortening sleep latency and increasing total sleep time suggest that this antidepressant compound may be of particular benefit in the treatment of depression associated with prominent insomnia. Additionally, effects of mirtazapine in shortening sleep latency, increasing total sleep time, and decreasing WASO raise the possibility that this agent may be of utility in the treatment of insomnia independent of clinical depression. Further studies will be needed to evaluate this possibility.

*Drug names:* bupropion (Wellbutrin and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), trimipramine (Surmontil), zaleplon (Sonata), zolpidem (Ambien).

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