Efficacy of Mirtazapine in Obstructive Sleep Apnea Syndrome

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Study Objectives: Decreased serotonergic facilitation of upper-airway motor neurons during sleep has been postulated as an important mechanism rendering the upper airway vulnerable to obstruction in patients with obstructive sleep apnea syndrome (OSA). Although serotonin reuptake inhibitors have been shown to produce modest reductions in the apnea-hypopnea index (AHI) during non-rapid eye movement (NREM) sleep, they have not been proven to be generally effective as treatments for OSA. Conversely, antagonists of type 3 (5-HT3) serotonin receptors effectively have been shown to reduce the frequency of central apneas during rapid eye movement (REM) sleep in a rodent model of sleep-related breathing disorder. We sought to determine whether mirtazapine, a mixed 5-HT2/5-HT3 antagonist that also promotes serotonin release in the brain would effectively reduce AHI during both NREM and REM sleep in patients with OSA.

Design: A randomized, double-blind, placebo-controlled, 3-way crossover study of mirtazapine in patients with OSA.

Setting: Laboratory studies were conducted in the Center for Sleep and Ventilatory Disorders at the University of Illinois Medical Center.

Patients: Seven adult men and 5 adult women with newly diagnosed (treatment-naive) and medically uncomplicated OSA were randomized into the study.

Interventions: Each subject self-administered oral medications 30 minutes before bedtime each night for 3 consecutive 7-day treatment periods. These treatments comprised (1) placebo, (2) 4.5 mg per day of mirtazapine, and (3) 15 mg per day of mirtazapine. The order of treatments was randomized for each subject, and orders were counterbalanced for the overall study.

Measurements and Results: Each subject charted his or her sleep-wake schedule throughout and completed the Stanford Sleepiness Scale every 2 hours during the seventh day of each treatment period. Subjects were studied by laboratory polysomnography on the seventh night of each treatment period. With respect to placebo treatment, 4.5 mg of mirtazapine significantly reduced the AHI in all sleep stages to 52%, with 11 of 12 subjects showing improvement over placebo; 15 mg of mirtazapine reduced the AHI to 46%, with 12 of 12 subjects showing improvement over placebo. Sleep fragmentation was reduced only by the higher dose of mirtazapine. Gross changes in sleep architecture were unremarkable.

Conclusions: Daily administration of 4.5 to 15 mg of mirtazapine for 1 week reduces AHI by half in adult patients with OSA. This represents the largest and most consistent drug-treatment effect demonstrated to date in a controlled trial. These findings suggest the therapeutic potential of mixed-profile serotonergic drugs in OSA and provide support for future studies with related formulations. Mirtazapine also is associated with sedation and weight gain—2 negative side effects in patients with OSA. In view of the above, we do not recommend use of mirtazapine as a treatment for OSA.

Keywords: Apnea, drug treatment, clinical trial, randomized, placebo-controlled, OSA, mirtazapine, serotonin

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EDITOR’S NOTE
The reader needs to be aware of the following information. On June 27, 2006, Cypress Bioscience Inc. announced “that the results of recently completed Phase IIa trials do not support continuing a development program evaluating combinations of mirtazapine with another approved drug as potential pharmaceutical treatments for obstructive sleep apnea (OSA). Cypress and Organon, the human healthcare business unit of Akzo Nobel, had each independently conducted Phase IIa trials that served as the basis for today’s announcement. A previous independently conducted small preliminary investigator sponsored pilot trial found that mirtazapine was able to reduce the number of abnormal respiratory events over the course of the night by roughly fifty percent. However, those data were not replicated in the recently completed Phase IIa trials.” (source: http://www.cypressbio.com/news/releases/20060627.pdf)

INTRODUCTION
THE PREVALENCE AND MORBID CONSEQUENCES ARISING FROM UNTREATED SLEEP-RELATED BREATHING DISORDERS (SRBDS) HAVE SPARKED AN ENORMOUS INCREASE IN INVESTIGATIONS OF THESE DISORDERS OVER THE PAST 4 DECADES. DESPITE THE INTENSITY OF THESE EFFORTS, THE PATHOGENIC MECHANISMS LEADING TO SRBDS AND THEIR CONSEQUENCES REMAIN POORLY UNDERSTOOD. UNCERTAINTY REGARDING SLEEP-RELATED CHANGES IN ESSENTIAL BRAINSTEM NETWORKS RESPONSIBLE FOR MAINTENANCE OF BOTH UPPER AIRWAY PATENCY AND A REGULAR RESPIRATORY RHYTHM HAS HINDERED EFFORTS TO DEVELOP EFFECTIVE PHARMACOTHERAPEUTICS FOR SRBDS.

Over the past 15 years, several animal model systems have been developed to complement human investigations of SRBDS.
Animal observations have suggested a putative therapeutic role for serotonin-promoting drugs in SRBDs. In particular, it is now established that during wakefulness serotonin, most probably acting through 5-HT3 receptors, provides a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway dilating muscles. It follows that withdrawal of this serotonergic input during sleep might predispose to airway obstruction in the form of apnea or hypopnea. Accordingly, systemic administration of 5-HT3 receptor antagonists to English bulldogs—an animal model of obstructive sleep apnea/hypopnea—reduced upper airway caliber and muscle tone. Conversely, serotonin promotion by a combination of trazadone and l-triptophan reduced the apnea-hypopnea index (AHI) in this model system. This therapeutic rationale has been tested in both open-label and blinded placebo-controlled clinical studies designed to promote serotonergic activity in the brain. Collectively, studies using either serotonin precursors or reuptake inhibitors have demonstrated limited promise for reducing SRBD severity during non-rapid eye movement (NREM) sleep, but no benefit has been observed during rapid eye movement (REM) sleep.

We hypothesized that, in the above studies, a putative benefit of serotonin-enhancing drugs in the brain may have been offset by an apnea-promoting effect of serotonin in the peripheral nervous system. Intravenous serotonin injection in anesthetized cats and rats produces immediate dose-dependent apnea by activation of the Bezold-Jarisch reflex. Intraperitoneal injection of serotonin produced no immediate apnea but caused an exacerbation of REM sleep-related apnea in a rodent model of central SRBD. As discussed by the authors, this effect most likely was mediated by the action of serotonin at 5-HT3 receptors on nodose ganglion cells. We subsequently screened a panel of 5-HT antagonist drugs, finding that ondansetron, a specific 5-HT3 antagonist, reduced the frequency of spontaneous central apneas during REM but not NREM sleep. Systemically delivered ondansetron was subsequently demonstrated to increase inspiratory activity in upper airway dilator motor neurons and to reduce the frequency of apnea and hypopnea during REM sleep in the bulldog model of obstructive SRBD. Conversely, mirtazapine, a mixed 5-HT2/S-HT3 antagonist that also promotes serotonin release in the brain, reduced the expression of central apnea by 50% during both NREM and REM sleep in the rat model of SRBD.

Here, we report the results of a double-blind, placebo-controlled, crossover study of 2 doses of mirtazapine on AHI in patients with obstructive sleep apnea (OSA) syndrome. As detailed below, mirtazapine again reduced AHI by approximately 50% during both NREM and REM sleep in this clinical pilot investigation.

METHODS

Seven male and 5 female patients with obstructive sleep apnea-hypopnea syndrome newly confirmed by polysomnography and naïve to any form of treatment participated in the present study. Subjects were aged from 18 to 67 years, and the mean age did not differ (p > 0.66) between men (39.0 ± 18.3 [SD]) and women (43.4 ± 14.2). Two women were postmenopausal and 3 were premenopausal. Neither of the postmenopausal women was receiving hormone replacement therapy. The body mass index for men (32.3 ± 9.7 kg/m2 [SD]) was significantly (p = 0.05) lower than for the women (45.5 ± 9.7 kg/m2). Upon prestudy diagnostic polysonmography, all subjects met the criteria for a diagnosis of sleep apnea syndrome according to American Academy of Sleep Medicine guidelines and were candidates for continuous positive airway pressure treatment (AHI for men = 22.0 ± 11.2; women = 24.1 ± 22.8). Significant cardiovascular, endocrine, hematologic, metabolic, neurologic, psychiatric, pulmonary, renal disorder, or sleep disorder other than obstructive sleep apnea (OSA), documented by history, physical, or laboratory examination, was excluded. Hypertension controlled to below 150 mm systolic and 90 mm diastolic by diuretics was permitted, but other antihypertensive regimens were excluded. Additional exclusion criteria included pregnancy, alcohol or drug abuse, a history of rotating or permanent night shift work within 6 months, and concomitant use of any central nervous system-active drug or any serotonergic drug. Before study entry, subjects received written and oral information and signed a consent document approved by the Institutional Review Board of the University of Illinois at Chicago. All procedures and protocols were conducted in compliance with the declaration of Helsinki and the standards of good clinical practice.

Upon meeting the above inclusion/exclusion criteria and providing informed consent, each subject participated in a randomized, double-blind, placebo-controlled, 3-way crossover study to evaluate the potential efficacy of mirtazapine (Remeron, Organon, Oss, Netherlands) as a treatment for OSA. Daily mirtazapine doses (taken by mouth 30 minutes before bedtime) of 4.5 mg and 15 mg were compared to placebo. For this, each subject completed 3 consecutive 7-day treatment periods with no washout interval between periods. The treatment order was randomized for each subject, with each of the 6 possible treatment sequences represented twice among the overall subject group. Compliance was assessed by interview and by accounting of all returned treatment units.

Throughout all treatment periods, subjects charted their time in bed, estimated their sleep times, and completed questionnaires relating to sleep quality each morning. In addition, on the final (seventh) day of each treatment period, subjects completed a Stanford Sleepiness Scale every 2 hours while they were awake. This scale provided a subjective retrospective assessment of sleepiness rated on a scale of 1 (alert, wide awake, and energetic) to 7 (cannot stay awake, sleep onset soon).

Each subject underwent overnight polysomnography in the Center for Sleep and Ventilatory Disorders at the University of Illinois Hospital on the final day of each treatment period. Subjects reported to the Center at 9 pm and were instrumented for electroencephalograms (C4/A1, C3/A2), bilateral electrooculograms, electromyograms (submental, bilateral anterior tibial), electrocardiogram, oronasal airflow (thermostat, EPM Systems, Midlothian, VA), thoracoabdominal motions (piezo-crystal, EPM Systems), arterial oxygen saturation by pulse oximetry, and body position. All signals, including digital infrared video, were acquired, processed and stored by a Sleepscan system (Biologic Systems Corp., Mundein, IL). Subjects were observed to take their medication (seventh dose) at 10:30 PM, and lights out was at 11:00 PM. All subjects were given an 8-hour sleep opportunity.

Sleep was scored according to standard criteria on 30-second epochs. Electroencephalogram arousals were scored according to American Academy of Sleep Medicine guidelines by a single polysomnographer blinded as to treatment and treatment-period. Time in bed was computed as the number of minutes in bed be-

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between lights out and lights on, total sleep time as the number of minutes of sleep between lights out and lights on, and sleep efficiency as the ratio of the two: total sleep time divided by time in bed. The distribution of sleep stages was separately determined as percentages of total sleep time scored as: (1) stage 1 or stage 2, (2) stage 3 or stage 4, and (3) REM sleep. Sleep latency was determined as the interval between lights out and the first of at least 3 successive epochs of sleep. REM sleep latency was determined as the interval between sleep onset and the first epoch of REM sleep.

Disordered breathing events were scored according to American Academy of Sleep Medicine guidelines with 1 addition: apneas were defined as respiratory events in which oronasal airflow decreased by more than 90%, whereas hypopneas were defined as events in which airflow decreased by 90% or less. This addition was necessitated by the fact that the American Academy of Sleep Medicine criteria do not specify any cutoff for discriminating apneas from hypopneas. Rather, obstructive apnea-hypopnea events are defined together as a clear decrease (> 50%) in the amplitude of breathing during sleep. Here, we scored hypopneas as clear decreases in airflow greater than 50% but less than 90% or as clear decreases less than 50% but associated with either an oxygen desaturation of more than 3% or an arousal. Quantitative airflow measured by a sealed facemask and pneumotachograph must be viewed as the gold standard both for detecting sleep disordered breathing events and for discriminating apneas from hypopneas. No other current measurement technique is fully adequate for both detecting and discriminating these events. Oronasal thermistors have been viewed as a strong method to discriminate hypopneas from apneas but inferior to nasal pressure measurements for detecting events.

In view of the above technologic limitations, and because AHI is a primary outcome variable, we sought to minimize variability of respiratory-event scoring by using a single polysomnographer blinded as to subject and treatment information. Additionally, after an interval of longer than 6 months, we had 5 randomly chosen subjects were excluded from the analysis.

Table 1—Effects of Mirtazapine on Sleep, Breathing, and Alertness in Patients With Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mirtazapine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.5 mg QD</td>
<td>15 mg QD</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>82.9 ± 6.4</td>
<td>87.7 ± 4.9</td>
<td>.05*</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>5.5 ± 1.3</td>
<td>3.8 ± 1.0</td>
<td>.01</td>
</tr>
<tr>
<td>REM latency, min</td>
<td>88.5 ± 13.8</td>
<td>103.8 ± 19.3</td>
<td>.01</td>
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<tr>
<td>Sleep stage, % of TST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>78.3 ± 3.2</td>
<td>76.9 ± 2.8</td>
<td>.02</td>
</tr>
<tr>
<td>3 or 4</td>
<td>5.1 ± 1.9</td>
<td>7.5 ± 1.8</td>
<td>.02</td>
</tr>
<tr>
<td>REM</td>
<td>16.6 ± 2.2</td>
<td>15.6 ± 1.3</td>
<td>.04*</td>
</tr>
<tr>
<td>Arousal Index, /h</td>
<td>41.1 ± 7.2</td>
<td>41.9 ± 9.4</td>
<td>.02*</td>
</tr>
<tr>
<td>Apnea Index, /h</td>
<td>9.0 ± 2.8</td>
<td>4.9 ± 1.9</td>
<td>.02*</td>
</tr>
<tr>
<td>Hypopnea Index, /h</td>
<td>13.3 ± 3.5</td>
<td>8.6 ± 2.6</td>
<td>.02*</td>
</tr>
<tr>
<td>AHI, /h</td>
<td>22.3 ± 4.8</td>
<td>13.5 ± 3.7</td>
<td>.04*</td>
</tr>
<tr>
<td>NREM AHI, /h</td>
<td>21.4 ± 5.1</td>
<td>13.6 ± 3.9</td>
<td>.01*</td>
</tr>
<tr>
<td>REM AHI, /h</td>
<td>26.8 ± 4.9</td>
<td>12.9 ± 3.4</td>
<td>.01*</td>
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<tr>
<td>AHI/Placebo AHI</td>
<td>1.0 ± 0</td>
<td>0.519 ± 0.460 ±</td>
<td>.0001*</td>
</tr>
<tr>
<td>Minimum SaO₂</td>
<td>81.7 ± 2.3</td>
<td>81.1 ± 2.7</td>
<td>.071</td>
</tr>
<tr>
<td>ODI, &gt;3%, /h</td>
<td>19.1 ± 4.8</td>
<td>10.6 ± 3.7</td>
<td>.031*</td>
</tr>
<tr>
<td>Stanford Sleepiness Scale</td>
<td>2.62 ± 0.34</td>
<td>2.18 ± 0.30</td>
<td>.033</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM for sleep, breathing, and subjective alertness variables in 12 subjects with obstructive sleep apnea syndrome. Each subject received each treatment for 7 days in randomized order and was studied by polysomnography at the end of each 7-day period. Treatment effects were tested by analysis of variance (ANOVA) with repeated measures. Planned comparisons of each active dose to placebo were controlled by Fisher protected least significant difference (PLSD). OSA refers to obstructive sleep apnea; REM, rapid eye movement sleep; TST, total sleep time; AHI, apnea-hypopnea index; NREM, non-rapid eye movement; ODI, oxygen desaturation index.

In view of the above technologic limitations, and because AHI is a primary outcome variable, we sought to minimize variability of respiratory-event scoring by using a single polysomnographer blinded as to subject and treatment information. Additionally, after an interval of longer than 6 months, we had 5 randomly chosen subjects were excluded from the analysis.

Statistical assessment of treatment effects on each study variable was performed using analysis of variance (ANOVA) with repeated measures. Planned contrasts between placebo and the 2 active treatments were controlled using the Fisher protected least significance difference (PLSD). ANOVA with repeated measures was also used to examine possible treatment order effects, and none were detected (p > 0.12 for each variable). All statistical analyses were performed at the University of Illinois at Chicago in consultation with the General Clinical Research Center statistician.

RESULTS

All twelve randomized subjects completed the trial, and no adverse events were reported. As summarized in Table 1, under placebo treatment, the mean apnea and hypopnea indexes were 9.0 (range: 0-30.2) and 13.3 (range: 0.8-44.1) per hour, respectively, while the AHI mean was 22.3 (range: 1.8-63.4), and the average minimum (nadir) oxygen saturation was 81.7%. Thus, the group of study subjects comprised newly diagnosed, medically uncomplicated patients with a wide range of severity in their OSA syndrome. Two subjects exhibited an AHI lower than 10 under placebo conditions: these subjects experienced 33 and 31 respiratory-event-related-arousals per hour, respectively. None of the significant findings detailed below were changed if these 2 subjects were excluded from the analysis.

Mirtazapine treatment at 15 mg per day reduced the hypopnea index by more than 50% (p = .02; Table), but the decrease in the apnea index was not statistically significant (p = .16) and nadir oxygen saturation during sleep was unchanged by either mirtazapine dose. However, as depicted in Figure 1 (left panel), the AHI was reduced with respect to placebo in 12 of 12 subjects during the 15 mg per day treatment period and in 11 of 12 subjects during the 4.5 mg per day treatment period. For the group, the mean AHI decreased from 22.3 for placebo treatment to 13.5 and 11.4 per hour for 4.5-mg and 15-mg doses, respectively (Figure 1, right panel). These treatment effects were highly significant (p ≤ .004 for each dose) when assessed by ANOVA with
repeated measures. When computed relative to the AHI during placebo treatment for each subject, the AHI was reduced to 52% and 46% of the placebo level by 4.5 and 15 mg per day of mirtazapine, respectively (Table 1). Again, these treatment effects were highly significant (p < .0001 for each). Five and 4 of the 12 subjects exhibited an AHI less than 5 during the 4.5-mg and 15-mg treatment periods, respectively. (Note that 2 of the 12 subjects exhibited an AHI < 5 during all 3 period, including placebo, as described above).

The pattern of treatment-related decreases was observed for NREM-related AHI and REM-related AHI (p < .01 for each; Table). Although subjects were not specifically instructed to sleep on their backs, analysis revealed that, on average, subjects spent 88.2% ± 7.7% of their sleep time in the supine position and that this was similar for all treatment periods (p > .5). The main treatment effect on AHI was equivalent for supine and nonsupine positions (p > .1 for the interaction of treatment × position by ANOVA). Additionally, although the number of female subjects was too small for appropriate statistical analysis, the decreases in AHI for male and female subjects appeared similar (58.5% ± 11.6% for men and 47.5% ± 8.0% for women). Further, the magnitude of the treatment effect (decrease in AHI with treatment) was significantly related to the baseline severity of the disorder (AHI during placebo treatment): r² for 4.5 mg of mirtazapine was 0.75 (p < .0001) and for 15 mg of mirtazapine was 0.79 (p < .0001).

The effects of mirtazapine treatment on sleep architecture were less prominent. Sleep efficiency and REM sleep percentage were increased by both doses, although only the 15 mg per day effects achieved statistical significance (p = .05 and p = .04, respectively; Table). In addition, the frequency of electroencephalographic arousals during sleep was decreased by 15 mg per day of mirtazapine to 65% of the placebo level (p = .02; Figure 2). In contrast to the effects on AHI, the decrease in arousal frequency with treatment by 15 mg of mirtazapine was only weakly related to the baseline (placebo) arousal frequency: r² = 0.17 (p = .04). Mirtazapine had no effect on the expression of any stage of NREM sleep and did not alter sleep latency or the latency to REM sleep (Table).

Analysis of the Stanford Sleepiness Scales revealed that the subjects felt relatively alert throughout the daytime even during the placebo treatment periods. The mean score during placebo was 2.62 (Table 1), corresponding to a self-assessment falling between “functioning at a high level, but not at peak; able to concentrate” (scale score = 2) and “awake, but not fully alert” (scale score = 3). Treatment with 4.5- and 15-mg doses of mirtazapine numerically reduced the mean scores to 2.18 and 2.24, respectively, but these effects did not achieve statistical significance.

**DISCUSSION**

The present double-blind, placebo-controlled, crossover study demonstrates that AHI is significantly reduced by oral mirtazapine in patients with OSA syndrome. This effect represents the largest and most consistent reduction of AHI so far demonstrated in any placebo-controlled test of a drug treatment for OSA. Another distinction from previous studies is that AHI was reduced to a similar extent during both NREM and REM sleep by mirtazapine, and this reduction was strongly correlated with the baseline severity of the AHI. Additionally, the treatment effects on AHI showed no clear body-position dependence and was similar among male and female subjects.

Despite the reduction in AHI during both active treatments (4.5-mg and 15-mg doses) with respect to placebo, the overnight nadir in oxygen saturation was unaffected by either dose of mirtazapine. This most probably reflects the fact that the residual
respiratory events were not shortened and, at least occasionally, were expressed in repetitive sequences such that the minimum oxygen saturation was not improved. Additionally, sleep quality and quantity were only slightly improved, despite a 50% reduction in respiratory events. Similarly, subjective daytime alertness was not significantly improved for either mirtazapine dose. Finally, it must be considered that the reduction in AHI could be an “artifact” of mirtazapine decreasing the number of arousals. However, this seems unlikely because, at the 4.5-mg dose, AHI and oxygen desaturation index were reduced by 48% and 44%, respectively, but the arousal index remain unchanged from placebo (Table 1).

Several previous studies have examined the effects of serotonin-related drugs in patients with OSA. Based on an uncontrolled study, Schmidt suggested that administration of the serotonin precursor L-tryptophan reduces sleep apnea7 and Hanzel et al reported an unblinded clinical trial showing that the reuptake inhibitor fluoxetine reduced AHI during NREM sleep.8 The latter finding was confirmed by Kraiczi et al, who conducted a double-blind, placebo-controlled, crossover study of paroxetine. This study demonstrated a 19% decrease in AHI during NREM sleep, but neither the overall AHI nor the AHI during REM sleep was significantly reduced.9

Animal studies have provided both a motivation and a theoretical basis for interpreting the above studies. If OSA is viewed as a disorder of excessive sleep-related upper airway collapsibility, then any factor contributing to or amplifying the decreased activation of upper airway dilator muscles during sleep is a potential pathogenic factor for the disorder. Serotonin receptors are expressed on hypoglossal motor neurons innervating the genio- glossus and other upper airway dilator muscles,21 and activation of these receptors, particularly 5-HT2A receptors, is excitatory.4 Further, with transitions from wake to NREM sleep, serotonin release from raphe neurons is reduced at various brainstem sites, including the hypoglossal motor nucleus, and release is minimal during REM sleep.22-24 These observations suggest that loss of serotonergic facilitation is one potential basis for the reduced upper airway muscle activation and increased collapsibility of the upper airway characteristic of REM sleep.

In this framework, the slight reduction in AHI during NREM sleep produced by serotonin reuptake inhibitors8,9 could be attributed to increased activity of endogenous serotonin in the hypoglossal motor nuclei. It could be further reasoned that because serotonin release is at a minimum during REM sleep, these drugs would be expected to have little effect during this sleep state.9 Still, more recent studies have questioned the importance of serotonergic inputs in the reduction of upper airway motor outputs during sleep, at least in the rat.3,25 In any case, it is clear that systemic manipulations of the serotonergic system can lead to complex and poorly understood effects on respiratory and upper airway motor outputs. The net effects of such interventions are likely to be target-tissue and receptor-subtype specific.26

For example, although brainstem serotonin networks may increase upper airway motor outputs, it appears that they may also be important inhibitors of respiratory chemoreflexes.27 Intracarotid 5-HT administration produces a biphasic ventilatory response comprising both excitation and inhibition,28 whereas intravenous or intracardiac infusion produces immediate dose-dependent apnea, an effect dependent upon activation of 5-HT1 receptors in or on nodose ganglion cell bodies.10 Moreover, intraperitoneal administration of 5-HT in conscious rats produced a 3-fold increase in the apnea index during REM sleep.12 This effect may also be attributable to nodose ganglion 5-HT1 receptors because peripherally administered serotonin does not cross the blood-brain-barrier and because the effect was blocked by pretreatment with ondansetron,12 a specific 5-HT1 receptor antagonist that penetrates the brain only poorly.29

On this basis, we speculated that endogenous activation of serotonin receptors in the peripheral nervous system may predispose

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Figure 2—The arousal index (ARI; electroencephalographic arousals per hour) determined by polysomnography and presented in the format of Figure 1. The ARI was consistently reduced only by the High (15 mg per day) dose of mirtazapine (left panel). On average, High-dose mirtazapine reduced ARI by 36% in comparison to the placebo-treatment period (p = .02 determined by analysis of variance with repeated measures and Fisher protected least significant difference).
to apnea, especially during REM sleep, whereas 5-HT activity in upper airway motor nuclei may protect against apnea, especially during NREM sleep. In accordance with this view, administration of ondansetron produced a dose-dependent REM sleep-specific suppression of apnea in the rodent and bulldog models of SRBD. Conversely, Stradling et al reported no effect of a single 16-mg dose of ondansetron on sleep architecture or disordered breathing in 10 patients with OSA.31 The difference between these animal and human studies may reflect differing species, differing effective doses, or other factors. It is also possible that daily administration of ondansetron would produce greater effects than a single dose.32 In any case, these studies serve collectively to underscore the potential complexities of serotonergic influences on sleep and breathing.

The present study represents the first controlled trial of a mixed-profile serotonergic agent in patients with OSA, though anecdotal evidence has been presented previously.33 Mirtazapine is a potent 5-HT2 and 5-HT3 receptor antagonist but also promotes serotonin release in the brain by blocking presynaptic inhibitory adrenergic heteroreceptors on serotonin nerve terminals.34-36 Thus, the net serotonergic profile of mirtazapine is promotion of 5-HT3 activity in the brain together with 5-HT2/5-HT3 blockade in the central and peripheral nervous systems. In light of the conceptual framework presented above, we may speculate that the reduction of NREM AHI reported here reflected the change in 5-HT3 activity in the brain. Consistent with this possibility is the report from Mendelson et al that the 5-HT1A agonist buspirone improved NREM AHI in 5 patients with OSA.37 Also of note is the finding by Berry et al that mirtazapine doses similar (on a mg/kg basis) to those tested here produced augmentation of genioglossus activity in anesthetized rats, whereas, at higher doses, upper airway muscle activity was suppressed.38 These and the present findings support the speculation that, at the doses tested, the ability of mirtazapine to increase brainstem serotonin or to block peripheral 5-HT3 receptors predominated over blockade of central 5-HT3 receptors. Moreover, Fenik et al demonstrated that blockade of 5-HT3 receptors via systemic ondansetron resulted in increased upper airway dilator activity, supporting the view upper airway motor neurons in the medulla may be tonically inhibited by vagus nerve afferent fibers.39 Further, we view that the reduction of AHI during REM sleep in the present study most probably reflected the antagonism of peripheral serotonin receptors by mirtazapine.

Still, the exact sites and relative importance of serotonergic effects for reducing AHI cannot be inferred from the present data. For example, 5-HT2 and 5-HT3 antagonism may have accentuated the 5-HT1A-mediated effects in the ventral respiratory group of the medulla. Also, we tested racemic mirtazapine, comprising an equal mixture of (+) and (-) enantiomers. However, these enantiomers have a differential pharmacology,36 and direct comparative tests of these isomers in both animal and human trials may help to elucidate the mechanisms by which mirtazapine influences respiration. Additionally, we cannot rule out other mechanisms, including the actions of mirtazapine at other targets, such as adrenergic autoreceptors or histamine receptors. The reduction of disordered respiration was not a result of changes in sleep architecture. Gross sleep architecture (Table) and microarchitecture (electroencephalogram arousals; Figure 2) were unchanged by 4.5 mg per day of mirtazapine, yet this dose was associated with a nearly 50% reduction in AHI.

Two limitations of the present study are immediately relevant to interpretation of the findings. First, the treatment periods were only 7 days. Due to the crossover study design, the delay in institution of conventional treatment for these patients with OSA was therefore 21 to 28 days; an interval deemed to be acceptable by the University of Illinois at Chicago Institutional Review Board. The decision to reduce the treatment period to 7 days was based on clinical data regarding the pharmacokinetics and onset of antidepressant action for mirtazapine. Steady-state plasma levels of mirtazapine are achieved within 4 days in adults taking a single daily dose.39 Furthermore, although the antidepressant effect of mirtazapine is not fully manifest until 14 to 28 days after initial dosing, there are clinically and statistically significant effects as early as the fourth day of treatment.40 Therefore it is reasonable to attribute the present reduction in AHI to the pharmacologic effects of mirtazapine on the central and peripheral nervous systems, but the present study may have underestimated the potential magnitude of reduction achievable under long-term treatment.

The study also is limited by the fact that washout periods were not included between treatment periods. Again, this decision was made to minimize the delay to institution of conventional treatment. Based on the pharmacokinetics of mirtazapine, we expect that steady-state plasma levels were achieved by day 4 of each treatment period. Similarly, the elimination half-life of 20 to 40 hours41 is in agreement with the view that a new and steady-state plasma level would be established within 4 days following crossover, even without an explicit washout period. Despite this, and the absence of a statistically significant treatment-order effect, we cannot completely rule out carryover effects due to the relatively limited number of subjects. We specifically examined the data for treatment-order effects, and none were detected by ANOVA with repeated measures and post hoc contrasts controlled by Fisher’s PLSD (p > .12 for each variable). In addition, carryover effects between treatment periods, if present, would have led us to underestimate the true treatment effects because the treatment sequences were counterbalanced.

Although this is the first controlled human trial, effects of mirtazapine on SRBD have been reported. In a case report of an 84-year-old man, Castillo et al described a reduction in AHI from 54.9 to 9.3 after 3 months of treatment with 15 mg daily of mirtazapine.33 In the rodent model of central SRBD, we described an approximate 50% reduction in the apnea index over a 50-fold dose range of mirtazapine.42 Despite the fact that rats express central apneas, the similar effects of mirtazapine in rat and man suggest the potential utility of the rodent model of SRBD as a screening tool to identify pharmacotherapeutic candidates for OSA.

In summary, the present study demonstrates the largest and most consistent improvement in AHI in a controlled trial for any drug to date—AHI was reduced by approximately 50% during all sleep stages. This finding supports the principle of treating OSA using mixed-profile serotonergic drugs. Despite the fact that all subjects demonstrated improvement with treatment, the AHI remained above 5 in a majority of subjects, sleep remained significantly fragmented, and slow-wave sleep time remained below normal. Mirtazapine also is associated with sedation and weight gain—2 negative side effects in patients with OSA. In view of the above, we do not recommend the use of mirtazapine as a treatment for OSA. Additional studies to evaluate other formulations designed to improve the responder rate and to decrease the negative side-effect potential will be necessary.
REFERENCES


