

## ORIGINAL CONTRIBUTIONS

# Effect of Esomeprazole on Nighttime Heartburn and Sleep Quality in Patients with GERD: A Randomized, Placebo-Controlled Trial

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- OBJECTIVES:** Sleep disturbances are common in patients with gastroesophageal reflux disease (GERD). This study examined the effects of esomeprazole on nighttime heartburn, GERD-related sleep disturbances, sleep quality, work productivity, and regular activities.
- METHODS:** This multicenter, randomized, double-blind, placebo-controlled trial included adults with GERD-associated sleep disturbances and moderate-to-severe nighttime heartburn (recorded by patient diary during screening). Patients received oral esomeprazole 40 mg (n = 220) or 20 mg (n = 226) or placebo (n = 229) once daily for 4 wk. The primary outcome was relief of nighttime heartburn. Secondary outcomes included resolution of sleep disturbances, sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI) questionnaire, and work productivity measured by the Work Productivity and Activity Impairment Questionnaire.
- RESULTS:** Nighttime heartburn was relieved in 53.1% (111/209), 50.5% (111/220), and 12.7% (28/221) of patients who received esomeprazole 40 mg, esomeprazole 20 mg, and placebo, respectively. Differences (95% CI) versus placebo were 40.5% (32.4%, 48.5%) and 37.8% (29.9%, 45.7%) and were highly significant ( $p < 0.0001$ ). GERD-related sleep disturbances resolved in significantly more ( $p < 0.0001$ ) patients who received esomeprazole 40 (73.7%) or 20 mg (73.2%) than in those who received placebo (41.2%). Both esomeprazole groups had greater PSQI global score changes from baseline ( $p < 0.0001$  vs placebo) and more ( $p < 0.0001$  vs placebo) work hours saved per week per patient compared with baseline (esomeprazole 40 mg, 11.6 h; esomeprazole 20 mg, 12.3 h; placebo, 6.2 h).
- CONCLUSIONS:** Esomeprazole reduced nighttime heartburn and GERD-related sleep disturbances and improved sleep quality and work productivity.

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## INTRODUCTION

Heartburn affects as many as 40% of adults in economically developed countries (1, 2). Heartburn and other gastroesophageal reflux disease (GERD) symptoms experienced during the night commonly cause sleep disturbances, including arousal from sleep, increased wakefulness, and overall poor sleep quality (3, 4). In a U.S. study of patients with GERD (5), 69% responded that they “experienced GERD symptoms when laid down to sleep at night”; 54% responded that they were “awakened at night by GERD symptoms”; and 29% responded that they were “awakened at night by coughing or choking because of fluid or an acid or bitter taste, or food in the throat.” A survey of patients with heartburn (6) found that 79% reported nighttime heartburn, and

of those, 75% had symptoms that affected their sleep, and 40% believed that nighttime heartburn impaired their ability to function the next day.

Health-related quality of life is more impaired in patients with nighttime symptoms of GERD than in healthy control subjects ( $p < 0.001$ ) or in patients with GERD and no nighttime symptoms (5). Additionally, heartburn symptom severity and nighttime heartburn are associated with reduced work productivity, particularly when nighttime heartburn interferes with sleep (7). Clinical trials in patients with GERD have shown that acid-suppressive therapy with proton pump inhibitors (PPIs) or ranitidine improves the sleep components of quality-of-life measures (8, 9). However, no previous study has focused on treatment efficacy in patients with GERD-related sleep disturbances and nighttime heartburn.

The objective of this randomized, placebo-controlled trial was to assess the efficacy of the PPI esomeprazole (40 and 20 mg, once daily) on nighttime heartburn, sleep disturbances, and sleep quality in patients with GERD and both sleep disturbances and moderate-to-severe nighttime heartburn.

## MATERIALS AND METHODS

### *Design and Setting*

This randomized, multicenter, double-blind, parallel-group, placebo-controlled study (D961AC00001/Study 319) was conducted in accordance with the ethical principles of Good Clinical Practice, the Declaration of Helsinki, and applicable regulatory requirements. Approval from the appropriate Institutional Review Boards for the participating centers and written informed consent were obtained before initiation of any study procedure. The study was conducted in clinical practices and research center settings in the United States.

### *Participants*

Enrolled patients were men and women aged 18–85 yr with a history of heartburn or acid regurgitation for  $\geq 3$  months or with any history of erosive esophagitis. Patients eligible for the screening period had to have an average of  $\geq 2$  episodes of nighttime heartburn symptoms per week. Patients also had a  $\geq 1$ -month history of GERD-associated sleep disturbances. Endoscopy was intentionally not performed so that the population would include patients with either symptomatic (nonerosive) or erosive GERD.

Patients who met the initial inclusion criteria entered a screening period that lasted a minimum of 7 and a maximum of 15 days. During this period, patients recorded on diary cards the severity of heartburn symptoms and whether or not they had GERD-associated sleep disturbances by answering a “yes” or “no” question. The same diary cards were used throughout the study. Patients with both GERD-associated sleep disturbances on  $\geq 3$  of the last 7 days of the screening period, and nighttime heartburn graded as moderate or severe on  $\geq 3$  of the last 7 nights of the screening period were eligible for randomization. GERD-associated sleep disturbances included, but were not limited to, trouble falling asleep, unwanted awakenings, or overall poor sleep quality caused by nocturnal heartburn, reflux, or any other GERD symptom.

Patients were excluded if they had any conditions other than GERD that could be the primary cause of or a significant contributor to the patient’s sleep disturbance. These conditions included, but were not limited to, severe anxiety, severe depression, panic attacks, sleep apnea, obstructed airways, chronic obstructive pulmonary disease requiring oxygen therapy or that was known to have disrupted the patient’s sleep, Pickwickian syndrome, restless leg syndrome, excessive need for nighttime urination, chronic insomnia of unknown cause, Buerger’s disease, and excessive caffeine use. Nighttime shift workers and patients planning to travel beyond three time zones during the study also were excluded.

Patients were eligible for trial participation while taking a stable regimen of any sleep medication, antihistamine, benzodiazepine, or antianxiety medication when use had been consistent for  $\geq 3$  months before trial entry and was expected to remain stable throughout the trial.

Exclusion criteria also included the following: use of a PPI within 1 wk before screening; active GI bleeding; any severe, unresolved, or unstable acute illness; any preexisting chronic illness likely to compromise assessment of efficacy or safety; need for continuous concurrent therapy with phenytoin, mephenytoin, warfarin, or antineoplastic agents for active cancer; known hypersensitivity to esomeprazole or antacid tablets (Gelusil<sup>®</sup>; 200 mg, aluminum hydroxide, 200 mg magnesium hydroxide, 25 mg simethicone; Warner-Lambert Consumer Healthcare [Parke-Davis], Morris Plains, NJ); and a history of drug addiction or alcohol abuse within the previous year. Women were required to be nonpregnant, nonlactating, and maintain effective contraception if of child-bearing potential.

### *Intervention*

After the screening period, all eligible patients were randomized sequentially in a 1:1:1 ratio to receive esomeprazole 40 mg, esomeprazole 20 mg, or placebo. The study sponsor provided a separate predetermined, computer-generated randomization schedule to each study center. All medications were provided as capsules of identical appearance to be ingested whole with water once daily in the morning, 30 min before breakfast, for 4 wk. Capsules were supplied in bottles with blinded and coded labels. The treatment code was not to be broken by the investigator except in medical emergencies.

No more than 6 antacid tablets (Gelusil<sup>®</sup>) per day or 21 tablets over any 7-day period were allowed as rescue medication for acute GERD symptoms during both the screening and treatment periods. Patients were expected to maintain usual sleep habits and consistent physical activity, caffeine intake, and nicotine-product use throughout the study. Patients were permitted moderate alcohol consumption if it was within the routine pattern for the individual before the study and remained consistent during the study. Compliance with study medications and use of rescue medication were measured by counting returned tablets. Patients were considered compliant with study treatments if they took between 75% and 125% of their study medication.

### *Outcomes*

The primary outcome variable was the relief of nighttime heartburn during the last 7 days of the trial as recorded by the patient on a diary card. Secondary outcome variables included change from baseline to week 4 in the global Pittsburgh Sleep Quality Index (PSQI) score (10), percentage of patients with complete resolution of sleep disturbances, relief of sleep disturbances, and percentage of days without GERD-associated sleep disturbances. Also assessed were the percentage of patients with complete resolution of daytime, nighttime, and 24-h heartburn symptoms, and the percentage

of patients with relief of daytime and 24-h heartburn symptoms. The Work Productivity and Activity Impairment Questionnaire: Sleep Disturbance-GERD (WPAI-SLEEP-GERD) (11) was used to assess work productivity.

### *Efficacy Assessments*

**HEARTBURN SYMPTOMS.** Patients assessed their symptoms on a diary card each morning during the screening period and before that morning's study medication dose during the treatment period. Severity of the most severe heartburn episodes experienced in the previous 24 h during daytime and nighttime were rated on a 4-point scale as: none (no heartburn); mild (awareness of heartburn, but easily tolerated); moderate (discomforting heartburn sufficient to cause interference with normal activities [including sleep]); severe (incapacitating heartburn with inability to perform normal activities [including sleep]). Nighttime was defined as the time between when the patient went to bed to try and go to sleep and when the patient got up in the morning to start daily activities. Heartburn was defined as a burning feeling, rising from the stomach or lower part of the chest toward the neck. Twenty-four-hour heartburn severity was derived from the worst response recorded by the patient for daytime or nighttime heartburn. Relief of heartburn was defined as a daily diary card response of "none" on at least 6 of 7 days, allowing for one "mild" response. Complete resolution of heartburn was defined as a response of "none" on 7 consecutive days. Symptom improvement was defined as any decrease in weekly symptom score from baseline compared with the last 7 days in the study.

**SLEEP DISTURBANCE.** On the same diary card, patients recorded "yes" or "no" answers to the question, "Did you have trouble sleeping last night due to your heartburn or other symptoms of GERD?" Study-center staff explained GERD symptoms to the patients and reviewed diary cards at each visit. Complete resolution of sleep disturbances was defined as a "no" response on 7 consecutive days, and relief of sleep disturbances was defined as a "yes" response on no more than 2 of 7 consecutive days.

**PSQI QUESTIONNAIRE.** The PSQI questionnaire (10) is a 19-item validated questionnaire completed by patients regarding the previous 1-month period. Items are grouped into seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score was weighted equally on a 0–3 scale, with 3 representing the worse effect, then summed to yield a global PSQI score, which could range from 0 to 21. Patients with a global score >5 are considered to have poor sleep quality (10). Patients completed the questionnaire at the randomization and final visits.

**WPAI-SLEEP-GERD QUESTIONNAIRE.** The WPAI-SLEEP-GERD Questionnaire (11) is a validated, self-administered, 6-question instrument that assessed whether the patient was currently employed, hours missed from work due to sleep disturbance from GERD, hours missed from work for other reasons, hours actually worked, the degree (1–10 scale) sleep disturbance secondary to GERD symptoms affected productivity while working, and the degree sleep disturbance due to GERD symptoms affected regular activities. Answers were based on the previous 7 days. Work hours lost due to GERD-related sleep disturbance were calculated as the sum of the hours missed due to GERD plus the actual hours worked multiplied by the degree (converted to a percentage) that GERD affected work productivity. The work hours saved were the differences between baseline and the week-4 values.

### *Safety Assessments*

Adverse events spontaneously reported by the patient or observed by the investigator were recorded and reviewed by the investigator. Laboratory measurement results (hematology and serum chemistry) were obtained at baseline and after 4 wk of treatment, and vital signs were measured at baseline and after 2 and 4 wk of treatment.

### *Statistical Analysis*

Efficacy analyses included all patients who were randomized to treatment and received  $\geq 1$  study dose and met the key enrollment criteria for nighttime heartburn and GERD-related sleep disturbances during the screening period (modified intention to treat). Because 7 days were needed to assess the primary endpoint, only patients who had data past 7 days were included in the analyses. Questionnaire analyses included patients who completed both baseline and postbaseline questionnaires.

The  $\chi^2$  test (SAS<sup>®</sup> procedure FREQ; SAS Institute, Inc., Cary, NC) was used to compare groups for the percentage of patients with relief or resolution of heartburn symptoms or sleep disturbances. Changes in the patient's PSQI scores from baseline to final visit were analyzed using analysis of covariance (SAS<sup>®</sup> procedure MIXED; SAS Institute, Inc.) using treatment as a factor and the baseline score as the covariate. Mean percentage of days without GERD-associated sleep disturbances were analyzed with a one-way analysis of variance model. The percentage of patients with poor sleep quality (PSQI score >5) was compared between groups using a Cochran-Mantel-Haenszel test stratified by whether or not they had a baseline PSQI score >5. Changes in WPAI-SLEEP-GERD variables were analyzed using analysis of variance. All statistical tests were two-sided. Nominal *p* values are presented for the secondary efficacy measures. Safety data are presented descriptively.

Calculations indicated that a sample size of 200 patients per treatment arm would provide at least 95% power to detect a 20% difference in nighttime heartburn relief rates (primary outcome), assuming a relief rate of 76% for each

esomeprazole group and 56% for the placebo group and using a two-sided test and an  $\alpha$  level of 0.025 for the two comparisons (each esomeprazole group compared with placebo).

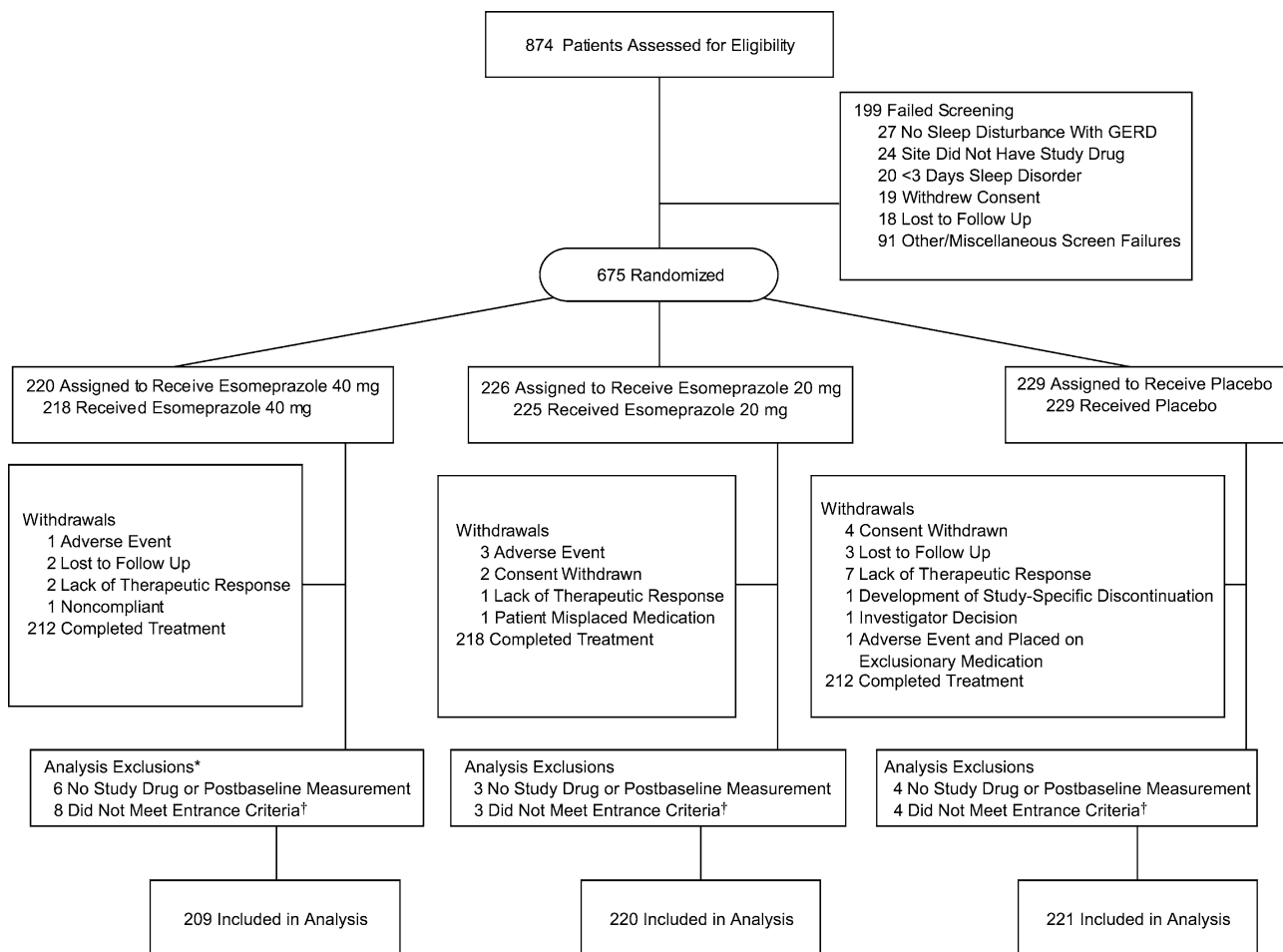
## RESULTS

Between April and August 2003, 874 patients were enrolled at 74 U.S. centers (Fig. 1). Of 675 patients randomized, 650 (96%) were included in efficacy analyses, and 642 (95%) completed the study. The main reasons for exclusion from efficacy analyses were lack of posttreatment data or lack of documented GERD-related sleep disturbances before randomization. Compliance was similar among groups (93.3% [195/209] in the esomeprazole 40-mg group, 94.5% [208/220] in the esomeprazole 20-mg group, and 94.1% [208/221] in the placebo group). The patients' demographic and clinical characteristics were similar among treatment groups (Table 1).

### Heartburn Symptoms and Sleep Disturbance

A significantly ( $p < 0.0001$ ) higher proportion of patients had relief of nighttime heartburn symptoms during the last 7 days of the trial (the primary trial outcome) in the esomeprazole 40- and 20-mg groups (53.1% and 50.5%, respectively) versus the placebo group (12.7%) (Fig. 2). The esomeprazole results were not significantly different from each other. The mean difference (95% confidence interval [CI] of the difference) between the esomeprazole 40-mg group and placebo was 40.4% (32.4%, 48.5%) and between the esomeprazole 20-mg group and placebo was 37.8% (29.9%, 45.7%). The average number of patients that a clinician must treat to relieve nighttime heartburn in 1 patient, or the number needed to treat (95% CI), was 3 (2.1, 3.1) for esomeprazole 40 mg and 3 (2.2, 3.4) for esomeprazole 20 mg.

Complete resolution and relief of GERD-associated sleep disturbances were similar in the esomeprazole 40- and 20-mg groups, and significantly higher ( $p < 0.0001$ ) in both groups than in the placebo group (Fig. 3). The percentages of



**Figure 1.** Patient disposition. \*Three patients are included in both categories. †Did not have heartburn or nighttime heartburn graded as moderate or severe on  $\geq 3$  of any consecutive 7 days of the screening period or did not have sleep disturbances associated with GERD on  $\geq 3$  of the last 7 days of the screening period.

**Table 1.** Demographic and Baseline Characteristics of Patients Included in Efficacy Analyses

Characteristic	Esomeprazole 40 mg (n = 209)	Esomeprazole 20 mg (n = 220)	Placebo (n = 221)
Mean age (SD), yr	46.3 (14.6)	46.8 (14.0)	46.5 (13.6)
Women (%)	125 (59.8)	132 (60.0)	131 (59.3)
Race, n (%)			
White	173 (82.8)	190 (86.4)	186 (84.2)
Black	18 (8.6)	16 (7.3)	17 (7.7)
Other	18 (8.6)	14 (6.4)	18 (8.1)
Mean nighttime heartburn severity score (SD)*	2.1 (0.53)	2.0 (0.54)	2.1 (0.50)
Mean number of days with sleep disturbances (SD) *	5.0 (1.5)	4.8 (1.4)	4.9 (1.4)
Patients using sleep medications (%) <sup>†</sup>	70 (34)	68 (32)	77 (36)
Prior PPI usage (%) <sup>‡</sup>	27 (13)	22 (10)	22 (10)

SD = standard deviation, PPI = proton pump inhibitor.

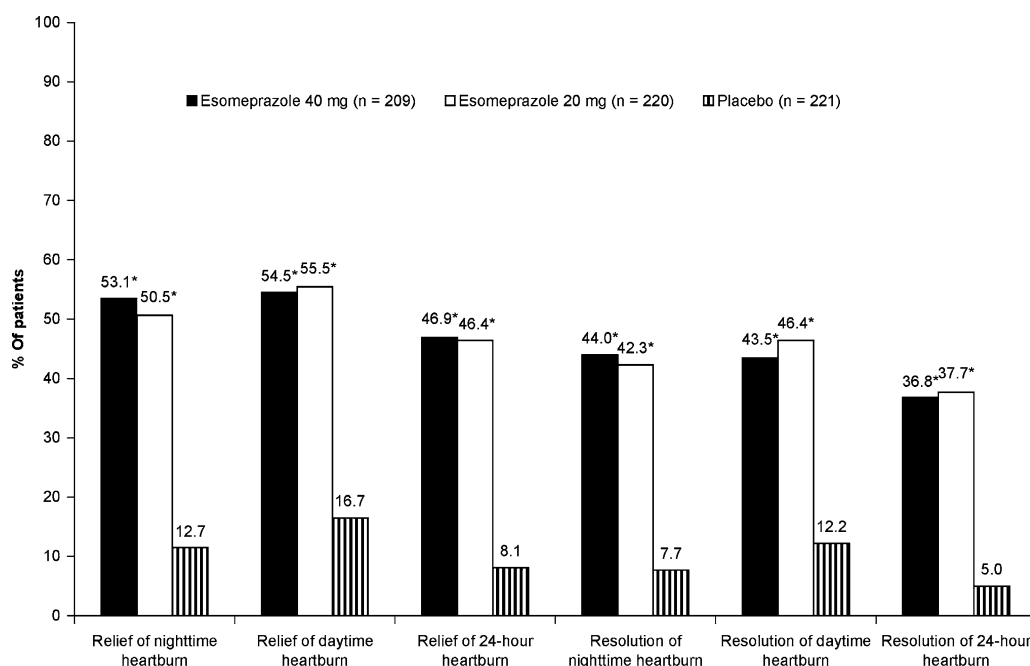
\*During the last 7 days of the screening period.

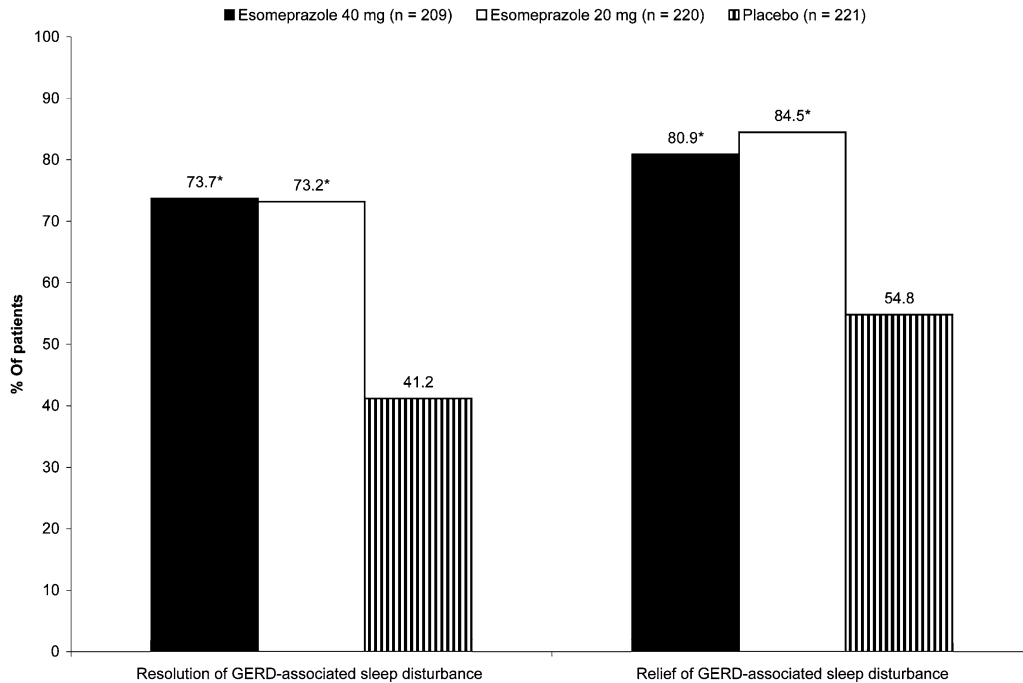
<sup>†</sup>The values shown are based only on the number of patients who completed the PSQI questionnaire at baseline (esomeprazole 40 mg, n = 204; esomeprazole 20 mg, n = 214; placebo, n = 214).<sup>‡</sup>Used >7 days before the initial enrollment visit.

patients who had complete resolution and relief of heartburn symptoms were also significantly higher ( $p < 0.0001$ ) in both esomeprazole groups than in the placebo group (Fig. 2). Significantly more patients in both esomeprazole groups than in the placebo group ( $p < 0.001$ ) had improvement (from baseline) during the last 7 days of treatment in nighttime heartburn symptoms: 175 of 209 (83.7%), 188 of 220 (85.5%), and 154 of 221 (69.7%) for the esomeprazole 40- and 20-mg and placebo groups, respectively. Similar numbers of patients, 174 of 209, 184 of 220, and 152 of 221, in the esomeprazole and placebo groups, respectively, (both  $p < 0.001$  vs placebo) had improvements in daytime symptoms. The numbers of patients with improvements in heartburn symptoms over 24 h

were 164 of 209 and 172 of 220 in the esomeprazole 40- and 20-mg groups compared with 102 of 221 in the placebo group (both  $p < 0.0001$  vs placebo). The mean (SD) percentages of days without sleep disturbances during the study were 83.2 (22.3)% and 84.1 (19.0)% in the esomeprazole 40-mg and 20-mg groups, respectively. Both percentages were significantly higher ( $p < 0.0001$ ) than the mean percentage of 61.5 (28.6)% in the placebo group.

Resolution of nighttime heartburn was predictive of sleep improvement. Of the 202 patients who had complete resolution of nighttime heartburn, only 8 did not also have complete resolution of GERD-related sleep disturbances during the same period. However, of the 406 patients who had complete

**Figure 2.** Percentage of patients with relief or resolution of heartburn during the last 7 days of the trial in the groups receiving esomeprazole 40 mg, esomeprazole 20 mg, and placebo. \* $p < 0.0001$  versus placebo.



**Figure 3.** Percentage of patients with resolution and relief of GERD-associated sleep disturbances during the last 7 days of the trial. \* $p < 0.0001$  versus placebo.

resolution of sleep disturbances, 212 did not have complete resolution of nighttime heartburn.

At the week-4 assessment, the mean (SD) number of rescue antacid tablets used daily by all randomized patients was similar between the esomeprazole 40-mg and 20-mg groups (1.0 [1.45] and 0.9 [1.41], respectively) but was significantly greater ( $p < 0.0001$ ) in the placebo group (1.7 [1.61]).

#### PSQI Questionnaire

At baseline, 527 of 632 (83%) of patients had poor sleep quality (global PSQI score,  $>5$ ). By week 4, 111 of 204 (54%) patients treated with esomeprazole 40 mg and 91 of 214 (43%) patients treated with esomeprazole 20 mg had poor sleep quality compared with 137 of 214 (64%) patients receiving placebo ( $p < 0.001$  for both treatments versus placebo). The least square mean (LSM) changes from baseline to week 4 in global PSQI score were similar between the esomeprazole 40-mg and 20-mg groups ( $-3.64$  and  $-4.00$ , respectively,

$p =$  not significant), and both improvements were significantly greater than in the placebo group ( $-2.19$ ;  $p < 0.0001$  for both comparisons) (Table 2).

#### WPAI-Sleep GERD Questionnaire

The degree to which sleep disturbance affected both work productivity and regular activities was significantly more reduced in the esomeprazole groups ( $p < 0.001$ ) than in the placebo group (Table 3). A total of 350 patients (54%) were employed, and the numbers employed were similar among groups. Approximately 16 work hours were lost due to GERD-related sleep disturbances at baseline (Table 3). After treatment, significantly more work hours were saved in both esomeprazole groups (11.6 and 12.3 h/wk/patient) compared with placebo (6.2 h/wk/patient) ( $p < 0.0001$ ) (Table 3). Using an average total employee compensation cost of \$24.59 from the U.S. Bureau of Labor Statistics for the fourth quarter of 2003 (12), the cost of hours saved per patient per week was \$286 and \$301 in the esomeprazole 40-mg and 20-mg

**Table 2.** PSQI Global Score

	Esomeprazole 40 mg (n = 204)	Esomeprazole 20 mg (n = 214)	Placebo (n = 214)
Baseline, mean (SD)	9.5 (4.1)	9.6 (3.9)	9.6 (3.8)
Week 4, mean (SD)	6.0 (3.8)	5.8 (4.0)	7.5 (4.0)
Change from baseline			
Mean (SD)	$-3.5$ (3.6)	$-3.8$ (3.8)	$-2.0$ (3.7)
LSM (SEM) [95% CI]	$-3.64$ (0.26) [ $-4.15$ , $-3.13$ ]*	$-4.00$ (0.26) [ $-4.50$ , $-3.50$ ]*	$-2.19$ (0.25) [ $-2.67$ , $-1.70$ ]

LSM = least squares mean; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; SEM = standard error of the mean.  
\* $p < 0.0001$  versus placebo.

**Table 3.** Mean (SD) Effects of Sleep Disturbance on Work Productivity, Work Hours Lost, and Regular Activities Based on Analyses of the WPAI-SLEEP-GERD Questionnaires

	Esomeprazole 40 mg (n = 114)	Esomeprazole 20 mg (n = 117)	Placebo (n = 119)
Degree sleep disturbance affected work productivity			
Baseline	4.0 (2.7)	4.0 (2.5)	3.9 (2.4)
Week 4	1.0 (1.5)	0.9 (1.7)	2.3 (2.2)
Change from baseline	-3.0 (2.9)*	-3.1 (2.5)*	-1.6 (2.6)
Work hours lost/week/patient			
Baseline	16.2 (12.3)	16.1 (10.7)	15.8 (13.0)
Week 4	4.5 (7.0)	3.8 (7.3)	9.6 (11.2)
Work hours saved/week/patient <sup>†</sup>	11.6 (13.3)*	12.3 (11.5)*	6.2 (12.9)
Degree sleep disturbance affected regular activities <sup>‡</sup>			
Baseline	4.8 (2.6)	4.7 (2.7)	4.9 (2.6)
Week 4	1.6 (2.2)	1.2 (2.0)	2.9 (2.7)
Change from baseline	-3.2 (3.1) <sup>§</sup>	-3.5 (2.8) <sup>§</sup>	-2.0 (2.8)

SD = standard deviation; WPAI-SLEEP-GERD = Work Productivity and Activity Impairment Questionnaire: Sleep Disturbance—Gastroesophageal Reflux Disease.

\* $p < 0.001$  versus placebo.

<sup>†</sup>Change from baseline in work hours lost.

<sup>‡</sup>Analysis included all patients who completed the questionnaires (esomeprazole 40 mg, n = 205; esomeprazole 20 mg, n = 214; placebo, n = 217).

<sup>§</sup> $p < 0.0001$  versus placebo.

groups, respectively, which represents a cost savings of approximately \$131 and \$148 per week per patient, respectively, compared with placebo.

### Safety

Both doses of esomeprazole were well tolerated (Table 4). Four patients experienced serious adverse events, but none of these was considered related to treatment. Five patients discontinued due to adverse events, and all but one (dry eye in the esomeprazole 20-mg group) was considered unrelated to treatment. Equal numbers of patients had adverse events considered to be treatment related in the esomeprazole groups, and fewer patients had treatment-related adverse events in the placebo group.

### DISCUSSION

The results of this prospective, randomized, placebo-controlled trial showed that esomeprazole 40 and 20 mg once

daily for 4 wk are similarly effective in reducing nighttime heartburn and related sleep disturbances. Additionally, both doses of esomeprazole improved sleep quality, reduced lost work hours, and increased work productivity.

This trial included patients with GERD who consistently had both moderate-to-severe nighttime heartburn and GERD-associated sleep disturbance before receiving trial treatment. Relief of nighttime heartburn (the primary outcome) during the last 7 days of the trial occurred in more than 50% of esomeprazole recipients compared with 13% of placebo recipients. Similar responses to esomeprazole and placebo were observed for secondary heartburn outcomes, such as complete resolution or relief of heartburn during nighttime, daytime, and 24-h periods. These results are consistent with those previously reported from studies investigating relief and resolution of heartburn symptoms in patients with symptomatic GERD receiving short-term PPI therapy (13, 14). In this trial, resolution of nighttime heartburn was predictive of resolution of GERD-related sleep disturbances. However, among those whose sleep disturbances were resolved, resolution of

**Table 4.** Number (%) of Patients with Adverse Events

	Esomeprazole 40 mg (n = 220)	Esomeprazole 20 mg (n = 226)	Placebo (n = 229)
Any AE	74 (33.6)	59 (26.1)	58 (25.3)
Treatment-related AE	15 (6.8)	15 (6.6)	7 (3.1)
Serious AE	2 (0.9)	1 (0.4)	1 (0.4)
Discontinuation due to AE	1 (0.5)	3 (1.3)	1 (0.4)
Most common AE*			
Diarrhea	5 (2.3)	11 (4.9)	7 (3.1)
Headache	11 (5.0)	4 (1.8)	5 (2.2)
Nausea	6 (2.7)	3 (1.3)	4 (1.7)
Flatulence	5 (2.3)	4 (1.8)	1 (0.4)
Abdominal pain	4 (1.8)	4 (1.8)	3 (1.3)

AE = adverse event.

\*Experienced by  $\geq 4$  patients in any treatment group.

nighttime heartburn was not always achieved. Therefore, asking about nighttime heartburn symptoms might predict sleep disturbances, but sleep dysfunction will resolve in many patients whose nighttime heartburn symptoms might not be severe enough to interfere with sleep. In this study, we did not assess the severity of other GERD symptoms that could have contributed to sleep disturbances. Further studies would be needed to determine the relative contributions of various GERD symptoms to sleep disturbances.

Previous studies also have indicated that GERD treatment can improve sleep as assessed by patients (3, 15, 16). Chand *et al.* (3) found significant improvements from baseline in the PSQI score in 18 patients with GERD who received esomeprazole 40 mg for 8 wk. In another study (15) in a sleep laboratory, a small number ( $n = 12$ ) of patients with GERD received a standardized provocative meal to induce nighttime heartburn and a single dose of a histamine<sub>2</sub>-receptor antagonist (ranitidine 75 mg) or placebo at 9 pm. Patient-assessed discomfort and sleep disturbances were significantly improved compared with placebo, but objective polysomnographic measurements did not change significantly. A large prospective, open-label study followed 6215 patients to assess the progression of GERD in patients under routine care (16), and the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire was used to evaluate quality of life. After 2 wk of standardized esomeprazole therapy, the sleep dysfunction subscale of QOLRAD was significantly improved in these patients.

A limitation of the current trial is that the favorable effects of PPI therapy on sleep would have been better defined if pH monitoring could have been done. With the development of pH-monitoring techniques that would have less potential effects on sleep, future studies may be able to more clearly define the effects of acid suppression. Another limitation that could affect the application of these results to the general GERD population is that the patients chosen for this trial had moderate-to-severe nighttime heartburn, and patients with less severe nighttime heartburn were excluded.

The high percentage of patients with resolution of sleep disturbances in the current trial is both statistically and clinically significant. As expected, these diary card assessments of sleep improvement were confirmed using the PSQI (10). The PSQI is a well-established and validated instrument that measures general sleep quality. It has become one of the most commonly used assessments in sleep research and has been shown to be an appropriate and valuable tool to define sleep disorders and assess responses to interventions measures (17). A limitation is that this assessment is subjective. However, objective measures of sleep would have been impractical in this large multicenter study, and the measurements themselves could disrupt sleep.

The WPAI-SLEEP-GERD questionnaire is also a validated instrument (11, 18). Respondents provide a subjective evaluation of time absent from work and reduced work productivity. GERD, as most functional disorders, has more of an effect on work productivity than it does on absenteeism. Previous re-

search using the WPAI-GERD questionnaire has shown that GERD can affect work productivity and that symptom severity and the amount of reduced work productivity reported are strongly correlated (18). In addition, Dean *et al.* (7) have reported that nocturnal heartburn is a predictor of reduced productivity, with an odds ratio of 1.24 ( $p < 0.01$ ). Health and productivity are inextricably linked, and, with increased medical costs, payors must be able to determine the value or return on investment of the health-care interventions that they pay for and that patients receive. Optimal pharmaceutical utilization that reduces productivity losses is of benefit to the patients and payors alike.

Sleep disorders may be one of the most prevalent extraesophageal complications of GERD (4, 6, 7) and are often unrecognized. It is apparent from the results of this study that sleep disturbance in patients with nighttime heartburn is a treatable condition that is very responsive to effective, acid-suppressive medical therapy for GERD. Esomeprazole is representative of a class of drugs (PPIs) that are potent acid-suppressive agents. In this trial, esomeprazole 40 or 20 mg effectively improved nighttime heartburn symptoms and sleep quality in patients with moderate-to-severe nighttime heartburn and reduced sleep disturbances associated with GERD. Additionally, these improvements were associated with improvements in patients' daily activities, including work productivity, which could have profound potential economic benefits. Therefore, treatment strategies for GERD should include improved sleep as an important goal if clinicians are to define "optimal therapy" as that which achieves the best clinical outcomes.

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