

# Effects of Omeprazole on Sleep Disturbance: Randomized Multicenter Double-Blind Placebo-Controlled Trial

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**OBJECTIVES:** Gastroesophageal reflux is considered to cause sleep disturbance, whereas proton pump inhibitor (PPI) administration is reported to improve insomnia associated with gastroesophageal reflux disease (GERD). The majority of patients with gastroesophageal reflux are asymptomatic and a significant number with erosive esophagitis are also reported to be asymptomatic. We examined whether PPI administration has a therapeutic effect for improving insomnia in patients without reflux symptoms in the same manner as patients with reflux symptoms.

**METHODS:** We performed a randomized multicenter double-blind placebo-controlled trial using 176 patients with insomnia regardless of the presence of reflux symptoms. The patients were divided into those administered omeprazole (20 mg) or a placebo for 14 days. Four self-reporting questionnaires, QOLRAD-J (Japanese translation of Quality of Life in Reflux and Dyspepsia), Pittsburg Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and a sleep diary, were used for evaluating GERD-related quality of life (QOL) and sleep disturbance.

**RESULTS:** We evaluated 171 patients with insomnia, of whom 69 had typical reflux symptoms. Omeprazole statistically significantly improved GERD-related QOL from  $30.8 \pm 0.7$  to  $33.0 \pm 0.5$  ( $P < 0.01$ ) (QOLRAD-J, total) and from  $6.0 \pm 0.2$  to  $6.6 \pm 0.1$  ( $P < 0.01$ ) (QOLRAD-J, sleep-related) when administered to patients with reflux symptoms. Omeprazole also improved insomnia significantly better than the placebo in patients with reflux symptoms; PSQI, from  $9.3 \pm 0.5$  to  $7.9 \pm 0.5$  ( $P < 0.01$ ) and sleep diary, from  $2.1 \pm 0.1$  to  $1.8 \pm 0.1$  ( $P < 0.01$ ). On the other hand, the therapeutic effects of omeprazole and the placebo were not different in patients without reflux symptoms.

**CONCLUSIONS:** Our results showed that PPI administration is effective only for insomnia in patients with reflux symptoms.

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**Subject Category:** Esophagus

## INTRODUCTION

Sleep disturbance is an important extraesophageal complication in patients with gastroesophageal reflux disease (GERD), and recently a close association between them has been reported by many investigators.<sup>1–3</sup> In an epidemiological study on GERD and sleep disorders conducted in Japan, sleep disturbance was significantly more prevalent in cases with frequent heartburn as compared with those without heartburn.<sup>4</sup> Jansson *et al.*<sup>1</sup> reported a positive association between GERD and the presence of insomnia, sleeplessness, and problems with falling asleep.

Many clinical studies have indicated that proton pump inhibitor (PPI) administration can improve sleep disorders associated with GERD, although the evidence presented has not always been adequate because of small sample size or inappropriate design.<sup>5–8</sup>

Various factors in addition to GERD are known to be involved in the pathogenesis of sleep disturbance, although the quantitative role of symptomatic GERD has not been fully investigated. In addition, GERD without typical reflux symptoms may have some role in sleep disturbance, as a large number of patients have endoscopy-proven asymptomatic reflux esophagitis. As silent patients with GERD frequently develop sleep disturbance, PPIs may improve that in patients with and without reflux symptoms.

We performed a multicenter randomized double-blind placebo-controlled trial of patients with primary insomnia, and with and without reflux symptoms who visited an outpatient clinic for treatment of sleep disturbance. We attempted to elucidate the percentage of patients with typical reflux symptoms among all who made a clinic visit with primary insomnia to clarify the effectiveness of PPI

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administration for treatment of insomnia in patients with and without reflux symptoms.

## METHODS

This multicenter randomized double-blind placebo-controlled prospective study of patients with sleep disturbance was conducted from 2010 to 2012 at Shimane University Hospital, and 13 affiliated hospitals and clinics. Based on previous reports, the therapeutic effects of PPIs on sleep disturbance are assumed to occur in ~70% of patients with GERD, whereas a placebo shows such an effect in ~40% of patients.<sup>9</sup> In addition, ~25% of patients with insomnia are reported to have GERD symptoms.<sup>10,11</sup> Therefore, the required sample size for the present study was estimated to be a minimum of 150, based on a two-tailed test with a significance level of 0.05 and power level of 0.80.

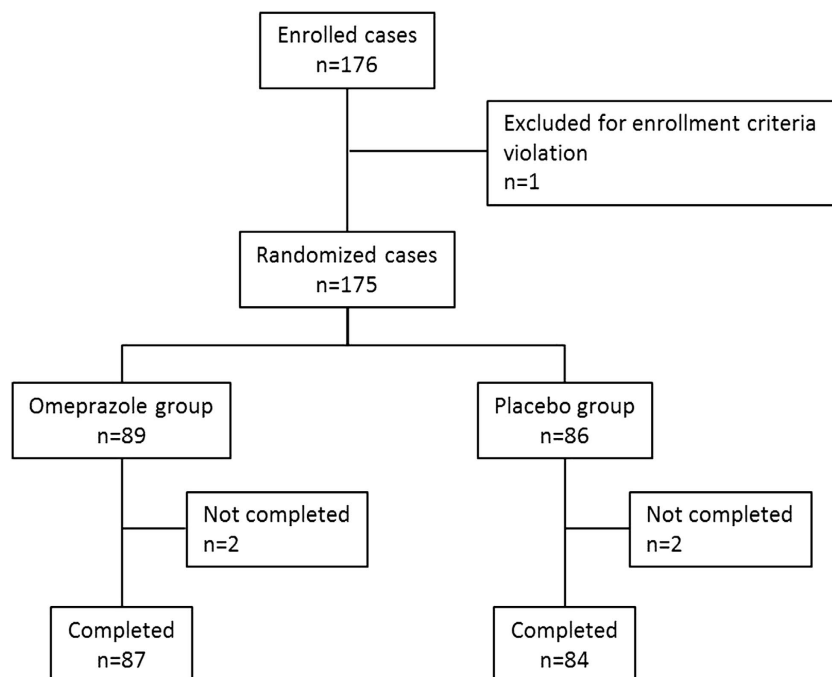
A total of 176 patients who visited outpatient clinics for management of primary insomnia were enrolled. Patients who took hypnotics, PPIs, and/or histamine H<sub>2</sub> receptor antagonists within 2 weeks before enrollment, those treated for mental disorders, and those with serious underlying diseases that may influence sleep quality were excluded. Women who were pregnant or had a high possibility of pregnancy, and patients allergic to omeprazole were also excluded. Written informed consent was obtained from all patients before starting the study that was carried out in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shimane University on 26 April 2010 and registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) under the number UMIN 000003626.

Background and clinical factors such as age, gender, height, body weight, body mass index, drinking, smoking,

presence of typical GERD symptoms (heartburn, acid regurgitation), throat discomfort, cough, chest pain, otalgia, and asthma were recorded at the time of enrollment.

The patients were randomly assigned to two groups according to a computer-assisted prefixed order, and then one group took 20 mg of omeprazole and the other an indistinguishable placebo 30 min before dinner once a day for 2 weeks. Evening administration of omeprazole was selected in this study in order to maximize its acid suppressive effect during the nocturnal period, as we previously showed.<sup>12</sup> Block randomization was used in this study. One block consisted of four samples, two of which were omeprazole and the other two were a placebo. The enrolled patients and physicians were blinded by providing all study drugs as tablets with an identical appearance in sequentially numbered opaque containers. This random allocation sequence was generated by a certified pharmacist (K.N.). The patients were enrolled by the physicians who participated in this study and allocated according to the prefixed sequence. Sleep disturbance and GERD-related quality of life (QOL) were evaluated before and after 2 weeks of treatment in all patients. Compliance to the drug treatment protocol was also evaluated.

Reflux symptom-related impairment of QOL was evaluated using the QOLRAD-J (Japanese translation of Quality of Life in Reflux and Dyspepsia questionnaire). QOLRAD is a disease-specific QOL instrument that includes 25 items in 5 domains: Emotional distress, Sleep disturbance, Food/drink problems, Physical/social functioning, and Vitality.<sup>13</sup> The scores for each were weighted equally from 1 to 7. Scores for the 5 domains were added to obtain a total score ranging from 7 to 35, with lower scores indicating worse GERD-related QOL. In addition, the score for the "Sleep disturbance" domain (ranging from 1 to 7) was also calculated to evaluate specific QOL impairment related to sleep in this study. We



**Figure 1** Enrolled patients.

**Table 1** Characteristics of enrolled patients

|                                       | Total (n = 171) | Omeprazole (n = 87) | Placebo (n = 84) | P value  |
|---------------------------------------|-----------------|---------------------|------------------|----------|
| Age                                   | 59.0 ± 1.1      | 59.0 ± 1.5          | 59.0 ± 1.6       | NS       |
| Gender (M/F)                          | 86/85           | 41/46               | 45/39            | NS       |
| Height (cm)                           | 159.7 ± 2.0     | 159.6 ± 2.1         | 159.9 ± 3.4      | NS       |
| Weight (kg)                           | 58.7 ± 1.2      | 59.1 ± 1.7          | 58.3 ± 1.7       | NS       |
| BMI                                   | 22.9 ± 0.4      | 23.1 ± 0.5          | 22.7 ± 0.6       | NS       |
| Smoking (+)                           | 27 (15.8%)      | 15 (17.2%)          | 12 (14.3%)       | NS       |
| Alcohol consumption (+)               | 68 (39.8%)      | 36 (41.4%)          | 32 (38.1%)       | NS       |
| <i>Symptoms (duplicates included)</i> |                 |                     |                  |          |
| Heartburn                             | 58 (33.9%)      | 31 (35.6%)          | 27 (32.1%)       | NS       |
| Acid regurgitation                    | 45 (26.3%)      | 21 (24.1%)          | 24 (28.6%)       | NS       |
| Throat discomfort                     | 35 (20.5%)      | 16 (18.4%)          | 19 (22.6%)       | NS       |
| Cough                                 | 25 (14.6%)      | 18 (20.7%)          | 7 (8.3%)         | P < 0.05 |
| Chest pain                            | 18 (10.5%)      | 9 (10.3%)           | 9 (10.7%)        | NS       |
| Otalgia                               | 12 (7.0%)       | 6 (6.9%)            | 6 (7.1%)         | NS       |
| Asthma                                | 7 (4.1%)        | 5 (5.7%)            | 2 (2.4%)         | NS       |
| <i>QOLRAD</i>                         |                 |                     |                  |          |
| Total                                 | 32.6 ± 0.3      | 32.7 ± 0.4          | 32.6 ± 0.5       | NS       |
| Sleep related                         | 6.4 ± 0.1       | 6.4 ± 0.1           | 6.4 ± 0.1        | NS       |
| <i>Sleep Scales</i>                   |                 |                     |                  |          |
| PSQI                                  | 9.6 ± 0.2       | 9.8 ± 0.3           | 9.4 ± 0.3        | NS       |
| ESS                                   | 5.7 ± 0.3       | 5.8 ± 0.5           | 5.7 ± 0.5        | NS       |
| Diary record                          | 2.1 ± 0.05      | 2.1 ± 0.1           | 2.1 ± 0.1        | NS       |

BMI, body mass index; ESS, Epworth Sleepiness Scale; M/F, male/female; NS, not significant; PSQI, Pittsburgh Sleep Quality Index; QOLRAD, Quality of Life in Reflux and Dyspepsia. Values are shown as mean ± s.e.

**Table 2** Effects of omeprazole and placebo on reflux and sleep indices

|                     | Omeprazole (n = 87) |            | P value  | Placebo (n = 84) |            | P value  |
|---------------------|---------------------|------------|----------|------------------|------------|----------|
|                     | Pre                 | Post       |          | Pre              | Post       |          |
| <i>QOLRAD</i>       |                     |            |          |                  |            |          |
| Total               | 32.7 ± 0.4          | 33.8 ± 0.2 | P < 0.01 | 32.6 ± 0.4       | 33.1 ± 0.4 | NS       |
| Sleep related       | 6.4 ± 0.1           | 6.7 ± 0.1  | P < 0.01 | 6.4 ± 0.1        | 6.6 ± 0.1  | NS       |
| <i>Sleep Scales</i> |                     |            |          |                  |            |          |
| PSQI                | 9.8 ± 0.3           | 8.0 ± 0.3  | P < 0.01 | 9.4 ± 0.3        | 8.0 ± 0.4  | P < 0.01 |
| ESS                 | 5.8 ± 0.5           | 5.2 ± 0.5  | NS       | 5.7 ± 0.5        | 5.0 ± 0.5  | P < 0.05 |
| Diary record        | 2.1 ± 0.1           | 1.9 ± 0.1  | P < 0.01 | 2.1 ± 0.1        | 1.9 ± 0.1  | P < 0.05 |

ESS, Epworth Sleepiness Scale; NS, not significant; PSQI, Pittsburgh Sleep Quality Index; QOLRAD, Quality of Life in Reflux and Dyspepsia. Values are shown as mean ± s.e.

also utilized the Epworth Sleepiness Scale (ESS) and a modified Pittsburgh Sleep Quality Index (PSQI) with the assessment period changed to 1 week, whereas diary records were used for evaluation of sleep quality. The ESS is a self-administrated questionnaire consisting of 8 self-rated items, each scored from 0 to 3, that measures sleep propensity.<sup>14</sup> With it, the habitual “likelihood of dozing or falling asleep” in common situations of daily living is measured. An ESS score ranging from 0 to 24 represents the sum of individual items, with values > 10 considered to indicate significant sleepiness.<sup>14</sup> The modified PSQI is also a self-administrated questionnaire that evaluates subjective sleep quality over the previous week. The self-rated items of the PSQI generate 7 component scores (range of subscale scores, 0–3); sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and

daytime dysfunction. The 7 component scores are added to obtain a global score ranging from 0 to 21, with higher scores indicating worse sleep quality.<sup>15</sup> Doi *et al.*<sup>15</sup> showed that a cutoff point of 5.5 in the Japanese version of the PSQI global score provided estimations of sensitivity and specificity of 85.7% and 86.6%, respectively, for primary insomnia. The diary record utilized was an original self-reporting tool developed by our group. Subjects evaluated sleep quality based on a 4-point Likert scale from 1 to 4 during the first 3 and final 3 days of the study period. The mean value of each 3-day period was calculated as a representative value. All investigators who participated in this study had access to the study data, and reviewed and approved the final manuscript.

**Statistical analysis.** The  $\chi^2$  test and Student’s *t*-test were used for comparing background factors, and a paired *t*-test

was used when comparing data obtained before and after treatment. All calculations were done with SPSS software (Abacus Concepts, Berkeley, CA) for Windows. Data are expressed as the mean  $\pm$  s.e.  $P < 0.05$  was considered to indicate statistical significance.

## RESULTS

**Enrolled patients.** This trial was ended in 2011, when the projected number of patients had been examined, with no adverse events reported. Originally, 176 patients were enrolled in the study, after which 1 patient was excluded because of an enrollment criteria violation, and thus a total of

175 patients were randomized into two groups to receive omeprazole or placebo. As two patients in each group were subsequently lost during the treatment period and excluded from analysis, 87 subjects in the omeprazole group and 84 in the placebo group were subjected to analysis of the therapeutic effect of PPI administration (Figure 1). Appropriate randomization was confirmed based on the lack of significant differences between the omeprazole and placebo groups, except for prevalence of cough (Table 1).

**Table 3** Characteristics of patients with and without heartburn and/or acid regurgitation

|   | Heartburn and/or acid regurgitation |                    | P value    |
|---|-------------------------------------|--------------------|------------|
|   | Positive (n = 69)                   | Negative (n = 102) |            |
| Age (years)                                 | 56.8 $\pm$ 1.6                      | 60.5 $\pm$ 1.4     | NS         |
| Gender (M/F)                                | 37/32                               | 49/53              | NS         |
| Height (cm)                                 | 161.7 $\pm$ 2.6                     | 158.3 $\pm$ 2.8    | $P < 0.05$ |
| Weight (kg)                                 | 60.8 $\pm$ 2.0                      | 57.4 $\pm$ 1.4     | NS         |
| BMI   | 23.1 $\pm$ 0.7                      | 22.8 $\pm$ 0.5     | NS         |
| Smoking (+)                                 | 7 (10.1%)                           | 20 (19.6%)         | NS         |
| Alcohol consumption (+)                     | 31 (44.9%)                          | 37 (36.3%)         | NS         |
| <i>Other symptoms (duplicates included)</i> |                                     |                    |            |
| Throat discomfort                           | 24 (34.8%)                          | 11 (10.8%)         | $P < 0.01$ |
| Cough                                       | 15 (21.7%)                          | 10 (9.8%)          | $P < 0.05$ |
| Chest pain                                  | 14 (20.3%)                          | 4 (3.9%)           | $P < 0.01$ |
| Otalgia                                     | 6 (8.7%)                            | 6 (5.9%)           | NS         |
| Asthma                                      | 5 (7.2%)                            | 2 (2.0%)           | NS         |
| <i>QOLRAD</i>                               |                                     |                    |            |
| Total                                       | 30.7 $\pm$ 0.5                      | 33.9 $\pm$ 0.2     | $P < 0.01$ |
| Sleep related                               | 6.0 $\pm$ 0.1                       | 6.6 $\pm$ 0.1      | $P < 0.01$ |
| <i>Sleep Scales</i>                         |                                     |                    |            |
| PSQI  | 9.1 $\pm$ 0.4                       | 10.0 $\pm$ 0.3     | NS         |
| ESS   | 6.6 $\pm$ 0.6                       | 5.2 $\pm$ 0.4      | NS         |
| Diary record                                | 2.1 $\pm$ 0.1                       | 2.2 $\pm$ 0.1      | NS         |

BMI, body mass index; ESS, Epworth Sleepiness Scale; M/F, male/female; NS, not significant; PSQI, Pittsburg Sleep Quality Index; QOLRAD, Quality of Life in Reflux and Dyspepsia.

Values are shown as mean  $\pm$  s.e.

**Prevalence of reflux symptoms in patients with insomnia.** The patients reported various symptoms including typical reflux symptoms. Heartburn was the most frequently reported, followed by acid regurgitation, as shown in Table 1. These are usually regarded as typical reflux symptoms, and suggest the presence of GERD with higher sensitivity and specificity. When patients who reported heartburn and/or acid regurgitation were defined as having GERD, 40.4% (69/171) of the present patients with insomnia were considered to have GERD.

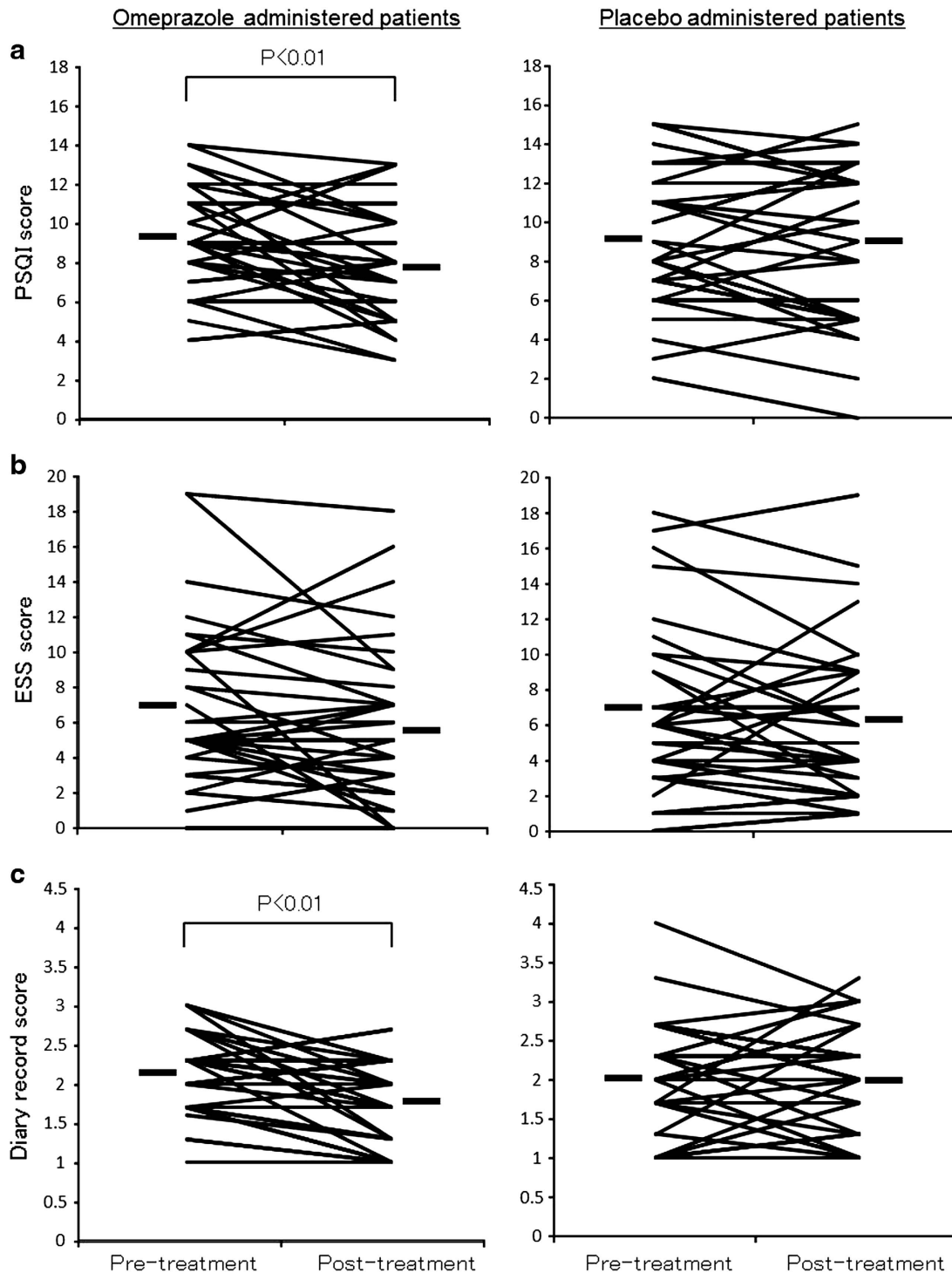
**Comparative efficacy of omeprazole and placebo for all patients.** GERD-related impairment of QOL as evaluated with total QOLRAD-J score was significantly improved in the omeprazole group (3.4% improvement), but not in the placebo group (1.5%) (Table 2). QOLRAD-J sleep-related score was also significantly improved by the administration of omeprazole, but not by the placebo (4.7% vs. 3.1%). These results confirmed the beneficial therapeutic effect of omeprazole for treatment of GERD. On the other hand, both omeprazole and the placebo showed similar effects on sleep disturbance when evaluated by ESS, PSQI, and the sleep diary records, with no remarkable differences seen between the groups. Thus, a large placebo effect for treatment of insomnia was unintentionally confirmed. For patients with insomnia as a whole, no beneficial effect of omeprazole over that of the placebo on improvement of sleep quality was found in our study.

**Stratified analysis of subjects with and without typical reflux symptoms.** Our patients with insomnia were then divided into reflux symptom-positive and -negative groups, and the effect of omeprazole was separately

**Table 4a** Effects of omeprazole and placebo on reflux and sleep indices in patients with heartburn and/or acid regurgitation

|                     | Omeprazole (n = 34) |                | P value    | Placebo (n = 35) |                | P value    |
|---------------------|---------------------|----------------|------------|------------------|----------------|------------|
|                     | Pre                 | Post           |            | Pre              | Post           |            |
| <i>QOLRAD</i>       |                     |                |            |                  |                |            |
| Total               | 30.8 $\pm$ 0.7      | 33.0 $\pm$ 0.5 | $P < 0.01$ | 30.7 $\pm$ 0.8   | 32.1 $\pm$ 0.6 | $P < 0.05$ |
| Sleep related       | 6.0 $\pm$ 0.2       | 6.6 $\pm$ 0.1  | $P < 0.01$ | 6.0 $\pm$ 0.2    | 6.3 $\pm$ 0.2  | NS         |
| <i>Sleep Scales</i> |                     |                |            |                  |                |            |
| PSQI                | 9.3 $\pm$ 0.5       | 7.9 $\pm$ 0.5  | $P < 0.01$ | 8.9 $\pm$ 0.6    | 8.6 $\pm$ 0.7  | NS         |
| ESS                 | 6.9 $\pm$ 0.8       | 5.8 $\pm$ 0.8  | NS         | 6.5 $\pm$ 0.8    | 6.0 $\pm$ 0.8  | NS         |
| Diary record        | 2.1 $\pm$ 0.1       | 1.8 $\pm$ 0.1  | $P < 0.01$ | 2.0 $\pm$ 0.1    | 2.0 $\pm$ 0.1  | NS         |

ESS, Epworth Sleepiness Scale; NS, not significant; PSQI, Pittsburg Sleep Quality Index; QOLRAD, Quality of Life in Reflux and Dyspepsia. Values are shown as mean  $\pm$  s.e.



**Figure 2** Effects of omeprazole and placebo on sleep scores in patients with heartburn and/or acid regurgitation. Omeprazole 20 mg in a day was administered for 2 weeks to 34 patients and a placebo to 35 patients with sleep disturbance and typical reflux symptoms. Pittsburg Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and diary record were used for the assessments of sleep quality. Each line connecting pretreatment and posttreatment period represents an investigated case. Broad horizontal lines represent mean values for each score. Only in omeprazole-treated cases, statistically significant improvement of sleep quality was observed. (a) Changes of PSQI score; (b) changes of ESS score; (c) changes of diary record score.

examined in them. Patients with typical reflux symptoms also more frequently had atypical reflux symptoms including throat discomfort, cough, and chest pain (Table 3). In addition, as expected, they had lower QOLRAD-J and

GERD-related QOL scores. As for quality of sleep evaluated by PSQI, ESS, and the diary records, there was no significant difference between the reflux symptom-positive and -negative groups.



**Table 4b** Effects of omeprazole and placebo on reflux and sleep indices in patients without heartburn or acid regurgitation

|                     | Omeprazole (n = 53) |            | P value  | Placebo (n = 49) |            | P value  |
|---------------------|---------------------|------------|----------|------------------|------------|----------|
|                     | Pre                 | Post       |          | Pre              | Post       |          |
| <b>QOLRAD</b>       |                     |            |          |                  |            |          |
| Total               | 33.9 ± 0.2          | 34.3 ± 0.2 | NS       | 33.9 ± 0.4       | 33.9 ± 0.4 | NS       |
| Sleep related       | 6.6 ± 0.1           | 6.8 ± 0.1  | P < 0.05 | 6.7 ± 0.1        | 6.8 ± 0.1  | NS       |
| <b>Sleep Scales</b> |                     |            |          |                  |            |          |
| PSQI                | 10.1 ± 0.3          | 8.1 ± 0.4  | P < 0.01 | 9.8 ± 0.4        | 7.6 ± 0.5  | P < 0.01 |
| ESS                 | 5.2 ± 0.6           | 4.8 ± 0.5  | NS       | 5.2 ± 0.6        | 4.3 ± 0.6  | P < 0.05 |
| Diary record        | 2.2 ± 0.1           | 1.9 ± 0.1  | P < 0.01 | 2.1 ± 0.1        | 1.9 ± 0.1  | P < 0.01 |

ESS, Epworth Sleepiness Scale; NS, not significant; PSQI, Pittsburg Sleep Quality Index; QOLRAD, Quality of Life in Reflux and Dyspepsia. Values are shown as mean ± s.e.

In patients with reflux symptoms, omeprazole statistically significantly improved GERD-related QOL from  $30.8 \pm 0.7$  to  $33.0 \pm 0.5$  ( $P < 0.01$ ) (QOLRAD-J, total) and from  $6.0 \pm 0.2$  to  $6.6 \pm 0.1$  ( $P < 0.01$ ) (QOLRAD-J, sleep-related). Omeprazole administration also statistically significantly improved sleep quality (PSQI 15.1%, ESS 15.9%, diary record 14.3% improvement), whereas administration of the placebo had no significant therapeutic effect (3.4%, 7.7%, and 0% respectively) (Table 4a and Figure 2). In contrast, in patients without reflux symptoms, there was no difference regarding the therapeutic effects of omeprazole and the placebo regarding improvement of sleep quality (PSQI 19.8% vs. 22.4%, ESS 7.7% vs. 17.3%, and diary record 13.6% vs. 9.5%; Table 4b). The placebo effect on sleep quality was especially large in this group of patients, and both placebo and omeprazole significantly improved sleep quality in patients without reflux symptoms. In patients with only atypical reflux symptoms ( $n = 22$ ), there was no significant difference regarding therapeutic effect on sleep disturbance between omeprazole and placebo. When sleep quality improvement after omeprazole treatment was compared between cases with and without sleep-related QOL impairment, only those with a lower QOLRAD-J sleep-related score showed consistent improvement in sleep quality measured by PSQI and ESS.

## DISCUSSION

We investigated the prevalence of reflux symptoms in patients with primary insomnia and conducted a randomized multicenter double-blind placebo-controlled trial of the effects of PPI treatment on insomnia. Our results showed that ~40% of the patients with insomnia had typical reflux symptoms such as heartburn and acid regurgitation. Omeprazole was effective for improving insomnia in these patients with reflux symptoms, whereas it was not more effective than the placebo for insomnia in patients without reflux symptoms.

GERD is known to be complicated by various extraesophageal conditions including asthma, dental erosion, and insomnia,<sup>16–18</sup> whereas insomnia is associated with impaired health-related QOL and frequently found in elderly individuals.<sup>19</sup> GERD is considered to be one of the most important pathogenetic factors of insomnia<sup>20</sup> and has increased in importance with its recent increase in prevalence. Furthermore, GERD may prevent sleep because of unpleasant reflux

symptoms. Symptomatic acid reflux may interrupt sleep and prevent falling asleep again, and thus it is easy to conclude that it can cause sleep disturbance. In the present study, we investigated the prevalence of reflux symptoms in patients with insomnia and found that as many as 40% with insomnia had typical reflux symptoms. This result suggested an important role of GERD as a possible pathogenetic factor in sleep disturbance.

The majority of gastroesophageal reflux occurrences do not cause reflux symptoms, a condition termed silent reflux. Martinez *et al.*<sup>21</sup> reported that <5% of gastroesophageal reflux events are perceived by patients with erosive as well as those with nonerosive reflux diseases. Furthermore, Lee *et al.*<sup>22</sup> found that ~43% of individuals with erosive esophagitis did not have any reflux symptoms, whereas Nagahara *et al.*<sup>23</sup> reported a high prevalence of asymptomatic reflux esophagitis in patients who underwent an upper gastrointestinal endoscopy examination, especially elderly patients. In our previous study, we showed that the majority of patients with erosive esophagitis identified by endoscopy had no reflux symptoms and were considered to be silent cases.<sup>24</sup> Silent gastroesophageal reflux may also impair sleep quality by disturbing sound or deep sleep, even without awakening the individual. In addition, it was reported that a significant number of subjects with sleep disturbance have abnormal acid exposure despite a lack of GERD symptoms.<sup>25</sup> Thus, asymptomatic gastroesophageal reflux may cause sleep disturbance in the same manner as symptomatic reflux.

For treatment of insomnia, various types of hypnotics are frequently administered for therapeutic intervention that increase the depth of sleep and prevent intermittent awakening. As swallow-induced primary peristalsis can only be observed when an individual is awake, administration of hypnotics to patients with insomnia caused by gastroesophageal reflux may impair the esophageal clearance mechanism and aggravate reflux esophagitis. Indeed, Gagliardi *et al.*<sup>26</sup> recently reported risks associated with hypnotic administration in GERD patients with insomnia. Thus, hypnotics may aggravate GERD, regardless of the presence of reflux symptoms.

PPI administration is considered to be a reasonable treatment option for patients with GERD-related sleep disturbance. Several double-blind randomized studies have investigated the effectiveness of PPIs for treatment of sleep disturbance in patients with symptomatic GERD and all concluded that they improved sleep quality for symptomatic

patients.<sup>9,27</sup> The results of our study also confirmed that PPI administration is effective for insomnia in patients with reflux symptoms. The beneficial effect of omeprazole on sleep disturbance in patients with typical reflux symptoms was statistically confirmed not only by the sleep domain in the QOLRAD-J score but also by the PSQI sleep scale results. Changes in ESS score tended to be greater after omeprazole administration in comparison with the placebo, although the difference did not reach a statistically significant level, probably because of the limited number of subjects enrolled. It is difficult to conclude the clinical benefit of changes in sleep scores observed in this study. However, the significant improvement in sleep-related QOL scores measured by the sleep-related QOLRAD-J suggest a clinical benefit of omeprazole for individuals with sleep problems and reflux symptoms.

We consider that the lack of PPI effect for improving sleep disturbance in cases without typical reflux symptoms is an interesting finding of the present study. Based on this result, we concluded that silent gastroesophageal reflux may not be a major factor causing sleep disturbance, in contrast to reflux symptoms. Furthermore, the presence of reflux symptoms may be a good indicator for predicting a good therapeutic effect of PPI administration for sleep disturbance.

Our results showed that as many as 40% of clinical patients with insomnia also have reflux symptoms and that PPI administration is effective for improvement of insomnia only in cases with typical reflux symptoms. Nevertheless, the following should be considered as limitations of this study. First, the PPI administration period was only 2 weeks, although a longer duration may be more effective to improve sleep disturbance, even in individuals without reflux symptoms. In addition, endoscopic examinations and intraesophageal pH monitoring studies were not performed to confirm the possible presence of esophageal erosions or pathological gastroesophageal acid reflux. To clearly identify the effects of PPIs on silent reflux, asymptomatic patients with endoscopy-proven reflux esophagitis should be investigated. Finally, the frequency and intensity of reflux symptoms were not graded, and the effects of PPIs on those should be examined in the future.

In summary, we found that ~40% of our clinical patients with insomnia had typical reflux symptoms. Their condition was effectively improved by administration of omeprazole, whereas patients without reflux symptoms were not improved by PPI administration.

## CONFLICT OF INTEREST

**Guarantor of the article:** Masahito Aimi, MD.

**Specific author contributions:** Study concept and design: Yoshikazu Kinoshita; acquisition of data: Yoshinori Komazawa, Koichiro Furuta, Yuko Yamane, Naoharu Hamamoto, Yasushi Uchida, Shozo Yano, Miwa Morita, Hiroaki Oguro, Tatsuya Miyake, and Goubaru Yoshiyuki; analysis and interpretation of data: Masahito Aimi; drafting of the manuscript: Masahito Aimi; critical revision of the manuscript for important intellectual content; Toshitsugu Sugimoto, Shunji Ishihara, and Yoshikazu Kinoshita;

statistical analysis: Masahito Aimi and Yoshikazu Kinoshita; obtained funding: Yoshikazu Kinoshita; administrative, technical, or material support: Seiichi Nagi and Kohji Naora; study supervision: Yoshikazu Kinoshita.

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## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

✓ Proton pump inhibitors are effective for the treatment of sleep disturbance in cases with reflux symptoms. The therapeutic effect of proton pump inhibitors on insomnia in cases without reflux symptoms is unclear.

### WHAT IS NEW HERE

✓ Omeprazole improves insomnia in patients with reflux symptoms but is not effective in cases without reflux symptoms.

- Jansson C, Nordenstedt H, Wallander MA *et al.* A population-based study showing an association between gastroesophageal reflux disease and sleep problems. *J Clin Gastroenterol Hepatol* 2009; **7**: 960–965.
- Khan BA, Sodhi JS, Zargar SA *et al.* Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. *J Gastroenterol Hepatol* 2012; **27**: 1078–1082.
- Orr WC, Goodrich S, Robert J. The effect of acid suppression on sleep patterns and sleep-related gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2005; **21**: 103–108.
- Kusano M, Kouzu T, Kawano T *et al.* Nationwide epidemiological study on gastroesophageal reflux disease and sleep disorders in the Japanese population. *J Gastroenterol* 2008; **43**: 833–841.
- Shaker R, Castell DO, Schoenfeld PS *et al.* Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gastroenterol* 2003; **98**: 1487–1493.
- Steward DL. Pantoprazole for sleepiness associated with acid reflux and obstructive sleep disordered breathing. *Laryngoscope* 2004; **114**: 1525–1528.
- Chand N, Johnson DA, Tabangin M *et al.* Sleep dysfunction in patients with gastro-oesophageal reflux disease: prevalence and response to GERD therapy, a pilot study. *Aliment Pharmacol Ther* 2004; **20**: 969–974.
- Dimarino AJ Jr, Banwait KS, Eschinger E *et al.* The effect of gastro-oesophageal reflux and omeprazole on key sleep parameters. *Aliment Pharmacol Ther* 2005; **22**: 325–329.
- Johnson DA, Orr WC, Crawley JA *et al.* Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *Am J Gastroenterol* 2005; **100**: 1914–1922.
- Fass R, Quan SF, O'Connor GT *et al.* Predictors of heartburn during sleep in a large prospective cohort study. *Chest* 2005; **127**: 1658–1666.
- Jung HK, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. *J Neurogastroenterol Motil* 2010; **16**: 22–29.
- Miki M, Adachi K, Azumi T *et al.* A comparative study of intragastric acidity during post-breakfast and pre-dinner administration of low-dose proton pump inhibitors: a randomized three-way crossover study. *Aliment Pharmacol Ther* 2006; **24**: 1445–1451.
- Hongo M, Kinoshita Y, Shimozuma K *et al.* Psychometric validation of the Japanese translation of the Quality of Life in Reflux and Dyspepsia questionnaire in patients with heartburn. *J Gastroenterol* 2007; **42**: 807–815.

14. Buysse DJ, Hall ML, Strollo PJ *et al.* Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. *J Clin Sleep Med* 2008; **4**: 563–571.
15. Doi Y, Minowa M, Uchiyama M *et al.* Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res* 2000; **97**: 165–172.
16. Picos A, Chisnoiu A, Dumitrasc DL. Dental erosion in patients with gastroesophageal reflux disease. *Adv Clin Exp Med* 2013; **22**: 303–307.
17. Moore JM, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease: real or imagined? *Curr Opin Gastroenterol* 2010; **26**: 389–394.
18. Saritas Yuksel E, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease: cough, asthma, laryngitis, chest pain. *Swiss Med Wkly* 2012; **142**: w13544.
19. Liu X, Uchiyama M, Kim K *et al.* Sleep loss and daytime sleepiness in the general adult population of Japan. *Psychiatry Res* 2000; **93**: 1–11.
20. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *J Gastroenterol* 2012; **47**: 760–769.
21. Martinez SD, Malagon IB, Garewal HS *et al.* Non-erosive reflux disease (NERD)-acid reflux and symptom patterns. *Aliment Pharmacol Ther* 2003; **17**: 537–545.
22. Lee D, Lee KJ, Kim KM *et al.* Prevalence of asymptomatic erosive esophagitis and factors associated with symptom presentation of erosive esophagitis. *Scand J Gastroenterol* 2013; **48**: 906–912.
23. Nagahara A, Hojo M, Asaoka D *et al.* Clinical feature of asymptomatic reflux esophagitis in patients who underwent upper gastrointestinal endoscopy. *J Gastroenterol Hepatol* 2012; **27**(Suppl 3): 53–57.
24. Mishima I, Adachi K, Arima N *et al.* Prevalence of endoscopically negative and positive gastroesophageal reflux disease in the Japanese. *Scand J Gastroenterol* 2005; **40**: 1005–1009.
25. Shaheen NJ, Madanick RD, Alattar M *et al.* Gastroesophageal reflux disease as an etiology of sleep disturbance in subjects with insomnia and minimal reflux symptoms: a pilot study of prevalence and response to therapy. *Dig Dis Sci* 2008; **53**: 1493–1499.
26. Gagliardi GS, Shah AP, Goldstein M *et al.* Effect of zolpidem on the sleep arousal response to nocturnal esophageal acid exposure. *Clin Gastroenterol Hepatol* 2009; **7**: 948–952.
27. Johnson D, Crawley JA, Hwang C *et al.* Clinical trial: esomeprazole for moderate-to-severe nighttime heartburn and gastro-oesophageal reflux disease-related sleep disturbances. *Aliment Pharmacol Ther* 2010; **32**: 182–190.



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