Esophageal reflux disease proton pump inhibitor therapy impact on sleep disturbance: a systematic review

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CRD summary
The authors concluded that, compared with placebo, proton-pump inhibitors improved some sleep disturbance-related outcomes in patients with oesophageal reflux disease. This was a generally well-conducted review and the authors’ conclusions reflected the findings. However, the limited combining of available evidence and the subjective outcome measures used suggest that the findings may not be reliable.

Authors’ objectives
To assess the impact of proton-pump inhibitors on sleep disturbance-related outcomes in patients treated for gastro-oesophageal reflux disease.

Searching
PubMed, Web of Science, and The Cochrane Library were searched from 1989 to October 2011 for English language publications. The search strategy was reported. References of relevant publications were scanned.

Study selection
Eligible for inclusion were placebo-controlled randomised controlled trials (RCTs) that assessed the impact of proton-pump inhibitors in patients with gastro-oesophageal reflux disease. Eligible outcomes were sleep time and quality, which were measured using polysomnography (with scales such as the Apnoea Hypopnoea Index) and/or non-polysomnography (with the Epworth Sleepiness Scale and other health-related quality of life questionnaires).

Included trials were conducted from 2004 to 2011. Half the trials used the proton-pump inhibitor esomeprazole (dose 20 to 40mg once or twice daily); the rest used dexlansoprazole, omeprazole, rabeprazole, or pantoprazole (20 to 40mg once or twice daily). Some trials permitted the use of additional rescue antacids or sleep medications. The mean age of participants was 47.4 years; 56% were women; and their mean body mass index was 29.4 (where reported.

Polysomnography outcome measures were used in two trials and included total sleep time (minutes), sleep onset latency (minutes), sleep efficiency (%), arousal per hour, and rapid eye movement. Non-polysomnography outcome measures were assessed in all trials, including sleep quality or the impact of treatment on work productivity, work hours lost, and regular activities. Non-polysomnography outcomes were measured using history and/or validated measures (Epworth Sleepiness Scale, Functional Outcomes of Sleepiness Questionnaire, Pittsburgh Sleep Quality Index) and non-validated measures (diaries or visual analogue scales).

Four reviewers independently screened articles for inclusion.

Assessment of study quality
Four reviewers independently assessed quality of trials using the 5-point Jadad scale. Trials were also assigned an Oxford level of evidence rating. Discrepancies were resolved by consensus.

Data extraction
Where possible, mean values and standard deviations (SDs) were extracted for baseline, final, and change from baseline measures.

It appeared that four reviewers independently extracted the data.

Methods of synthesis
Data were presented as a narrative synthesis and in tables organised by outcome measure.

Results of the review
Eight RCTs (1,345 patients; range 15 to 642) were included in the review. Six RCTs scored 3 or more on the Jadad scale (suggesting moderate to high quality); two RCTs scored two or less (suggesting poor quality). Polysomnography outcomes were measured after one week; non-polysomnography outcomes were measured at two to eight weeks.

**Polysomnography** (two RCTs): None of the measures (total sleep time, sleep onset latency, sleep efficiency, arousal per hour, or rapid eye movement) showed statistically significant differences between treatment and placebo groups.

**Non-polysomnography** (eight RCTs): Four RCTs used the Pittsburgh Sleep Quality Index; three were high quality and one was poor quality. All four trials demonstrated a significant improvement using treatment compared with placebo (p values 0.034 or less). However, two trials reported scores at four weeks duration of over 5, which indicated poor sleep quality.

Three high quality RCTs used the Work Productivity and Activity Impairment questionnaire; all three trials showed that treatment compared with placebo showed a statistically significant reduction in the degree to which sleep disturbance affected work-related outcomes (p values 0.04 or lower than 0.01).

Results from non-validated measures were reported in the review.

**Authors’ conclusions**
Compared with placebo, proton-pump inhibitors improved non-polysomnography sleep disturbance-related outcomes in patients with oesophageal reflux disease.

**CRD commentary**
The review question and supporting inclusion criteria were clearly stated. A few appropriate sources were searched for relevant literature, but as this was limited to the English language, potentially relevant papers may have been missed. Each stage of the review process was undertaken in duplicate, which reduced the potential for reviewer error and bias.

Appropriate methods were used to assess trial quality; quality was referred to in the results. However, only an overall score was reported, which made it difficult to judge individual item results. There were clinical and methodological differences among trials. Therefore, a narrative synthesis was appropriate. The authors highlighted that only two trials used objective outcome measures, although assessment was only after a very short time period. The authors acknowledged that the impact of additional medication on outcomes remained unclear.

This was a generally well-conducted review and the authors’ conclusions reflected the findings. However, given the limited synthesis, short durations, and subjective nature of most outcome measures, the findings may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the evidence supported the use of proton-pump inhibitors as a treatment to improve oesophageal reflux disease symptoms and associated quality of life sleep-disturbance related outcomes.

**Research:** The authors stated that further research was warranted to evaluate the impact of proton-pump inhibitors on polysomnography outcomes, as well as to examine the relationship between polysomnography and non-polysomnography outcomes in patients with gastro-oesophageal reflux disease and sleep disorders.

**Funding**
Supported in part by a Cochrane Scholars Grant.

**Bibliographic details**

**PubMedID**
22307577

**DOI**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.