Systematic review: Clinical effectiveness of interventions for the treatment of nocturnal gastroesophageal reflux

Jeroen M. Schuitenmaker | Thijs Kuipers | André J.P.M. Smout | Paul Fockens | Albert J. Bredenoord

Abstract

Background: Nocturnal gastroesophageal reflux symptoms have a major impact on sleep quality and are associated with complicated gastroesophageal reflux disease (GERD). We performed a systematic review to assess the data on the effectiveness of the currently available interventions for the treatment of nocturnal reflux symptoms.

Methods: We searched PubMed, EMBASE, and the Cochrane Library. All prospective, controlled, and uncontrolled clinical trials in adult patients describing interventions (lifestyle modifications, surgical and pharmacological) for nocturnal gastroesophageal reflux symptoms were assessed for eligibility. A narrative descriptive summary of findings is presented together with summary tables for study characteristics and quality assessment.

Key Results: The initial reference search yielded 3067 citations; 66 citations were screened in full text, of which 31 articles were included. Studies on lifestyle modifications include head of bed elevation (n = 5), prolonging dinner-to-bed time (n = 2), and promoting left lateral decubitus position (n = 2). Placebo-controlled clinical trials investigating proton pump inhibitors (PPIs) (n = 11) show success rates ranging from 34.4% to 80.8% in the PPI group versus 10.4%–51.7% in the placebo group. Laparoscopic fundoplication is reserved for severe disease only. There is insufficient evidence for a recommendation on the use of nasal continuous positive airway pressure (nCPAP), hypnotics, baclofen and adding bedtime H2 receptor antagonists for reducing nocturnal reflux.

Conclusion Inferences: A sequential treatment strategy, including head of bed elevation, prolonging dinner-to-bed time, promoting left lateral decubitus position and treatment with acid-suppressive medication is recommended for nocturnal gastroesophageal reflux symptoms. Currently, there is insufficient evidence for the use of nCPAP, hypnotics, baclofen and adding bedtime H2 receptor antagonists.
1 | INTRODUCTION

The presence of nocturnal gastroesophageal reflux symptoms, such as heartburn and/or regurgitation, can have a major impact on sleep quality. Patients with nocturnal reflux symptoms often report difficulty falling asleep, a fragmented sleeping pattern, and/or wake up in the middle of the night. Up to 80% of patients with gastroesophageal reflux disease (GERD) experience symptoms at night, which interferes with daytime functioning, work, and social activities and has a negative effect on health-related quality of life.5–3

Physiological changes during sleep make the esophagus more susceptible to damage caused by acidic reflux. Important esophageal clearance mechanisms such as primary peristalsis, salivary excretion, and secondary peristalsis are inhibited during sleep.6 Although reflux episodes occur less frequent during sleep than when awake,5 the nocturnal reflux episodes are often prolonged, causing an increased esophageal acid contact time leading to more mucosal damage.6 Indeed, nocturnal acid reflux has been associated with esophageal complications such as reflux esophagitis, peptic stricture, Barrett esophagus, and adenocarcinoma.7 Furthermore, nocturnal reflux is associated with several extra-esophageal manifestations of GERD, including asthma, dental erosions, and chronic cough.9

Lifestyle modifications, such as raising the head end of the bed and avoiding meals 2–3 h before bedtime, can be very effective but often do not provide sufficient relief. The use of proton pump inhibitors (PPIs) are very effective for daytime symptoms, but have limited efficacy for nocturnal reflux symptoms.10,11 Because nocturnal reflux symptoms are associated with impaired sleep quality, reduced quality of life and more severe forms esophageal diseases, effective treatment of these troublesome nocturnal symptoms is key.12,13 The aim of this study is to systematically identify, evaluate, and summarize the current available interventions (lifestyle modifications, pharmacological and surgical interventions) for the treatment of nocturnal gastroesophageal reflux symptoms.

2 | METHODS

2.1 | Literature search

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.14 The systematic review protocol was prospectively registered at the PROSPERO registry (CRD42020220289). Electronic literature databases MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Library (Cochrane Central Register of Controlled Trials) were last searched on the November 23, 2021. The full search strategy is described in Appendix S1: no filters and/or limits were used. Reference lists of the included studies and previous (systematic) reviews were searched manually to identify additional studies.

2.2 | Study selection

All prospective, controlled, and uncontrolled clinical trials in adult patients describing interventions (lifestyle modifications, surgical, pharmacological or others) for nocturnal gastroesophageal reflux symptoms were assessed for eligibility. For pharmacological studies, only randomized controlled trials were included. Nocturnal gastroesophageal reflux symptoms were defined as the occurrence of troublesome typical reflux symptoms (heartburn and/or regurgitation) between going to bed at night and upon awakening in the morning (during recumbent position). All non-English and studies published before 1985 were excluded, as well as studies with healthy volunteers or with interventions that have been withdrawn from the market (such as cisapride). Studies with only intragastric acid suppression as outcome (with no esophageal reflux parameters available) or pharmacological studies where nocturnal reflux or reflux symptoms were not the primary outcome measure were also excluded. The predefined selection criteria of the studies are shown in Appendix S2. Two authors independently screened the titles and abstracts of all references retrieved by the literature search. Studies not meeting the predefined selection criteria and duplicates were removed. The remaining citations were retrieved in full text and screened independently by the same two reviewers. A third author resolved disagreements between judgments. If the full text was not available, the corresponding author was not contacted. Screening and study selection were performed in Rayyan15 and Endnote.16
2.3  |  Assessment of methodologic quality, data extraction, and data reporting

For the risk of bias assessment, the Cochrane risk of bias tool was used in case of a randomized controlled trial and the ROBINS-I tool was used to assess non-randomized studies of interventions. Two reviewers independently performed the quality assessment. If no consensus was reached, a third author resolved disagreements between judgments. Outcome data from the full texts were extracted into Microsoft Excel independently by the same two reviewers and merged after data extraction. As significant heterogeneity in the data was expected (e.g., different kind of interventions), a narrative descriptive summary of findings is presented together with summary tables for study characteristics and quality assessment.

3  |  RESULTS

3.1  |  Study selection

The initial reference search yielded 3067 citations after removal of duplicates. Sixty-six citations were screened in full text, of which 31 were included in this systematic review (Figure 1). A list of the excluded articles is presented in Appendix S3. Studies on interventions for nocturnal reflux symptoms include head of bed elevation (n = 5), early versus late dinner (n = 2), left lateral decubitus sleep position (n = 2), nasal continuous positive airway pressure (nCPAP) (n = 7), pharmacological (n = 14), and surgery (n = 1) (Table 1). As expected, there was a significant heterogeneity in the data due to the different interventions for nocturnal gastroesophageal reflux. The risk of bias assessment is presented in Appendix S4 and in Table 1. Recommendations for effective treatments are displayed in Figure 2.

3.2  |  Head of bed elevation

Raising the head end of the bed, using bed blocks or a wedge, is a widely recommended lifestyle modification for the reduction of nocturnal reflux symptoms. We identified five randomized clinical trials and one non-randomized clinical trial that investigated the effect of head of bed elevation on nocturnal reflux (Table 1).19-23 Two studies used esophageal pH parameters as outcome measure. In a cross-over study with 15 endoscopically proven reflux esophagitis patients, patients slept three consecutive nights, in random order, in a hospital bed with a wedge (22° angle), bed blocks (20 cm), or without elevation (one pillow). Compared to control, sleeping on a foam wedge led to a significant reduction of time pH < 4, but no significant effect on the total number of reflux episodes or acid clearance time was seen.21 Interestingly, no effect on pH-reflux parameters was observed when using the bed blocks of 20 cm. In a non-randomized trial in 20 patients with confirmed nocturnal esophageal reflux by pH testing, two weeks of bed blocks led to a minimal, but significant, reduction in time with pH < 4 (%) from 15.0 ± 8.4 versus to 13.7 ± 7.2 (p = 0.001).23 These studies suggest...
that head of bed elevation has minimal to no effect on esophageal pH-reflux parameters.

However, several studies suggest a positive effect on symptom reduction. In severe reflux esophagitis, treatment with 20-cm bed blocks for six weeks reduced reflux symptoms, but the endoscopic appearance did not improve significantly. Head of bed elevation also led to a significant reduction of reflux symptoms in patients that underwent esophagectomy with gastric tube reconstruction. Unfortunately, these studies are hampered by severe methodological limitations with high risk of bias (Table 1). We identified one high-quality clinical trial with 39 patients with nocturnal symptoms at least three nights a week and confirmed esophageal erosions. In this cross-over trial, patients were randomised to six weeks of lying flat followed by six weeks with a 20-cm elevated head end of the bed (with a washout period of two weeks). Treatment success, defined as change of ≥0.6 points in Reflux Disease Questionnaire score, was observed in 69.2% in the intervention group versus 33.3% in the control group (RR: 2.08; 95% CI: 1.19–3.61). No improvement in quality of life was observed.

3.3 | Early versus late night dinner

International GERD treatment guidelines advise avoiding the intake of a meal in the three hours before recumbency. Two randomized, unblinded, cross-over clinical trials investigated the effect of the timing of dinner on nocturnal reflux episodes and esophageal acid exposure time. Orr and colleagues investigated this by providing a late evening meal to 20 symptomatic reflux patients with positive Bernstein acid perfusion test and measured pH, using a pH probe, in a sleep laboratory. They found no difference between the number of reflux episodes, esophageal acid exposure time, or duration of reflux episodes between the early (19.00 h) or late night dinner (21.00 h). However, the early dinner meal was not standardized and the two measurement nights could be up to three weeks apart, which might affected the results and resulting in high risk of bias. Furthermore, no information on the nocturnal period is provided as they combined the postprandial and the nocturnal period in the analysis. In a study using wireless pH monitoring, a late night meal led to a significantly higher esophageal acid exposure time and higher number of reflux episodes compared to an early evening meal. This effect was observed especially in patients with a hiatal hernia, esophagitis, and overweight patients.

3.4 | Sleep positional therapy (left lateral decubitus position)

Experimental studies suggest that the body position during sleep plays a role in occurrence of reflux. The left lateral decubitus position is associated with significantly shorter esophageal acid exposure time and faster esophageal acid clearance compared with the supine and right lateral decubitus positions. Therefore, interventions aiming to promote the left lateral decubitus sleep position have the potential to reduce nocturnal reflux symptoms. In a study by Allampati and colleagues, 27 patients with nocturnal heartburn and/or regurgitation ≥2 per week were instructed to sleep with a positional therapy device for two weeks. The positional therapy device consists of an inclined wedge, creating a 15–20° angle for the entire torso, and a cushion to promote the left lateral decubitus position. After two weeks of treatment, it significantly reduced nocturnal reflux symptoms and GERD-Health Related Quality of Life. Another study with the same positional therapy device concludes it was also effective in reducing laryngopharyngeal reflux symptoms. Both studies had serious risk of bias due to methodological limitations.

3.5 | Continuous positive airway pressure (CPAP)

The obstructive sleep apnea syndrome (OSAS) is characterized by repetitive partial or complete collapse of the upper airway during sleeping leading to obstructive apneas, hypopneas, and/or arousals from sleep. Symptoms include daytime sleepiness, excessive snoring, and gasping during sleep. Continuous positive airway pressure (CPAP) is the gold standard for the treatment of OSAS. CPAP increases intrathoracic pressure and prevents the upper airway to collapse: effectively reducing apneas, hypopneas, and arousals from sleep. It is hypothesized that by raising intrathoracic pressure CPAP might reduce the occurrence of nocturnal gastroesophageal reflux as well. We identified seven clinical trials investigating the effect of nasal continuous positive airway pressure (nCPAP) on nocturnal gastroesophageal reflux. All of these are non-blinded, non-randomized cross-over trials or observational studies. Five studies were performed in OSAS patients with subsequent nocturnal reflux symptoms and were at serious or critical risk of bias. Two studies were performed in non-OSAS population, with moderate or low risk of bias.

The first trial investigated six OSAS patients, who complained of regular nocturnal heartburn and/or regurgitation, in a sleep laboratory for two consecutive nights using polysomnography and esophageal pH testing. Patients had not previously received treatment for their reflux complaints. During the first night, patients underwent polysomnography and esophageal pH monitoring, with no treatment for either OSAS or GERD. During the second night, patients were treated with nasal CPAP, which was titrated to the pressure at which all the obstructive apneas and hypopneas were within normal range. The apnea hypopnea index was reduced from 45.0 ± 10.0 to 8.6 ± 4.6 (p < 0.005). The mean percentage of time with pH <4 was reduced from 6.3 ± 2.1 to 0.1 ± 0.1 (p < 0.025). Furthermore, the total number of reflux episodes dropped from 10.1 ± 3.5 to 0.6 ± 0.3 (p < 0.03). A subsequent study by the same study group investigated the effect in six non-OSAS GERD patients (nocturnal acid exposure time >5%) using a similar study protocol. The mean percentage of time with pH <4 dropped significantly from 27.7 ± 10.0 to 5.8 ± 2.6 (p < 0.004) with no effect on sleep efficiency or incidence.
| Author and year   | Study design                          | N  | Population | Intervention                                | Outcome measure(s)                      | Effect               | Risk of bias   |
|------------------|---------------------------------------|----|------------|---------------------------------------------|-----------------------------------------|----------------------|----------------|
| Head of bed elevation |                                       |    |            |                                             |                                        |                      |                |
| Harvey et al. 1987 | Factorial, randomized controlled trial | 71 | GERD       | Bed blocks (20 cm)                          | 1. Symptom                              | Improved            | High risk      |
| Hamilton et al. 1988 | Randomized, cross-over                | 15 | GERD       | Bed blocks (20 cm) Foam wedge (22° angle)   | 1. Intraesophageal pH                   | No effect            | Some concerns  |
| Khan et al. 2012  | Non-randomized, cross-over            | 20 | GERD       | Bed blocks (20 cm)                          | 1. Symptom                              | Improved            | Serious        |
| Huang et al. 2019 | Randomized, cross-over                | 14 | Post-esophagectomy Foam wedge (20° angle)   | 1. Symptom                              | Improved on wedge. No improvement on bed blocks | Low risk            |
| Villamil Morales et al. 2020 | Randomized, single-blind, 2 × 2 cross-over | 39 | GERD       | Bed blocks (20 cm)                          | 1. Symptom                              | Improved            | Low risk       |
| Early vs. late dinner |                                       |    |            |                                             |                                        |                      |                |
| Orr et al. 1998   | Randomized, unblinded, cross-over     | 20 | GERD       | Early vs. late dinner                       | 1. Intraesophageal pH                   | No effect            | High risk      |
| Piesman et al. 2007 | Randomized, unblinded, cross-over     | 30 | GERD       | Early vs. late dinner                       | 1. Intraesophageal pH                   | Improved (early)     | Low risk       |
| Positional therapy (left lateral decubitus position) |                                       |    |            |                                             |                                        |                      |                |
| Allampati et al. 2017 | Non-randomized, cross-over          | 27 | GERD       | Positional therapy device                   | 1. Symptom                              | Improved            | Serious        |
| Tierney et al. 2017 | Non-randomized, cross-over            | 33 | LPR        | Positional therapy device                   | 1. Symptom                              | Improved            | Serious        |
| Continuous positive airway pressure (CPAP) |                                       |    |            |                                             |                                        |                      |                |
| Kerr et al. 1992  | Non-randomized, cross-over            | 6  | OSAS, GERD | nCPAP                                       | 1. Intraesophageal pH                   | Improved            | Serious        |
| Kerr et al. 1993  | Non-randomized, cross-over            | 6  | GERD       | nCPAP                                       | 1. Intraesophageal pH                   | Improved            | Moderate       |
| Shoenut et al. 1994 | Non-randomized, cross-over           | 13 | Achalasia, Scleroderma | nCPAP                                   | 1. Intraesophageal pH                   | Improved in achalasia. No effect in scleroderma patients | Low             |
| Ing et al. 2000   | Non-randomized, cross-over            | 22 | OSAS, non-OSAS | nCPAP                                  | 1. Intraesophageal pH                   | Improved            | Critical       |
| Green et al. 2003 | Observational study                   | 165| OSAS, GERD | nCPAP                                       | 1. Symptom                              | Improved            | Critical       |
| Tawk et al. 2006  | Non-randomized, cross-over            | 16 | OSAS, GERD | nCPAP                                       | 1. Intraesophageal pH                   | Improved            | Serious        |
| Shepherd et al. 2011 | Non-randomized, cross-over           | 8  | OSAS, GERD | nCPAP                                       | 1. Intraesophageal pH                   | Improved            | Critical       |

(Continues)
| Author and year         | Study design                          | N   | Population | Intervention                              | Outcome measure(s)                           | Effect          | Risk of bias |
|-------------------------|---------------------------------------|-----|------------|-------------------------------------------|----------------------------------------------|-----------------|--------------|
| Proton pump inhibitors  |                                       |     |            |                                           |                                              |                 |              |
| Johnson et al. 2005     | Double-blind, parallel, placebo-      | 675 | GERD       | Esomeprazole 20, 40 mg                    | 1. Symptom  
2. Sleep disturbances  
3. Sleep quality  
4. Work productivity | 1. Improved  
2. Improved  
3. Improved  
4. Improved | Low           |
| Johnson et al. 2010     | Double-blind, parallel, placebo-      | 262 | GERD       | Esomeprazole 20 mg                        | 1. Symptom  
2. Sleep disturbances  
3. Sleep quality  
4. Work productivity | 1. Improved  
2. Improved  
3. Improved  
4. Improved | Low           |
| Fass et al. 2009        | Double-blind, parallel, placebo-      | 947 | NERD       | Dexlansoprazole 30, 60 mg                  | 1. Symptom  
2. Quality of life | 1. Improved  
2. Improved | Low           |
| Fass et al. 2011        | Double-blind, parallel, placebo-      | 305 | GERD       | Dexlansoprazole 30 mg                      | 1. Symptom  
2. Sleep disturbances  
3. Sleep quality  
4. Work productivity | 1. Improved  
2. Improved  
3. Improved  
4. Improved | Low           |
| Orr et al. 2005         | Double-blind, cross-over, placebo-    | 42  | GERD       | Rabeprazole 20 mg                         | 1. Intraesophageal pH  
2. Symptom  
3. Polysomnography | 1. No effect  
2. No effect  
3. No effect | High          |
| Orr et al. 2007         | Double-blind, cross-over, placebo-    | 15  | GERD       | Esomeprazole 40 mg                         | 1. Intraesophageal pH (+impedance)  
2. Polysomnography | 1. Improved  
2. No effect | High          |
| Peura et al. 2009       | Double-blind, parallel, placebo-      | 864 | GERD (self-treating) | Lansoprazole 15, 30 mg | 1. Symptom | 1. Improved | Low           |
| Adding bedtime H2RA     |                                       |     |            |                                           |                                              |                 |              |
| Janiak et al. 2007      | Double-blind, cross-over, placebo-    | 14  | Systemic sclerosis | Omeprazole 20 mg b.d. + ranitidine 300 mg | 1. Intraesophageal pH  
2. Symptom  
3. Quality of life | 1. No effect  
2. No effect  
3. No effect | Some concerns |
| Orr et al. 2003         | Double-blind, cross-over, placebo-    | 19  | GERD       | Omeprazole 20 mg b.d. + ranitidine 150 mg | 1. Intraesophageal pH  
2. Polysomnography | 1. No effect  
2. No effect | Some concerns |
| Evening vs. morning dose|                                       |     |            |                                           |                                              |                 |              |
| Pehlivanov et al. 2003  | Double-blind, cross-over, RCT         | 20  | GERD       | Rabeprazol 20 mg                          | 1. Intraesophageal pH | 1. Improved (evening) | Low           |
| Comparing PPIs          |                                       |     |            |                                           |                                              |                 |              |
| Miner et al. 2010       | Single-blind (investigator), cross-    | 52  | GERD       | Rabeprazol 20 mg vs. pantoprazole 40 mg   | 1. Intraesophageal pH | 1. No effect | Some concerns |
| Hypnotics               |                                       |     |            |                                           |                                              |                 |              |
| Gagliardi et al. 2009   | Double-blind, cross-over, placebo-    | 24  | GERD       | Zolpidem                                  | 1. Intraesophageal pH | 1. Worsened | Low           |
of arousals. It was hypothesized that by raising intrathoracic pressure using nCPAP (pressure = 8 cm H₂O), nocturnal reflux could be reduced. Indeed, midesophageal pressure was raised from 2.0 ± 0.4 to 5.2 ± 1.3 mm Hg (p < 0.01) and low esophageal sphincter (LES) pressure from 14.6 ± 1.4 to 24.3 ± 4.1 mm Hg (p < 0.02) using six healthy volunteers. Prolonged treatment (one week) with nCPAP also led to a significant drop in nocturnal acid exposure from 16.3 ± 18.8 to 3.8 ± 7.6 (p < 0.01) in a study investigating 16 OSAS patients with nocturnal GERD (>6% time pH <4). However, in this study, the two nights were performed in different conditions. The first pH prolonged monitoring was performed under ambulatory conditions; the second pH prolonged monitoring test was performed in the sleep laboratory and no specific diet instructions during the study, which might have affected the pH monitoring results.

In an observational study in 165 OSAS patients, the nocturnal reflux symptom score was significantly reduced after nCPAP treatment, which might indicate that nCPAP also improves nocturnal reflux symptoms. In addition, patients with a higher CPAP pressure showed a greater improvement in nocturnal reflux symptom score (p < 0.001). Interestingly, in patients with an aperistaltic esophagus and low LES resting pressure (2.4 ± 1.3 mm Hg) due to systemic sclerosis, nCPAP did not improve reflux parameters on pH monitoring, suggesting that some residual resting pressure is needed for the beneficial effect. Indeed, in patients with an aperistaltic esophagus due to achalasia but with a high resting LES pressure (mean 17.1 ± 5.8 mm Hg), nCPAP led to a reduction in time with pH <4 (%) from 38.5 ± 20.6 to 2.9 ± 5.6 (p = 0.014). Other studies also show improvement in nocturnal reflux parameters after nCPAP treatment, but have serious methodological limitations.

### 3.6 Acid-suppressive medication

Antacids neutralize gastric acidity and have a rapid and short-term effect in relieving reflux symptoms. Antacids are available over-the-counter and contain different combinations such as aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate, and alginate. We identified no studies on antacids that met the inclusion criteria of our study. There are three classes of acid-suppressing medication available: H₂ receptor antagonist (H2RA), proton pump inhibitors (PPIs), and more recently potassium channel acid-blocking drugs (P-CABs). We identified 11 randomized clinical trials investigating the effect of acid-suppressive medication on nocturnal gastroesophageal reflux symptoms and/or nocturnal esophageal pH parameters. These include studies on PPIs versus placebo (n = 7), adding bedtime H2RA (n = 2), comparing two PPIs (n = 1), and comparing evening or morning dose PPI (n = 1). No studies P-CABs were identified that met our inclusion criteria.

Currently available PPIs include esomeprazole, omeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole (which is the R-enantiomer of lansoprazole). When compared to placebo, PPIs are highly effective for the treatment of nocturnal reflux. Antacids neutralize gastric acidity and have a rapid and short-term effect in relieving reflux symptoms. Antacids are available over-the-counter and contain different combinations such as aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate, and alginate. We identified no studies on antacids that met the inclusion criteria of our study. There are three classes of acid-suppressing medication available: H₂ receptor antagonist (H2RA), proton pump inhibitors (PPIs), and more recently potassium channel acid-blocking drugs (P-CABs). We identified 11 randomized clinical trials investigating the effect of acid-suppressive medication on nocturnal gastroesophageal reflux symptoms and/or nocturnal esophageal pH parameters. These include studies on PPIs versus placebo (n = 7), adding bedtime H2RA (n = 2), comparing two PPIs (n = 1), and comparing evening or morning dose PPI (n = 1). No studies P-CABs were identified that met our inclusion criteria.

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reflux symptoms. Johnson and colleagues performed a large clinical trial in 675 patients with symptomatic and/or endoscopic GERD and nighttime heartburn at least two times per week. Treatment with esomeprazole 40 mg, 20 mg or placebo for 4 weeks led to a complete resolution of nighttime heartburn in 53.1%, 50.5%, and 12.7% of the patients, respectively. A follow-up study in 262 patients with symptomatic and/or endoscopic GERD concludes that treatment with 20 mg of esomeprazole led to relief of nighttime heartburn in 34.3% of the patients compared to 10.4% in the placebo group. Furthermore, both studies show reduction in reflux-related sleep disturbances and improvement in sleep quality and work productivity.

Fass and colleagues treated 947 symptomatic, non-erosive reflux patients with dexlansoprazole 60 mg, 30 mg or placebo for 4 weeks. In the three groups of patients, the percentage of nights without nighttime heartburn was 80.8%, 76.9%, and 51.7%, respectively. Similar rates of heartburn-free nights were observed in a follow-up trial in 305 patients treated with dexlansoprazole 30 mg for four weeks: 73.1% in the dexlansoprazole group versus 35.7% in the placebo group. Lansoprazole has also shown to be effective in reducing nighttime heartburn (30 mg: 61.7% vs. placebo: 47.8%).

Due to pharmacokinetics, PPIs are the most effective when taken on an empty stomach and approximately half an hour before the breakfast and/or dinner. In a small study comparing evening and morning dose of rabeprazole on nocturnal esophageal pH, rabeprazole led to a significantly lower nocturnal esophageal pH (0.2%) when taken before dinner compared to when taken before breakfast (3.4%).

Adding bedtime H2RA to twice-daily PPI therapy has been shown to reduce nocturnal intragastric acid; however, this effect is only temporary and its clinical significance on esophageal reflux has been debated. We identified two randomized clinical trials, and they conclude that adding bedtime H2RA to omeprazole 20 mg twice daily does not improve esophageal pH parameters in patients with nocturnal GERD or systemic sclerosis.

### 3.7 Muscle relaxant (baclofen)

Baclofen significantly inhibits gastroesophageal reflux episodes by inhibition of transient lower esophageal sphincter relaxation (TLESR). TLESRs allow gas to vent from the stomach, but are also the major mechanism behind gastroesophageal reflux. For the treatment of nocturnal reflux, baclofen has been shown to reduce the number of reflux episodes during a one-night sleep laboratory study; however, no difference on esophageal acid exposure time was seen.
When compared to placebo. Furthermore, the clinical use of baclofen is limited due to its gastrointestinal and neurological side effects, such as drowsiness, dizziness, and nausea.

### 3.8 | Hypnotics

Ramelteon is a highly selective melatonin receptor type 1 and type 2 agonist and is prescribed for insomnia that is characterized by difficulty with sleep onset. Treatment with ramelteon for 4 weeks reduced nocturnal heartburn symptoms compared to placebo in a small clinical trial in 16 patients, with erosive esophagitis or abnormal esophageal pH (>4.2% pH <$<$4) and concomitant insomnia. However, the effect on esophageal pH parameters is unclear and caution is warranted during sleep, crucial esophageal clearance mechanisms such as primary peristalsis, salivary excretion, and secondary peristalsis as a response to refluxed gastric content are inhibited. Suppressing these protective mechanisms using hypnotics might improve symptoms, but further aggravates GERD by increasing esophageal acid exposure time. Indeed, zolpidem, a GABA<sub>A</sub> receptor agonist and a commonly prescribed sedative and hypnotic, prolongs esophageal acid clearance time by impairing the reflux-associated awakenings and arousals. In this double-blind, randomized clinical trial, Zolpidem led to an increase of mean esophageal acid clearance time from 37.8 to 363.3 seconds compared to placebo. Therefore, caution is warranted when using hypnotic medication for patients with nocturnal reflux symptoms.

### 3.9 | Surgery

GERD patients who have failed pharmacological (PPI) therapy, especially in the setting of persistent troublesome regurgitation, are often referred for anti-reflux surgery. Laparoscopic fundoplication is the standard surgical therapy for GERD and is highly effective for relieving long-term heartburn and regurgitation. We identified only one case-control study that investigated the specific effect of Nissen fundoplication on nocturnal gastroesophageal reflux. In 11 GERD patients, with abnormal preoperative Johnson-DeMeester scores on esophageal pH testing, laparoscopic fundoplication improved self-reported sleep quality parameters such as daytime drowsiness and numbers of hours of sleep. However, no effect was observed on objective parameters measured by polysomnography.

### 4 | DISCUSSION

There is a complex bi-directional relationship between sleep and nocturnal gastroesophageal reflux. The presence of nocturnal reflux symptoms can negatively affect sleep quality by waking up patients from sleep. Indeed, reflux-related sleep disturbances interfere with daytime functioning, work, and social activities and have a negative effect on health-related quality of life. On the contrary, poor sleep quality seems to further worsen reflux symptoms by increasing esophageal acid contact time. Therefore, effective treatment of nocturnal reflux and the troublesome nocturnal symptoms is key. In this systemic review, we identified, evaluated, and summarized the current available literature on clinical trials for the treatment of nocturnal gastroesophageal reflux symptoms.

Similar to daytime GERD, a step-up treatment strategy is warranted for nocturnal reflux. Lifestyle modifications, such as raising the head end of the bed and avoiding meals 2–3 h before bedtime, are often the first step in the treatment of troublesome symptoms. Although widely recommended, we identified a limited number of high-quality clinical trials for the use head of bed elevation and avoidance of meals 2–3 h before bedtime for the treatment of nocturnal reflux symptoms. However, these pragmatic, safe, easy-to-adopt, and low-risk lifestyle modifications seem legitimate from a physiological perspective. Raising the head end of the bed allows gravity to keep acid in the stomach and improves the esophageal clearance of acid in case reflux occurs. In addition, prolonged pH monitoring studies show that reflux is most often a postprandial event; the gastric distention after eating induces a TLESR. Nocturnal reflux episodes occur mostly during the first half of the night. The concept of advising patients against late night meals, drinks, and snacks seems therefore logical. Indeed, shorter dinner-to-bed time is associated with an increased risk for GERD. Therefore, head of bed elevation and avoidance of meals 2–3 h before bedtime should be advised to all patients that present themselves to their physician with (nocturnal) reflux symptoms. Naturally, other lifestyle modifications against GERD, although not specific for nocturnal reflux, should also be recommended. These include weight loss, smoke cessation, avoiding fatty meals, carbonated beverages, and other reflux-provoking foods.

Interestingly, patients often recall having more reflux symptoms when sleeping in the right decubitus position. Recently, our group confirmed that the left lateral decubitus position is associated with significantly shorter esophageal acid exposure time and faster esophageal acid clearance compared with the supine and right lateral decubitus positions. A proposed mechanism to explain this is the esophagogastric junction anatomy; in the left lateral decubitus position, the stomach is positioned below the esophagus, resulting in less reflux. Anti-reflux pillows, aiming to maintain the left lateral decubitus position and head of bed elevation, have been found to result in less recumbent acid exposure and less self-reported nocturnal reflux symptoms as well. These data suggest that promoting the left lateral decubitus position can be recommended together with other lifestyle modifications for nocturnal reflux.

If lifestyle modifications are not sufficient, acid-suppressive medications are often the next step. The discovery of H2RAs and PPIs is considered medical milestones, and they have changed the practice of gastroenterology and its treatment of gastric acid-related conditions.
disorders. PPIs are the most effective pharmacological treatment for GERD, both in healing erosive esophagitis and reflux symptoms.\textsuperscript{60} We identified several large, high-quality placebo-controlled clinical trials with success rates ranging from 34.4% to 80.8% in the PPI group versus 10.4%-51.7% in the placebo group (depending on definition of treatment success).\textsuperscript{36-40} This suggests that PPIs are more effective than placebo when treating nocturnal reflux, but a substantial group with persistent symptoms persist. In a survey investigating symptom control among GERD patients, more than 80% still experienced nocturnal reflux symptoms under PPI treatment.\textsuperscript{11} Of those, nearly a quarter rated these nocturnal symptoms as severe or very severe and almost 30% of these patients experienced ≥6 nocturnal symptoms in the 30 days preceding the survey. Furthermore, in approximately 40% of the patients that used PPI once daily, the reason for increasing the dosing frequency was the persistence of nocturnal reflux symptoms.\textsuperscript{11}

It has been suggested that nocturnal acid breakthrough plays a role in nocturnal reflux. Nocturnal acid breakthrough is defined as the presence of intragastric pH <4 during the overnight period for at least 60 continuous minutes in patients taking PPI twice daily.\textsuperscript{61} Pharmacological strategies to tackle this phenomenon, such as the development of novel PPIs, delayed-release formulations and adding bedtime H2RA, have been shown to increase nocturnal intragastric pH.\textsuperscript{62,63} However, several studies show that nocturnal acid breakthrough is an isolated gastric phenomenon and does not correlate with clinically more meaningful parameters such as esophageal acid exposure and nocturnal reflux symptoms.\textsuperscript{64-66} Indeed, in our systematic review, we found no beneficial effect of adding bedtime H2RA on esophageal pH parameters. Furthermore, the tachyphylaxis associated with repeated usage of H2RA on top of PPIs limits the role of H2RA for nocturnal reflux symptoms.\textsuperscript{67} Nocturnal acid breakthrough might play a role in complicated nocturnal GERD, for example in patients with major motility disorders or Barrett's esophagus; however, this should be further investigated. Therefore, pharmacodynamics studies on novel treatments for (nocturnal) GERD should not only include intragastric pH measurements, but also esophageal pH measurements to establish their clinical effect on nocturnal reflux.

Laparoscopic fundoplication is indicated for patients who have proven persistent symptoms despite maximum PPI therapy or have significant anatomical abnormalities, such as a large hiatal hernia. Interestingly, studies on the specific effect of fundoplication on GERD-related sleep disturbances are scarce.\textsuperscript{51} However, long-term control of heartburn and acid regurgitation symptoms is often between 80 and 90% in patients with GERD.\textsuperscript{68,69}

In patients with OSAS, there is a high prevalence of nocturnal GERD, ranging from 38% up to 76%.\textsuperscript{70,71} Both OSAS and GERD share similar risk factors such as (old) age, obesity, smoking, and alcohol consumption. However, the exact relationship between these two multifactorial conditions has not been fully understood. It was previously assumed that the pressure gradient between negative intrathoracic pressure and positive gastric pressure during an obstructive sleep apnea event might facilitate reflux. CPAP increases intrathoracic pressure and prevents the upper airway to collapse; therefore, CPAP therapy might reduce the occurrence of nocturnal reflux. Indeed, we identified several small, uncontrolled experimental studies that show marked improvement in esophageal acid exposure during nCPAP therapy. Interestingly, Ing and colleagues concluded that only 12% of the reflux episodes occurred simultaneously with apneas or hypopneas.\textsuperscript{35} More recent data suggest that nocturnal reflux in OSAS patients is mainly caused by TLESRs and not by a negative intraesophageal pressure due to obstructive apnea events.\textsuperscript{72} The intraesophageal pressure does decreases during obstructive apnea events; however, this is compensated by an increase in the gastroesophageal junction pressure, acting as a natural anti-reflux barrier.\textsuperscript{73} TLESRs mainly occur during awake state or are preceded by arousals.\textsuperscript{72} Therefore, the beneficial effect of nCPAP might be explained by reducing the number of arousals, leading to less TLESR and less nocturnal reflux. Larger, high-quality randomized clinical trials are needed to evaluate whether nCPAP has a role in the therapeutic armamentarium of nocturnal reflux.

We identified several treatments that are not effective for the treatment of nocturnal reflux. We do not recommend the use of muscle relaxants (baclofen), as the evidence of its effect is limited and it is associated with many gastrointestinal and neurological side effects.\textsuperscript{74} Although nocturnal reflux negatively affects sleep quality and hypnotics might reduce nocturnal reflux symptoms, these drugs lead to an increased esophageal acid exposure time by impairing the reflux-associated awakenings and arousals.\textsuperscript{48,50} Therefore, we do not recommend the use of hypnotics to treat nocturnal reflux symptoms.

A potential limitation of this study is that we excluded clinical trials that only measured intragastric pH without measurement of esophageal pH or reflux parameters as outcome measures. As intragastric pH poorly correlates with esophageal reflux, we felt that this led to a better overview of treatments with proven effect on nocturnal gastroesophageal reflux. Furthermore, this systematic review focused on interventions specifically targeting nocturnal reflux symptoms. This does not mean, however, that interventions that are not specific for nocturnal reflux, such as weight loss in overweight patients, smoke cessation, and antacids, should not be recommended to patients who present with nocturnal reflux symptoms. GERD is a multifactorial disease and should be treated as such.

5 | CONCLUSION

This systematic overview provides clinicians with an overview of treatment strategies that specifically target nocturnal reflux symptoms. A step-up treatment strategy, including head of bed elevation, prolonging dinner-to-bed time, promoting left lateral decubitus position and treatment with acid-suppressive medication is recommended. Currently, there is insufficient evidence for the use of nCPAP, hypnotics, baclofen and adding bedtime H2RA for the treatment of nocturnal gastroesophageal reflux symptoms.
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AUTHOR CONTRIBUTIONS
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ORCID
Jeroen M. Schuitenmaker https://orcid.org/0000-0002-1213-3551
Thijs Kuipers https://orcid.org/0000-0002-5503-5505
André J.P.M. Smout https://orcid.org/0000-0001-7796-6282
Paul Fockens https://orcid.org/0000-0002-2382-0672
Albert J. Bredenoord https://orcid.org/0000-0001-5918-2062

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