Nocturnal Gastroesophageal Reflux Disease

Case Study and Commentary, Ronnie Fass, MD, Michael Shapiro, MD, and Anmarie Moore, MD

Gastroesophageal reflux disease (GERD) is a chronic disorder and the most common disease that affects the esophagus. Approximately 20% of U.S. adults experience GERD-related symptoms at least once per week, and a considerable percentage of GERD patients experience nighttime symptoms. Nocturnal GERD is an underappreciated clinical problem that impacts sleep, daytime function, and work productivity. Nocturnal gastroesophageal reflux has been demonstrated to be an important underlying mechanism for the development of complicated GERD and extraesophageal manifestations of GERD. Physicians need to be aware of the prevalence and impact of this disabling condition.

Educational Objectives
1. Recognize the symptoms of nocturnal GERD
2. Describe the pathophysiology of nocturnal GERD
3. Understand the relationship between nocturnal GERD and sleep disturbances
4. Describe the available treatments for nocturnal GERD

The epidemiology of nocturnal gastroesophageal reflux has only recently been examined. According to a Gallup poll from 1988 in which 1000 GERD patients completed a survey, 79% of the respondents reported nocturnal heartburn [2]. In a study by Farup et al, 74% of GERD patients with frequent GERD symptoms reported nocturnal GERD symptoms [3]. In contrast, Locke et al found in a community-based survey that 47% and 34% of the GERD sufferers reported nocturnal heartburn and nocturnal acid regurgitation, respectively [1]. Fass et al in a large prospective cohort study of subjects evaluated for sleep disturbances demonstrated that 24.9% reported heartburn during sleep [4].

Acid reflux episodes are divided into daytime reflux and nighttime reflux. However, because there is no clear definition of nighttime reflux, some prefer to divide episodes into reflux during the awake period and reflux during the sleep period. The latter division underscores the impact of sleep physiology on gastroesophageal reflux. Acid reflux during awake time tends to be more frequent but of shorter duration. In contrast, acid reflux during sleep is generally less frequent but of a significantly longer duration [5].

Nocturnal gastroesophageal reflux has been demonstrated to be an important underlying mechanism for the development of complicated GERD and extraesophageal manifestations of GERD. The latter may include oropharyngeal, laryngeal, and pulmonary manifestations [6,7]. The former may include erosive esophagitis, peptic stricture, esophageal ulcerations, Barrett’s esophagus, and adenocarcinoma of the esophagus. Furthermore, recent reports have demonstrated that nocturnal GERD is associated with poor quality of sleep and a variety of sleep disturbances [8,9].

Nocturnal reflux is also associated with reduced health-related quality of life as compared with the general population. In addition, patients with nighttime symptoms of GERD have a substantially diminished quality of life as compared with individuals without GERD symptoms during nighttime [3].
CASE STUDY
Initial Presentation
A 48-year-old salesman presents to his primary care physician with the complaint of daily episodes of heartburn as well as repeated short episodes of chronic cough over the past 6 months. He also reports awakening during the night with heartburn at least twice per week. He has been taking H₂ blockers for the past 2 weeks with little improvement in his symptoms.

What are the symptoms and signs of nocturnal GERD?

Nocturnal GERD should be suspected in every patient that presents with typical or extraesophageal manifestations of GERD (Table 1). Specific questions that address different potential manifestations of nocturnal GERD should be used. Reports of typical GERD symptoms during nighttime are indicative of nocturnal GERD, but these are not always present. Patients reporting waking up during the night with heartburn, acid regurgitation, sour or bitter taste in the mouth as well as waking up in the morning with these symptoms should be considered as having nocturnal gastroesophageal reflux. Additionally, nocturnal gastroesophageal reflux may present with nighttime cough, wheezing, sore throat, choking, and other symptoms. Furthermore, insomnia, repeated awakening, snoring, tossing and turning, and even night-mares have all been related to nocturnal gastroesophageal reflux. In other patients, the sole manifestation of nocturnal gastroesophageal reflux can be awakening in the morning and feeling unrefreshed, dozing off, daytime sleepiness, and other sleep-related disturbances. In one series it was demonstrated that nighttime heartburn occurring twice a week or more was associated more with respiratory symptoms or sleep complaints [10].

Recent studies have suggested that nocturnal gastroesophageal reflux is more common during the early phase of the sleep period, which may be related to bedtime meals, consumption of alcohol and/or carbonated beverages, and use of sleeping pills (specifically, benzodiazepines) [4,11].

A careful physical examination should be performed at the first clinical visit and on subsequent visits as needed. However, most patients with nocturnal GERD will not demonstrate any disease-related physical findings. Additionally, signs that could be found in any GERD patient may be present, such as increased body mass index, obesity, submandibular adenopathy (GERD-related pharyngeal involvement), caries and poor oral hygiene (GERD-related oral involvement), cachexia, and anemia (GERD complications). However, most of these signs are rarely found in patients with GERD.

Further History
The patient is questioned about the duration of his symptoms and he reports a 15-year history of heartburn and occasional acid regurgitation that usually occurs at night. He complains about daytime sleepiness, dozing off occasionally, inability to concentrate, and irritability. He denies dysphagia, odynophagia, nausea, vomiting, weight loss, or gastrointestinal bleed. He smokes 20 cigarettes a day, drinks 24 oz of beer at least twice a week, and eats large late-evening meals.

What is the definition of nocturnal GERD and what are the pathophysiologic mechanisms?

Definition
Currently, we are still devoid of an accepted definition for nocturnal GERD. Interestingly, studies that assessed either prevalence or therapeutic response of patients with nighttime heartburn lacked a clear definition of nocturnal GERD [1,2,12]. Farup et al offered that nighttime GERD could be defined as the presence of any 1 of the following [3]:

- Nocturnal awakening by GERD symptoms
- Nocturnal awakening caused by coughing or
choking, regurgitation of fluid or food, and acidic/bitter taste

• GERD symptoms while in the supine position
• Morning awakening secondary to GERD symptoms

This is an inclusive definition that may include patients who experience GERD-related symptoms in the supine position while still awake. In contrast, Fass et al suggested that nighttime heartburn should be defined as heartburn that awakens patients from sleep during the night [4]. While this is a more restrictive definition, it underscores the importance of having GERD-related symptoms during sleep.

Pathophysiology
Normal sleep physiology results in many changes in gastroesophageal function that contribute to the pathogenesis of GERD. Sleep may alter physiologic mechanisms responsible for normal esophageal clearance, resulting in impairment of esophageal acid clearance. Rate of swallowing is reduced during sleep leading to decrease in primary peristalsis, a pivotal defense mechanism that is responsible for volume clearance of refluxate from the esophagus [13]. Diminished salivary production during sleep as well as reduced delivery of saliva to the distal esophagus due to decreased primary peristalsis delay alkalization and thus normalization of esophageal pH after acid reflux has occurred. The upper esophageal sphincter basal pressure is significantly reduced, resulting in an increased risk for aspiration, which may lead to upper airways exposure to gastroesophageal reflux and consequently extraesophageal manifestations. In addition, gastric acid secretion is increased and gastric emptying is delayed during nighttime. Moreover, there is less conscious awareness of gastroesophageal reflux during sleep, resulting in reduction in symptom perception and thus alteration in conscious defensive behavior against gastroesophageal reflux (eg, antacid consumption, assuming the upright position, initiating a swallow) [14].

The overall weakening in esophageal defense mechanisms during sleep leads to prolonged esophageal acid exposure during nighttime, resulting in a more serious injury to the esophageal mucosa. Several studies have demonstrated that nocturnal GERD is associated with increased risk of having severe gastroesophageal disease, such as erosive esophagitis, peptic stricture, Barrett’s esophagus, and even adenocarcinoma of the esophagus [15]. DeMeester et al [16] studied GERD manifestations in 100 patients with reflux-related symptoms and demonstrated that patients with supine reflux had a higher incidence of erosive esophagitis than those with predominantly upright reflux. Robertson et al [17] compared pH testing results in patients with uncomplicated versus complicated GERD. The authors concluded that complicated GERD is associated with prolonged nocturnal acid exposure of the esophagus. They further stipulated that nocturnal acid exposure may be the cause of peptic stricture, esophageal ulceration, or Barrett’s metaplasia. Another study has demonstrated a significant nocturnal acid exposure in patients with Barrett’s esophagus as compared with those with erosive esophagitis or nonerosive reflux disease (Figure 1) [18]. Furthermore, patients with long-segment Barrett’s esophagus (≥ 3 cm) demonstrated a significantly higher nighttime acid exposure as compared with those with short-segment Barrett’s esophagus (< 3 cm) [19,20]. Overall, there was an increase in total as well as supine esophageal acid exposure, as documented by pH testing, from nonerosive reflux disease to erosive esophagitis and then to Barrett’s esophagus [18].
Lastly, the risk of esophageal adenocarcinoma is 8 times higher among patients with weekly reflux symptoms in comparison with asymptomatic subjects. The risk is even higher in patients reporting nocturnal heartburn [15].

**What is the relationship between nocturnal GERD and sleep disturbances?**

There are some data supporting a close association between nocturnal GERD and sleep disturbances. Sleep disturbances in patients with GERD are poorly recognized and rarely elicited during clinic visits. Despite the significant impact of these disturbances on patients’ quality of life and (probably) on their perception of the severity of their disease, questions regarding sleep disturbances are not usually asked during a routine history taken from patients with reflux disease. When 759 patients with endoscopy-negative reflux disease and enrolled in the esomeprazole clinical trial program [21] were assessed by a quality-of-life tool for “sleep disturbances for at least some of the time,” 50% reported that symptoms of GERD were responsible for difficulties in getting a good night’s sleep. Other indicators of sleep disturbance were “feeling tired/worn out due to lack of sleep” (42%), “failure to wake up feeling refreshed” (41%), “having trouble falling asleep” (40%), and “heartburn/acid regurgitation waking the patient and preventing him/her from falling asleep” (35%) [21].

In a national survey of 1000 subjects with GERD, 75% of the participants reported that GERD symptoms affected their sleep, and 63% believed that heartburn negatively affected their ability to sleep well [2]. The prevalence of sleep disturbances among respondents increased with increase in frequency of the nighttime heartburn episodes during the week. Additionally, 42% could not sleep through the night and 39% took naps whenever possible. Green et al reported that GERD patients that sleep less during the night are more likely to have symptoms that correlate with acid reflux events [22]. Additionally, the extent of distal esophageal acid exposure has a significant effect on patients’ reported sleep experience [8]. The higher the acid exposure, the lower the overall reported quality of sleep (supine) and the higher the number of nocturnal awakenings (total and supine). Dekel et al demonstrated that the frequency and severity of GERD symptoms were correlated with patients’ quality of sleep. Patients with erosive esophagitis reported more nocturnal awakenings due to heartburn than those with nonerosive reflux disease but otherwise reported similar sleep abnormalities and quality of sleep. Other investigators have demonstrated that nighttime gastroesophageal reflux may result in anamnestic short awakenings that lead to sleep fragmentation and feeling unrefreshed the next morning, dozing off, and daytime sleepiness [9].

Obstructive sleep apnea (OSA) is a breathing disorder that occurs during sleep in which the patient experiences respiratory pauses lasting at least 10 seconds and occurring at least 5 times per hour of sleep [23]. OSA is characterized by excessive daytime sleepiness, snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia leading to memory problems, irritability, and depression. The exact association between OSA and GERD remains controversial. In one study, OSA was not influenced by severity of GERD. Additionally, objective measures of disordered sleep had a stronger association with age, smoking, and alcohol use than with GERD in men and a stronger association with age and body mass index than with GERD in women [24]. Kerr et al have demonstrated that precipitous drops in pH were frequently preceded by arousal (98.4%), movement of the patient (71.9%), and swallowing (80.4%) [25]. In this case, arousal is theorized to be caused by increased ventilatory effort [26]. Arousal and movement may trigger gastroesophageal reflux by causing transient alteration in the pressure gradient across the lower esophageal sphincter (LES). Additionally, the lowered intrathoracic pressure that accompanies OSA may itself predispose the patient to gastroesophageal reflux by exacerbating the LES pressure gradient. Treatment with nasal continuous positive airway pressure showed dramatic reduction in the frequency of gastroesophageal reflux by elevating intrathoracic pressure [25].

Investigators have suggested that GERD causes OSA, and OSA has been linked to GERD [24]. Other studies could not demonstrate a causal relationship between GERD and OSA. In a study by Penzel et al, 37 of 52 reflux events that occurred during sleep involving either apnea or hypopnea were found prior to the reflux event [27]. The sequence in time did not prove a causal relationship between the respiratory and reflux events. Patients subjectively report that the quality of sleep is affected by the severity of GERD; however, objective correlation between GERD and OSA is lacking, which may suggest that both are common entities sharing similar risk factors but may not be causally linked [24].

**What is the approach to diagnostic evaluation and initial treatment in nocturnal GERD?**

Upper endoscopy should be performed in all patients with classic symptoms of GERD who also report alarm symptoms (dysphagia, odynophagia, weight loss, anorexia, evidence of gastrointestinal bleeding, or iron deficiency anemia) [28]. All patients with chronic symptoms of GERD, particularly those...
who are 50 years and older, are at increased risk for Barrett’s esophagus and thus should undergo an upper endoscopy at least once during their lifetime to rule out the presence of Barrett’s mucosa [29]. Patients who are found to have Barrett’s esophagus should undergo regular surveillance using a standard esophageal mucosal biopsy protocol. Presently, the sole presence of nocturnal heartburn is not an indication for an upper endoscopy, unless alarm symptoms are also elicited. Similarly, pH testing should be reserved only for individuals who are not responding to potent antireflux treatment (on therapy).

Patients with symptoms of nocturnal GERD may be treated with diet, lifestyle modifications, and medications without prior endoscopic evaluation. A step-up approach may be adopted, starting with a histamine type-2 receptor antagonist (H₂RA) and upgrading to a proton pump inhibitor (PPI) if nocturnal symptoms are not improved. Others may elect either a step-in or a step-down approach. The former suggests initiating and maintaining subjects on a PPI, while the latter proposes initiating patients on a PPI and then tapering them down to the least potent antireflux modality that can still control their symptoms (Figure 2).

**Further Evaluation and Management**

After completing the history and physical examination, lifestyle modifications and dietary changes are recommended. While no alarm symptoms were elicited, the physician orders an upper endoscopy prior to starting

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**Figure 2. Management algorithm for nocturnal GERD. LA = Los Angeles classification; NERD = nonerosive reflux disease; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.**

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**Table 2. Lifestyle Modifications in the Treatment of GERD**

- Elevate the head of the bed
- Avoid assuming the supine position up to 4 hours after a meal
- Avoid medications that exacerbate gastroesophageal reflux (eg, anticholinergics, tricyclics and other antidepressants, calcium channel blockers, benzodiazepines)
- Avoid smoking or drinking alcohol
- Avoid eating large fatty meals, spicy food, chocolate, peppermint, coffee, onions, and citrus juices
- Avoid carbonated beverages
- Reduce weight (if overweight)
- Avoid tight-fitting garments

Medical therapy. The test reveals Los Angeles classification grade B erosive esophagitis.

- **What are treatment options?**

Generally, the main goals of treatment for nocturnal GERD are resolution or improvement of reflux-related symptoms; resolution or improvement of extraesophageal manifestations if present (including sleep deprivation); healing of esophageal inflammation if present; resolution or improvement of quality of life; and prevention of GERD-related complications.

Overall, studies that assessed treatment effect on nocturnal symptoms (clearly defined) are relatively scarce. The current adopted therapeutic approach to nocturnal GERD is similar to that for GERD. In general, nocturnal acid regurgitation is less common and also less easily controlled with pharmacologic therapy than nocturnal heartburn. Additionally, nocturnal atypical and extraesophageal manifestations of GERD are more difficult to control, and thus aggressive use of potent antireflux treatment (PPIs) is often warranted.

**Lifestyle Modifications**

Lifestyle modifications include weight loss, smoking cessation, avoidance of postprandial recumbency for a period of 3 to 4 hours, elevation of the head of the bed, avoidance of tight-fitting garments, and avoidance of food and drink that exacerbate GERD symptoms (Table 2). Although of limited value as sole treatment of GERD, lifestyle modifications are an important adjunct to medical therapy [30,31]. The role of lifestyle modifications in nocturnal GERD remains to be elucidated. Recent studies have suggested that late night meals may provoke nocturnal GERD; thus, avoiding meals 3 to 4 hours before bedtime is recommended [11]. The association between increased body mass index, consumption of carbonated soft drinks, and use of benzodiazepines and reports of heartburn during sleep suggests that following lifestyle modifications may improve nocturnal GERD [32,33]. Shaker et al. demonstrated that 61% of the patients with nighttime heartburn avoided food before bed and 44% elevated the head of the bed, but only 33% and 23%, respectively, rated these methods as completely satisfactory [2]. For many patients, lifestyle modifications may be difficult to follow long term and many also adversely affect their quality of life.

**Antacids and Alginates**

Antacids are basic compounds composed of different combinations of acid-neutralizing agents such as aluminum and magnesium hydroxide, calcium carbonate, sodium citrate, and sodium bicarbonate. Considered the standard medical treatment for peptic ulcer disease for more than a century, antacids have been the most widely used remedy for GERD symptoms [34,35]. They provide transient symptom relief but do not contribute to the healing or prevention of GERD complications [34,36]. Nevertheless, antacids are a very popular on-demand treatment for patients seeking rapid symptom relief.

Alginates create a foamy raft above the gastric contents. With both alginic acid and antacid present, the raft acts as an alkaline barrier between the acid gastric contents and the esophagus, while the antacid serves to neutralize the gastric contents. This mechanism is thought to protect the esophageal epithelium and to alleviate GERD symptoms. However, as with antacids alone, alginates provide rapid, transient relief of symptoms but play no role in healing erosive esophagitis or preventing symptom relapse or GERD complications.

There are no specific studies that assess the specific role of antacids or alginates in nocturnal GERD. In one study, 71% of the patients with reported nighttime heartburn were using over-the-counter (OTC) medication (primarily antacids) to relieve their symptoms, but only 29% rated this therapeutic modality as satisfactory [2].

**Promotility/Prokinetic Drugs**

Motility-modifying drugs may affect gastroesophageal reflux by increasing LES pressure, improving esophageal peristalsis and thus acid clearance, and facilitating gastric emptying. All may improve nighttime gastroesophageal reflux. At present, metoclopramide and tegaserod are available as promotility drugs, both with no clear effects on nocturnal GERD documented. Both drugs should be considered in patients with nocturnal GERD and evidence of delayed gastric emptying.

Metoclopramide is a dopamine antagonist and a cholinomimetic that crosses the blood–brain barrier and neutralizes the inhibitory effect of dopamine in the central nervous system and on the gastrointestinal smooth muscle. Its
therapeutic efficacy in GERD, however, is limited because of multiple adverse effects of a neurologic or psychotropic nature, including lethargy, mental status changes, and extrapyramidal abnormalities [37]. Elderly subjects are particularly vulnerable to these effects, and some (extrapyramidal) effects are not reversible after discontinuation of the drug. Additionally, metoclopramide has demonstrated little effect on esophageal healing.

Tegaserod, a partial 5-hydroxytryptamine-4 receptor agonist, has been prescribed primarily for women with constipation-predominant irritable bowel syndrome or those with chronic constipation. A potent promotility agent throughout the gastrointestinal tract, tegaserod may improve delayed gastric emptying in patients with GERD. Although its role in GERD has not been clearly established, early studies have demonstrated a limited transient lower esophageal sphincter relaxation reducing effect that may result in fewer reflux events [38].

**Histamine Type-2 Receptor Antagonists**

H2RAs, or H2 blockers as they are commonly known, are still widely used for the treatment of GERD. This class of drugs reduces gastric acid output by competitive inhibition of histamine at H2-receptors on the parietal cells. H2RAs reduce pepsin output by an unknown mechanism and reduce gastric acid volume as well [39]. As a class, the different H2RAs are considered equivalent in suppressing gastric acid output when administered in equipotent doses. The pharmacokinetic differences among the agents appear to be clinically insignificant [40]. Although H2RAs are effective in controlling basal acid secretion, they are less effective in suppressing postprandial acid secretion. Standard doses have been proven to be effective in controlling symptoms and healing mild to moderate erosive esophagitis. The more severe forms of erosive esophagitis require greater acid suppression, which the H2RAs are less able to provide. Clinical trials with higher doses of H2RAs to address this concern have yielded conflicting results. Ranitidine 300 mg twice daily was proven to be no better than the standard dose of 150 mg twice daily [41]. Cimetidine 800 mg twice daily was likewise shown to have a similar outcome to 400 mg twice daily [42]. In a multicenter trial comparing ranitidine 300 mg 4 times/day with 150 mg twice daily, healing rates among patients with grades I to III erosive esophagitis were much higher in those receiving the higher dose (75% versus 54%) [43]. However, the authors neglected to elaborate on the increased cost of multiple dosing as well as the impact on patient compliance. In contrast, Kahrilas et al [44] demonstrated that doubling the standard dose of ranitidine (from 150 mg twice daily to 300 mg twice daily) failed to improve symptom control in more than 50% of patients who persistently experienced heartburn symptoms after 6 weeks of standard H2RA therapy.

The potential effect of H2RAs on the nighttime histamine-driven surge of gastric acid secretion led to the popular use of these drugs at bedtime by patients who continued to be symptomatic on a standard or double-dose PPI [45]. However, pharmacokinetic tachyphylaxis develops quickly with H2RAs, limiting their regular use in clinical practice [46]. The main appeal of H2RAs is their usage as an on-demand therapy. Their rapid effect on GERD symptoms, unsurpassed by any of the currently available PPIs, makes this class of drugs a very popular OTC remedy for many GERD sufferers who never seek medical attention.

As part of the OTC antireflux armamentarium, many nocturnal GERD sufferers will use on-demand H2RAs for nighttime heartburn [2].

**Proton Pump Inhibitors**
PPIs (pantoprazole, omeprazole, lansoprazole, rabeprazole, and esomeprazole) are the most potent gastric acid suppressants because of their ability to inhibit the proton pump H+, K+-ATPase, the enzyme that constitutes the final common pathway of gastric acid secretion. They suppress nocturnal and daytime as well as food-stimulated gastric acid secretion [47]. Because of their profound and sustained acid inhibition, PPIs are now the most successful antisecretory agents in terms of symptom relief and mucosal healing [39,48]. Additionally, PPIs provide faster symptom resolution and healing of the esophageal mucosa compared with the H2RAs [48]. The main impact of PPIs has been on advanced erosive esophagitis, complications of GERD (such as peptic stricture), atypical/extrasophageal manifestations of GERD, and Barrett’s esophagus.

Therapeutic studies using PPIs have shown an excellent control of nighttime heartburn (Table 3). In fact, nighttime heartburn appears to be more responsive to PPI therapy than daytime heartburn. Furthermore, in GERD patients with primarily nighttime symptoms, a PPI prior to dinner is likely to be more efficacious in controlling nocturnal symptoms than if a dose is taken prior to breakfast [49].

Studies with pantoprazole have focused on clinical efficacy of the medication on nighttime acid exposure as well as nighttime heartburn. Pantoprazole has been shown to provide nighttime heartburn relief in 76% of patients on day 7 and 81% on day 14 [50]. However, comparative studies with other PPIs are still lacking.

**Treatment of Laryngeal Manifestations**

Wo et al [51] recently reviewed some of the therapeutic trials in patients with GERD-related otolaryngeal manifestations. The reviewers pointed out that any comparison of the different studies was limited due to the use of various doses of PPIs, standard doses of H2 blockers, and surgery over different periods of time, which ranged from 4 to 24 weeks.
Regardless of the mode of therapy, the response rates in these studies ranged from 50% to 96%. One study that used omeprazole 40 mg daily for 8 weeks as empirical therapy for posterior laryngitis demonstrated that two thirds of the patients were either symptom-free or satisfied with their symptom improvement at the conclusion of the study. The remaining patients were classified as nonresponders, and when ambulatory 24-hour esophageal pH monitoring was performed, 80% still demonstrated an abnormal amount of esophageal acid exposure. This finding raises the question of adequate compliance in the latter group [52].

In a recent randomized, double-blind, placebo-controlled study, the effect of lansoprazole 30 mg twice daily was evaluated in patients with idiopathic chronic laryngitis; 20 patients were randomly assigned to lansoprazole or placebo for 3 months. The groups were matched by pH test results, endoscopic findings, and laryngeal signs and symptoms. At the end of the study, 50% of the patients in the lansoprazole group but only 10% in the placebo group reported complete resolution of their laryngeal symptoms. Laryngeal signs completely or partially resolved in 58% of the patients in the lansoprazole group but only in 30% of the patients in the placebo group. The investigators concluded that the use of an empiric trial of PPIs as the first line of therapy is an effective therapeutic approach in patients with chronic recurrent laryngitis [53].

As with therapeutic trials in GERD-related asthma, patients with GERD-related otolaryngeal abnormalities benefit the most from PPIs at least double the standard dose for a minimum period of 8 to 12 weeks. H2RAs have no role in this patient population.

In patients with chronic cough, it is advisable that after excluding common non–GERD-related causes (eg, postnasal drip, asthma) aggressive treatment with PPIs should be initiated, lifestyle modifications recommended, and promotility drugs considered as an additive modality. Treatment should be continued for at least 3 months before re-evaluation. After 3 to 6 months of therapy, ambulatory 24-hour esophageal pH monitoring on PPI therapy should be considered in nonresponders to identify those with inadequate acid control who consequently need a high-dose PPI. As with other manifestations of GERD, long-term and possibly lifelong treatment with PPIs would likely be needed to prevent recurrence [54].

Recently, Irwin and Madison [55] reviewed retrospectively and prospectively conducted uncontrolled trials that used PPIs or H2RAs to treat chronic cough. Response rates with acid-suppressive therapy were between 70% and 100% in these studies. PPIs (omeprazole 20 mg or 40 mg daily) provided a much faster response rate (mean, 53 days), and many patients already had responded during the first 1 to 2 weeks of treatment. In contrast, the response time of H2RAs was longer and occurred over a period of 3 to 6 months. A

### Table 3. Effect of Proton Pump Inhibitor (PPI) Therapy on Nighttime versus Daytime Heartburn*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration, wk</th>
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**Complete Relief**

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*Studies include erosive esophagitis patients only.
2-week trial of omeprazole 40 mg twice daily was found to be an excellent diagnostic approach for GERD-related chronic cough as well as a clinical predictive factor for successful response to antireflux treatment [56].

**Surgical Treatment**

Improvement of nighttime heartburn has been used as one of the clinical outcomes that assessed the effectiveness of surgical intervention in GERD. There are no specific surgical studies that evaluated nocturnal GERD only.

Antireflux surgery is offered to patients in the hope of obviating the need for continuous medical therapy, which may result in inconvenience, increased costs, and concerns about safety [57]. Nissen fundoplication remains the most commonly performed surgery and consists of a 360° wrap of the gastric fundus around the distal esophagus, which results in augmentation of LES basal pressure and a decrease in the rate of transient lower esophageal sphincter relaxation. At this time, fundoplication is commonly done laparoscopically, which, compared with open surgery, is less costly, has less postoperative morbidity, and requires a shorter hospital stay. Postoperatively, however, dysphagia appears to be more common in patients who underwent laparoscopic Nissen fundoplication. Complications due to antireflux surgery are also determined by the expertise of the surgeon, which has been shown to closely correlate with the number of procedures performed.

Offering surgery to young patients because of the prospect of long-term medical therapy should be individualized and discussed in an unbiased approach. Ultimately, the success of antireflux surgery depends on selecting the appropriate patients and surgeon. Presurgical evaluation includes an esophageal manometry, primarily to exclude achalasia and ineffective peristalsis (amplitude of esophageal body contractions < 30 mm Hg), upper endoscopy, and 24-hour esophageal pH monitoring in those patients without erosive esophagitis [58].

Positive response to medical therapy is the best predictor of successful surgical outcome. Additionally, age younger than 50 years and the presence of typical GERD symptoms were also found to be positive clinical predictors. However, approximately half of the patients referred for antireflux surgery are referred because medical therapy has failed [59]. When clinical outcome of antireflux surgery and treatment with omeprazole were compared, as long as patients were allowed to adjust the needed dose no great difference in rates of treatment failure was observed between the 2 therapeutic strategies [60]. However, a recent publication has reported that more than 10 years after antireflux surgery, more than half of patients require medical therapy (many on PPIs) to control their GERD symptoms [61].

Practitioners should be aware of the side effects that patients may encounter after antireflux surgery, which may include persistent dysphagia, “gas-bloat” syndrome, inability to vomit, vagal nerve injury, and diarrhea.

**Case Resolution**

The patient was initiated on a PPI given once daily 30 minutes before breakfast. On a follow-up visit 1 month later, he reports significant improvement in GERD symptoms. He does admit to having occasional nocturnal GERD symptoms and daytime sleepiness. An additional evening dose (30 minutes before dinner) of the PPI is recommended, and this regimen results in complete resolution of nighttime symptoms over the following month.

**CONCLUSION**

Nocturnal heartburn is very common, affecting most patients with GERD. However, patients may not report nocturnal symptoms unless specifically asked. In a subset of GERD patients, nocturnal symptoms may not be present but patients may display other manifestations of nocturnal gastroesophageal reflux, such as nighttime choking, cough, wheezing, and sleep disturbances. Nocturnal GERD requires special attention from treating physicians because of its association with complicated GERD and atypical/extrasophageal manifestations of GERD. Any therapeutic intervention for GERD should also aim at ameliorating nocturnal GERD symptoms. PPIs are an effective therapeutic modality in controlling nocturnal heartburn symptoms in most sufferers.

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**References**


Nocturnal Gastroesophageal Reflux Disease

DIRECTIONS: Each of the questions below is followed by 4 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following symptoms have been related to nocturnal reflux?
   (A) Snoring  
   (B) Sore throat  
   (C) Nightmares  
   (D) All of the above

2. Which of the following statements about nocturnal GERD is FALSE?
   (A) Nocturnal GERD is associated with an increased risk of complicated GERD  
   (B) Nocturnal GERD is present in less than half of patients with GERD  
   (C) Nocturnal GERD is a risk factor for esophageal adenocarcinoma  
   (D) Nocturnal GERD is associated with reduced quality of life

3. A benefit offered by H₂ receptor antagonist use in GERD is
   (A) Increases lower esophageal sphincter pressure  
   (B) Rapid effect on GERD symptoms  
   (C) Improves laryngeal manifestations  
   (D) All of the above

4. What is appropriate initial therapy in 45-year-old man with chronic GERD symptoms?
   (A) Initial H₂ receptor antagonist therapy  
   (B) Initial PPI therapy, then taper down  
   (C) Initiate and maintain on PPI therapy  
   (D) Any of the above

5. Which of the following is recommended as a next step in a patient whose GERD symptoms are uncontrolled after 1 month on once daily PPI therapy?
   (A) Continue current therapy  
   (B) Have patient undergo 24-hour pH monitoring  
   (C) Increase dose of PPIs  
   (D) Add an H₂ receptor antagonist
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   _Very helpful _Somewhat helpful _Not at all helpful

4. Please tell us how well the article achieved each of the following objectives.
   Participants will be able to:
   - Recognize the symptoms of nocturnal GERD
     _Achieved _Partially achieved _Not achieved
   - Describe the pathophysiology of nocturnal GERD
     _Achieved _Partially achieved _Not achieved
   - Understand the relationship between nocturnal GERD and sleep disturbances
     _Achieved _Partially achieved _Not achieved
   - Describe the available treatments for nocturnal GERD
     _Achieved _Partially achieved _Not achieved

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