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Review article: diagnosis and management of night-time reflux

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SUMMARY

Symptoms of gastro-oesophageal reflux disease (GERD) range from mild to severe and, when they occur during night-time hours, can interfere with sleep patterns and reduce overall quality of life. The clinical presentation of GERD is characterized by oesophageal as well as supra-oesophageal symptoms, including otolaryngologic and pulmonary complications. However, GERD may be overlooked as the cause of a patient's supra-oesophageal symptoms because these complaints can occur in the absence of oesophageal symptoms or endoscopic changes. The role of available tools used for GERD diagnosis, including endoscopy, oesophageal pH monitoring and an empirical course of proton pump inhibitor therapy, is discussed. Interventions available to achieve the therapeutic goals of symptom relief and prevention include specific lifestyle modifications and over-the-counter as well as prescription pharmacological agents. Patient-initiated, as-needed treatment may not be the best choice for managing persistent night-time reflux because it requires patient arousal from sleep. Proton pump inhibitor therapy remains the treatment of choice for patients with more severe symptoms and those with erosive oesophagitis. Few studies have specifically evaluated the role of pharmacological agents in the management of night-time reflux and comparisons are difficult due to the variability in study design and endpoints assessed.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a chronic disorder and a common reason for visits to primary care physicians, gastroenterologists and, more recently, otolaryngologists. Population-based studies estimate that GERD symptoms occur weekly in 8–20% of the population.[1, 2] Among those individuals reporting heartburn at least weekly, 79% report night-time heartburn.[3] Approximately 60% of individuals with night-time symptoms experience interference with sleep, which may affect daytime activities in as many as 40% of these patients.[3]

Symptoms of GERD are not limited to the oesophageal complaints characteristically associated with reflux. Atypical chest pain and otolaryngeal and pulmonary problems are common in GERD patients. Unfortunately, these symptoms are often treated without recognition that GERD is potentially contributing to the underlying problem. Night-time symptoms have also been associated with increased prevalence and severity of GERD complications.[4–8] Despite its prevalence and potentially

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serious consequences, there are few epidemiological reports, sleep studies or clinical efficacy trials specifically addressing the diagnosis and management of night-time GERD.

DIAGNOSIS

Recognizing oesophageal symptoms

Oesophageal symptoms that are highly specific for reflux include heartburn, regurgitation or both, often occurring after meals (especially large or fatty meals) (Table 1). Typically, symptoms are aggravated by recumbency or bending and are relieved by antacids. Although symptom severity does not necessarily correlate with the extent of damage to the mucosa, most patients with severe or complicated oesophagitis experience persistent heartburn, regurgitation or dysphagia.[9] Based on the results of a population-based study that found a positive association between severity and frequency of symptoms ($P < 0.001$) and between symptom frequency and number of physician visits (odds ratio, 6.2; 95% confidence interval, 3.6–10.7), one can conclude that seeking the assistance of a physician for symptom relief may be a good indicator that GERD symptoms are severe.[1] However, many patients may not judge their symptoms to be severe enough to warrant medical attention. A survey of patients experiencing heartburn at least once a week found that 42% believed their symptoms were not serious enough to seek medical help.[3]

Table 1. Conditions associated with gastro-oesophageal reflux disease

Oesophageal	Supra-oesophageal
Heartburn	Hoarseness
Regurgitation	Asthma (related to aspiration and vagal reflex)
	Aspiration
	Cough
	Carcinoma of the larynx
	Laryngitis and damage to larynx
	Pulmonary fibrosis
	Bronchiectasis
	Pneumonia
	Excessive throat clearing
	Globus sensation
	Laryngospasm
	Post-nasal drip sensation
	Exacerbation of reactive airway disease
	Decreased vocal pitch
	(secondary to vocal fold oedema)

Recognizing supra-oesophageal symptoms

Otolaryngeal symptoms of GERD, which include hoarseness, laryngitis, laryngospasm, cough, globus sensation, excessive throat mucus, chronic throat clearing and chronic sore throat, can present in the absence of classic reflux symptoms or endoscopic changes. As many as 50% of all patients who have symptoms of excessive salivation, hoarseness, sore throat or persistent cough attributable to acid reflux do not exhibit any typical reflux symptoms.[1] In one study of 225 consecutive patients with otolaryngeal disorders suspected of having GERD, 24-h pH monitoring showed that 62% of the patients had abnormal oesophageal acid exposure and 30% had reflux into the pharynx, even though 57% had no oesophageal symptoms.[10] Although these statistics may be at the high end of the range for patients with supra-oesophageal symptoms (the overall association is likely to be less than one-third of patients having documented reflux), physicians should consider GERD in patients presenting with a history of repetitive throat clearing, recurrent hoarseness (particularly in the morning) or cough—even in the absence of heartburn.[11, 12]

Similarly, a large proportion of non-allergic asthma patients may have reflux without having heartburn or dyspepsia. GERD should be considered in patients with adult-onset asthma and in those whose asthma is refractory to customary asthma treatment. The exact contribution of reflux to the pathogenesis of asthma, or vice versa, has not been fully elucidated, but some studies demonstrate symptomatic improvement in response to empirical proton pump inhibitor treatment in asthmatic patients.[13, 14] In a study of asthmatic patients with nocturnal wheezing and chronic cough, but no reflux symptoms, 62% had abnormal 24-h oesophageal pH tests. No demographic variables were predictive of reflux in the asymptomatic patients, which underscores the importance of 24-h pH testing for a more accurate diagnosis.[15] The question of improved 24-h pH profiles in response to better asthma treatment is also now being studied.

Complaints of sleep disturbances may also serve as a warning sign in patients with GERD. Oesophageal and supra-oesophageal symptoms may cause loss of sleep, fatigue, snoring and breathlessness, which lead to reduced quality of life and work productivity.[5, 16]

Diagnostic methods

Symptom relief is an important goal of treatment, but many patients with heartburn have no abnormality seen at endoscopy, therefore empirical treatment has been advocated for transient or intermittent symptoms.[17, 18] Relief of symptoms with 1 week of therapy with omeprazole 20 mg b.d. is associated with a diagnostic sensitivity of 75% and specificity of 55% compared with endoscopy and ambulatory pH monitoring.[19] Compared with 24-h oesophageal pH testing, a therapeutic trial using omeprazole 40 mg once-daily yielded positive and negative predictive values of 68% and 63%, respectively.[20] In most cases where proton pump inhibitor therapy has been used as a diagnostic test for reflux as a cause of symptoms, a twice-daily omeprazole dosing regimen was employed.[21] In general, failure to improve after 2 weeks of proton pump inhibitor therapy warrants referral to a gastroenterologist for diagnostic evaluation.

Although empirical treatment can be helpful in identifying GERD, a recent meta-analysis failed to support proton pump inhibitor therapy as a reliable diagnostic procedure. In that study, proton pump inhibitor therapy was found to correlate only weakly with more objective diagnostic measures such as ambulatory pH and endoscopy.[22] In addition, a response to empirical proton pump inhibitor therapy does not exclude or identify Barrett's oesophagus or GERD complications. Empirical proton pump inhibitor therapy may be appropriate for patients in whom the diagnosis of GERD appears straightforward, but should not be used in patients presenting with alarm symptoms suggesting the possibility of serious complications (Table 2).[17] Those patients need to undergo upper endoscopy and be treated promptly.

The duration of reflux has been directly associated with an increased risk of complications, therefore endoscopic screening should be considered in patients over age 50 who exhibit chronic GERD symptoms. No further surveillance is required in the absence of Barrett's oesophagus at the first endoscopy.[17] Endoscopy with biopsy is the only reliable method of diagnosing Barrett's oesophagus.[17, 23] Availability of ultra-thin flexible endoscopes facilitate endoscopic diagnosis and may offer a more cost-effective approach than conventional endoscopy.[24]

GERD symptoms result from acidic gastric contents entering the oesophagus and not just from excessively low pH of the gastric contents in the absence of reflux. Thus, gastric pH monitoring is not of direct utility in the diagnosis of GERD. In contrast, ambulatory oesophageal pH monitoring enables evaluation of the frequency and duration of episodes during which the oesophagus is exposed to pH < 4. A dual oesophageal probe is sometimes used, which involves a second probe placed in the upper oesophagus allowing documentation of proximal reflux (Figure 1).[25, 26] Although increased acid reflux into the proximal oesophagus can be demonstrated in many GERD patients with laryngeal symptoms, technical limitations remain and the association of such reflux and symptoms requires clarification. One such limitation is the lack of consensus for the location and placement of the proximal probe, which can have an impact on the results of the test.[27] In various studies, the proximal pH probes have been placed 20 cm above the lower oesophageal sphincter, just below the upper oesophageal sphincter, or in the hypopharynx. Normal values of acid exposure, for each position of the probe, remain to be established in adequate numbers of subjects. At present, these kinds of measurements are largely confined to a research setting and are of little use in ordinary practice. General consensus among otolaryngologists is that in order to diagnose supraesophageal reflux, a pH probe needs to be placed outside the confines of the oesophagus, in the hypopharynx.[28]

In many instances, physicians use the response to empirical treatment with acid-suppressive therapy for deciding whether or not a symptom (i.e. hoarseness) is attributable to reflux, reserving pH monitoring mainly for refractory cases. Among patients who do not respond to an aggressive therapeutic trial of proton pump inhibitors, pH monitoring may be helpful in clarifying the existence or absence of GERD. Caution should be used in interpreting negative results of pH

Table 2. Warning or alarm symptoms of gastro-oesophageal reflux disease

Dysphagia
Bleeding/anaemia
Weight loss
Choking (acid causing coughing, shortness of breath, or hoarseness)
Chest pain

Adapted with permission from DeVault K.R. & Castell D.O. Am J Gastroenterol 1999; 94: 1434–1442.[17]

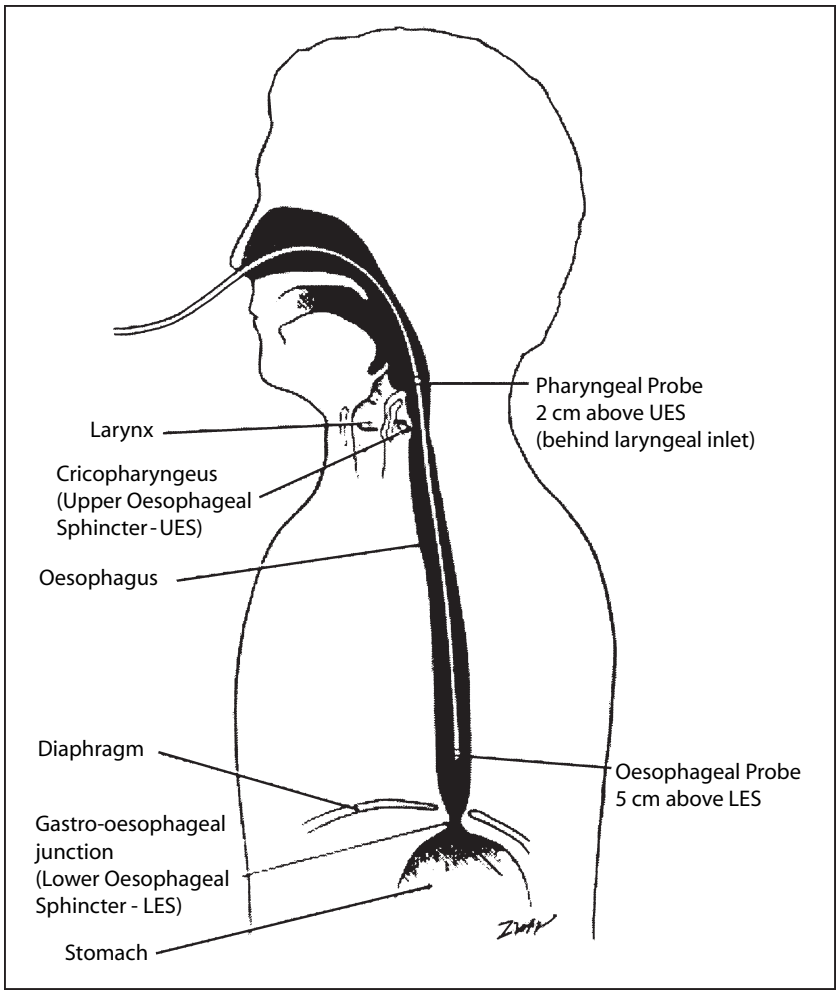

Figure 1. Example of dual probes. Positioning of dual probes using an oesophageal probe and a second probe in the pharynx for 24-h ambulatory monitoring. Adapted with permission from Richter J.E. Am J Med 1997; 103: S130–4.[101]

monitoring because of the intermittent nature of reflux. A negative study should prompt a careful search for an alternative cause of symptoms.

MANAGEMENT OF REFLUX

The goals of therapy for GERD are symptom relief and prevention, healing and maintenance of healing, prevention of oesophagitis or prevention of recurrent oesophagitis, and reduction in the risk of developing long-term complications (e.g. strictures, oesophageal ulcers).

Lifestyle changes

Although few studies have assessed the benefits of lifestyle changes in reducing the symptoms and severity of GERD, patient education regarding such changes is considered an important adjunct to any pharmacological intervention (Table 3).[29–33] Elevation of the head of the bed on 6- or 8-inch blocks (not the use of pillows) should be considered in the management of GERD patients with supine or nocturnal symptoms.[29] Additional recommendations include controlling weight,

Table 3. Lifestyle recommendations

Elevate the head of the bed
Avoid chocolate, peppermint, alcohol, spicy foods and coffee
Avoid eating later than 2–3 h before bedtime
Control weight
Avoid smoking and alcohol

Sources: Johnson L.F. & DeMeester T.R. Dig Dis Sci 1981; 26: 673–80[29]; Murphy D.W. & Castell D.O. Am J Gastroenterol 1988; 83: 633–6[33]; Pehl C. *et al.* Dig Dis Sci 1993; 38: 93–6[32]; Sigmund C.J. & McNally E.F. Gastroenterology 1969; 56: 13–8[30]; Wendl B. *et al.* Aliment Pharmacol Ther 1994; 8: 283–7[31].

ingesting small meals, eating a low-fat diet, avoiding certain offending foods and allowing at least 3 h after ingesting a meal before reclining. Certain foods, including chocolate, mints, alcohol and coffee, among others, may exacerbate reflux.[30–33]

Pharmacological therapy

Several pharmacological agents are used in the treatment of GERD. Some agents can be taken as symptomatic therapy to relieve heartburn or other symptoms as they occur. Other medications are used long-term on a daily basis to heal the oesophageal mucosa and/or prevent the occurrence of symptoms. In those with night-time heartburn, one must carefully weigh 'as-needed' or 'prn' regimens against standard regimens that are aimed at preventing symptoms; because for night-time symptoms, as-needed regimens rely on the patient being awakened from sleep and taking corrective action. In the absence of full arousal, acid exposure and tissue injury continue.[34] For more information, see the paper by Orr *et al.*[35] in this supplement.

In order to optimize therapy, an understanding of the basic pharmacology of the agents available for the treatment of GERD is necessary. For example, the fact that histamine-$_2$ receptor antagonists (H_2RAs) reduce postprandial gastric acid secretion[36, 37] may lead the clinician to choose these agents in the management of patients with intermittent symptoms that occur only after meals. All proton pump inhibitors work in a similar manner, inhibiting only H^+,K^+ ATPase that is active. Moreover, maximal recruitment of proton pumps to the parietal cell apical surface takes several days to achieve, and maximal acid inhibition is not achieved until the third to fifth day of therapy (Figure 2).[38–40] All of the proton pump inhibitors are prodrugs absorbed in the small intestine. Four of the currently available agents (omeprazole, lansoprazole, pantoprazole and rabeprazole) are marketed as racemic mixtures that contain equal amounts of *R* and *S* enantiomers. The fifth, esomeprazole, contains only the *S*-isomer of omeprazole.[41] Only after the proton pump inhibitor is absorbed and directed into the acidic environment of the parietal cell does it become protonated and converted into the active moiety that binds to cysteine residues on the H^+,K^+ ATPase enzyme, thereby inhibiting acid secretion.[42] Insufficient data are available to conclude whether structural or pharmacokinetic differences among proton pump inhibitors translate into clinical superiority for any one proton pump inhibitor. However, the key concepts that should be kept in mind when using a proton pump inhibitor to treat night-time heartburn are outlined in Table 4.[38, 40, 42–53] Several excellent review articles describe the pharmacological properties of antacids, H_2RAs and proton pump inhibitors in considerably more detail.[42, 54–56]

Comparative efficacy

Twenty-four hour ambulatory pH monitoring has been used to compare the effects of different proton pump inhibitors. The level of intra-oesophageal pH is a reasonable measure of success in treating GERD, but it is not a reliable surrogate for symptom relief. This was apparent in a study examining the effects of lansoprazole or pantoprazole on intra-oesophageal pH. All 45

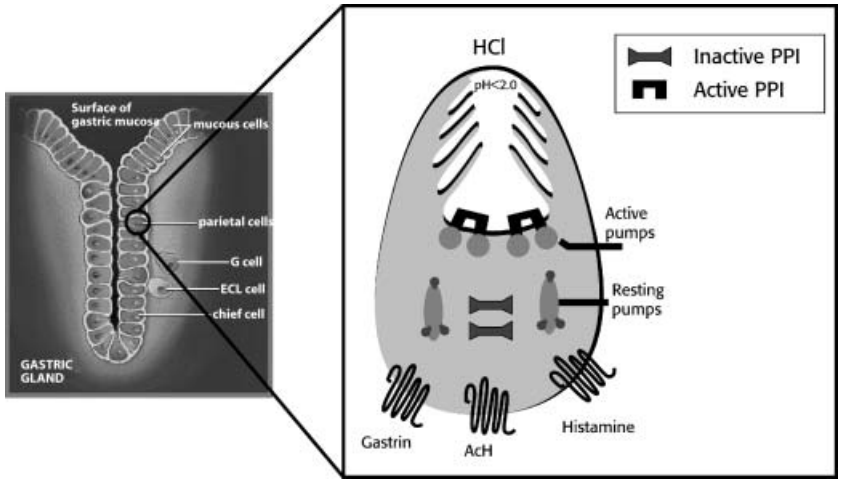

Figure 2. Steps to the mechanism of action of proton pump inhibitors. The pumps depicted are H^+,K^+ ATPase pumps. AcH, acetylcholine. Adapted from Huber *et al.* (1995)[40]; GERD Information Resource Center, http://www.gerd.com/media/micview.gif; with permission. *Source*: Kromer W. Digestion 1995; 56: 443–54.[102]

Table 4. Pharmacological considerations of antacids, H_2RAs and proton pump inhibitors

	Pharmacological considerations
Antacids	• Provide rapid onset, short-term relief • Useful in managing mild, intermittent symptoms
H_2RAs (Cimetidine, Ranitidine, Famotidine, Nizatidine)	• Competitively inhibit H_2 receptors on basolateral membrane of parietal cell • Can be combined with antacids to offer prompt and sustained relief of mild intermittent episodes of heartburn • Continued use is associated with development of tolerance • Rebound in acid secretion may occur following discontinuation of therapy
Proton pump inhibitors (Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole)	• Block the final step in acid secretion, the active H^+,K^+ ATPase enzyme, producing profound acid secretion • Offer long duration of action. Restoration of acid secretion depends on pump protein turnover and reversibility of the disulphide bond to the H^+,K^+ ATPase enzyme • Provide greater symptom relief and faster oesophageal healing than H_2RAs • Maximum acid suppression may take 3–4 days of therapy • Tolerance does not occur • Rebound in acid secretion may occur after discontinuation of therapy • Data suggest a mg per mg equivalency among proton pump inhibitors • Should be taken 30–60 min before breakfast to maximize effect, in that proton pump inhibitors only inhibit active proton pumps. If a second dose is required, it should similarly be given before the evening meal • Should not be taken with H_2RAs, prostaglandins, or other antisecretory agents

H_2RA, H_2-receptor antagonist.
Sources: Chiba N. *et al.* Gastroenterology 1997; 112: 1798–810;[50] De Graef J. & Woussen-Colle M.C. Gastroenterology 1986; 91: 333–7;[53] Fullarton G.M. *et al.* Gut 1989; 30: 449–54;[49] Huang J.Q. & Hunt R.H. Baillieres Best Pract Res Clin Gastroenterol 2001; 15: 355–70;[44] Huber R. *et al.* Aliment Pharmacol Ther 1995; 9: 363–78;[40] Kromer W. *et al.* Pharmacology 1999; 59: 57–77;[51] Kromer W. Scand J Gastroenterol 2001; 36(suppl. 234): 3–9;[52] Lachman L. & Howden C.W. Am J Gastroenterol 2000; 95: 57–61;[46] Robinson M. *et al.* Aliment Pharmacol Ther 2001; 15: 1365–74;[45] Shin J.M. *et al.* Biochim Biophys Acta 1993; 1148: 223–33;[38] Simon T.J. *et al.* Am J Ther 1995; 2:304–313;[43] Wilder-Smith C.H. *et al.* Dig Dis Sci 1990; 35: 976–83;[48] Wilder-Smith C. *et al.* Aliment Pharmacol Ther 1990; 4(Suppl. 1): 15–27;[47] Wolfe M.M. & Sachs G. Gastroenterology 2000; 118: S9–31.[42]

patients with heartburn/acid regurgitation at baseline were reported as being symptom-free at the end of the study; however, oesophageal acid exposure remained abnormal in 44% of patients.[57]

The number of studies assessing the efficacy of pharmacological therapy specifically for night-time GERD is limited, and comparisons between them are difficult due to variability among study designs and endpoints. Few studies have specifically addressed the relief of night-time GERD symptoms by proton pump inhibitors. Typically, these studies asked patients to rate the severity of their symptoms based on the duration, frequency and extent of interference with daily activities. The ratings and the symptoms addressed varied, with some studies addressing only the presence of heartburn,[58–60] whereas others included additional symptoms such as regurgitation, dysphagia and belching.[61–64] In some studies, the effect of therapy on night-time symptoms may be inferred from endpoints such as a 24-h symptom-free period.[57, 60] There are no studies assessing supra-oesophageal manifestations of GERD that occur in association with night-time reflux. The definition of what constitutes complete or sustained symptom relief varies from trial to trial. In one study comparing pantoprazole 20 mg and 40 mg daily with nizatidine 150 mg twice daily, patients were considered to have complete symptom resolution on the first day in which they reported no symptoms if they remained symptom-free for the remainder of the 8-week study period.[65] In contrast, other studies defined sustained resolution as 7 consecutive heartburn-free days, regardless of when this occurred.[58, 59] Table 5 summarizes characteristics of comparative studies that include data pertaining to the effect of proton pump inhibitors on night-time GERD symptoms.[58, 59, 63, 64, 66–69]

Overall, based on the available information, all the proton pump inhibitors are safe and have beneficial effects in patients with GERD. However, it cannot be

Table 5. Summary of proton pump inhibitor studies addressing night-time heartburn*

Comparators (*n*)	Patient population	Study length and endpoints	Symptom evaluation	Effect on night-time symptoms
PAN 10 mg q.d.s. (88) PAN 20 mg q.d.s. (93) PAN 40 mg q.d.s. (94) RAN 150 mg b.d. (96)	Healed EE, with at least one typical GERD symptom	• 12-month period • Relapse of EE • Number of symptom-free days/nights	• Daily diary recordings using a 4-point scale • Symptoms assessed: heartburn, regurgitation, dysphagia	• PAN 40 mg resulted in a greater proportion of heartburn-free nights compared with RAN ($P = 0.002$) • Patients receiving PAN 40 mg reported daytime and night-time symptoms eliminated in > 90% of days
LAN 30 mg q.d.s. (402) LAN 15 mg q.d.s. (208) OME 20 mg q.d.s. (418) PLA (198)	EE	• 8 weeks • Mucosal healing • Symptom relief (endpoint definition not specified)	• Daily diary recordings using a 4-point scale • Investigator assessment of symptom frequency and severity • Symptoms assessed: heartburn, belching, regurgitation, dysphagia	• LAN 30 mg resulted in significantly less proportion of nights with heartburn and significantly less patients with night-time heartburn ($P < 0.05$ vs. LAN 15 mg and vs. OME)
ESO 40 mg q.d.s. (1216) OME 40 mg q.d.s. (1209)	EE	• 8 weeks • Mucosal healing • Frequency and severity of heartburn • Time to resolution and sustained resolution • Sustained resolution defined as a rating of '0' for 7 consecutive days	• Daily diary recordings using a 4-point scale • Investigator assessment of heartburn severity during 7 days before study evaluation	• ESO-treated patients reported 90.8% of heartburn-free nights compared with 87.9% in the OME-treated patients ($P < 0.001$) • Proportion of patients with sustained resolution was higher in the ESO group (68.3% at week 4; $P < 0.001$)
LAN 30 mg q.d.s. (1754) OME 20 mg q.d.s. (1756)	EE with at least one episode of moderate-to-very-severe heartburn during the 3 days before study screening	• 8 weeks • Mucosal healing • Frequency and severity of heartburn on days 1–3; and weeks 1, 2, and 8 • Time to resolution and sustained resolution • Sustained resolution defined as 7 consecutive heartburn-free days	• Daily diary recordings using a 5-point scale	• LAN provided greater relief of night-time heartburn throughout week 1 (69% vs. 64% heartburn-free nights; $P < 0.0001$), which persisted through 8 weeks • Higher proportion of LAN patients reported sustained resolution at days 1, 3, 7, and 14. Difference became smaller at days 28 and 56

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Table 5. *Continued*

Comparators (*n*)	Patient population	Study length and endpoints	Symptom evaluation	Effect on night-time symptoms
PAN 40 mg q.d.s. (112) ESO 40 mg q.d.s. (105)	Endoscopically proven moderate-to-severe GERD	• 4 weeks • Symptom relief • Night-time defined as the sleeping period at night	• Daily diary recordings using a 5-point scale and/or telephone interviews every 3 days • Symptoms assessed: heartburn, regurgitation, gastric complaints, epigastric pressure, flatulence, early satiety	• 99% of PAN patients and 98% of ESO patients reported no or mild heartburn after 28 days • Time to first onset of night-time symptom relief was 1.73 days with PAN compared with 3.45 days with ESO ($P = 0.012$)
ESO 40 mg q.d.s. (654) ESO 20 mg q.d.s. (656) OME 20 mg q.d.s. (650)	Endoscopically proven GERD	• 8 weeks • Mucosal healing • Time to resolution and proportion of patients achieving sustained resolution • Sustained resolution defined at 7 consecutive days with no reported symptoms	• Investigator assessment at weeks 4 and 8 • Daily diary recordings using a 4-point scale	• Both ESO groups reported significantly greater proportion of heartburn-free nights (84.7%, and 83.6% for 40 and 20 mg, respectively) compared with OME • Proportion of patients achieving sustained resolution by day 28 was 74.2%, 70.1%, and 66.6% for ESO 40 mg, ESO 20 mg, and OME, respectively
ESO 40 mg (2624) LAN 30 mg (2617)	EE experiencing heartburn ≥2 days in the 7 days before study randomization	• 8 weeks • Mucosal healing • Complete heartburn relief • Sustained resolution defined at 7 consecutive days with no reported symptoms	• Investigator assessment of symptoms at week 4 • Daily diary recordings using a 4-point scale	• Complete heartburn relief at week 4 reported by 62.9% ESO vs. 60.2% LAN patients ($P < 0.05$) • Mean number of heartburn-free nights: 87.1 vs. 85.8 ($P < 0.05$) • Median time to sustained resolution of night-time heartburn was 1 day for ESO and 2 days for LAN ($P < 0.01$)

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Table 5. *Continued*

Comparators (*n*)	Patient population	Study length and endpoints	Symptom evaluation	Effect on night-time symptoms
PAN 20 mg q.d.s. (73) PAN 40 mg q.d.s. (76) NIZ 150 mg b.d. (72)	EE experiencing heartburn or regurgitation on at least 4 of the past 7 days	• 8 weeks • Mucosal healing • Complete elimination (achieved on the first day on which no symptoms were reported on that day or any subsequent days) of daytime or night-time heartburn, regurgitation or dysphagia	• Daily diary recording noting the presence or absence of reflux symptoms	• Persistent absence of night-time heartburn was greater among PAN-treated patients compared with NIZ ($P < 0.05$) • Median time to complete elimination of night-time symptoms was 21 days vs. 51 days for PAN- and NIZ-treated patients, respectively

*Studies not designed to assess only night-time heartburn. Refer to individual trials for overall efficacy and daytime symptom data.
EE, erosive oesophagitis; ESO, esomeprazole; GERD, gastro-oesophageal reflux disease; LAN, lansoprazole; NIZ, nizatidine; OME, omeprazole; PAN, pantoprazole; PLA, placebo; RAN, ranitidine.
Sources: Castell D.O. *et al.* Am J Gastroenterol 2002; 97: 575–83;[68] Castell D.O. *et al.* Am J Gastroenterol 1996; 91: 1749–57;[63] Kahrilas P.J. *et al.* Aliment Pharmacol Ther 2000; 14: 1249–58;[67] Kovacs T.O.G. *et al.* Aliment Pharmacol Ther 2002; 16: 2043–52;[65] Metz D.C. & Bochenek W.J. Aliment Pharmacol Ther 2003; 17: 155–64;[66] Richter J.E. *et al.* Am J Gastroenterol 2001; 96: 656–65;[58] Richter J.E. *et al.* Am J Gastroenterol 2001; 96: 3089–98;[59] Scholten T. *et al.* Aliment Pharmacol Ther 2003; 18: 587–94.[64]

concluded that one agent is significantly better than another. Although it has been suggested that some proton pump inhibitors may have a faster initial onset than others,[70] there are no differences in long-term effectiveness.[71] Data are now emerging regarding the impact of proton pump inhibitor therapy on sleep disturbances in GERD patients that suggest significant benefits of treatment over no treatment, but evaluation of the clinical implications of these findings awaits full publication of trial results.[72–74]

TREATMENT STRATEGIES

Management of breakthrough symptoms

In an effort to reduce the costs of long-term care of GERD patients, various approaches to dosing have been used. For some patients who have mild and/or occasional symptoms, antacids and/or H_2RAs may be used as needed for symptom relief.

Persistent night-time symptoms

For patients with more serious and/or more persistent symptoms, a traditional approach has been to start with lifestyle modifications and use progressively more intense antisecretory therapy. Alternatively, patients may be started on relatively high doses of antisecretory medication and gradually 'stepped-down' to a less potent maintenance dose. Intermittent treatment programmes involving proton pump inhibitors have been used, in which treatment is initiated by the patient when symptoms occur. In such cases, the medication is administered as a short course of daily treatment, customarily of 2–4 weeks' duration. Treatment is then discontinued until symptoms return. Intermittent therapy may be particularly well suited to patients with uncomplicated GERD and may be effective in reducing costs.[75]

Mathematical models have suggested that step-down therapy may be cost effective when compared with step-up treatment.[21] However, comparative evaluations of step-up vs. step-down vs. fixed-dose therapy have yielded inconclusive results regarding efficacy. In a community-based study, 593 heartburn patients were randomized to receive either ranitidine 150 mg b.d. or lansoprazole 30 mg once daily for 20 weeks (fixed-dose); ranitidine 150 mg b.d. for 8 weeks followed by lansoprazole 30 mg once daily for 12 weeks (step-up);

or lansoprazole 30 mg once daily for 8 weeks followed by ranitidine 150 mg b.d. for 12 weeks (step-down).[60] Fixed-dose proton pump inhibitor treatment provided more consistent heartburn relief than H_2RA, step-up or step-down treatments after 20 weeks of follow-up.[60] In contrast, another study of 73 patients treated in a primary care setting assessing step-down therapy found that most patients who were 'stepped-down' from proton pump inhibitor treatment to no therapy or high-dose H_2RA therapy with or without prokinetic drug added after initial symptom relief were maintained successfully at 1-year follow-up.[76] Patients were included in this study if they had been prescribed proton pump inhibitors for more than 8 weeks.[76] In this study the response to step-down from proton pump inhibitors differed with the primary symptom (heartburn as the dominant symptom was associated with a need for continued proton pump inhibitor therapy[76]) and with the duration of proton pump inhibitor treatment before the study.[77] Based on these data, the benefit of fixed-dose treatment with proton pump inhibitor therapy needs to be evaluated on an individual basis until optimal treatment strategies for specific patient groups are defined.[78] When proton pump inhibitors are used to control symptoms, using the lowest effective maintenance dose as early as possible in the treatment programme is recommended.[79] In patients with night-time reflux, symptoms may be more subtle and varied than those associated with daytime reflux and close attention to their response to the medication is required.

Treatment options for symptomatic GERD

Over-the-counter medications. As noted earlier, changes in lifestyle that may potentially improve GERD symptoms are considered to be important in all patients. Over-the-counter medications including antacids, H_2RAs or a combination of the two can provide prompt, relatively transient relief of symptoms such as heartburn or regurgitation, but their short duration of action limits their daily use in many cases.

Omeprazole is now available over the counter. Its maximum effect is not achieved for 3–5 days into therapy, similar to other proton pump inhibitors, thus it is not considered an effective choice for immediate relief. This carries a significant risk of improper dosing by the public. Pharmacokinetic principles dictate that proton pump inhibitors should be taken approximately 30 min before a meal (before breakfast for once-daily dosing) and not be taken with a variety of other drugs, including H_2RAs (Table 4).[38, 40, 42–53] The importance of proper dosing should not be underestimated. Despite widespread use of proton pump inhibitors for more than 15 years and their immense popularity, a lack of understanding still exists with regard to the proper use of these drugs—even among physicians. A recent survey found that only 28% of primary care physicians, who comprise nearly 80% of proton pump inhibitor prescribers, appropriately directed their patients to take their proton pump inhibitor before breakfast.[80] Furthermore, although gastroenterologists recommended that their patients take proton pump inhibitors before breakfast more often than their primary care colleagues, 11% of those specialists responded that the time of administration did not matter.[80] Effective use of over-the-counter proton pump inhibitors would seem to require that patients do better than physicians seem to do in understanding the importance of timing the ingestion of the drug in relation to meals.

The use of over-the-counter proton pump inhibitors raises several additional concerns, most notably the delay in diagnosis of more serious conditions. Beyond this, results from a survey commissioned by the American Pharmacy Association reveal that patients often do not read over-the-counter product labels and may not be aware of potential risks associated with the use of nonprescription products.[81] This survey arouses concern because inappropriate treatment of reflux can lead to serious consequences.

Proton pump inhibitors are metabolized via cytochrome P450 isoenzymes 2C19 and 3A4 (CYP2C19 and CYP3A4, respectively), therefore a small potential exists for drug interactions. The genetically determined rate at which proton pump inhibitors are metabolized by CYP2C19 has implications for the duration of acid suppression. For example, in pharmacodynamic studies, the area under the curve for omeprazole has been shown to be greater in poor metabolizers than in extensive metabolizers,[82] and the former may be at increased risk for adverse effects.[83, 84] Up to 22% of Japanese people may fall into this 'slow metabolizer' category owing to a genetic mutation in CYP2C19.[85]

Prescription medications. For patients with persistent night-time reflux symptoms who do not respond to lifestyle modification and over-the-counter medications, prescription medication is required. Patient-initiated therapy using over-the-counter or intermittent treat-

ment is not sufficient or appropriate for these patients, because without medical evaluation and supervised treatment, erosive oesophagitis may occur or progress in a small, but significant, percentage of cases.[86]

H_2RAs provide symptom relief but are not as effective as proton pump inhibitors in achieving mucosal healing. A meta-analysis of studies enrolling patients with GERD grades II–IV found that healing mild-to-moderate erosive oesophagitis requires 8–12 weeks of treatment with H_2RAs, whereas time to healing is 4–6 weeks with proton pump inhibitor treatment. Moreover, the rate of healing at 2 weeks associated with proton pump inhibitor use in this study was superior to that with H_2RAs after 12 weeks (Figure 3).[50]

Lower oesophageal sphincter mechanism incompetence, poor oesophageal acid clearance, decreased salivary secretion of bicarbonate, and delayed gastric emptying can be important in producing or exacerbating night-time reflux symptoms in patients with GERD. Promotility therapy has been found to be beneficial in treating GERD.[87–89] The dopamine antagonist metoclopramide may provide symptom relief by improving gastric motility. However, this agent is not effective in inducing oesophageal mucosal healing and its long-term use is seriously limited by the occurrence of serious side-effects. The efficacy of cisapride, which stimulates acetylcholine release from the mesenteric plexus indirectly affecting gut motility, is similar to H_2RAs in achieving symptom relief and mucosal healing. However, cisapride has been associated with rare, but sometimes fatal, cardiac arrhythmias. As a result, the manufacturer removed cisapride from the US market in July 2000, but continues to make it available for patients meeting the specific eligibility requirements of a limited access protocol.[90] There is currently no prokinetic drug with a recognized indication in GERD or gastroparesis available on the US market.

Treatment options for healing endoscopically proven GERD

Healing therapy. Traditionally, daily treatment with standard doses of proton pump inhibitors for 8 weeks has been used for initial management of endoscopically proven GERD. Although not approved by the Food and Drug Administration, twice-daily dosing may provide superior inhibition of acid secretion in patients with severe or resistant symptoms or with supra-oesophageal manifestations of reflux, which have been reported to be more common in those with night-time reflux.[5] Gastric acid suppression has been found to be superior in response to omeprazole 20 mg b.d. compared with either omeprazole 20 mg or 40 mg once daily.[91] However, although gastric acid suppression may be more effective with twice-daily dosing, mucosal healing over a period of weeks has not been shown to be improved by twice-daily dosing: rabeprazole 20 mg once daily and 10 mg twice daily and omeprazole 20 mg once daily were shown to have similar efficacy in inducing oesophageal mucosal healing as determined by endoscopy.[92]

Maintenance therapy. After 6 weeks of proton pump inhibitor therapy in patients with erosive oesophagitis, oesophageal mucosa has been reported to be healed in more than 80% of patients.[50] However, relief of some supra-oesophageal symptoms, often associated with substantial night-time reflux, may require a longer duration (6 months or more) of treatment.[93, 94]

The proton pump inhibitor dose required for maintenance of healing and symptom relief seems to be similar to the healing dose. In a study of patients successfully treated initially with healing doses of esomeprazole (40 mg or 20 mg) or omeprazole (20 mg), fewer than 60% of those receiving a smaller subsequent maintenance dose of esomeprazole 10 mg were still in remission at the end of the study.[95] Similar results were found

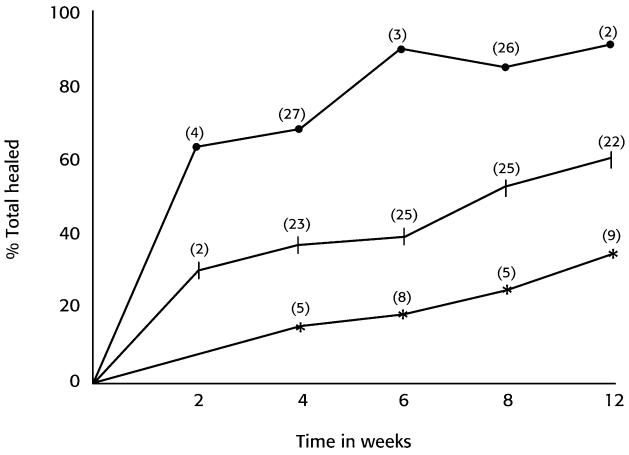

Figure 3. Erosive oesophagitis healing-time curves for proton pump inhibitors and H_2-receptor antagonists vs. placebo, expressed as mean total healing for each drug class per evaluation time in weeks. •, proton pump inhibitors; |, H_2-receptor antagonists; *, placebo. Adapted with permission from Chiba *et al.* (1997).[50]

with pantoprazole in patients randomized to a maintenance regimen of ranitidine 150 mg b.d. or pantoprazole 10 mg, 20 mg or 40 mg q.d.s. and followed for 12 months.[66] Endoscopic examination at 12 months found that 33% of those receiving ranitidine were still healed compared with 82% and 68% of those receiving pantoprazole 40 mg or 20 mg, respectively. Only 40% of patients who took pantoprazole 10 mg remained healed.[66]

Although stepping-down to low-dose therapy may seem initially to be less costly, the ramifications of relapse for the patient and the utilization of medical resources must be considered. To that end, evidence-based treatment protocols looking at total costs and patient outcomes should be used by third-party payers to determine formulary approvals and first-tier co-payment level.

Proton pump inhibitor therapy has been used extensively in patients with night-time reflux. Reduction of night-time intragastric pH to less than 4 for more than 1 h has been reported in both normal volunteers receiving twice-daily proton pump inhibitor therapy and in as many as 73% of patients with GERD.[96] This night-time decrease in gastric pH of more than 1 h in duration is referred to as nocturnal acid breakthrough. The relevance of nocturnal acid breakthrough to oesophageal disease or GERD symptoms has not been established.[97, 98] A retrospective review of patients receiving ranitidine, famotidine or nizatidine added to omeprazole b.d. or lansoprazole b.d. at bedtime showed a reduced incidence of nocturnal acid breakthrough and reduced oesophageal exposure to acid during nocturnal acid breakthrough, but these results have been neither confirmed nor shown to have an impact on clinical outcomes.[99] A crossover study found that the addition of ranitidine 300 mg to treatment with omeprazole 20 mg twice daily did not enhance proton pump inhibitor efficacy in nocturnal gastric pH control.[97] Nocturnal acid breakthrough was found to persist in 59–91% of patients despite elimination of oesophageal acid reflux and symptoms in 90% and 100% of patients, respectively.[97]

Use of defined short-term or intermittent proton pump inhibitor therapy. As noted earlier, defined durations of intermittent courses of therapy, used when required, have been proposed as a treatment option for some patients with uncomplicated GERD. These treatment regimens involve the use of short, defined, but limited sequences of daily proton pump inhibitor therapy. A multicentre, randomized study found that omeprazole was superior to ranitidine when administered as intermittent courses of 2–4 weeks' duration in patients with uncomplicated GERD.[100] This study showed that three 2-week courses per year controlled GERD symptoms in most patients. However, the impact of short-course intermittent therapy on disease progression has not been evaluated.

CONCLUSIONS

Symptoms from night-time reflux range from mild to severe. They may be similar to those of daytime reflux and exacerbated by recumbency, or may differ in their presentation, with symptoms such as nocturnal cough, nocturnal restlessness, night-time awakenings, or fatigue. Supra-oesophageal symptoms including pulmonary and otolaryngologic complaints, common in patients with night-time symptoms, may be easily overlooked. Endoscopy is appropriate in some cases to evaluate the presence, extent or severity of oesophagitis, but endoscopic findings are normal in many patients, even when symptoms are severe. In general, 24-h oesophageal pH monitoring is of value in confirming the presence of reflux in patients with suggestive symptoms. Endoscopy may be helpful in evaluating patients who have failed empirical therapy or in screening for Barrett's oesophagus. In all, 24-h oesophageal pH monitoring is of greatest value in establishing the presence or absence of reflux and the response to proton pump inhibitor therapy.

Mild-to-moderate reflux with occasional or intermittent symptoms can often be managed with a combination of lifestyle changes and as-needed use of H_2RAs and/or antacids. Use of over-the-counter proton pump inhibitor treatment (e.g. omeprazole) is readily available but requires careful patient counselling to ensure that the drug is being used appropriately and dosing is adequate. More severe, persistent and complicated disease requires continued treatment with a prescription proton pump inhibitor.

Studies indicate that night-time reflux is associated with a longer duration of oesophageal exposure to gastric acid, leading to more severe oesophageal and supra-oesophageal injury, therefore increased awareness on the part of both physicians and patients and more aggressive treatment may be needed. Proton pump inhibitors are the treatment of choice for healing

GERD and managing patients with severe night-time reflux. The dosing regimen selected for maintenance therapy should be dictated by assessment of the patient's requirements, and rarely differs from the dose required for the initial response in that same patient.

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REFERENCES

1 Locke GRI, Talley NJ, Fett SL, Zinsmeister AR, Melton LJI. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112: 1448–56.
2 Frank L, Kleinman L, Ganoczy D, *et al.* Upper gastrointestinal symptoms in North America: prevalence and relationship to healthcare utilization and quality of life. Dig Dis Sci 2000; 45: 809–18.
3 Shaker R, Castell DO, Schoenfeld P, Spechler SJ. 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: 1487–93.
4 Cibella F, Cuttitta G. Nocturnal asthma and gastroesophageal reflux. Am J Med 2001; 111(Suppl. 8A): S31–6.
5 Gislason T, Janson C, Vermeire P, *et al.* Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries. Chest 2002; 121: 158–63.
6 Harding SM. Nocturnal asthma: role of nocturnal gastroesophageal reflux. Chronobiol Int 1999; 16: 641–62.
7 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825–31.
8 Robertson D, Aldersley M, Shepherd H, Smith CL. Patterns of acid reflux in complicated oesophagitis. Gut 1987; 28: 1484–8.
9 Okamoto K, Iwakiri R, Mori M, *et al.* Clinical symptoms in endoscopic reflux esophagitis: evaluation in 8031 adult subjects. Dig Dis Sci 2003; 48: 2237–41.
10 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101: 1–78.
11 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981; 123: 413–7.
12 Batch AJ. Globus pharyngeus: (Part II), Discussion. J Laryngol Otol 1988; 102: 227–30.
13 Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW, Bradley LA. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. Am J Med 1996; 100: 395–405.
14 Larrain A, Carrasco E, Galleguillos F, Sepulveda R, Pope CE. Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. Chest 1991; 99: 1330–5.
15 Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. Am J Respir Crit Care Med 2000; 162: 34–9.
16 Dean BB, Crawley JA, Schmitt CM, Wong J, Ofman JJ. The burden of illness of gastro-oesophageal reflux disease: impact on work productivity. Aliment Pharmacol Ther 2003; 17: 1309–17.
17 DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1999; 94: 1434–42.
18 Johansson KE, Ask P, Boeryd B, Fransson SG, Tibbling L. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. Scand J Gastroenterol 1986; 21: 837–47.
19 Johnsson F, Weywadt L, Solhaug JH, Hernqvist H, Bengtsson L. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. Scand J Gastroenterol 1998; 33: 15–20.
20 Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, *et al.* Omeprazole as a diagnostic tool in gastroesophageal reflux disease. Am J Gastroenterol 1997; 92: 1997–2000.
21 Ofman JJ, Dorn GH, Fennerty MB, Fass R. The clinical and economic impact of competing management strategies for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2002; 16: 261–73.
22 Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004; 140: 518–27.
23 Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. J Am Med Assoc 2002; 287: 1972–81.
24 Dean R, Dua K, Massey B, Berger W, Hogan WJ, Shaker R. A comparative study of unsedated transnasal esophagogastroduodenoscopy and conventional EGD. Gastrointest Endosc 1996; 44: 422–4.
25 Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. Am J Gastroenterol 1993; 88: 25–9.
26 Fisher RS, Sher DJ, Donahue D, Senior J, Krevsky B. A single intragastric pH electrode does not accurately measure intragastric acidity. Am J Gastroenterol 1996; 91: 1167–72.
27 Anggiansah A, Sumboonnanonda K, Wang J, Linsell J, Hale P, Owen WJ. Significantly reduced acid detection at 10 centimeters compared to 5 centimeters above lower esophageal sphincter in patients with acid reflux. Am J Gastroenterol 1993; 88: 842–6.

28 Postma GN. Ambulatory pH monitoring methodology. Ann Otol Rhinol Laryngol Suppl 2000; 184: 10–4.
29 Johnson LF, DeMeester TR. Evaluation of elevation of the head of the bed, bethanechol, and antacid form tablets on gastroesophageal reflux. Dig Dis Sci 1981; 26: 673–80.
30 Sigmund CJ, McNally EF. The action of a carminative on the lower esophageal sphincter. Gastroenterology 1969; 56: 13–8.
31 Wendl B, Pfeiffer A, Pehl C, Schmidt T, Kaess H. Effect of decaffeination of coffee or tea on gastro-oesophageal reflux. Aliment Pharmacol Ther 1994; 8: 283–7.
32 Pehl C, Wendl B, Pfeiffer A, Schmidt T, Kaess H. Low-proof alcoholic beverages and gastroesophageal reflux. Dig Dis Sci 1993; 38: 93–6.
33 Murphy DW, Castell DO. Chocolate and heartburn: evidence of increased esophageal acid exposure after chocolate ingestion. Am J Gastroenterol 1988; 83: 633–6.
34 Orr WC, Allen ML, Robinson M. The pattern of nocturnal and diurnal esophageal acid exposure in the pathogenesis of erosive mucosal damage. Am J Gastroenterol 1994; 89: 509–12.
35 Orr WC, Heading R, Johnson LF, Kryger M. Sleep and its relationship to gastroesophageal reflux. Aliment Pharmacol Ther 2004; 20(Suppl. 9): 39–46.
36 Hamilton MI, Sercombe J, Pounder RE. Control of intragastric acidity with over-the-counter doses of ranitidine or famotidine. Aliment Pharmacol Ther 2001; 15: 1579–83.
37 Bruley des Varannes S, Duquesnoy C, Mamet JP, Slama A, Galmiche JP, Scarpignato C. Effects of tablet and effervescent formulations of ranitidine 75 mg and cimetidine 200 mg on gastric acidity and oesophageal acid exposure in healthy humans. Aliment Pharmacol Ther 1998; 12: 1155–61.
38 Shin JM, Besancon M, Simon A, Sachs G. The site of action of pantoprazole in the gastric H+/K(+)-ATPase. Biochim Biophys Acta 1993; 1148: 223–33.
39 Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. J Biol Chem 1997; 272: 22 4438–46.
40 Huber R, Kohl B, Sachs G, Senn-Bilfinger J, Simon WA, Sturm E. The continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol Ther 1995; 9: 363–78.
41 Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 411–26.
42 Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118: S9–31.
43 Simon TJ, Berlin RG, Gardner AH, Stauffer LA, Gould AL, Getson AJ. Self-directed treatment of intermittent heartburn: a randomized, multicenter, double-blind, placebo-controlled evaluation of antacid and low doses of an H(2)-receptor antagonist (famotidine). Am J Ther 1995; 2: 304–13.
44 Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician. Baillieres Best Pract Res Clin Gastroenterol 2001; 15: 355–70.
45 Robinson M, Rodriguez-Stanley S, Ciociola AA, *et al.* Synergy between low-dose ranitidine and antacid in decreasing gastric and oesophageal acidity and relieving meal-induced heartburn. Aliment Pharmacol Ther 2001; 15: 1365–74.
46 Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. Am J Gastroenterol 2000; 95: 57–61.
47 Wilder-Smith C, Halter F, Ernst T, *et al.* Loss of acid suppression during dosing with H2-receptor antagonists. Aliment Pharmacol Ther 1990; 4(Suppl. 1): 15–27.
48 Wilder-Smith CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS. Tolerance to oral H2-receptor antagonists. Dig Dis Sci 1990; 35: 976–83.
49 Fullarton GM, McLauchlan G, Macdonald A, Crean GP, McColl KE. Rebound nocturnal hypersecretion after four weeks treatment with an H2 receptor antagonist. Gut 1989; 30: 449–54.
50 Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997; 112: 1798–810.
51 Kromer W, Horbach S, Luhmann R. Relative efficacies of gastric proton pump inhibitors: their clinical and pharmacological basis. Pharmacology 1999; 59: 57–77.
52 Kromer W. Relative efficacies of gastric proton-pump inhibitors on a milligram basis: desired and undesired SH reactions. Impact of chirality. Scand J Gastroenterol 2001; 36(Suppl. 234): 3–9.
53 De Graef J, Woussen-Colle MC. Influence of the stimulation state of the parietal cells on the inhibitory effect of omeprazole on gastric acid secretion in dogs. Gastroenterology 1986; 91: 333–7.
54 Maton PN, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. Drugs 1999; 57: 855–70.
55 Sandvik AK, Brenna E, Waldum HL. Review article: the pharmacological inhibition of gastric acid secretion—tolerance and rebound. Aliment Pharmacol Ther 1997; 11: 1013–8.
56 Welage LS. Pharmacologic features of proton pump inhibitors and their potential relevance to clinical practice. Gastroenterol Clin North Am 2003; 32: S25–S35.
57 Frazzoni M, De Micheli E, Grisendi A, Savarino V. Effective intra-oesophageal acid suppression in patients with gastro-oesophageal reflux disease: lansoprazole vs. pantoprazole. Aliment Pharmacol Ther 2003; 17: 235–41.
58 Richter JE, Kahrilas PJ, Johanson J, *et al.* for the Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96: 656–65.

59 Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol 2001; 96: 3089–98.
60 Howden CW, Henning JM, Huang B, Lukasik N, Freston JW. Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. Am J Gastroenterol 2001; 96: 1704–10.
61 Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96: 2849–57.
62 Sontag SJ, Hirschowitz BI, Holt S, *et al.* Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. multicenter study. Gastroenterology 1992; 102: 109–18.
63 Castell DO, Richter JE, Robinson M, Sontag SJ, Haber MM. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. Am J Gastroenterol 1996; 91: 1749–57.
64 Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Aliment Pharmacol Ther 2003; 18: 587–94.
65 Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W. Comparison of the efficacy of pantoprazole vs. nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16: 2043–52.
66 Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther 2003; 17: 155–64.
67 Kahrilas PJ, Falk GW, Johnson DA, *et al.* for the Esomeprazole Study Investigators. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther 2000; 14: 1249–58.
68 Castell DO, Kahrilas PJ, Richter JE, *et al.* Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97: 575–83.
69 Kovacs TOG, Wilcox CM, DeVault K, *et al.* Comparison of the efficacy of pantoprazole versus nizatidine in the treatment of erosive esophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16: 2043–52.
70 Robinson M, Fitzgerald S, Hegedus R, Murthy A, Jokubaitis L. Onset of symptom relief with rabeprazole: a community-based, open-label assessment of patients with erosive oesophagitis. Aliment Pharmacol Ther 2002; 16: 445–54.
71 Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther 2001; 23: 998–1017.
72 DiMarino AJ Jr, Banwait KS, Eschinger E, Greenberg A, Doghramji K, Cohen S. Sleep efficiency; effect of PPI therapy in patients with marked sleep disturbance. Gastroenterology 2004; 126(Suppl. 2): A–340.
73 Banwait KS, Greenberg A, Eschinger E, Doghramji K, Cohen S, DiMarino AJ. The effect of proton pump therapy on disturbed sleep mechanics induced by esophageal acid exposure. Gastroenterology 2004; 126(Suppl. 2): A–335.
74 Johnson D, Orr W, Cuccia A, Traxler B, Brown K, Roth T. Esomeprazole for the relief of moderate to severe nighttime heartburn and associated sleep disturbance in patients with GERD: a multicenter, randomized, double-blind, placebo-controlled, 4-week study. Gastroenterology 2004; 126(Suppl. 2): A–336.
75 Stalhammar NO, Carlsson J, Peacock R, *et al.* Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-oesophageal reflux disease. Pharmacoeconomics 1999; 16: 483–97.
76 Inadomi JM, Jamal R, Murata GH, *et al.* Step-down management of gastroesophageal reflux disease. Gastroenterology 2001; 121: 1095–100.
77 Inadomi JM, McIntyre L, Bernard L, Fendrick AM. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. Am J Gastroenterol 2003; 98: 1940–4.
78 McGuigan JE. Treatment of gastroesophageal reflux disease: to step or not to step. Am J Gastroenterol 2001; 96: 1679–81.
79 Metz DC. Therapy for gastroesophageal reflux disease: more is not necessarily better. Am J Gastroenterol 2003; 98: 1913–5.
80 Barrison AF, Jarboe LA, Weinberg BM, Nimmagadda K, Sullivan LM, Wolfe MM. Patterns of proton pump inhibitor use in clinical practice. Am J Med 2001; 111: 469–73.
81 APhA. APhA and Prevention magazine national survey shows too many Americans put themselves at risk through self-medication. 2004: http://www.aphanet.org/
82 Chang M, Tybring G, Dahl ML, *et al.* Interphenotype differences in disposition and effect on gastrin levels of omeprazole—suitability of omeprazole as a probe for CYP2C19. Br J Clin Pharmacol 1995; 39: 511–8.
83 Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. J Am Pharm Assoc (Wash) 2000; 40: 52–62.
84 McCarthy DM, McLaughlin TP, Griffis DL, Yazdani C. Impact of cotherapy with some proton pump inhibitors on medical claims among HMO patients already using other common drugs also cleared by cytochrome P450. Am J Ther 2003; 10: 330–40.
85 Horai Y, Nakano M, Ishizaki T, *et al.* Metoprolol and mephenytoin oxidation polymorphisms in Far Eastern Oriental subjects: Japanese versus mainland Chinese. Clin Pharmacol Ther 1989; 46: 198–207.

86 McDougall NI, Johnston BT, Kee F, Collins JS, McFarland RJ, Love AH. Natural history of reflux oesophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. Gut 1996; 38: 481–6.
87 Castell DO, Sigmund C Jr, Patterson D, *et al.* Cisapride 20 mg b.i.d. provides symptomatic relief of heartburn and related symptoms of chronic mild to moderate gastroesophageal reflux disease. CIS-USA-52 Investigator Group. Am J Gastroenterol 1998; 93: 547–52.
88 McCallum RW, Fink SM, Winnan GR, Avella J, Callachan C. Metoclopramide in gastroesophageal reflux disease: rationale for its use and results of a double-blind trial. Am J Gastroenterol 1984; 79: 165–72.
89 Vigneri S, Termini R, Leandro G, *et al.* A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med 1995; 333: 1106–10.
90 Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001; 96: 1698–703.
91 Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol 1996; 91: 1532–8.
92 Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastrooesophageal reflux disease. Scand J Gastroenterol 2000; 35: 1245–50.
93 Belafsky PC, Postma GN, Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical findings. Laryngoscope 2001; 111: 979–81.
94 Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg 2002; 127: 32–5.
95 Vakil NB, Shaker R, Johnson DA, *et al.* The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther 2001; 15: 927–35.
96 Peghini PL, Katz PO, Bracy NA, Castell DO. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. Am J Gastroenterol 1998; 93: 763–7.
97 Ours TM, Fackler WK, Richter JE, Vaezi MF. Nocturnal acid breakthrough: clinical significance and correlation with esophageal acid exposure. This work was presented in part as an oral communication at Digestive Disease Week, Atlanta, GA, May 21–23, 2001. Am J Gastroenterol 2003; 98: 545–50.
98 Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology 2002; 122: 625–32.
99 Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. Aliment Pharmacol Ther 2001; 15: 1351–6.
100 Bardhan KD, Muller-Lissner S, Bigard MA, *et al.* Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. BMJ 1999; 318: 502–7.
101 Richter JE. Ambulatory oesophageal pH monitoring. Am J Med 1997; 103: S130.
102 Kromer W. Similarities and differences in the properties of substituted benzimidazoles: a comparison between pantoprazole and related compounds. Digestion 1995; 56: 443–54.