GASTROENTEROLOGY

UNMET NEEDS IN PPI THERAPY FOR GERD

GERD: Current Challenges in Control

David Armstrong, MD
McMaster University
Hamilton, ON

Nighttime GERD: Implications for Clinical Practice

Marc Bradette, MD
Pavillon Hôtel-Dieu de Québec
Centre Hospitalier Universitaire de Québec
Québec, QC

GERD : The Era of PPIs

Brian Bressler, MD
University of British Columbia
Vancouver, BC

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David Armstrong, MA, MB BChir, FRCP(UK), FACG, AGAF, FRCPC
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Marc Bradette, MD, FRCP
Chief of Service, Department of Gastroenterology
Pavillon Hôtel-Dieu de Québec
Centre Hospitalier Universitaire de Québec
Québec, Québec

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Brian Bressler, MD, M. S., FRCPC
Clinical Assistant Professor of Medicine, Division of Gastroenterology
University of British Columbia
Vancouver, British Columbia

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Guest Editor

David Armstrong, MA, MB BChir, FRCP(UK) FACG, AGAF, FRCPC

Associate Professor, Division of Gastroenterology
McMaster University
Hamilton, Ontario

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GERD: Current Challenges in Control

The reasons that patients with gastroesophageal reflux disease (GERD) fail to achieve adequate symptom relief with proton pump inhibitors (PPIs) have proven surprisingly complex. While high rates of healing are achieved in patients with erosive esophagitis on conventional once-daily doses of PPIs, the proportion of patients with persistent symptoms despite healing is substantial. Relative to those with esophagitis, the proportion of patients with inadequate symptom control is even higher in patients with endoscopy-negative GERD (NERD). The large body of research exploring the relationship of acid- and non-acid reflux to symptoms of GERD has expanded the understanding of pathophysiological mechanisms. Insights from this research are guiding strategies with the potential to address deficiencies of current therapies. In essence, GERD has proven to be a heterogeneous entity with contributing etiological factors not limited to excess gastric acid secretion. A systematic approach toward understanding the key mechanisms of symptom genesis may improve treatment success.

Definition and Epidemiology

Gastroesophageal reflux disease (GERD) is a product of the reflux of gastric contents into the esophagus. As most individuals have occasional episodes of reflux, the threshold at which these episodes become pathologic is when the associated symptoms are troublesome.[1] This patient-centered definition recognizes that GERD is a symptom-based disease even if complications can include erosive esophagitis, Barrett's esophagus, and extra-esophageal symptoms such as laryngitis and chronic cough. By definition, GERD requires retrograde movement of gastric contents but it does not exclude the co-existence of other conditions affecting the upper gastrointestinal (GI) tract; furthermore, reflux may be associated with symptoms other than those considered typical of GERD. In a Canadian study of dyspepsia that excluded patients whose symptom description was limited to complaints of heartburn or regurgitation, 54.7% were found to have esophagitis when endoscopy was performed. [2] Even though a large proportion of these patients reported heartburn or regurgitation within their constellation of symptoms, this study reinforces the notion that GERD is common in uninvestigated dyspepsia patients who have symptoms that are not limited to heartburn.

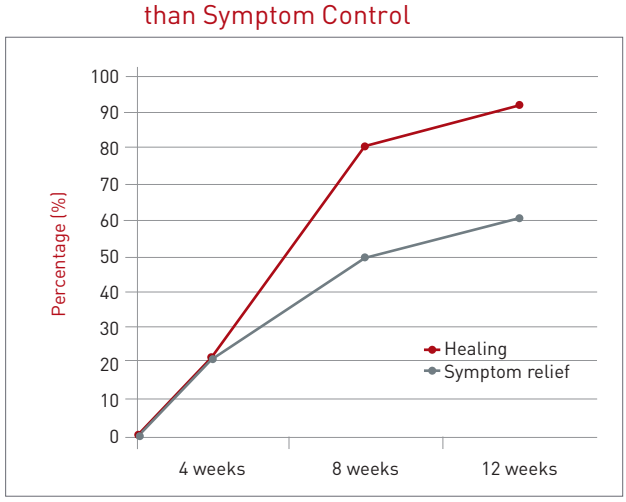
When extrapolated to Canada, incidence rates of approximately 5 per 1000 patient years in the United States (US) and United Kingdom (UK), predict about 170,000 new diagnoses of GERD per year.[3] Although a recent review of population-based studies was unable to corroborate a previous assertion that the incidence of GERD increases with age, it did suggest that older patients are more likely to develop erosive esophagitis.[4] That analysis also concluded that GERD symptoms become less severe and less characteristic with age. Due to the heterogeneity of GERD symptom expression, these findings are potentially relevant to clinicians delivering care in countries, like Canada, with a growing proportion of the population older than age 60 years.

Despite recent attention to the role of non-acid or weakly acidic reflux as a source of GERD symptoms,[5] acid control remains the fundamental principle of therapy. Response to acid control is so characteristic of GERD, that a trial of antisecretory therapy, particularly a proton pump inhibitor (PPI), has been defined by the Canadian Association of Gastroenterology (CAG) as a positive diagnostic test. [6] However, failure to respond to a PPI, particularly if prescribed once daily, does not rule out GERD. Although lack of response should prompt efforts to identify an alternative cause of symptoms, a diagnosis of refractory GERD can be considered if twice-daily PPI therapy does not adequately relieve symptoms and if no alternative etiology can be identified.[3]

There is a substantial proportion of patients with GERD who fail conventional, once-daily PPI therapy when symptom control is the endpoint. In contrast to healing rates, which have typically exceeded 90% in outcome trials of 8 to 12 weeks, rates of symptom control have been in the order of 50% to 65% (Figure 1).[7] In patients with non-erosive esophageal reflux disease (NERD), rates of symptom control are generally reported to be lower than those achieved in patients with esophagitis. [8] However, most treatment trials in patients with NERD have been limited to 4 weeks and there are data, at least in uninvestigated patients with heartburn, to show that the proportion of patients with symptom relief increases with continued therapy, up to 12 weeks. [9] Although the rates of symptom control have been far greater with PPIs than with any other therapy used in the treatment of GERD, the need for better treatments is driven by the important relationship between symptoms and diminished quality of life.[10]

There is a substantial proportion of patients with GERD who fail conventional, once-daily PPI therapy when symptom control is the endpoint.

FIGURE 1 | PPIs: More Effective for Healing of GERD than Symptom Control



Adapted from Dekel R. et al. *Drugs* 2004;64(3):277-95

GERD versus NERD

The CAG guidelines endorse empirical treatment of heartburn and regurgitation in the absence of alarm symptoms, such as unexplained weight loss or signs of bleeding, on the presumption of underlying GERD.[6] In responders, no further investigations may ever be conducted, precluding subclassification of GERD into its erosive esophagitis and NERD subtypes. Although it is possible that NERD is best characterized as an early stage or mild form of GERD, it has been proposed that

Although it is possible that NERD is best characterized as an early stage or mild form of GERD, it has been proposed that NERD is a distinct entity that has a modest risk of progression to esophagitis and complications.

NERD is a distinct entity that has a modest risk of progression to esophagitis and complications.[11] However, our understanding of NERD is hampered by the fact that there is no objective test to confirm reflux – acid or non-acid – in NERD patients since, by definition, they have no endoscopic evidence of injury. In the absence of reflux, antireflux therapy would not be expected to be effective. If, however, the symptoms are caused by reflux of gastric constituents other than acid, which are perhaps less likely to cause erosive esophagitis, gastric acid control may also be ineffective. Although antisecretory therapies are effective in the majority of NERD patients, only about half of patients with NERD have acid levels in the lower esophagus that are above the physiological range.[12] Overall, the pathophysiology and natural history of NERD remain unclear.

Unlike esophagitis, where the straightforward relationship between excess acid and inflammation is apparent in the high rates of healing achieved by raising lower esophageal pH, the more complex relationship between acid control and symptom relief may be valuable to efforts to improve successful empirical management of GERD. Of several plausible explanations for NERD in the absence of elevated acid levels, visceral hypersensitivity is among the strongest.[13] There are several mechanisms by which nociceptive receptors in the esophageal mucosa in patients with NERD may generate the pain signals that underlie symptoms. In addition to hypersensitivity to weakly acidic reflux,[14] these include microscopic impairments in mucosal integrity that may increase access of acid or other gastric constituents to nerves, producing symptoms at levels of pH not normally considered pathologic (Table 1).[15]

The complex relationship between acid control and symptom relief may be valuable to efforts to improve successful empirical management of GERD.

TABLE 1 | Etiologic Factors: Erosive Esophagitis vs. NERD

Erosive Esophagitis	NERD
Excess gastric acid in the esophagus	Excess gastric acid in the esophagus
Insufficient LES Function	Insufficient LES Function
Abnormal esophageal motility	Abnormal esophageal motility Hypersensitivity to weakly acidic reflux Non-acid reflux Microscopic damage to esophageal mucosa

Not all symptoms may be acid related in patients with symptoms consistent with GERD. For example, patients with a sensitive esophagus may complain of GERD symptoms when they drink citrus juices or alcohol or eat tomatoes or spicy foods. These exposures do not necessarily exacerbate GERD or reflux. Rather, they may simply irritate an esophagus that is already sensitive or injured. In addition, changes in motility due to impaired peristaltic function can cause upper GI symptoms. Although motility disorders are a far less common source of upper GI symptoms than acid-driven heartburn, this source of symptoms is now more easily detected with the introduction of high-resolution manometry.[16] For non-acid-related symptoms, pH monitoring, impedance monitoring, and manometry are useful for identifying the underlying causes of symptoms in non-responders to PPI therapy, but these tools are generally reserved for patients whose symptoms persist after several trials of pharmacologic therapy, particularly higher or more frequent doses of PPIs.

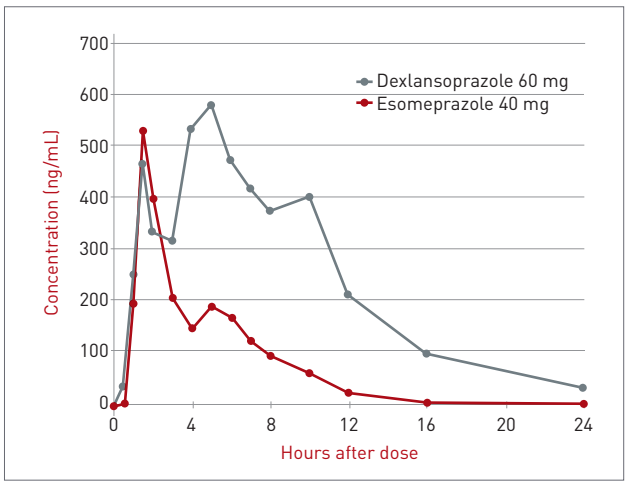
Treatment: Improving Response with Acid Control

The CAG guidelines recommend once-daily PPI therapy in a standard dose for symptoms of persistent GERD.[6] The standard dose of the first drug in this class, omeprazole, is 20 mg. The standard doses of subsequently marketed PPIs, which differ modestly in metabolism and pharmacokinetics, have ranged from 20 mg to 40 mg. In general, the efficacy differences, if any, between the first generation PPIs did not appear to be substantial. Although there were no large-scale, head-to-head comparisons with clinical endpoints until the introduction of esomeprazole, the S-enantiomer of the parent compound omeprazole, healing rates of esophagitis and symptom control in uninvestigated GERD were of the same order of magnitude. In trials with esomeprazole, which increased the proportion of each 24-hour dosing period with pH >4.0,[17] healing rates have been superior relative to the previously available PPIs, which, in addition to omeprazole, included lansoprazole, pantoprazole, and rabeprazole.[18]

The advantage of greater acid control for GERD management, demonstrated with the relative advantage of esomeprazole over previous PPIs, has fostered other strategies to more effectively suppress acid over each dosing period to improve clinical benefit. These strategies have included doubling the dose of PPIs, typically by twice-daily administration,[19] or adding a histamine H_2-receptor antagonist.[20] One of the potential disadvantages of these strategies is that they forsake the compliance advantage inherent in a once-daily therapy. More recently, an alternative strategy has been introduced with a new PPI, dexlansoprazole, that employs a dual-delayed release delivery technology which produces two plasma peaks.[21] In a randomized study, evaluating intragastric pH, dexlansoprazole produced an improvement over the standard dose of esomeprazole which was similar to that which esomeprazole had produced over previous PPIs (Figure 2).[22] While the mean pH over 24 hours was superior for dexlansoprazole (4.3 vs. 3.7; $P<0.003$), the significant differences

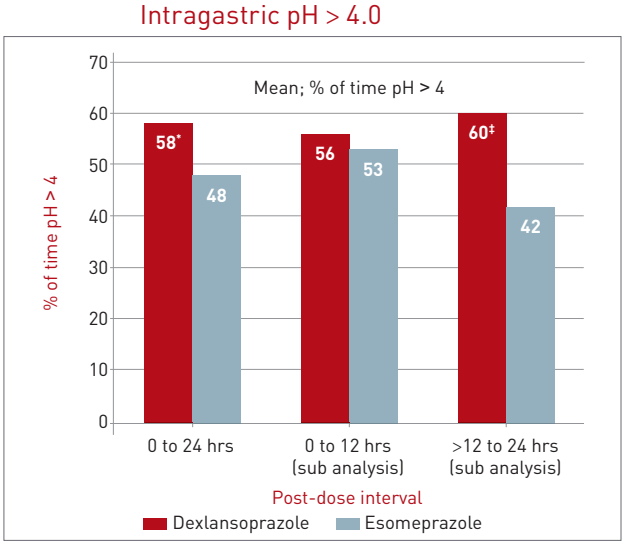
between 12 and 24 hours post-dose for time with pH >4.0 (60% vs. 42%; *P*<0.001) and average mean pH (4.5 vs. 3.5; *P*<0.001) predict better control of the acid-driven symptoms of GERD (Figures 3 and 4).

FIGURE 2 | Mean Plasma Concentration-time Curves



Adapted from Kukulka M, et al. *Clin Exp Gastroenterol.* 2011; 4:213-220.

FIGURE 3 | Mean Percentage of Time with Intragastric pH > 4.0



*$P < 0.01$; ‡$P < 0.001$.
Adapted from Kukulka M, et al. *Clin Exp Gastroenterol.* 2011;4:213-220.

For empirical therapy of GERD, there is a reasonable expectation that the greatest likelihood of symptom control will be achieved with greater acid control over each dosing period. Improved acid suppression during the nighttime hours is particularly important, because up to 80% of patients with GERD report nighttime symptoms and, nearly half of those report impaired quality of sleep. [23] Based on the modest therapeutic gain from increasing the dose of once-daily PPIs, the patterns of inadequate symptom relief from traditional PPIs suggest that the deficiency occurs because acid

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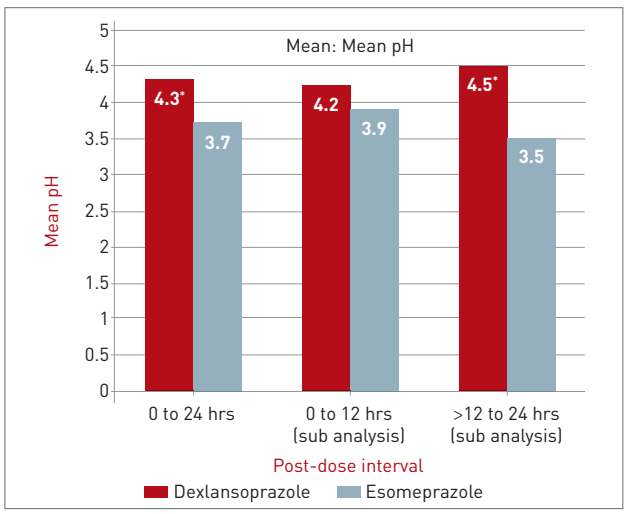
FIGURE 4 | Mean Intragastric pH over 24-hour Post-dose Period



*$P < 0.001$.
Adapted from Kukulka M, et al. *Clin Exp Gastroenterol.* 2011;4: 213-220.

suppression is not sustained adequately. This is consistent with the formation of new proton pumps after serum levels of PPIs are no longer high enough to irreversibly block pump function; the re-emergence of actively-secreting proton pumps during the latter part of the 24-hour dosing period is susceptible to treatment by longer-acting PPIs that can sustain high levels for longer periods. So far, other pharmacologic strategies, such as drugs designed to improve tone of the lower esophageal sphincter (LES), have not yet proven to be clinically viable but may prevail in ongoing clinical studies.[24] While surgery to improve LES function remains a therapeutic option for GERD, benefits are not necessarily superior to PPI for acid-driven symptoms.[25-26] This makes strategies for delivering active drugs over a longer period of acid proton formation one of the most attractive methods for improving symptom control.

Conclusion

In patients presenting with GERD, in the absence of alarm symptoms, empiric treatment with PPIs serves as both a diagnostic study and a treatment. For esophagitis, PPIs have a very high rate of success, healing most patients in standard doses. While there is no pharmacologic therapy superior to PPIs for control of symptoms, the limitation of standard doses of PPIs has been a growing concern because of the strong relationship between persistent symptoms and diminished quality of life. While acid may not always be the critical factor in patients with inadequately controlled GERD-like symptoms, incremental improvements in acid control with more effective PPIs or more effective delivery of PPIs promise greater efficacy and should be considered before pursuing additional diagnostic studies to rule out non-acid sources of symptomatology.●

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Guest Editor

Marc Bradette, MD, FRCP

Chief of Service, Department of Gastroenterology
Pavillon Hôtel-Dieu de Québec
Centre Hospitalier Universitaire de Québec
Québec, Québec

UNMET NEEDS IN PPI THERAPY FOR GERD

Nighttime GERD: Implications for Clinical Practice

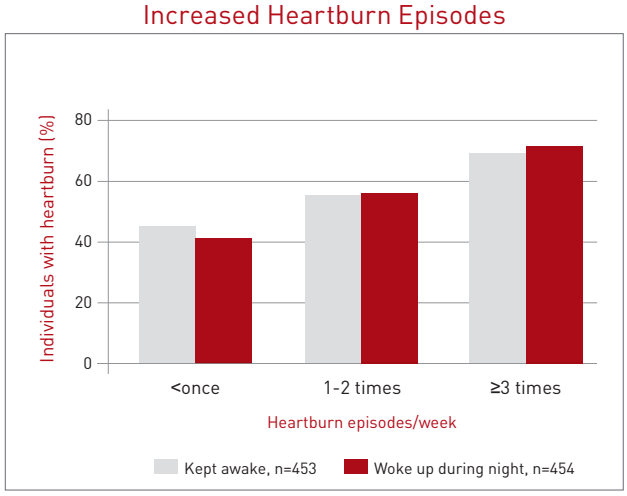
Of patients who report at least once-weekly episodes of heartburn, most also report nighttime symptoms. Although both the daytime and nighttime subtypes of gastroesophageal reflux disease (GERD) are produced when acidic gastric contents reflux into the lower esophagus, nighttime reflux has the potential to be a more severe form. Probably due to the loss of gravity that increases acid dwell time in the esophagus in the supine position, nocturnal reflux is associated with a higher risk of esophagitis and its long-term complications. Effective treatment of daytime reflux is not necessarily effective for nighttime episodes for a variety of reasons, including diminishing pharmacologic effect from proton pump inhibitors (PPIs) that are typically taken once daily in the morning. In many patient groups, such as those with sleep apnea, nocturnal GERD can contribute substantially to complications such as daytime fatigue. Due to its distinct features and risks, nocturnal GERD should be addressed specifically with the goal of complete symptom control.

Definition and Epidemiology

By the most commonly-used definition, patients have nocturnal gastroesophageal reflux disease (GERD) when heartburn or other symptoms adversely affect sleep quality.[1] This can refer to difficulty getting to sleep, mid-sleep awakenings, or a sense of next-day fatigue. Large surveys of patients with GERD suggest that about 80% of patients with daytime GERD also have nighttime symptoms.[2-3] In one survey of patients with GERD, 47% reported that symptoms sometimes or frequently woke them in the middle of the night.[4] In another, 63% reported that GERD symptoms adversely affected the quality of their sleep, and 40% reported that nocturnal heartburn affected their ability to function the next day.[5] The likelihood of nocturnal symptoms increased with the frequency of daytime symptoms (Figure 1).

Large surveys of patients with GERD suggest that about 80% of patients with daytime GERD also have nighttime symptoms.

FIGURE 1 | Sleep Disturbances More Frequent with Increased Heartburn Episodes



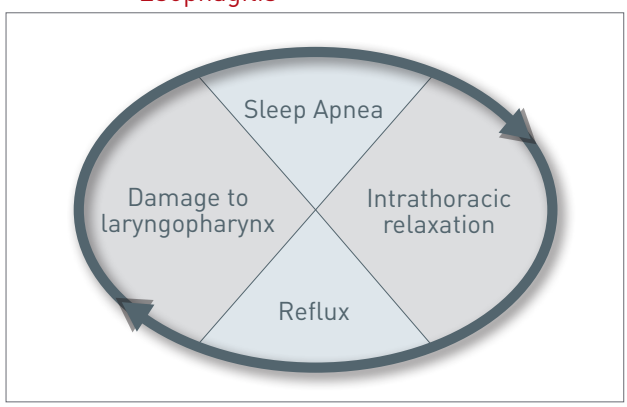
Adapted from Shaker R et al. *Am J Gastroenterol.* 2003;98(7): 1487-93.

Although most surveys have focused on heartburn as the source of sleep disturbances, other GERD symptoms, such as regurgitation, may make important contributions. In particular, there is a strong association between GERD and sleep apnea.[6-7] It has been hypothesized that this association is the result of a vicious cycle when gastric contents reach the upper airways to cause inflammatory damage.[8-9] According to this theory, sleep apnea which is induced or exacerbated by this damage, reduces intrathoracic pressure to increase reflux events, thereby increasing the risk for further reflux, further inflammation, and persistent apnea risk (Figures 2 and 3). Other extraesophageal symptoms of GERD, such as chronic cough, may also be involved in clinically significant disturbances of sleep or sleep quality.[10]

Impact of Nocturnal GERD on Quality of Life

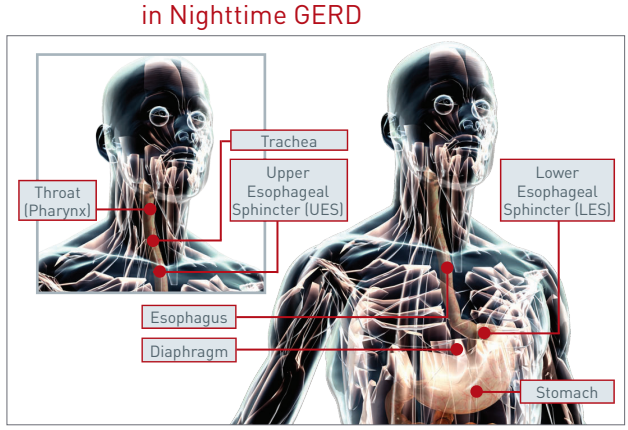
The adverse impact of nocturnal GERD on quality of life has been demonstrated repeatedly,[11-12] but there is also substantial evidence that GERD episodes at night are more serious than GERD events during the day. Nocturnal GERD is associated with a greater risk of esophagitis and severe forms of esophagitis,[13] including a greater risk of Barrett's esophagus.[14] The likely explanation is that the events occurring in the supine position produce slower clearance of the reflux so that longer acid contact increases the risk of damage.[15-16] The reduction in gravitational forces inherent in the supine position may also increase the likelihood that reflux will extend higher into the esophagus, reaching the airways to exacerbate sleep apnea and other extraesophageal manifestations.[17]

FIGURE 2 | Vicious Cycle between Sleep Apnea and Esophagitis



Nighttime symptoms have also been associated with diminishing next-day work productivity.[18] In a study which compared 476 individuals with GERD who had nocturnal symptoms to 526 individuals with GERD but no nocturnal symptoms and 513 controls, the reduction in work productivity and GERD-related work loss were highly significant ($P<0.0001$) relative to either the GERD group without nocturnal symptoms or controls.[19]

FIGURE 3 | Gastro-esophageal Anatomy Implicated in Nighttime GERD



Pathophysiology

Although the vast majority of patients with daytime GERD also have clinically significant nocturnal symptoms, risk factors for nocturnal symptoms may differ. In relatively large surveys, nocturnal GERD risk factors have included more daily

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symptoms of heartburn, severe daytime symptoms, predominant symptom of regurgitation, long duration of GERD symptoms, and higher body mass index (BMI).[20-21] Sleep apnea, as previously mentioned, is also associated with nocturnal GERD, and there is a correlation between greater severity of apnea and greater likelihood of GERD.[6] While the correlation between severe or frequent symptoms of daytime heartburn symptoms may relate to a weaker barrier to reflux episodes, such as hiatal hernia,[21] the increase in BMI is likely to not only increase the risk of GERD but the proximal extent of the rise in gastric contents.[22]

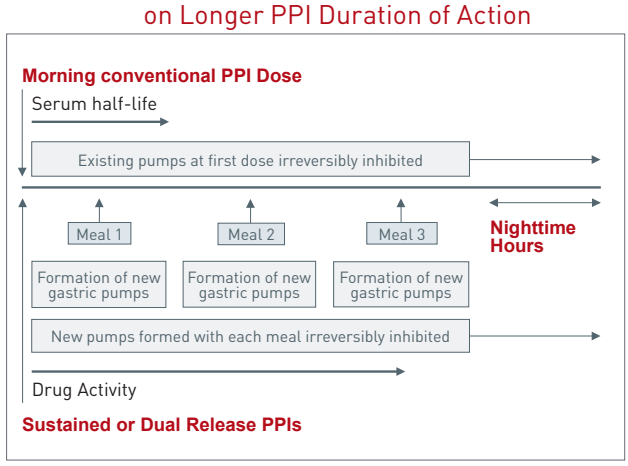
The basic mechanism of GERD, which includes a greater or more prolonged acid exposure in the lower esophagus after otherwise normal transient lower esophageal sphincter relaxations (TLESR),[23] is likely to be similar in daytime and nighttime GERD, but the precipitating factors may vary. For example, late night meals have been shown to be a risk factor for nocturnal GERD, [24] and agents that increase muscle relaxation, such as benzodiazepines, may also have a more deleterious effect at night than in the day when patients are no longer upright.[21]

Impaired barrier function due to a hiatal hernia or other cause may be important to nocturnal GERD in some individuals, but there is some evidence TLESRs are similar in patients with or without GERD and that the difference in risk is mediated by the greater acid content of the reflux, the slower clearance of the acid, or both.[23, 25] This reinforces the importance of anti-secretory therapy to lower gastric acid levels, a step that may be poorly suited to once-daily proton pump inhibitor (PPI) therapy taken in the morning. PPIs irreversibly bind to meal-stimulated proton-pumps, which is the final step for gastric acid secretion, but have a relatively short half-life in the serum. [26] Consequently, when new proton pumps are formed with meals later in the day, gastric acid suppression diminishes (Figure 4). This may explain why nocturnal GERD is often more difficult to control and is more likely to produce severe esophagitis.[13]

Treatment

Effective acid control is associated with a reduction in nocturnal GERD, including sleep disturbances,[27] but once-daily PPIs are unable to control nocturnal GERD consistently.[28] This has led to a variety of strategies to improve outcome, including twice-daily PPI therapy,[29] once-daily PPI therapy combined with an H_2-receptor antagonist at night,[30] and sustained-release or dual-release PPIs.[31-32] Although twice-daily PPIs are effective and are likely to be superior to the combination of a PPI and an H_2-receptor antagonist, which would provide weaker acid control at night, this approach is burdened by a more demanding regimen that might diminish compliance.

FIGURE 4 | Control of Nocturnal GERD May Depend on Longer PPI Duration of Action



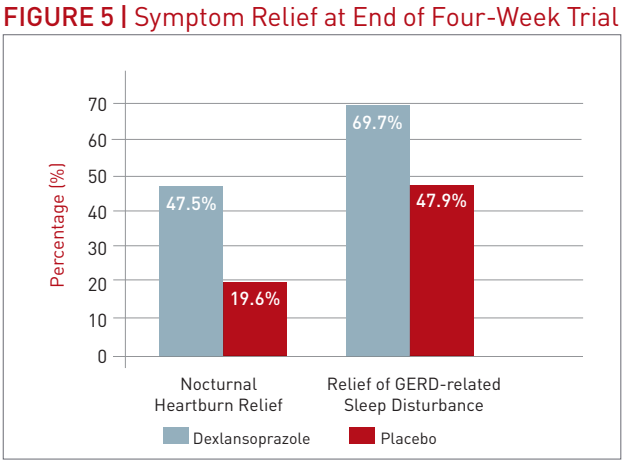
The potential advantages of a sustained- or dual-release PPI for the treatment of nocturnal GERD are substantial based on the pathophysiology of GERD and the pharmacokinetics of antisecretory agents. In a study that compared a sustained-release once-daily dose of 50 mg rabeprazole to a conventional dose of 40 mg once daily esomeprazole, the esophagitis healing rates were slightly greater at 8 weeks for Los Angeles (LA) grade C esophagitis with rabeprazole as compared with esomeprazole (80% vs. 75%), but the symptom relief was comparable (48.3% vs. 48.2%).[33] However, this study did not look at nocturnal symptoms specifically. In contrast, a study of dexlansoprazole modified release (MR), which employs a dual-release technology to separate peak plasma levels, that was conducted specifically in individuals with nocturnal GERD did demonstrate a highly significant reduction in sleep-related symptoms as well as an improvement in work productivity.[32] In this 305-patient trial, relief of sleep disturbances was 69.7% and 47.9% ($P<0.001$) in placebo in the two study groups, favouring dexlansoprazole (Figure 5).

The potential advantages of a sustained- or dual-release PPI for the treatment of nocturnal GERD are substantial based on the pathophysiology of GERD and the pharmacokinetics of antisecretory agents.

Other strategies can be helpful alone or in combination with acid control for reducing nocturnal GERD and its adverse effects on sleep. Avoiding late evening meals is one reasonable approach, while elevating the head of the bed has a documented benefit on symptom improvement. [1] These mechanical approaches are important, but acid control has been fundamental to the

treatment of GERD in both its daytime and nighttime manifestations. Surgical control of fundoplication has been specifically associated with improvement in sleep disturbances due to GERD,[34] but other methods of acid control if effective in the evening hours would be expected to provide meaningful clinical benefit.

FIGURE 5 | Symptom Relief at End of Four-Week Trial



Adapted from Fass R, et al. *Am J Gastroenterol* 2011;106(3):421- 31.

Conclusion

Nocturnal GERD is an extremely common disorder that deserves specific attention because of its important role in diminishing quality of life as well as the threat it poses to development of esophagitis and its complications, including Barrett's esophagus and esophageal adenocarcinoma. It cannot be assumed that treatments effective for control of daytime GERD symptoms will be effective in the evening for several reasons, particularly the physiology of meal-stimulated acid pump development. Patients treated for GERD should be asked specifically about nighttime symptom control. Adjustments in treatment, including use of longer-acting agents, may be appropriate if there is a presence of nocturnal GERD. Controlling nocturnal GERD presents a major opportunity to improve patient wellbeing.●

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Guest Editor

Brian Bressler, MD, MS, FRCPC

Clinical Assistant Professor of Medicine, Division of Gastroenterology
University of British Columbia
Vancouver, British Columbia

UNMET NEEDS IN PPI THERAPY FOR GERD

GERD: The Era of PPIs

Proton pump inhibitors (PPIs) replaced previous options for the treatment of gastroesophageal reflux disease (GERD) because of superior acid control, a fundamental component of GERD pathophysiology. However, despite the high rates with which PPIs heal esophagitis, it is now well recognized that a substantial proportion of individuals do not achieve complete or even adequate relief of symptoms. Alternative strategies to improve symptom control which interferes with a patient's quality or life include high dose or twice-daily PPIs, newer delivery methods to improve pharmacologic effect over each dosing interval and the introduction of adjunctive treatments, including lifestyle modifications, to augment PPI activity. Pharmacologic targets other than acid control are being pursued but have not yet yielded marketable alternatives. Clinicians need to develop an awareness of the frequency with which patients on conventional PPI treatment are dissatisfied with treatment in order to consider strategies that may be effective for improving quality of life.

Epidemiology

Transient reflux of gastric contents into the esophagus is a normal and frequent physiologic event.[1] Although the majority of episodes are symptomless, periodic episodes of heartburn may occur in otherwise healthy individuals. The point at which episodes of heartburn meet the threshold of an empirical diagnosis of gastroesophageal reflux disease (GERD) is based on frequency, chronicity, and the degree of the symptom burden. In Canada, consistent with other North American and European countries, approximately 17% of adults experience moderate to severe symptoms of GERD at least once weekly.[2]

The symptoms of GERD have a significant adverse impact on quality of life whether or not they are associated with esophagitis,[3-4] which need not be present for a diagnosis of GERD.[5] Rather, while it was once thought that non-erosive GERD, often called NERD, was an early stage or milder form of GERD, there is growing evidence that NERD, GERD with esophagitis, and Barrett's esophagus, characterized by metaplasia of the squamous epithelium, are related but independent phenotypes with distinct natural histories.[6] It is estimated that 50% to 85% of patients with GERD will not demonstrate esophagitis on endoscopy.[7] Of patients with NERD, only about 10% progress to esophagitis if followed long term.[5] The pathophysiology of functional heartburn, which is defined by heartburn in the absence of lesions or abnormalities in acid exposure on pH studies, is unknown and may incorporate several subgroups, including those with abnormalities of motility.[8]

There is growing evidence that NERD, GERD with esophagitis, and Barrett's esophagus are related but independent phenotypes with distinct natural histories.

Other evidence suggesting that NERD and erosive esophagitis are related but independent entities include differences in dominant risk factors. Although the list of risk factors overlap, elevated body weight and hiatal hernia are more closely associated with esophagitis, while psychological co-morbidities and extraesophageal symptoms are more commonly presented by patients with NERD.[9] In addition, NERD patients are less responsive to proton pump inhibitor (PPI) therapy.[9] In one study, the proportion of patients refractory to PPIs was more than three times greater in those with NERD relative to those with esophagitis (16.7% vs. 6%).[10]

In typical practice, treatment is offered without first differentiating NERD from esophagitis. According to Canadian guidelines, endoscopic investigation is not necessary unless patients present with alarm symptoms, which include involuntary weight loss, evidence of blood in the gastrointestinal (GI) tract, or unexplained anemia, or if the goal is to rule out Barrett's esophagus.[5] Endoscopy or other types of diagnostic studies, such as esophageal pH monitoring, may also be appropriate in patients with atypical symptoms, such as dysphagia, chest pain, or vomiting.

The rising rate of GERD over the past two decades [11] are not fully understood and may be due to multiple factors, including the growing rates of obesity, a risk factor for GERD.[12] While the increasing prevalence of GERD may be associated with increases in Barrett's esophagus and esophageal adenocarcinoma,[13] GERD by itself can be considered a serious disease for which the goal should be complete symptom control. While there is good data demonstrating that GERD is associated with substantial direct and indirect health costs,[14] uncontrolled or inadequately controlled symptoms not only have an adverse impact on numerous domains of quality of life, such as general perception of overall health status, they can interfere with diet, impair sleep, and reduce productivity.[15-16]

Pathophysiology of Acid

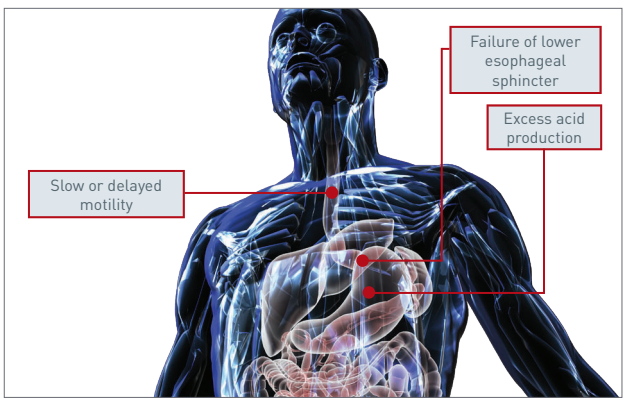
Although there is an association between symptoms and the degree and duration of refluxed acidic gastric contents,[17] there also appears to be substantial variability for the threshold at which symptoms are experienced, whether defined by pH or reflux duration. [18] When PPIs were introduced, they replaced H_2- receptor antagonists because, acting on the final common pathway of gastric acid production in the parietal cell, they provided greater acid inhibition for a longer duration.[19] A direct relationship between acid control and both symptom control and healing of esophagitis is relevant to pharmacologic agents as well as surgical interventions used in the treatment of GERD.[20]

PPIs act by irreversibly binding to the proton pump in the parietal cell, thereby impeding the hydrogen-potassium exchange fundamental to acid secretion.[21] Due to the irreversibility, acid secretion is restored only when new pumps are formed, which occurs with meal stimulation.[22] As the serum half-life of PPIs is only two to three hours,[21] the window of time in which proton pump binding and inhibition takes place is relatively short. Although higher doses may bind a higher proportion of existing proton pumps, the incremental benefit is small.[23] Acid suppression persists because of the irreversible binding; there is a diminishing effect over time as new proton pumps are formed.[21]

The goal of reducing gastric acid production with PPIs is to increase the pH of the refluxate into the esophagus to reduce risk of damage and acid-driven symptoms. Another approach is to improve the barrier to reflux from the stomach into the

esophagus. This is the mechanism of benefit from fundoplication and the strategy behind numerous endoscopic procedures, most of which have not yet demonstrated convincing benefit over sustained periods.[24] Pharmacologic therapies to strengthen the lower esophageal sphincter (LES), which is the primary physiologic barrier to reflux, have been pursued.[25] These efforts, like alternative pharmacologic approaches to acid suppression, have not yet generated an effective and safe treatment (Figure 1).

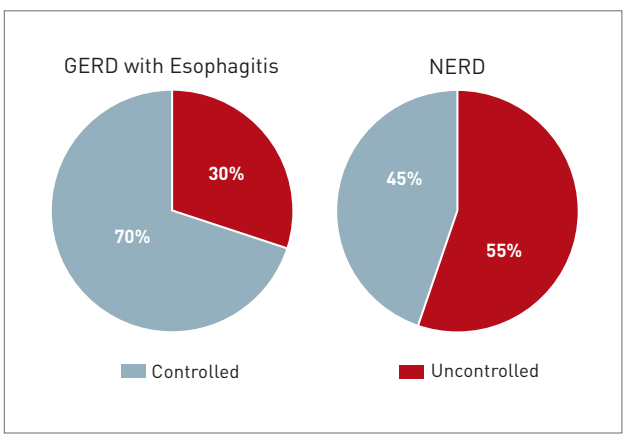
FIGURE 1 | Reasons for Persistent GERD



Unmet Needs in GERD Therapy

The need to improve therapy for GERD is driven by the substantial proportion of patients who do not achieve adequate symptom relief on conventional doses of PPIs. In patients with esophagitis on endoscopy, 20% to 30% continue to experience symptoms even if the esophagitis is healed.[26] In patients with NERD, less than 50% of patients achieve complete symptom resolution on a standard dose of PPI (Figure 2).[7] Patients achieving complete resolution of nocturnal symptoms on standard doses of PPIs is worse in both groups.[27] In one survey conducted in the United States of patients taking a PPI, 80% reported that they had symptoms within the previous 30 days.[28] Of these, 22% were on twice-daily PPIs, and almost half supplement that PPI with another agent, such as an H_2-receptor antagonist or an antacid.

FIGURE 2 | Patients with Inadequate Symptom Control



Although a more rapid and complete symptomatic response is more common in patients with esophagitis, the presence or absence of inflammation is not typically known to the treating physician. However, the goal should include symptom relief whether or not patients have esophagitis. Persistent symptoms produce a reduction in quality of life on the order of that experienced by patients who have survived a coronary event.[29] In those with symptoms described by patients as disrupting, GERD is associated with significant increases in absenteeism, reduced work productivity, and higher consumption of healthcare services.[30]

The need to improve therapy for GERD is driven by the substantial proportion of patients who do not achieve adequate symptom relief on conventional doses of PPIs.

In patients who undergo endoscopy and receive a diagnosis of esophagitis, healing is an important goal. The risk of untreated GERD includes Barrett's esophagus and esophageal adenocarcinoma.[31] Patients who undergo endoscopy may be reassured by the absence of lesions, but symptoms of GERD should not be considered benign when they interfere with functions of daily life. The efficacy of PPIs relative to previous options for the treatment of GERD may have initially diverted attention from the substantial proportion of patients who do not obtain adequate relief from these agents, but this unmet need has now generated increasing attention in clinical research. More attention is also needed for understanding the causes and the potential treatments for functional heartburn. PPIs are not typically effective in patients with this diagnosis,[8] which may incorporate an array of disorders including those stemming from problems of motility or the consequences of psychogenic mood disorders.

Next Steps in GERD Therapy

In addressing inadequate relief of GERD symptoms in patients who are being treated with a PPI, it is important to consider adherence to therapy and alternative sources of pain or discomfort, not the least of which includes angina. However, in an otherwise healthy and adherent patient, the problem may simply be one of inadequate acid control. One explanation for persistent symptoms in some but not all individuals with GERD who receive a conventional dose of PPI is the variability in sensitivity of the esophageal mucosa to acid contact. Although symptoms do correlate with the extent of acid exposure in patients with NERD, as in those with esophagitis, the threshold of sensitivity differs.[32] This is the reason that the focus on improving symptom control has remained largely on improving acid control.

Unlike higher doses of PPIs, which provides limited additional benefit for control of acid,[33] twice-daily

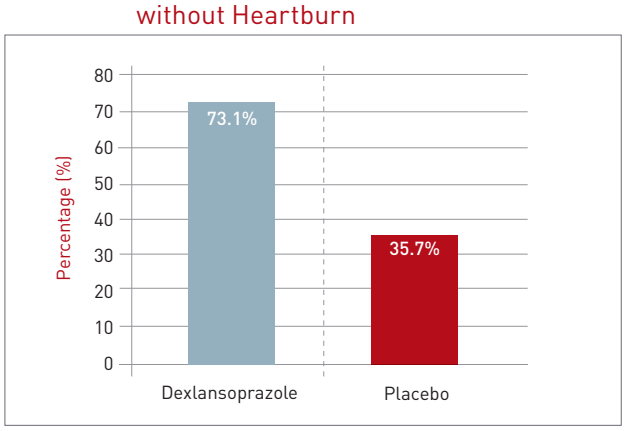
regimens address the formation of new proton pumps and have been shown to improve symptom control, including nocturnal symptoms.[34] However, twice-daily regimens increase the burden on patient compliance, particularly as timing of medication relative to meal-stimulated formation of pumps is important.

An alternative that is conceptually appealing is to extend the activity time of a once-daily PPI by prolonging its antisecretory effect. Several PPIs with unique pharmacokinetics have been evaluated in clinical testing, including dexlansoprazole, which is now licensed in Canada. Dexlansoprazole, a PPI that is structurally related to, but more potent than, lansoprazole [35] has been formulated in a capsule that employs a mixture of two types of enteric-coated granules, allowing it to provide two distinct peak concentrations.[36] One occurs, like other PPIs, one or two hours after administration, and the second peak at three to four hours later, permitting this agent to extend its activity over a longer period when acid pumps are being formed.

An alternative that is conceptually appealing is to extend the activity time of a once-daily PPI by prolonging its antisecretory effect.

While the licensing of dexlansoprazole was based on conventional double-blind, placebo-controlled trials that associated this agent with both safety and efficacy,[37] more recent studies have focused on the role on this agent for indications where other PPIs have been less effective, particularly nocturnal GERD. In the most recent study, 305 patients with nocturnal heartburn were randomized to 30 mg dexlansoprazole or placebo.[38] Dexlansoprazole was not only highly effective for the primary endpoint of nights without heartburn (73.1% vs. 35.7%; $P<0.001$) (Figure 3), but was associated with significant improvements in sleep quality and work productivity.

FIGURE 3 | Reaching Primary Endpoint of Nights without Heartburn



Similar approaches to improving the pharmacokinetics of PPI delivery have been attempted with tentaprazole and a prodrug of omeprazole.[39-40] These studies have reinforced the feasibility of this approach, which is encouraging because of the limited alternatives. Although other pharmacologic approaches once seemed promising, such as potassium-competitive acid blockers, and agents that inhibit transient lower esophageal relaxations, much of the work in these areas has been stopped because of unanticipated side effects. While both concepts are based on the goal of reducing the amount of acid that reaches the lower esophagus, the effort to improve the pharmacokinetics of PPIs appears to provide the best current pharmacologic option for improving GERD therapy.

Conclusion

The efficacy of PPIs in the treatment of GERD, as well as other acid-related GI disorders, relative to previous options may have delayed the attention now being paid to those who are not achieving adequate symptom relief on conventional doses of these agents. While PPIs do provide very high rates of esophagitis healing, approximately 30% of patients with inflammation and an even higher proportion without esophagitis remain symptomatic. The inadequacy of control is greatest for nocturnal symptoms. Although more frequent dosing may be a solution for some proportion of individuals, modified pharmacokinetics to lengthen the availability of drug available for proton pump binding is another. Efforts to identify patients with persistent symptoms to offer alternative treatment approaches can be expected to be rewarded with substantial improvements in quality of life and wellbeing.

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