


The Medical Management of Gastroesophageal Reflux Disease: A Narrative Review

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Abstract

Objective: The medical management of gastroesophageal reflux disease (GERD) continues to evolve. Our aim was to systematically assess the literature to provide an updated review of the evidence on lifestyle modifications and pharmacological therapy for the management of GERD. **Background:** The cornerstones of GERD medical management consist of lifestyle modifications and pharmacologic agents. Most recently, evidence has emerged linking anti-reflux pharmacologic therapy to adverse events, such as kidney injury, metabolic bone disease, myocardial infarction, and even dementia, among others. **Methods:** A systematic search of the databases of PubMed/MEDLINE, Embase, and Cochrane Library was performed for articles on the medical management of GERD between inception and March 1, 2021. **Conclusion:** Although pharmacological therapy has been associated with potential adverse events, further research is needed to determine if this association exists. For this reason, lifestyle modifications should be considered first-line, while pharmacologic therapy can be considered in patients in whom lifestyle modifications have proven to be ineffective in controlling their symptoms or cannot institute them. Naturally, extra-esophageal causes for GERD-like symptoms must be considered on suspected high-risk patients and excluded before considering treatment for GERD.

Keywords

GERD, lifestyle modifications, management, PPI, esophageal cancer

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Introduction

Gastroesophageal reflux disease (GERD) affects 10% to 20% of people in the Western world.¹ It is the most common gastrointestinal disorder, leading to an overall spending of 15 to \$20 billion yearly.² The disease is defined by the presence of recurrent reflux of stomach contents causing troublesome symptoms. Most patients present with repeated episodes of heartburn and/or regurgitation. Chest pain is also common, and less common symptoms include a chronic cough, asthma, dysphagia, and belching. Gastroesophageal reflux disease is caused by the dysfunction of the lower esophageal sphincter whereby frequent and/or prolonged relaxations lead to regurgitation of gastric acid.

Over time, the acid leads to damage and dysplasia of the gastroesophageal mucosa. Risk factors for GERD include obesity, tobacco smoking, and genetic predisposition.³ Untreated GERD can lead to complications, including esophageal (esophagitis, Barrett's esophagus, esophageal strictures, or esophageal adenocarcinoma) or extra-esophageal (asthma exacerbations, chronic laryngitis, hypersalivation).

The prevalence of GERD associated complications is 18% to 25% for esophagitis, 7% to 23% for esophageal strictures, and 7.2% for Barrett's esophagus.³

The majority of healthcare spending for GERD concentrates around the spending for acid suppressing medications, amounting to \$5.2 billion for esomeprazole alone.² Recent evidence, however, have suggested potential harm from long-term acid suppression prompting a reassessment of the evidence behind the medical management of GERD. Lifestyle modifications, such as weight loss, dietary changes, and mealtime practices, remain the preferred initial approach for the management of GERD, followed by pharmacological therapy for those who fail conservative

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Table 1. Lifestyle Modifications in the Treatment of GERD.

Lifestyle modifications	Strength of recommendation taxonomy (SORT)
1. Weight loss	Grade A (level of evidence 1)
2. Avoidance of trigger foods/beverages	Grade C (level of evidence 2)
3. Avoid alcohol and tobacco	Grade B (level evidence of 1 and 2)
4. Elevation of the head of the bed	Grade A (level of evidence 1)
5. Avoidance of meals for at least 3 h before bedtime	Grade B (level of evidence 2)

measures. In this article, we provide a comprehensive review of the current guidelines on the medical management of GERD. A summary of the recommendations and their respective grades based on the Strength of Recommendation Taxonomy (SORT)⁴ are presented in (Table 1). We present this article in accordance with the narrative review reporting checklist.

Methods

The databases of PubMed/MEDLINE, Embase, and Cochrane Library were interrogated for articles published between database inception and March 1, 2021. All studies on case reports, pediatric patients, or those published in a language other than English were excluded. Guidelines, reviews, comparison studies, and meta-analyses were included for assessment. The phrases “GERD” (title), “lifestyle modifications” (all fields), and “medical management” (all fields) were used to search the databases. In addition, articles referenced in review articles or guidelines were reviewed for inclusion.

Discussion

Lifestyle Modifications

The interest in lifestyle modifications has been reinvigorated by recent evidence of potential adverse reactions of pharmacologic therapy. Lifestyle modifications that have been proven to play a role in the management of GERD include weight loss, avoiding meals in proximity to bedtime, elevation of the head of the bed, and avoidance of toxic habits or foods that can potentially exacerbate symptoms. Lifestyle changes should remain the first line of therapy.

Weight loss. More than one third of patients with overweight or obesity report GERD symptoms.⁵ Traditionally, the hallmark symptomatology of GERD has been shown in various studies to be directly correlated to the body mass index (BMI).⁶⁻⁸ The proposed mechanism involves an elevation of the gastroesophageal pressure gradient in combination with transient lower esophageal relaxation (TLER) that leads to higher frequency of reflux episodes.

The symptoms of GERD have been reported to be more frequent the greater the BMI is.^{9,10} This holds true even for patients who are categorized as having a normal BMI (18.5-24.9 kg/m²), as the symptoms occur irrespective of whether patients have a normal weight or obesity. In addition, a growing body of evidence also suggests a positive association between the BMI and erosive esophagitis, Barrett’s esophagus, and esophageal neoplasia.^{7,10} More recent data suggests that the waist-to-hip ratio and abdominal diameter correlate better with esophageal acid exposure and risk of Barrett’s esophagus than BMI does.^{11,12} This evidence is further supported by the fact that patients who achieve weight loss report a decrease in GERD symptoms.⁹

In the United States, the prevalence of overweight and obesity continues to increase at an alarming rate. According to the 2015 to 2016 Centers for Disease Control and Prevention (CDC), 31.8% and 39.8% of the US population has overweight or obesity, respectively (total of 71.6%). Dire estimates predict that an excess of 85% of the US population will have overweight or obesity by the year 2030.¹³

Considering that one-third of patients with overweight or obesity have GERD symptoms, this accounts for over 87 million patients with GERD symptoms in the US.⁵ Given the magnitude of this issue and the direct correlation of obesity with other comorbidities such as cardiovascular disease, weight loss is encouraged. Patients with GERD that achieve weight loss report a significant reduction of symptoms, and up to 27% can have complete resolution of symptoms with weight loss alone.¹⁴ Other studies report that a reduction in BMI of just 3.5 kg/m² led to the decrease of 40% of frequent GERD symptoms.¹⁵ The cornerstones of weight loss are dietary interventions and increase in physical activity.

Several meta-analyses have found consistent findings on the direct correlation of BMI and GERD (level of evidence 1) and current guidelines strongly recommend encouraging weight loss in patients with symptoms, especially those with BMI over 25 kg/m².¹⁶ The strength of the recommendation to encourage weight loss for managing GERD symptoms should be Grade A.

Dietary factors. Dietary interventions in patients with GERD are not only aimed at weight loss but also at avoiding foods that potentially may trigger symptoms. Several

foods and beverages have been traditionally linked to GERD symptoms, although high-quality evidence still lacks and is, moreover, conflicting.

Acidic foods such as those containing citrus or tomatoes have been noted to have different ingestion dynamic than that of pH-neutral fluids, which may exacerbate GERD symptoms.¹⁷ Ingestion of fatty meals, soft drinks, and chocolate have been suggested to reduce the pressure of the lower esophageal sphincter, increase esophageal acid exposure times, and increase gastric acid production in some studies. Furthermore, saturated fat and cholesterol consumption have been noted to have a dose-response link with GERD symptoms.¹⁸ Unfortunately, formal studies examining the effects of both consumption and abstinence of coffee, tea, soft drinks, acidic beverages like citrus, spearmint, chocolate, or spicy meals have either yielded mixed results or are lacking, for which current guidelines recommend only on selectively eliminating foods that clearly trigger symptoms on selected patients.^{16,19}

Diets consisting of low carbohydrate content have reported decreases in scores of symptomatic scales as well as the lower esophageal exposure to acid as measured by pH monitoring.²⁰ The Mediterranean diet has been evaluated in prospective trials and suggested to have properties that decrease GERD symptomatology. A study from southeastern Europe found that patients not adhering to a Mediterranean diet were more than twice as likely to report GERD symptoms after adjusting for confounders including eating habits.²¹ Diets that have elevated protein and fiber content have also been suggested to reduce GERD symptoms by causing an increased tone of the lower esophageal sphincter.²²

While several observational studies (level of evidence 2) have suggested avoidance of certain foods and recommended alternative diets (such as Mediterranean, low carbohydrate, and fiber-rich), high-quality evidence, such as a well-designed randomized controlled trial, is lacking. The strength of the recommendation to avoid trigger foods or beverages should be Grade C.

Toxic habits. Alcohol and tobacco consumption have been directly implicated in triggering GERD symptoms. The underlying mechanism is believed to involve lower esophageal sphincter (LES) relaxation, as evidence of prolonged acid exposure time in patients who smoke and consume alcohol has been found. Specifically, cessation of tobacco smoking has been linked to significant improvement in reported reflux symptoms in patients with a normal BMI who are on antisecretory therapy in a large population-based cohort study of 29 610 individuals.²³ A systematic review of 100 studies on lifestyle measures for the management of GERD, however, found the cessation of alcohol (16 studies, level of evidence 2) and tobacco (12 studies, level of evidence 2) in patients with obesity and GERD did not

confer improvement in their symptoms or esophageal acid exposure times in patients with obesity.¹⁹ Nonetheless, alcohol and tobacco use are independent risk factors for the development of esophageal squamous cell carcinoma and adenocarcinoma, respectively.^{24,25} Irrespective of symptoms or BMI, all patients should be provided counseling on cessation of alcohol and tobacco product consumption.

A large prospective cohort (level of evidence 2) and systematic review (level of evidence 2) have found conflicting evidence on the benefits of abstaining from alcohol and tobacco. However, a meta-analysis (level of evidence 1) and a large case-control study (level of evidence 2) found cigarette smoking and alcohol increase the risk of esophageal cancer. The strength of the recommendation to abstain from alcohol and cigarette smoking should be Grade B.

Body posture. The 2 main factors that influence esophageal acid exposure are the pressure gradient that exists between the gastric cavity and the esophagus, and the LES. The pressure gradient itself is a factor that may propel or drive acid through the esophagus, while the LES pressure creates a mechanical barrier to acid. Studies have shown that the supine position substantially decreases the LES pressure while increasing the frequency of TLERS to a degree that it facilitates the passage of acid into the esophagus.²⁶ A postulated mechanism to explain this is the effect of the gastric distension on mechanoreceptors located in the fundus. When stimulated, it is believed that these facilitate TLERS, therefore promoting reflux.

The beneficial effects of elevating the head of the bed with either blocks or wedges when sleeping have been described for over 40 years now.²⁷ The rationale for elevating the head of the bed is to elevate the gastroesophageal junction sufficiently enough to avoid submersion of the area below liquid gastric contents.²⁸ Initial studies demonstrate that up to two-thirds of patients that sleep with an elevated head of the bed have improvement in esophageal acid clearance times, as measured by intraesophageal pH monitoring. This did translate into decreased esophageal acid exposure times, although it did not decrease the frequency of reflux episodes in patients that had elevation of the head of the bed while sleeping.²⁷ This has shown to correlate with decreased reported frequency of reflux symptoms in patients with GERD.²⁹⁻³²

Three randomized controlled trials (level of evidence 1) have consistently shown esophageal pH values and GERD symptoms improve with elevation of the head of the bed. The strength of this recommendation to elevate the head of the bed should be Grade A.

Meal timing in relation to bedtime. As described above, gastric distension stimulates mechanoreceptors that increase the frequency of TLERS. Ingesting a meal causes the gastric cavity to accommodate to the volume of it, causing

Table 2. Pharmacologic Therapies for GERD.

Medical therapeutic options	Over the counter?
Proton pump inhibitors	
Deslansoprazole	No
Esomeprazole	Yes
Lanzoprazole	Yes
Omeprazole	Yes
Pantoprazole	No
Rabeprazole	No
Histamine-2 Receptor Antagonists	
Cimetidine	Yes
Famotidine	Yes
Ranitidine	Yes
Nizatidine	Yes
Prokinetics	
Metoclopramide	No
GABA _B Receptor Antagonists	
Baclofen	No
Antacids	
	Yes

distension. This in itself causes an increase in transient relaxations of the LES, facilitating the occurrence of reflux.³³ A Japanese prospectively-designed study found that the odds of experiencing GERD symptoms in patients with a meal-to-bed time of less than 4 h was over 7-fold compared to patients with a meal-to-bed time of 4 h or more.³⁴ Therefore, it is recommended that patients avoid going to sleep at least within 3 h after a meal.

In addition, it has been noted that frequent night-time awakenings and sleep deprivation may also contribute to exacerbating GERD symptoms. These sleep disturbances are not uncommonly a result of nocturnal GERD symptoms, for which interventions to improve sleep hygiene and help break this vicious cycle should also be sought.³⁵

A matched case-control study (level of evidence 2) found more than a 7-fold increase in the odds of experiencing GERD symptoms with meal-to-bed of 4 or more. Larger studies, including randomized controlled trials, however, are needed to confirm this finding. The strength of this recommendation to avoid eating dinner for at least hours before bedtime should be Grade B.

Pharmacologic therapy

Patients in whom lifestyle modifications are ineffective in controlling GERD symptoms can benefit from pharmacologic therapy. (Table 2). Acid suppression is the mainstay of pharmacological management of GERD. Therapeutic agents that have been traditionally used in the treatment of GERD not only include acid suppressants like proton pump inhibitors (PPIs), histamine-2-receptor blockers (H₂B) and antacids, but also medications that can have an effect on gastrointestinal motility, such as prokinetics and baclofen.³¹

Pharmacologic therapy for GERD has recently been the focus of interest as multiple studies reporting on the potential adverse effects of long-term therapy have emerged, namely for PPI therapy.

The PPIs have been in the market for over 25 years and are currently the most effective therapeutic agent in the treatment of GERD. In the United States, they currently rank in the top 10 prescribed medications with 15.2 million monthly prescriptions for esomeprazole alone in the year 2015.³⁶ They not only have a therapeutic role, but can also play a role in establishing a presumptive diagnosis of GERD.

In patients with erosive reflux disease (ERD), the rates of healing, symptomatic relief, and speed of healing are higher in patients on PPIs compared to H₂B, sucralfate and placebo, as evidenced by a 1997 meta-analysis. Specifically, the mean healing proportion of patients treated with PPIs was 83.6% compared to 51.9% on H₂B, 39.2% with sucralfate, and 28.2 in placebo. Erosive esophagitis healing rates were also faster for patients taking PPIs (12% per week) as compared to H₂B (6% per week), sucralfate and placebo (3% per week).³⁷

Patients with ERD have been noted to respond more favorably to acid-suppression therapy with PPIs when compared to patients with non-erosive reflux disease (NERD).³⁸ A Cochrane systematic review found that PPIs are more effective than H₂B in improving reflux symptomatology in patients treated empirically for GERD and in those patients with proven NERD.³⁹

Treatment failure or incomplete response in patients who have been prescribed PPIs is not uncommon. Several factors that may lead to treatment non-response have been described and include anatomical factors (ie, hiatal hernia), extraesophageal symptoms, underdosing, and lack of adherence to treatment. All patients who do not respond to lifestyle modifications and basic pharmacologic therapy should be referred to a gastroenterologist for further evaluation and management, which may include upper endoscopy, functional testing, abdominal imaging, and *H. pylori* testing, among others.

Adherence to the PPI regimen comprises taking the medication and adhering to the specific schedule at which it is taken in relation to meals and time of day. A study noted that only 60% of patients with GERD actually fill their prescription for PPI. For this reason, taking a good history with emphasis on adherence to medication can potentially avoid a patient from having therapy escalated unnecessarily.^{40,41} With the exception of dexlansoprazole and omeprazole-sodium bicarbonate, it is recommended that all patients on PPIs take the medication 30 to 60 min before breakfast to achieve efficacy.¹⁶ It is also worth noting that considering the pharmacokinetics of PPIs, the maximum acid-suppressing effect is typically achieved after 3 days of uninterrupted therapy.⁴² This is clinically important to consider, as the

therapeutic efficacy in patients taking PPIs on an as-needed basis for less than 3 days may be suboptimal. Since several PPIs can currently be obtained by patients without medical prescription, it is paramount for patients to be appropriately educated not only on the risks of long-term use, but on their correct use.

Some patients that have incomplete response may respond favorably to twice-daily dosing.⁴³ One study supports switching lansoprazole for esomeprazole in non-responders, although no further data is available involving efficacy of switching PPIs more than once.⁴³ Other patients with incomplete response to maximal-dose PPI therapy alone or with nocturnal acid breakthrough may benefit from adding a second agent to the regimen. Adding an H₂B at bedtime to the twice-daily PPI regimen has been shown to reduce nocturnal acid breakthrough in patients with GERD.⁴⁴ However, it must be noted that tolerance to H₂B can quickly develop, rendering nocturnal acid breakthrough control effective only for 1 week after induction.⁴⁵ This leads to consider carefully selecting patients with symptoms or proven nocturnal acid breakthrough for adding H₂B therapy on an as-needed basis.

In patients with conditions requiring long-term acid suppression therapy, the objective should be to use the lowest effective dose of the least expensive medication available. These conditions include complications of GERD, such as Barrett's esophagus, peptic strictures, prevention of relapse, PPI-responsive esophageal eosinophilia, erosive esophagitis, and Zollinger-Ellison syndrome among others.

Patients that have had their symptoms adequately controlled on PPI therapy or those who do not have a definite indication to be taking a PPI can be considered to be switched (ie, "stepped down") from the PPI to a less expensive medication. A well-designed study suggests that more than half of patients with reflux symptoms can be maintained in remission with no need of PPI use. Of these patients, 27% required no further medications, while the remaining 73% remained in remission with the use of an H₂B.⁴⁶ Rebound acid hypersecretion has been described in patients who discontinue long-term PPI therapy abruptly. The mechanism behind this is believed to be a hypergastrinemic state that is caused by the gastric cavity's hypoacidity due to long-term blockade of the hydrogen/potassium ATPase (ie, the "proton pump") by the PPIs.⁴⁷ This is a well-recognized effect that has been replicated in randomized control trials and can last from 8 to 26 weeks.^{48,49} High-quality evidence to address this issue is lacking, but 1 study reduced the dose to half for 2 weeks before discontinuing.⁴⁶ A recent personal recommendation from Targonwik suggests to first decrease the PPI frequency to every other day for 2 weeks, then only twice in a week for 2 more weeks and then to discontinue.⁴⁹

In an effort to accelerate gastric emptying and decrease the occurrence of reflux, the use of prokinetic agents has

been described in the past. Traditionally, 5-HT₄ antagonists (mosapride and cisapride) and selective dopamine-2 antagonists (metoclopramide and domperidone) have been used. Unfortunately, the side effect profile of both of these groups limits its use, with 5HT₄ antagonists being associated with cardiac side-effects. While metoclopramide is still available in the American market, its association with the potential development of tardive dyskinesia and other neuropsychiatric side effects limits its use. Domperidone is considered to have similar efficacy to metoclopramide but is not available in the United States.

The use of baclofen, a GABA receptor agonist, has also been described in selected cases of patients with GERD. Its effects on decreasing the frequency of TLERs have in theory made it an attractive option in addition or substitution to acid suppression. Some studies have found that patients taking baclofen can have decreased reflux symptoms and belching, for which it is currently a therapeutic option in patients with rumination syndrome.⁵⁰ However, data on actual symptomatic improvement in patients with GERD is mixed, and believed to be secondary to the fact that baclofen also paradoxically decreases the initiation and frequency of esophageal secondary peristalsis, increasing the esophageal acid exposure time and hence GERD symptoms.⁵¹ Patients considered for baclofen or prokinetics therapy must have exhaustive diagnostic testing performed to exclude other causes.

Antacids act locally and react with the gastric or esophageal hydrochloric acid to neutralize it. Although this can provide symptomatic relief in patients with pyrosis, the effect is short-lived, and symptoms may recur rapidly. Furthermore, this temporality of their effects usually results in patients resorting to frequent dosage, which is cumbersome to the majority of patients. Alginates, such as sucralfate, form a viscous barrier that temporarily coats the esophagus and prevents gastric contents from coming into direct contact with the esophageal tissue. It is estimated that a mere 25% of patients with GERD experience symptomatic relief with the use of antacids. In addition, antacids and alginates have not been associated with mucosal healing in patients with ERD.⁵²

Side effects include decreased absorption of calcium potentially leading to increased rates of osteoporosis and hip fractures, infections (ie, *C. difficile* and food-borne pathogens), renal disease, myocardial infarction, and dementia. However, the quality of data behind these claims are only associations and not necessarily link to actual causality. Therefore, higher quality of evidence is necessary to better understand these entities and truly elicit causality, if existent.⁴⁹

Conclusion

The prevalence of GERD continues to increase with the increasing obesity epidemic in the United States. The

mainstay of treatment involves lifestyle modifications, including weight loss, dietary changes, and mealtime practices. Although there are multiple pharmacologic therapies available, proton pump inhibitors remain the most effective therapy for symptomatic management. Before prescribing proton pump inhibitors, however, the correct way to administer these medications and their potential side effects should be reviewed. Despite evidence showing possible associations with kidney injury, dementia, and bone mineral disease, further research is required to understand if a causality actually exists.

Declaration of Conflicting Interests

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