



# Pharmacological Management of Gastro-Esophageal Reflux Disease: An Update of the State-of-the-Art

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**Abstract:** Gastro-esophageal reflux disease (GERD) is a highly prevalent, chronic disorder, whose knowledge remains limited and the management of these patients changes continuously. This review provides a summary of the most recent advancements in the pathogenesis of this disease and the new drugs introduced into the market to overcome some of the unmet needs of traditional therapies. Nowadays, the most fruitful diagnostic examinations are 24-hour impedance-pH monitoring, which allows us to separate true NERD from esophageal functional disorders and high-resolution manometry, which helps to exclude the existence of motility disorders sharing the same symptoms of GERD. Proton pump inhibitors (PPIs) remain the first-choice therapy in the treatment of GERD, but a consistent proportion of these patients continue to experience symptoms despite their intake. These cases pertain mainly to the subpopulation with non-erosive reflux disease (NERD) and represent very challenging clinical situations, because it is mandatory to understand the reasons for PPI failure. The management of these difficult patients requires necessarily to test them and avoid the use of empiric treatments that are often unsuccessful, costly and potentially dangerous. Recently, several new drugs have been used to increase the defensive properties of this mucosa with promising results in randomized clinical trials.

**Keywords:** medical management of GERD, proton pump inhibitors, potassium competitive acid blockers, PPI-refractory patients, esophageal mucosal resistance, mucosal protective agents, bile acid sequestrant drug

## Introduction

Gastroesophageal reflux disease (GERD) is defined as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”.<sup>1</sup> Typical esophageal symptoms include heartburn and regurgitation and, more rarely, chest pain and dysphagia. Extra-esophageal symptoms or signs with an established association with GERD on the basis of population-based studies are chronic cough, hoarseness, asthma and dental erosions. However, these symptoms have potential etiologies other than GERD and, in the absence of concomitant typical GERD symptoms, the causal role of reflux remains difficult to prove. GERD complications are mainly represented by mucosal injury, the most common being reflux esophagitis, strictures, Barrett’s esophagus and adenocarcinoma.

The prevalence of GERD is high in Western countries and ranges from 13% to 20% in the USA and from 9.8% to 18% in Europe, while it is lower in Asia (2.5–4.8%).<sup>2</sup> Obesity, increasing age, a family history of reflux disease and chronic consumption of certain drugs (nitrates, calcium antagonists, benzodiazepines, etc.) are significant risk factors.<sup>3–5</sup>

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GERD is a chronic disease with phases of recurrence and remission overtime, but it can be considered a benign disorder from a prognostic point of view.<sup>6</sup>

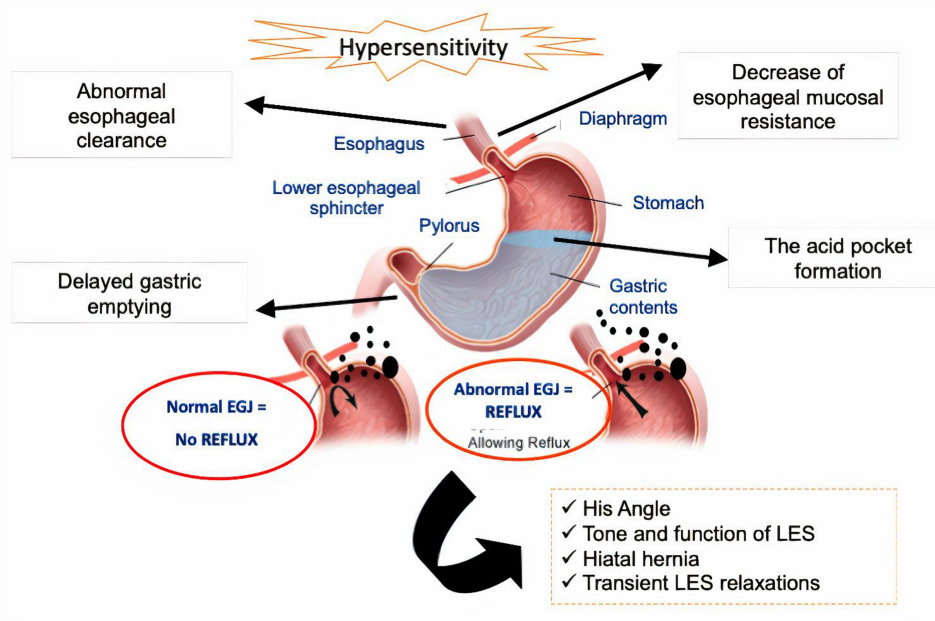
The aim of this review is to provide a summary of the most recent studies on the unmet needs and the pharmacological management of GERD with particular attention to the new molecules that have enriched our therapeutic armamentarium. A computerized (PubMed databases) literature research was performed with focus on the last five years (2016–2020). We used the following terms: “GERD”, “GORD”, “gastroesophageal reflux disease treatment or therapy” “functional heartburn”, “reflux hypersensitivity”, “PPI-refractory GERD”, “PPI failure”, “impedance-pH monitoring”, “esophageal pH-metry”, “Bravo system”, “high resolution manometry”, “proton pump inhibitors”, “PPIs”, “H<sub>2</sub> antagonists”, “potassium competitive acid blockers”, “P-CABs”, “GABA<sub>b</sub> agonists, anti-depressants”, “pain modulators”, “esophageal mucosal integrity”, “esophageal mucosal resistance”, “esophageal mucosal protective drugs”, “alginates”, “hyaluronic acid”, “esophageal medical devices”, “add-on therapy to PPIs”. We critically reviewed all full-text papers, including clinical trials, systematic reviews and meta-analyses, published in English language. The number of clinical trials we considered in this review was 19 and that of systematic reviews was 14.

## Pathophysiology of GERD

GERD is due to multiple mechanisms and motor alterations predominate, as shown in Figure 1. The anti-reflux barrier is thought to consist of the intrinsic pressure of the lower esophageal sphincter (LES), the extrinsic compression of the LES by crural diaphragm and the acute angle of His. There are three prevalent mechanisms of reflux: transient LES relaxations (TLESRs), LES hypotension and anatomical disruption of the esophago-gastric junction (EGJ), that is hiatus hernia.<sup>7</sup>

TLESRs represent the most important mechanism of reflux in healthy subjects and in a very large part of GERD patients; they occur during swallows to allow the passage of a bolus from the esophagus into the stomach and are also induced by secondary peristalsis, which starts from mid esophagus as effect of a vago-vagal reflex commencing with activation of gastric receptors primarily placed in the sub-cardiac region. Therefore, the primary stimulus which triggers a TLESR is gastric distension, often due to gastric air or the presence of meal and this explains why TLESRs are mainly a postprandial phenomenon.<sup>8</sup>

A second mechanism is LES hypotension and episodes of free reflux are observed only when the LES pressure is lower than 5 mmHg measured by manometry. This mechanism is particularly frequent in patients with scleroderma.<sup>9</sup>



**Figure 1** The complex pathogenesis of GERD.

As third factor, the presence of hiatal hernia favors gastroesophageal reflux by increasing the severity of esophageal acid exposure. It alters the position of LES with respect to the crural diaphragm because these two important factors of the anti-reflux barrier are no longer coupled.<sup>10</sup>

In addition to the above mechanisms, an impaired esophageal clearance of refluxate may prolong the contact time with the mucosa of the distal part of the esophagus and this contributes to generate symptoms or to damage the epithelium. Primary (swallow-induced) and secondary (distension-induced) peristalses are the main clearance events to clear the refluxate. Esophageal motility disorders occur in about 30% of patients with GERD, with ineffective esophageal motility being the most prevalent alteration.<sup>11</sup> Although less relevant, also chemical clearance due to bicarbonates contained in saliva is decreased in GERD.<sup>12</sup> Recently, the relevance of esophageal clearance has been shown even in neonates, where it enables to predict the response to PPI therapy. In a study by Nobile et al<sup>13</sup> a more efficient and rapid esophageal clearance assessed by impedance-pH monitoring was significantly associated with a positive clinical response to anti-reflux therapy with omeprazole among newborns with increased acid esophageal exposure time (AET).

Finally, a delayed gastric emptying has been demonstrated in about 40% of GERD patients and this can favor the backflow of the material retained in the stomach.<sup>14</sup>

Although GERD treatment is mainly based at present on the use of antisecretory drugs to reduce acid reflux, there is no evidence of gastric acid hypersecretion in these patients.<sup>15</sup> In fact, acid remains the most aggressive factor in determining mucosal damage or reflux symptoms. Chronic smoking is also considered a risk factor for GERD development.

In summary, the alteration of the anti-reflux barrier is sometimes associated with an inadequate clearing of refluxate and a delayed gastric emptying; in addition, dietetic factors, drugs able to reduce competence of LES and obesity contribute to induce the reflux of too much acid in the wrong place, that is the esophagus, the mucosa of which is not familiar with this aggressive element.

In recent years, another mechanism, such as the reduction of defensive properties of esophageal mucosa has been advocated in the pathogenesis of GERD.<sup>16</sup>

There are many studies showing that the mucosal resistance of the esophagus is impaired in most patients

with GERD, particularly in those with non-erosive reflux disease (NERD), who do not present mucosal lesions at endoscopy.<sup>16,17</sup> Indeed, the presence of dilated intercellular spaces (DIS) is common in patients with true NERD and reflux hypersensitivity (RH) because of the presence of an impaired mucosal barrier.<sup>18</sup> In patients with NERD it has been shown that microscopic esophagitis, including DIS, is significantly lower in controls (15%) and in patients with functional heartburn (FH) (13%) than in patients with RH (65%) and in those with excess of acid (77%).<sup>19</sup>

## Phenotypic Presentation of GERD

At the end of the second millennium erosive esophagitis (EE) was identified with GERD, but in the last two decades we have realized that patients with esophagitis represent only a minority (25–30%) of the entire spectrum of this disease, because about 70–75% of them pertain to the NERD phenotype, that is patients with typical reflux symptoms and devoid of any esophageal lesion visible at endoscopy.<sup>20</sup> Two large population-based epidemiological studies have demonstrated that the rate of endoscopy-negative cases can be as high as 75%.<sup>21,22</sup>

Current pathophysiological studies performed with the modern 24-hour impedance-pH monitoring have demonstrated that NERD population is greatly heterogeneous from a pathophysiological point of view and can be subdivided into several subgroups<sup>23</sup>: about 40% of them have an excess of acid in their esophagus (true NERD), while the remaining part (60%) have normal esophageal acid exposure. This latter population can be further distinguished in the following subgroups: 1) patients with RH to both acid and weakly acidic reflux (about 40%) and patients with FH (about 20%). Patients with RH have a positive association between symptoms and episodes of reflux, while those with FH do not have any relationship with reflux events. According to Rome IV criteria for functional esophageal disorders,<sup>24</sup> patients with RH and FH are no more considered in the GERD population, but this has been questioned.<sup>25,26</sup>

## Pharmacological Treatment of GERD

The multiple factors implicated in the pathogenesis of GERD and the various forms of clinical presentation of this disease do not permit to manage our patients in the same way and to use a unique pharmacological treatment, which can be of benefit in each situation we may face with in our routine daily practice. Therefore, the most practical

therapeutic approach relies on targeting the individual elements of GERD pathophysiology according to each clinical situation and implies that our medical treatment will be always palliative, because it is unable to control the functional alterations representing the real mechanisms of the disease. In this review we will list the most frequently used drugs to ameliorate the single or combined mechanisms of reflux, taking into consideration their chance of success in the different clinical presentations of GERD.

## Acid Control

### Proton Pump Inhibitors

Although gastric acid secretion is not increased in patients with GERD and the main pathophysiological alterations of this disease are represented by motility dysfunctions, the contact of acid with esophageal mucosa remains a key factor in the generation of symptoms and in the induction of inflammatory lesions at the distal part of the esophagus.<sup>27</sup> Therefore, it is not surprising that the dominant medical treatment of patients with GERD focuses on inhibiting acid secretion.

Proton pump inhibitors (PPIs) are the most powerful antisecretory drugs available, because they bind to the  $H^+K^+$  ATP-ase, which is the final step in the production of acid by the gastric parietal cell and therefore they have rapidly replaced the less potent  $H_2$ -receptor antagonists ( $H_2$ RAs) as first-choice drugs in the control of this relevant element in the pathogenesis of GERD.<sup>28</sup> Table 1 shows a list of  $H_2$ -RAs and PPIs used for treatment of GERD.

**Table 1** List of  $H_2$ -Receptor Antagonists and Proton Pump Inhibitors Used for Treatment of GERD

<b><math>H_2</math>RAs</b>
Cimetidine
Ranitidine
Famotidine
Nizatidine
Roxatidine
<b>PPIs</b>
Omeprazole
Lansoprazole
Pantoprazole
Rabeprazole
Esomeprazole
Dexlansoprazole
Ilaprazole
Tenatoprazole
IR (immediate release)-omeprazole
Dexlansoprazole-MR (modified release)

Despite the greater antisecretory activity of PPIs compared to  $H_2$ RAs, their efficacy is variable, depending on the degree to which the clinical manifestations of the disease are more or less attributable to acid.

There is no doubt that the most responsive form of GERD is EE, particularly when it presents with the more severe degrees of mucosal damage, ranging from B and D of the well-known Los Angeles classification.<sup>29</sup> There are many randomized clinical trials, systematic reviews and meta-analyses showing that PPIs are able to achieve a very high healing rate, proximal to 80–90% in these patients within 8–12 weeks of treatment.<sup>30,31</sup> This effectiveness in healing esophageal mucosal alterations is associated with a quick resolution of typical symptoms of the disease, particularly heartburn, when PPIs are compared with placebo and  $H_2$ RAs. However, their optimal control of symptoms is reduced in the case of regurgitation, which can continue to persist despite these powerful antisecretory drugs.<sup>32</sup> The efficacy of PPIs has been shown to be high also in patients with reflux-induced chest pain, as shown in a recent meta-analysis, in which six randomized controlled trials on patients studied with 24-hour esophageal pH-metry, found a benefit in 56–85% of GERD positive patients compared with 0–17% of GERD negative ones.<sup>33</sup> Also, dysphagia, which occurs in about one-third of patients with EE without strictures or cancer, resulted to resolve in 83% of cases using PPI therapy.<sup>34</sup>

The excellent results of PPIs in EE are lower by a factor of 20%–30% in patients with the non-erosive form of GERD<sup>35</sup> and this is due to the reduced pathogenetic role of acid in this population.<sup>36</sup> In fact, we have already mentioned that patients with NERD are greatly heterogeneous from a pathophysiological point of view and acid is not responsible of heartburn in cases of RH to weakly acidic reflux and FH. These categories do not respond to antisecretory drugs because their symptoms are generated by factors other than increased or normal esophageal acid exposure.

However, NERD patients with excess of acid in their esophagus show the same benefit of the EE ones by PPI therapy.<sup>37</sup>

As GERD is a chronic condition with more or less frequent clinical relapse, maintenance therapy is needed for continued symptom control and esophagitis remission. Independently of the modality of maintenance therapy, on demand or continuous, PPIs have been superior to  $H_2$ RAs, prokinetics and placebo in preventing relapses of symptoms and esophageal lesions over periods of times of one or more years.<sup>38,39</sup>

As to the management of extra-esophageal symptoms of GERD (chronic cough, hoarseness, asthma), this aspect is highly controversial because the diagnosis of atypical GERD is very difficult and the risk of other etiologies sustaining these symptoms remains possible. Anyway, PPI therapy can be successful also in these patients, particularly when typical symptoms are concomitant, and therefore support the existence of gastroesophageal reflux as the cause of them.<sup>40</sup>

The PPI safety has been questioned in last years by the publication of many studies, mainly observational, on the occurrence of multiple adverse events,<sup>41</sup> including hypomagnesemia, enteric infections, ischemic heart disease, kidney injury, pneumonia, dementia and nutritional deficiencies. However, this alarmism has been rejected in great part in recent reviews,<sup>42,43</sup> due to the important methodological flaws of observational and retrospective studies performed to show the above adverse reactions and the lack of biological plausibility in the majority of risks reported in published papers.

## PPI-Refractory GERD

Many studies have reported that a great number of patients with GERD symptoms, particularly heartburn, ranging from 19% to 44%, report either partial or complete lack of response to a standard PPI dose.<sup>44,45</sup> In addition to an incorrect dosage or timing of PPI intake, various mechanisms may induce this phenomenon, such as weakly acidic or bile reflux, mutations of hepatic cytochrome P-450, esophageal hypersensitivity to physiological reflux, the presence of FH, which does not pertain anymore to the GERD realm.<sup>46</sup> The main population responsible for PPI refractoriness is represented by NERD patients, who include both RH and FH, that is two clinical conditions in which the pathogenetic role of acid is reduced or absent.<sup>47</sup>

The management of non-responsive GERD patients is a challenging task in routine clinical practice and requires the use of objective diagnostic tools (Table 2) and among them the most useful appear to be the prolonged registration of acid exposure time (AET) up to 96 hours by the Bravo system or 24-hour impedance-pH monitoring, in order to detect the real cause of PPI failure.<sup>48,49</sup> In particular, FH has been found to be associated with both functional dyspepsia and irritable bowel syndrome, thus suggesting that these three conditions might share the same pathogenetic mechanism, that is increased visceral perception.<sup>46,50</sup>

**Table 2** Diagnostic Tools for Studying PPI-Refractory Patients

Upper GI endoscopy (+ histology)	Absence of pathognomonic features
	Exclusion of other causes
High resolution manometry (HRM)	Identification of major motor abnormalities as possible causes of GERD-like symptoms
Esophageal pH-metry	Assessment of abnormal reflux and its association with GERD symptoms
	No chance to detect gaseous and weakly acidic refluxes
Impedance-pH monitoring	Lack of pathognomonic patterns for PPI failure
	Persistence of increased acid refluxes or absence of abnormal reflux and presence or not of any association between symptoms and either acid or weakly acidic refluxes
Bravo system	This technique permits to perform up to 96- hour telemetry capsule pH monitoring and to overcome the day-to-day variability of esophageal acid exposure. It does not detect gaseous and weakly acidic refluxes.

The therapeutic approach to these patients is complex and several options are available, although they are not sustained by a large body of randomized clinical trials. Table 3 shows the list of major treatments reported in international medical literature. Increasing PPI dosage or the use of surgical therapy should be adopted in patients with insufficient control of acid excess.<sup>51,52</sup> Several attempts to use add-on therapies to PPIs have obtained good results, particularly those combining mucosal protection and acid inhibition, as shown in few controlled studies. In patients with poor response to 8-week PPIs, switching to vonoprazan 20 mg/die allowed to obtain an enhanced symptom control and a faster healing of mucosal lesions, probably due to the longer-lasting acid

**Table 3** Management of Patients with PPI-Refractoriness

<ul style="list-style-type: none"> <li>• Optimize PPI therapy and check for patients' compliance</li> <li>• Add-on options to PPIs:               <ul style="list-style-type: none"> <li>(a) Alginate</li> <li>(b) Medical devices containing hyaluronic acid</li> <li>(c) H<sub>2</sub>-receptor antagonists</li> <li>(d) Bile acid sequestrant (IWX-3718)</li> </ul> </li> <li>• Consider vonoprazan in alternative to PPIs</li> <li>• Consider pain modulators in case of hypersensitivity</li> <li>• Consider anti-reflux surgery</li> </ul>
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suppression of the P-CAB,<sup>53,54</sup> but these studies were uncontrolled.

In presence of esophageal functional disorders, pain modulators may be the best therapeutic option, but their efficacy has not been strongly demonstrated.<sup>26</sup>

Also, the prolonged exposure of the esophagus to bile acids may be responsible for PPI refractoriness, because duodeno-gastro-esophageal reflux has been shown in 65% of patients who continued to complain of GERD-related symptoms despite PPI treatment.<sup>55</sup> The diagnosis of ambulatory duodeno-gastro-esophageal reflux is difficult to obtain and the mostly used method remains the measurement of bilirubin levels as a surrogate marker for bile reflux by means of Bilitec, which is generally adopted in the majority of investigational studies in this field.<sup>56</sup> The modern MII-pH is able to measure weakly alkaline reflux events, but this diagnostic approach has not been validated either in research or in clinical studies. Farré et al<sup>17</sup> showed that a mix of acid and biliary salts induced more intercellular dilated spaces (DIS) on esophageal mucosa compared with acid alone. The same authors observed a progressive reduction in transepithelial resistance (TEER) associated with increase in concentration of biliary salts; the same results were not recorded with acid alone.

IW-3718 is a novel, gastric-retentive, extended-release formulation of the bile acid sequestrant colesevelam, which is able to bind bile acids in the stomach and, thus, may reduce their backflow into the esophagus. Vaezi et al<sup>57</sup> performed a randomized clinical trial to evaluate the efficacy and safety of different doses of IW-3718 as an adjunct therapy to PPIs in patients who showed lack of, or only partial, response to PPI treatment and found that this combination, given for 8 weeks, significantly reduced heartburn symptoms compared with adding placebo to PPIs. The dose of 1500 mg/daily of IW-3718 resulted to achieve the best results and was well tolerated. The mean change from baseline to week 8 in weakly heartburn severity score was reduction of 46% in the placebo group and 58% in the 1500 mg IW-3718 and the mean change in weakly regurgitation frequency score in the same time period in the group with active drug was a reduction of 17.5% compared with placebo. These findings suggest that IW-3718 may provide a further therapeutic option in improving both reflux typical symptoms in patients with refractory GERD, an important area of unmet need.

## Neutralization of the Acid Pocket

Acid reflux episodes usually occur in the post-prandial periods,<sup>58</sup> although intragastric pH is high because of the buffering effect of meals.<sup>59</sup> This paradoxical phenomenon was first observed by Fletcher et al,<sup>60</sup> who found that the average pH in the body of the stomach was remarkably higher (4.7 units) than the pH of esophageal refluxate (1.6 units). They explained this great difference in pH values by identifying a pocket of unbuffered gastric acid immediately below the EGJ. This phenomenon is exclusively post-prandial and can be found in both normal subjects and GERD patients. Moreover, it becomes supra-diaphragmatic more in reflux patients than in healthy individuals, particularly when a large hiatal hernia is present.<sup>61</sup> Several studies have shown that alginate, a hetero-polysaccharide extracted from an ocean seaweed, is able to neutralize or displace the acid contained in the pocket and ready to backflow into the esophagus.<sup>62</sup> This action contributes to justify the post-prandial intake of alginate used as anti-reflux therapy.

## Potassium Competitive Acid Blockers (P-CABs)

These novel antisecretory drugs differ from PPIs because they compete with K<sup>+</sup> and induce a selective and reversible inhibition of the proton pump in a dose-dependent manner.<sup>63</sup> They are not pro-drugs that must be activated in the parietal cells, like PPIs, and therefore their onset of action is immediate and the control of gastric acid secretion occurs after the first dose and within the first day of administration.<sup>64</sup> Moreover, their dissociation rate from the proton pump is slow and its retention time in the gastric mucosa is 24 hours or more, thus the acid inhibitory activity covers both daytime and nighttime,<sup>65</sup> differently from PPIs which are less effective during the nocturnal period.<sup>66</sup> The main differences in the mechanisms of action between P-CABs and PPIs are reported in Table 4.

There are many molecules pertaining to this drug category (veraprazan, linaprazan, vonoprazan, tegoprazan, etc.), but vonoprazan is certainly the most studied in the treatment of GERD. It is marketed mainly in Asian countries, such as Japan, China, South Korea, Taiwan and Malaysia and Phase III studies are in progress in Europe and US. This drug has been shown to be effective and not inferior to PPIs in patients with the mild or moderate degrees of EE,<sup>67</sup> and its healing rate was even significantly better than that of lansoprazole in patients with the grades C and D of esophagitis,<sup>68</sup> a superiority maintained in CYP2C19 metabolizers.<sup>69</sup> This

**Table 4** Main Differences in the Mechanisms of Action Between PPIs and P-CABs

Proton Pump Inhibitors (PPIs)	Potassium Competitive Acid Blockers (P-CABs)
Pro-drugs that need to be transformed to the active form	Direct action on H <sup>+</sup> -K <sup>+</sup> ATP-ase
Binding covalently to H <sup>+</sup> -K <sup>+</sup> ATP-ase	Binding to K <sup>+</sup> site of H <sup>+</sup> -K <sup>+</sup> ATP-ase
Irreversible binding to the proton pump	Reversible binding to the proton pump
Full effect after 3–5 days	Full effect after the first dose
Affected by genetic polymorphism	Not affected by genetic polymorphism
Pharmacodynamic effect greater during the daytime	Pharmacodynamic effect lasting for both the daytime and nocturnal hours

drug has also been shown to induce lower recurrence rates of esophagitis than lansoprazole, when used as maintenance therapy.<sup>70</sup> However, GERD symptom relief with vonoprazan 20 mg/daily did not differ from that obtained with esomeprazole 20 mg/daily, even though this effect appeared more quickly.<sup>71</sup> It is important to emphasize that significantly more patients with esophagitis achieved a complete resolution of nocturnal heartburn with vonoprazan than with lansoprazole, due to its prolonged ability to keep intragastric pH >4.0 units during the nighttime.<sup>72</sup> Finally, the safety of vonoprazan does not differ from that of PPIs in a meta-analysis by Cheng et al.<sup>73</sup> However, the remarkable acid suppression induced by vonoprazan needs a careful control of possible adverse events, particularly in patients treated in the long term. In fact, the short-term safety of this drug is good and comparable with that of PPIs, while the chronic use of vonoprazan 10 mg and 20 mg daily over 52 weeks in patients treated to prevent reflux esophagitis recurrence determined a progressive increase of serum gastrin up to 678 pg/mL on average, with the higher dose, even though there were no relevant effects on gastric neuroendocrine cells.<sup>69</sup> As to other adverse events, changes in the gut microbiome have been documented with vonoprazan, thus increasing the risk of enteric infections in patients travelling to tropical areas.

## Reflux Inhibitors

It is well known that TLESRs represent the most relevant mechanism in the pathophysiology of GERD and therefore its control has become a therapeutic target in the therapy of this

disease. Baclofen, a gamma-amino-butyric acid (GABA) receptor type B agonist, has been identified as the first reflux inhibitor and, as such, is able to reduce the number of TLESRs and all types of reflux events, both acid and weakly acidic, as shown by means of impedance-pH monitoring.<sup>74</sup> A meta-analysis of nine studies has found that baclofen decreased the number and the length of reflux episodes as well as the incidence of TLESRs.<sup>75</sup> However, its clinical use is very limited because of its poor tolerability due mainly to neurological adverse events.<sup>76</sup> Other similar agents (lesogaberan and arbaclofen placarbil) did not show a relevant therapeutic efficacy compared with placebo and their development has been stopped.<sup>77</sup>

## Enhancing Esophageal Clearance and Defensive Properties

We have already said that GERD patients exhibit greater volume of refluxate and longer acid clearance times than normal subjects and therefore limiting the contact time between refluxate and esophageal mucosa by improving peristaltic function may be a useful therapeutic attempt. Moreover, reducing the mucosal permeability by means of drugs able to reinforce the defensive properties of esophageal lining, thus blocking the toxic effect of the gastric substances contained in the refluxate, is a further potentially adequate therapeutic proposal.

## Prokinetics

A list of currently used prokinetic compounds is reported in Table 5. These drugs have the potential to enhance esophageal clearance of refluxate by stimulating a valid peristalsis and accelerating gastric emptying. Although these possible good actions aimed at reducing the contact time of refluxate with esophageal mucosa and preventing the backflow of meals and secretions retained for more time than usual in the stomach, there is no high-quality evidence for their use in GERD patients, as either

**Table 5** List of Prokinetic Agents Used for Treatment of GERD

Metoclopramide
Clebopride
Domperidone
Erythromycin
Mosapride
Itopride
Prucalopride
Tegaserod
Acotiamide

monotherapy or adjunctive therapy.<sup>78</sup> Not surprisingly, the US guidelines published in 2018 do not recommend these drugs as a therapeutic option for PPI-refractory GERD patients.<sup>79</sup> In addition, almost all prokinetic agents available present a certain risk of cardiac toxicity (mainly arrhythmias) or neurologic adverse events.<sup>80</sup> In fact, many of these agents approved for the management of GI motility disorders carry a small but increased risk of drug-induced arrhythmia. Epidemiologic studies have identified many important patient-specific and drug-specific risk factors that, when present, typically in combination, exponentially increase the risk of drug-induced long QT syndrome, which is associated with the great risk of cardiac arrest and death.

Only prucalopride was proven to be safe from the cardiac standpoint, thanks to its high selectivity for 5-HT<sub>4</sub> receptors,<sup>81</sup> and enables to accelerate gastric emptying and reduce AET, but clinical trials assessing its efficacy in GERD treatment are lacking.

## Mucosal Protection

Many studies have recently shown that an impaired mucosal integrity is involved in the pathogenesis of GERD and in the generation of typical symptoms, particularly heartburn. In the last years, mucosal baseline impedance measured by the modern impedance-pH monitoring, has emerged as a novel method to assess the alterations of mucosal integrity in GERD patients.<sup>82,83</sup> A recent study has shown that this metric varies with the GERD phenotype, because it tends to decrease from FH to NERD and, even more, in EE, thus confirming the value of mucosal integrity as a marker of weakened mucosal protection and opening a new avenue for GERD treatment.<sup>84</sup> In addition, an elegant study by Woodland et al<sup>85</sup> has demonstrated that the intramucosal distribution of nerve fibers is more superficial in NERD than in EE and Barrett's esophagus and this provides a reasonable explanation for the higher sensitivity of the first population toward all substances bathing the mucosa of the organ.

Among the few compounds displaying a mucosal protective activity there is alginate, which was found to coat *in vitro* the luminal surface of esophageal mucosa for about 1 hour<sup>86</sup> and *in vivo* this protective effect was shown to be as long as 10 min, on average.<sup>87</sup> This long-lasting adhesion is particularly relevant in relation to the fast transit time of liquids through the esophagus (less than 16 s), even in a supine position.<sup>88</sup>

The association of mucosal protection with acid inhibition with PPI has been assessed in a randomized clinical trial in NERD patients and resulted to achieve a percentage of heartburn-free days significantly higher than that of PPI alone.<sup>89</sup> Moreover, the use of alginate as add-on therapy to PPIs in GERD patients with partial response to the latter drugs was shown to relieve heartburn and to ameliorate the quality of life significantly better than PPIs alone.<sup>90</sup> Therefore, the bio-adhesive properties of alginate permit to improve the success of PPIs in the treatment of GERD, when these two compounds are used combined in both NERD patients and in those who are partially unresponsive to these powerful antisecretory drugs.

A new medical device containing hyaluronic acid and chondroitin-sulfate (Esoxx<sup>TM</sup>, Alfasigma, Italy) has been developed as esophageal protective agent. The European Council classified this formulation as class III medical device, which should be used in human beings for the purpose of treatment or alleviation of disease. It is dispersed in a bio-adhesive carrier (poloxamer 407), which prolongs its residence time in the lumen and creates a mechanical barrier against noxious agents of refluxate over the esophageal lining.<sup>91</sup> Both compounds exhibit multiple functions, such as anti-inflammatory effect, wound repair, tissue regeneration and modulation of cytokines expression.<sup>16</sup> A prospective, randomized clinical trial performed in Italy in NERD patients compared Esoxx<sup>TM</sup> combined with a standard PPI dose to PPI plus placebo.<sup>92</sup> The combined therapy protracted for 14 days was significantly better than the latter one in relieving symptoms and improving the quality of life of recruited patients. The treatment was well tolerated and no serious adverse events were registered.

## Visceral Hypersensitivity

The Committee of Rome IV criteria for esophageal functional disorders sustained that both RH and FH have to be included in this category and only NERD patients with abnormal AET pertain to the population with GERD.<sup>24</sup> This new classification was based on the assumption that RH and FH are due to visceral hypersensitivity, without taking under consideration that the former is characterized by a positive association between symptoms and reflux episodes, although the esophageal acid exposure is normal, whereas the latter does not exhibit any relationship of this type.

**Table 6** List of Pain Modulators Used in Randomized Clinical Trials for Treating Functional Esophageal Disorders

Imipramine
Amitriptyline
Venlafaxine
Sertraline
Paroxetine
Citalopram
Gabapentin

Even though the reduction of visceral hypersensitivity is a reasonable therapeutic target in these functional patients, the results of clinical trials using neuromodulators (Table 6) have provided conflicting findings, because some studies have shown the benefit of these drugs,<sup>93,94</sup> while others did not find any difference between antidepressants, particularly tricyclic compounds at low dosage, and placebo.<sup>95,96</sup> On the contrary, surgical therapy has provided promising results in both uncontrolled<sup>97-99</sup> and controlled clinical studies<sup>100</sup> performed in patients with RH. These good results were also maintained over a follow-up of 3–5 years.<sup>98,101</sup> These findings contribute to question the above-mentioned Rome IV criteria and support the need of maintaining RH and FH as separate entities, thus re-classifying most RH patients within the GERD spectrum<sup>25,26</sup> in order to adopt the right therapeutic decisions.

## Conclusions

PPIs remain the first-choice therapy in both short- and long-term medical treatment for EE due to their well-documented benefit in controlling heartburn, healing esophagitis and preventing disease recurrences. Despite their effectiveness, there is a consistent proportion of GERD patients who respond only partially to them and the majority pertain to the NERD population, particularly the RH and FH subgroups. It is mandatory to test these patients in order to understand the various reasons for PPI failure and accordingly to adopt the most useful treatments instead of managing them empirically with frequent unsuccessful and potentially dangerous attempts.

PPIs present several drawbacks, such as the slow onset of action, short bio-availability, insufficient control of nocturnal acid secretion, which can impair their benefit. In the last decade, a new class of acid-suppressive agents, the P-CABs, have been introduced on the market, especially in Asian countries, and have been shown to be successful in the treatment of GERD, because they seem

to be able to overcome some PPI pitfalls, but more clinical comparative studies are needed in North America and European populations with the various manifestations of GERD. In patients with NERD, the benefit of PPIs is lower because of their pathophysiological heterogeneity, because esophageal hypersensitivity seems to prevail on the damage due to acid. However, the results of the few randomized clinical trials using the current pain modulators are far from being satisfactory.

## Expert Opinion

PPIs remain the standard therapeutic approach to GERD patients, although 20%–40% of them do not respond adequately to these antisecretory drugs. The majority of PPI non-responders pertain to the NERD population, but also up to 15% of patients with EE do not achieve full remission of their inflammatory lesions after at least 8 weeks of treatment. This high proportion of GERD patients with incomplete or null response to PPIs represents the most challenging population for physicians. Nowadays it is recommended to investigate them with appropriate examinations in order to understand why they continue to have persistent symptoms instead of managing them empirically with the risk of increased costs and adverse events using long-lasting and higher than usual doses of PPIs.

Endoscopy is useful to rule out other causes of esophagitis (pill-induced esophagitis, eosinophilic esophagitis, etc.), but ambulatory impedance-pH monitoring and high-resolution manometry have become the tests of choice to identify patients with excess of acid despite PPI therapy or those with symptoms not due to GERD or finally, those with motility disorders who can manifest the same disturbances of GERD patients.

In cases with partial response to PPIs, several clinical studies have shown that a consistent therapeutic gain can be achieved by combining PPIs with mucosal protective drugs (alginate, formulations containing hyaluronic acid and chondroitin-sulfate) or recently with a bile acid sequestrant drug. In alternative to PPIs, also the use of vonoprazan, the most studied among the antisecretory drugs blocking the K<sup>+</sup> exchange channel of the proton pump (P-CABs), has been found to increase the rate of response in patients with persistent symptoms despite taking PPIs. It must be stressed that prokinetics, which continue to be used frequently by many physicians, are devoid of any therapeutic help in the treatment of GERD, both alone and in co-prescription with PPIs.

P-CABs are interesting drugs for future use because they have shown a faster onset of action and a longer-lasting increase of intragastric pH compared with PPIs, so that they can be used in alternative to the latter ones in order to improve the healing rates of EE, particularly the most severe grades (C and D) of erosive lesions. They have been used so far mainly in Asian countries and should be more evaluated in western populations, especially in patients with NERD.

Finally, a greater attention than in the past has been paid in last years toward the use of drugs able to protect esophageal mucosa and reinforce its defensive properties, a therapeutic target that has been overlooked for long time. These drugs have been found to be not inferior to PPIs in relieving GERD symptoms and improving the quality of life of NERD patients, as either monotherapy or combined with PPIs. They seem to have opened a new avenue in the continuous search for medications able to solve the actual unmet needs of medical anti-reflux therapy.

However, the future of GERD management, particularly for challenging cases, will not rely on the development of new drugs, but on the better identification by means of the objective diagnostic tests available (impedance-pH monitoring, Bravo system and high-resolution manometry) of patients with suspected symptoms of GERD or those who do not respond satisfactorily to standard antisecretory therapy with PPIs. Last but not least is the appropriate indication for surgical therapy, which remains the only approach able to control the pathophysiological alterations leading to the development of GERD.

## Disclosure

The authors report no conflicts of interest in this work.

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