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GERD: Latest update on acid-suppressant drugs

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ABSTRACT

GERD is a very familiar diagnosis among health care providers due to its massive spread, and its symptoms can affect the quality of life for a respectable slice of its patients. Therefore, what can only be described as a logical consequence, a pursuit of a treatment that can both relieve symptoms and have minimal side effects is still ongoing to cover the large demographic affected by GERD. In the following review, analysis will be made of GERD, including possible regulatory activity, of certain drugs to the already discussed pathways involved in GERD patients.

1. Introduction

GERD is considered a common disease with the typical symptom of heartburn, which affects more than 40% of the population among U.S. residents (Eisen, 2001). This spread of the disease, in addition to its well-documented effect on patients' quality of life (Eslick and Talley, 2009), is the reason behind substantial efforts both financially and scientifically in the pursuit of relief and reduced symptoms (Scarpignato et al., 2020), supported by speculations that GERD is even more common than previously thought due to the different definitions of heartburn among different communities and that GERD may present in an atypical way (e.g., Chronic cough, Sore throat, hoarseness.etc) (Malfertheiner and Hallerbäck, 2005).

Although proton pump inhibitors are very effective at treating GERD and relieving its symptoms (Klok et al., 2003), advancements have yet to stop after the FDA recently approved the use of the potassium competitive acid blocker vonoparzan, as it has been shown to be a more prominent and efficient root for treatment (St. Onge and Phillips, 2023).

Medical treatments for GERD include antacids, Histamine-h2 receptor antagonists, Proton Pump inhibitors, potassium-competitive acid blockers, and Prokinetics. Not to forget that lifestyle modifications should always be considered the first-line treatment and that surgical options are available (Kaltenbach et al., 2006).

2. Methods and materials

We conducted a review by searching the Google Scholar, PubMed, and Directory Open access Journal databases for relevant information using keywords such as GERD, pressure, hypertension, antihestamine, antiacids, PPI's, Potassium competitive acid blockers, Prokinetics, pain, blenching, vonoparzan, GERD symptoms, to identify primary comparative studies on treatment and management options for GERD. The quality and strength levels of the results were considered and when available meta-analyses and systematic reviews, large epidemiological studies and randomized control trials represented the main source of data.

3. Results

3.1. Lifestyle modifications

Lifestyle modifications are considered the first-line treatment for GERD (Kaltenbach et al., 2006); however, there has been some controversy regarding the efficacy of these modifications and their role in symptom relief. Studies have advised that the Triggers of GERD (e.g., citrus, tomatoes, highly spiced foods, fatty foods, fried foods, and chocolate) be identified and avoided in patients (Heidarzadeh-Esfahani

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et al., 2021; Zhang et al., 2021). In regards to Tobacco smoking, the only group that demonstrated an improvement in severe GERS upon cessation was healthy individuals with a normal BMI and who used antireflux medication at least weekly (Ness-Jensen et al., 2014).

it's worth noting that GERD symptoms can be aggravated by consuming nonvegetarian food and alcohol, as can the consumption of carbonated beverages (Seremet et al., 2015). Greasy food is often associated with nonerosive reflux disease, while high fat intake has been linked to the development of Barret's esophagus (Chirila et al., 2016). Conversely, the Mediterranean diet decreases the risk of GERD (Mone et al., 2016).

Improvements in GERD and esophagitis were noted in IBS patients when a strict gluten-free diet was applied (GOMES and DANTAS, 2014).

Stress plays a major role in triggering GERD; therefore, stress management strategies are recommended to help reduce symptoms (Yuan et al., 2019).

Postprandial reflux symptoms are managed by steering away from prostration after meals, consuming food within 3 h before sleeping, and overeating. The lateral decubitus position during sleep is recommended (Kaltenbach et al., 2006; Yuan et al., 2019; Piesman et al., 2007; Albarqouni et al., 2021; Schuitenmaker et al., 2022; Gerson and Fass, 2009; Ness-Jensen et al., 2016).

Exercising and losing weight have a significant impact on reducing symptoms of GERD, especially among overweight and obese individuals (de Bortoli et al., 2016; Nilsson et al., 2004).

3.2. Antacid

Accounting for a major class of OTC drugs sold globally, antacid drugs are worth billions of dollars spent by GERD patients in search of relief of heartburn, hyperacidity, and indigestion, as well as other symptoms related to this condition (Mbatchou et al., 2017; Mandel and Brodie, 2000).

Antacids work by counterpoising excess HCL in the stomach and inhibiting pepsin (Peterson et al., 1977). They showed to not just help with symptom relief but also to boost the effect of other acid suppression drugs, such as PPIs (Higuera-de-la-Tijera, 2018). Regarding their composition, salts of magnesium, aluminum, calcium, sodium, carbon, or bismuth are the main components of antacid products, they come in powders, tablets, or liquid forms. However, most antacids are composed of a mixture of two salts (Brown et al., 2012; Aggarwal et al., 2017). The most common compositions of antacids include the following:

Calcium carbonate: calcium carbonate abates GERD symptoms via two mechanisms. After reacting with gastric HCL, the formed calcium ions induce peristalsis in the esophagus, thus moving acid back to the stomach, while carbonate anions act as a buffer for excess H+ protons from HCL, hence decreasing H+ concentrations and raising ph. calcium carbonate can cause constipation and flatulence, systemic alkalosis and hypercalcemia on long-term use, and milk-alkali syndrome when it is overdosed (Mejia and Kraft, 2009).

Sodium bicarbonate: Sodium bicarbonate is often combined with citric acid, and the combination is fast to react with water to produce a sodium citrate solution, which releases carbon dioxide. Sodium citrate can increase stomach pH rapidly by neutralizing acid. Mild gas or bloating is expected due to stomach irritation (Carr et al., 2011).

Magnesium salts: Magnesium hydroxide Magnesium carbonate Magnesium trisilicate. The main side effects of magnesium salts are dose-related diarrhea, flushing, hypotension, vasodilation, and hypermagnesemia (Green et al., 1975).

Aluminum salts: Aluminum hydroxide, aluminum carbonate, and aluminum phosphate can cause hypomagnesemia, hypophosphatemia, constipation, and anemia.

3.3. H2 blockers

Since the FDA approved the use of the imidazole derivative cimetidine (the least potent H2 blocker, which requires a dose of approximately 800 mg (Somogyi and Gugler, 1983)) for the treatment of GERD in 1977, H2 blockers became one of the most common treatment regimens for GERD, followed by ranitidine, a basic substituted furan, in 1983, which has now raised great concerns regarding its safety, as it has been linked to the carcinogenic effect of NDMA (McGwin, 2020) and was withdrawn from markets in the U.S. (Aschenbrenner, 2020). In 1986, guinidinothiazole group member Famotidine, the most potent H2 blocker requiring a dosage of 40 mg (Schunack, 1987a), appeared. There was thought to be a correlation between famotidine and clinical improvement among COVID-19 patients (Freedberg et al., 2020), but further studies affirmed no link (Sethia et al., 2020). Finally, nizatidine was introduced in 1988 and has also been linked to excess NDMA exposure (Shaik et al., 2022). These drugs (excluding nizatidine) have the advantage of being available orally, intravenously, or intramuscularly (Schunack, 1987b). They can be prescribed or taken over the counter.

H2 receptors in parietal cells are the main targets of H2 blockers, which act as antagonists of histamine and block histamine receptors, consequently inhibiting histamine stimulation in parietal cells and acid secretion.

Although PPIs demonstrate a clear advantage in treating acid related esphoageal diseases, the use of H2RAS is continuedly used as an augmentation therapy for patients who have PPI resistant Acid disorders (Pandolfino et al., 2023).

H2 blockers are well tolerated (Lewis, 1991)and have a lower risk of causing bacterial overgrowth and infections than PPIs (Untersmayr, 2015). The main side effect of these drugs, headache, is their ability to cross the blood–brain barrier, and other side effects include drowsiness, fatigue, abdominal pain, constipation, and diarrhea (Pinto-Sanchez et al., 2017). It is worth noting that there are no absolute contraindications for H2 blockers.

3.4. PPI

PPIs have been the main treatment for acid disorders since the introduction of omeprazole in 1989. Six PPIs are currently available for use (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole) (Robinson, 2005).

All PPIs are benzimidazole derivatives: heterocyclic organic molecules that include both a pyridine and benzimidazole moiety linked by a methylsulfinyl group (Orel et al., 2021; Savarino et al., 2021).

The use of tenatoprazole has undergone preliminary preclinical and clinical evaluation. With clinical use approval yet to come, this new form of PPI that has an adventitiously prolonged half-life can be superior to its benzimidazole relatives (Pati et al., 2020).

PPIs are membrane-permeable, acid-labile weak bases. With early activation and degradation by luminal gastric acid being the first problem to address in mind, a variety of delivery systems have been used to package these drugs, including enteric-coated tablets, gelatin capsules, or coated granules in powder form. packaging in combination with bicarbonate is also an option. Once clear of the stomach, PPIs are metabolized in the first parts of the small bowel. Lansoprazole, pantoprazole, and esomeprazole can be administered intravenously, which provides immediate acid suppression and is a natural fit for hospitalized patients for whom the oral route of administration is not appropriate (Sachs et al., 2006). Single-release PPIs have a short serum half-life (1–2 h), and considerable effort has been made to develop dual-release/or delayed-release formulations to counteract this shortcoming (Morelli et al., 2011; Vakily et al., 2009).

Once inside the body, proton pump inhibitors (PPIs) travel to activated gastric parietal cells, where they accumulate in acidic secretory canaliculi. When proton pump inhibitors (PPIs) enter the acidic environment of the stomach, they undergo a chemical reaction in which a chiral sulfoxide bond is cleaved due to the action of an acid catalyst. This process causes PPIs to become effective in reducing the production of

acid in the stomach. - It is important to note that some PPIs, such as esomeprazole and dexlansoprazole, do not undergo this acid-catalyzed cleavage of the chiral sulfoxide bond. This process leads to the production of active sulfenic acid and/or sulfonamide compounds, which then bind covalently to cysteine residues on the H+/K + ATPase to prevent acid secretion. This inhibition can last for up to 36 h until new pumps can be synthesized. Although PPIs are generally thought to be equally effective in terms of clinical outcomes, their distinct pharmacologic properties may differ among individuals.

Unfortunately, up to 50% of patients taking PPIs for nonerosive GERD are dissatisfied with their treatment due to unresolved symptoms (Fass et al., 2005), and among patients taking PPIs twice per day, nearly 40% increase their dosage because of persistent nocturnal symptoms (Chey et al., 2010). This leads us to define the term.

"Nocturnal acid breakthrough" for the reactivation of gastric acid secretion overnight is a frequently encountered disadvantage for single-release PPI users receiving a single morning dose (Tutuian and Castell, 2004). Note that the escalation of dosing to twice daily is often performed in accordance with both the American Gastroenterology Association (Chen et al., 2023) and the American College of Gastroenterology (Katz et al., 2022) Practice Guidelines. Despite the frequency of this intervention, breakthrough symptoms are still observed among many patients (Chey et al., 2009). Pharmacologically, in healthy individuals, an intragastric pH below 4 is still present for 15% of the day despite a dosage of 40 mg esomeprazole given twice per day (Yuan and Hunt, 2008).

The prolonged-release PPI "rabeprazole-ER" is a 50 mg capsule containing 5 separate 10 mg tablets that are absorbed at intervals throughout the small intestine and colon. Compared with esomeprazole and conventional delayed-release rabeprazole, the ER of rabeprazole has been shown to be more effective at controlling nocturnal gastric acid secretion [48]. Imidazopyridines, such as tenatoprazole, possess a serum half-life of 7–8 h and may potentially offer an added advantage in clinical settings. These compounds have the potential to enhance efficacy and assist in overcoming certain limitations. The future implications of these findings could be significant in the field, warranting further investigation. (Sachs et al., 2006), Tenatoprazole showed a superior inhibitory effect on H+/K + ATPase and a substantially longer half-life of 7–8 h (which can increase to 14 h if taken in multiple doses) (Galmiche et al., 2005; Hunt et al., 2005; Thomson et al., 2006).

When comparing PPIs several studies have pointed out that esomeprazole is favorable over other PPIs when it comes to erosive esophagitis with a healing probability rate of 98% (Li et al., 2017).

However the nearest competitor is dexlansorpazole as it is seen as the best option for controlling nuctornal breakthrough acid symptoms (Dumra et al., 2023).

Some studies suggest that there might be a genetic component in overall patient response to PPI treatment relying on differences in CYP2C19 metabolism, ofcourse genetic testing is not clinically indicated in the course of GERD treatment, however rabeprazole is considered the best choice to tackle this obstacle as it does not depend on CYP2C19 for primary metabolism.

The side effects and complications of proton pump inhibitors (Fig. 1) are related to the long-term use of PPIs for Clostridium difficile, other enteric infections, and potentially community-acquired pneumonia according to retrospective observational studies (Eom et al., 2011); however, additional investigations are needed (Filion et al., 2014). In addition, suppressing acid release and elevating pH in the gastric lumen is one of the mechanisms underlying the disruption of the innate immune system. Therefore, susceptibility to maltitude of enteric infections is increased, including small intestinal bacterial growth (Lo and Chan, 2013; Bavishi and Dupont, 2011). PPIs can rarely cause hypomagnesemia, a condition where magnesium levels drop significantly, leading to serious complications like tetany, seizures, muscle weakness, delirium, and cardiac arrhythmias (Eom et al., 2011; Mackay and Bladon, 2010; Melloni et al., 2015; McDonald et al., 2015; Cheungpasitporn et al., 2015). Discontinuing PPIs after prolonged use can lead to higher acid levels than before treatment, a phenomenon known as rebound acid secretion (Ahmed, 2023). This is due to increased gastrin levels stimulating acid production. However, there are conflicting data on the association between PPI use and osteoporosis, bone fractures, dementia, kidney disease, and heart disease. Most evidence comes from retrospective studies with potential confounding factors, and prospective studies have not consistently supported these links. Concerns about malignancy due to prolonged gastrin elevation have not been substantiated in human studies, though fundic gland polyps may increase with long-term PPI use without a link to malignancy (Ahmed, 2023).

3.5. Potassium competitive acid blockers

Developed first in the 1980s, P-CAPS showed rapid effective reversible inhibition of the proton pump (H+/K + ATPase). However, most P-CAPs, such as the imidazopyridine compound SCH28080 from the Schering-Plough Corporation and linaparzan (Sugano, 2018), which showed no superiority over esomeprazole in the management of heartburn, were not available on the market because of its correlation with hepatotoxicity, so it was discontinued. Currently, there are three P-CAPSs on the market: Revaparzan, a pyrimidine derivative;

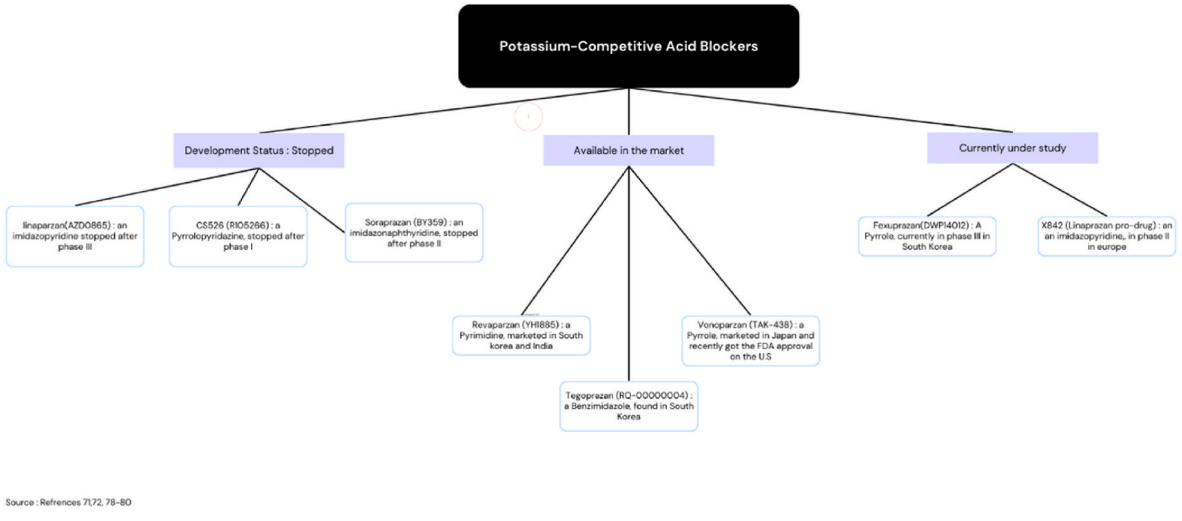

Fig. 1. Current status of different p-CABS drugs.

Vonoparzan, a pyrrole derivative; and Tegoprazan, a benzimidazole (Fig. 2).

Increasing worries and concerns about the safety profile of PPIs and the associated side effects of prolonged use have led to increased attention being given to P-CAPS as a potential dethroner of PPIs in the field of acid suppression (Moore and Vaezi, 2010; Rettura et al., 2021).

Potassium plays an essential role in the activation of the H+/K + ATPase in the apical membrane of parietal cells because it is required for its function. While resting the proton pump is confined to tubulovesicular regions of a parietal cell with low K+ concentrations and membranes that are impermeable to K+ and therefore incapable of activating and transporting H+ ions, when the parietal cell is stimulated, the tubulovesicular components merge with the cell apical membrane. After being exposed to K + -containing luminal fluid, the H+/K + -ATPase enzyme can begin to exchange H+ for K+ (Engevik et al., 2020; DuBose and Codina, 1996; Sakai et al., 2016).

Although there is a variety of classes of P-CAPS (imidazopyridine derivatives [BY841], imidazo-naphthyridine derivatives [soraprazan], imidazo-thienopyridines [SPI-447], and quinolone derivatives [SK&F96067]) (Tsukimi et al., 2000; Wurst and Hartmann, 1996; Simon et al., 2007). However, the mechanism of action remains similar. The characteristics of P-CAPS being lipophilic weak bases with limited pH stability gives them the ability to accumulate in acidic environments, such as those found in the canaliculi of parietal cells, there P-CAPS can bind ionically to the H+/K + ATPase and prevent further activation by K+.

Compared with conventional PPIs, which require 3–5 days to achieve maximal steady inhibition of acid secretion, P-CAPS are effectively absorbed and quickly accumulate in parietal cells (Andersson and Carlsson, 2005; Williams et al., 1998). For example, a single dose of Vonoparzan (20 mg) can increase the intragastric pH to nearly 7 in 4 h (Jenkins et al., 2015). Furthermore, vonoparzan has superior effects on nocturnal GERD symptoms compared with PPIs, as the mean nighttime pH above 4 after the administration of 20 mg vonoparzan on day 1 was greater than that after the administration of 20 mg esomeprazole or 10 mg rabeprazole (Oshima and Miwa, 2018).

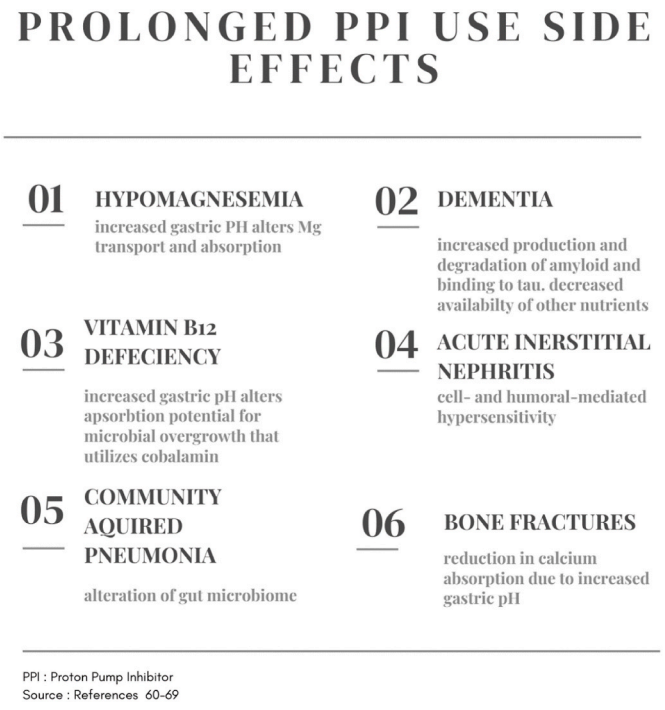

Fig. 2. illustrates the prevalent complications and adverse reactions associated with prolonged PPI usage, along with the fundamental mechanisms responsible for each complication.

The superiority of vonoprazan over conventional PPIs has extended to H.pylori treatment regimens as seen in (Chey et al., 2022) also it was found that vonprazan can even reduce treatment duration compared to PPI (1 week vs 2 weeks) (Ang et al., 2022).

That stated, the comparison between P-CABS and PPIs needs more investigation as most studies are focused in Asiatic populations, the superiority of PCABs over ppi is documented in westren studies regarding H.pylori eradication regimns, and severe esophagitis (Cheng et al., 2021), other acid related diseases require more research among western communities.(Table 1)

The safety profile of short- and moderate-term use of P-Cabs is remarkable, and shows clear superiority over PPis (Xiao et al., 2020; Mizuno et al., 2020; Akiyama et al., 2020; Ashida et al., 2016, 2018; Yamashita et al., 2017). However, long-term usage may be associated with hypergastronemia (Uemura et al., 2018) and intestinal microbiome changes (Cochet and Peri, 2017; Marcus et al., 2012).

3.6. Prokinetics

Prokinetics are not considered acid-suppressant drugs. They work differently from acid-suppressing medications like proton pump inhibitors (PPIs) or H2 blockers. They are medications that stimulate contractions and motility in the gastrointestinal (GI) tract through some mechanism such as increasing lower esophageal sphincter pressure, enhancing esophageal peristalsis, accelerating gastric emptying, and Promoting overall GI motility.

While prokinetics may be used in treating certain gastrointestinal disorders, including some cases of GERD, they are not first-line treatments but sometimes used in combination with PPIs for certain patients. However, their use is limited due to potential side effects and varying efficacy. Some examples of prokinetic agents include.

3.6.1. Acotiamide

Acotiamide works on enhancing gastric emptying (Kusunoki et al., 2012; Nakamura et al., 2017) although it is mainly a cholinesterase inhibitor, Acotiamide has been shown to improve acetylcholine release. When acotiamide was added to patients on either PPIs or p-CABs, there was no difference in overall treatment compared to the placebo group, and the major difference occurred in the field of symptom-specific response for regurgitation (Yamashita et al., 2019).

3.6.2. Bethanechol

Bethanechol is a parasympathomimetic choline carbamate that selectively stimulates muscarinic receptors and has no effect on nicotinic receptors, urinary retention, postpartum urinary retention, or overflow incontinence caused by neurogenic atony of the bladder. The use of bethanechol in the treatment of GERD has been controversial, as although significant improvement was found in patients on bethanechol in a study by (Thanik et al., 1980), later studies by (Saco et al., 1982) showed no important relief, and not using bethanechol remains the preferred option (Bor et al., 2024).

3.6.3. Domperidone

Domperidone works as a peripheral D-2 receptor antagonist, based on a meta-analysis (Maddern et al., 1986), a combination of domperidone and PPI was shown to significantly reduce GERD and its symptoms (Zamani et al., 2022).

3.6.4. Itopride

Mainly in Asia, this acetylcholine esterase inhibitor and D-2 receptor antagonist is used for dyspepsia, demonstrated in GERD symptoms and a reduction in its recurrence when added to PPIs (Ezzat et al., 2011).

3.6.5. Metoclopramide

Metoclopramide works as a dopamine D2 and muscarine receptor blocker in the gastric pathway, three studies affirmed the positive effect

Table 1
Investigations in the efficacy and safety of PCABs vs PPIs in gastric acid related diseases.

Gastric acid related disease	Study conductor	Country	Treatment used	Results
Erosive esophagitis	Lee et al. (2019) Lee et al. (2019)	South korea	Tegoprazan (100 mg) Tegoprazan (50 mg) Esomeprazole (40 mg)	Both doses of tegoprazan were non-inferior to esomeprazole 40 mg in treating EE
	Xiao et al. (2020) Xiao et al. (2020)	56 centers in China, South Korea, Taiwan, and Malaysia	Vonoprazan (20 mg) Lansoprazole (30 mg)	Vonoprazan is non-inferior in terms of EE healing when compared to Lansoprazole
Gastric ulcer	Cho et al. (2020) Cho et al. (2020)	South Korea	Tegoprazan (100 mg) Tegoprazan (50 mg) Lansoprazole (30 mg)	Both doses of Tegoprazan used were non-inferior to lansoprazole in the treatment of Gastric ulcers
	Miwa et al. (2017) Miwa et al. (2017)	Japan	Vonprazan (20 mg) Lansoprazole (30 mg)	Vonoprazan is non-inferior to lansoprazole in treating both gastric and duodenal ulcers
GERD	NCT02743949	33 centers in Belgium, Bulgaria, Czech Republic, Estonia, Poland, and the UK	Vonprazan (40 mg) Vonprazan (20 mg) Esomeprazole (40 mg)	No significant difference between both vonoprazan doses and esomeprazole in terms of 24-h heartburn free periods and >1 sustained resolution of heartburn

of metoclopramide either as a sole treatment for heartburn (McCallum et al., 1977) or as a helpful aid to the H2 blocker cimetidine (Bright-Asare and El-Bassoussi, 1980; Lieberman and Keeffe, 1986).

3.6.6. *Mosapride*

Several studies have shown that a selective serotonin receptor agonist can provide minimal help as an adjuvant therapy to PPIs (Hsu et al., 2010; Cho et al., 2013).

3.6.7. *Tegaserod*

An aminoguanidine indole, which showed prokinetic potential in animals first in 1995 (Camilleri and Atieh, 2021), reached the market in 2002 as a possible treatment of choice for irritable bowel syndrome, but then it was removed by the FDA in 2007 due to concerns regarding its cardiovascular safety, which did not hold in place, as it was reapproved in 2019 before it was finally removed from the market by the manufacturer in 2022. Mainly two studies searched On the topic of tegaserod as a possible choice for GERD treatment, (Kahrilas et al., 2000) showed a significant impact of using tegaserod on reflux events compared to placebo, however, (Tutuian et al., 2006) reported no difference (2 days of therapy).

4. Conclusion

Although there seems to be a period in which every newly developed drug, such as H2 blockers and PPIs, has been used as the main treatment for GERD, p-CABS treatment is still needed. However, the downside of these drugs is very similar due to their shared function of acid suppression; other drugs that work to protect the mucosal layer of the GI tract are available but are less effective and can be used as adjunct therapies with PPIs or p-CAPS (Nishizawa et al., 2015). Surgical intervention should always be considered in the occurrence of stumbling upon persistent unresponsive GERD due to the risk of dangerous yet rare complications, such as Barrett's esophagus and esophageal adenocarcinoma (Lee et al., 2024).

Author contribution form Author's contribution

ZAF is the first Author, contributed to conceptualization editing & reviewing, Investigation,Original draft. NM contributed to conceptualization, investigation, original draft, editing & reviewing. AE contributed to conceptualization, investigation, original draft, editing & reviewing. DAF contributed to conceptualization, investigation, original draft, editing & reviewing. SY is the corresponding author, contributed to investigation, original draft, editing, reviewing & bibliography. MH is the supervisor, contributed to editing and reviewing, validation, supervision, and resources.

All authors reviewed and accepted the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work responsed in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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