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A REVIEW OF PHARMACOLOGICAL ADVANCES IN THE MANAGEMENT OF GERD, 2015-2025

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) remains one of the most prevalent gastrointestinal disorders worldwide. Between 2015 and 2025, advances in understanding its multifactorial pathophysiology have driven significant changes in pharmacological management.

Aim: This review summarizes key developments in GERD pathophysiology and evaluates significant pharmacological advances from 2015 to 2025, including comparative safety profiles, limitations of current therapies, and emerging treatment directions.

Methods: A structured search of PubMed, Google Scholar, and major open-access databases was performed using keywords related to GERD, pathophysiology, proton pump inhibitors, P-CABs, prokinetics, neuromodulators, and novel therapies.

Results: Proton pump inhibitors remain first-line therapy but show variable efficacy in non-erosive disease and refractory symptoms. Newer agents such as potassium-competitive acid blockers, modern prokinetics, alginate-based formulations, neuromodulators, and mucosal protectants offer therapeutic benefits in selected phenotypes. Comparative analyses highlight the importance of optimizing long-term PPI use and monitoring potential adverse effects. Advances in diagnostics and improved understanding of sensory and functional mechanisms have enabled more individualized treatment strategies.

Conclusions: Pharmacological management of GERD has evolved substantially over the past decade, shifting toward mechanism-based and patient-specific therapy. Future progress will depend on integrating high-resolution diagnostics, refining reflux phenotypes, and developing novel treatments that target mucosal integrity, hypersensitivity, and non-acid reflux.

KEYWORDS

GERD, Proton Pump Inhibitors, Potassium-Competitive Acid Blockers, Prokinetics, Neuromodulators, Mucosal Protectants, Refractory GERD

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Introduction

Gastroesophageal reflux disease is a common chronic disorder characterized by bothersome symptoms and/or complications resulting from the retrograde flow of gastric contents into the esophagus [1]. Its prevalence remains high globally, making it a significant public health concern and a frequent reason for gastroenterology consultations [2]. Indeed, over 40% of the U.S. population experiences GERD symptoms, highlighting its widespread impact on public health and quality of life [3]. The continuous evolution of diagnostic methods, such as 24-hour impedance-pH monitoring and high-resolution manometry, has refined the understanding of GERD subtypes and improved patient stratification for targeted therapies [1]. Despite these advancements, a substantial proportion of patients, estimated between 30% and 40%, experience refractory GERD, necessitating ongoing research into novel pharmacological interventions beyond traditional proton pump inhibitors [4] [1]. Thus, this review examines pharmacological innovations from 2015 to 2025, encompassing novel acid suppressants, mucosal protectants, and neuromodulators that target the multifaceted pathophysiology of GERD and address the shortcomings of current therapies [1]. This will include an in-depth examination of the mechanisms of action, efficacy, safety profiles, and clinical applicability of these newer pharmacological agents, comparing them against established therapies. Furthermore, the review will consider the implications of these advancements for personalized medicine approaches, addressing the diverse clinical presentations and underlying mechanisms of GERD [1].

Methodology

This review comprehensively analyzes pharmacological developments in GERD management from 2015 to 2025, specifically focusing on innovations that address the limitations of existing treatments and offer new avenues for managing refractory cases. The methodology employed an extensive search across major medical databases, including PubMed, Google Scholar, and Directory of Open Access Journals. The search strategy incorporated the following terms: “GERD”, “prokinetics”, “H₂-receptor antagonists”, “potassium-competitive acid blockers”, “proton pump inhibitors”, “neuromodulators” and “mucosal protectants”.

Pathophysiology of GERD and Current Diagnostic Approaches

The pathophysiology of GERD is complex, involving multiple mechanisms that contribute to the retrograde flow of gastroduodenal content into the esophagus [1]. These mechanisms primarily include transient lower esophageal sphincter relaxations, hypotensive lower esophageal sphincter pressure, impaired esophageal peristalsis, and delayed gastric emptying [1]. Indeed, while the esophagogastric junction typically functions as an effective antireflux barrier, transient lower esophageal sphincter relaxations are the most frequent mechanism of reflux in both healthy individuals and GERD patients. However, in GERD patients, these relaxations are often more frequent or prolonged, leading to increased esophageal exposure to gastric content [5]. Moreover, emerging evidence suggests that the composition of the refluxate, beyond just its acidity-including bile acids and pepsin-can also contribute significantly to esophageal mucosal damage and symptom generation, further diversifying the pathophysiology of GERD [6]. Furthermore, compromised esophageal mucosal defense mechanisms and the presence of a hiatal hernia can exacerbate the severity of GERD symptoms and increase the risk of complications [6][7].

In addition to these mechanical and chemical factors, recent research emphasizes the role of visceral hypersensitivity and alterations in the gut-brain axis in the manifestation of GERD symptoms, particularly in non-erosive reflux disease, where objective evidence of mucosal injury is absent [4]. For instance, the heterogeneity in non-erosive reflux disease patients-with some exhibiting excess esophageal acid and others

demonstrating normal acid exposure but reflux hypersensitivity-underscores the need for refined diagnostic approaches to guide treatment [8]. Accordingly, current diagnostic techniques, such as esophageal pH-impedance monitoring, are crucial for distinguishing between acid-related reflux, weakly acidic reflux, and functional heartburn, thereby enabling more precise therapeutic strategies [1]. This detailed understanding of GERD's varied pathophysiological underpinnings is crucial for developing and implementing personalized management plans [4]. Moreover, identifying comorbidities and considering gut-brain axis disorders are essential components of the diagnostic workup for patients with persistent reflux symptoms [2]. Building on this, the Lyon Consensus 2.0 further refines diagnostic criteria, categorizing patients into distinct GERD phenotypes such as non-erosive reflux disease and reflux hypersensitivity, which often do not respond to conventional acid-suppressive therapies alone [9]. These phenotypic distinctions highlight the multifactorial nature of GERD, extending beyond mere acid-related mechanisms to encompass compromised mucosal defense and visceral hypersensitivity [1][10]. In turn, the heterogeneity of refluxate composition underscores the need for diagnostic modalities, such as multichannel intraluminal impedance-pH monitoring, which can differentiate between various reflux events- including acid, weak acid, and non-acid reflux-and access their association with patient symptoms [11]. Ultimately, this comprehensive diagnostic approach is vital for tailoring treatment strategies, particularly for those cases where traditional proton pump inhibitor therapy proves ineffective [12][13]. Consequently, novel diagnostic tools focusing on impedance, neuropathophysiology, and psychometrics are advancing to more precisely and practically identify GERD phenotypes, aiding in understanding the diverse underlying mechanisms of GERD [11].

Pharmacological Agents for GERD Management Proton Pump Inhibitors (PPIs)

Proton pump inhibitors remain the cornerstone of GERD treatment, effectively reducing gastric acid secretion by irreversibly binding to and inhibiting the H⁺/K⁺ ATPase pump in gastric parietal cells [14]. This mechanism renders them the most potent antisecretory drugs available, leading to their widespread adoption as first-line therapy for various acid-related disorders [1]. However, despite their efficacy, a significant proportion of patients- particularly those with non-erosive reflux disease or refractory GERD-do not achieve complete syndrome relief with PPI monotherapy [4][15]. In fact, up to 40% of GERD patients exhibit inadequate responses, a condition termed PPI-refractory GERD [1][8]; response rates are especially poor in cases of regurgitation, which persist despite potent antisecretory regimens [1]. Suboptimal outcomes often stem from patient-related factors, such as incorrect dosage or timing of PPI intake, weakly acidic or bile reflux, genetic variations in hepatic cytochrome P-450 metabolism, poor adherence, and misdiagnosis [1][2]. Beyond these, PPIs have inherent limitations-including delayed onset of action, low bioavailability, variable acid-suppressing efficacy, and incomplete control of nighttime acidity- that contribute to unmet needs in acid-related disease management and persistent symptoms even with twice-daily dosing, where intragastric pH fails to exceed 4 for ~15% of the day [3][16][17][18]. For instance, conventional PPIs require several days for maximal effect, with up to two-thirds of patients lacking sufficient relief after the initial dose, and healing rates varying from 50-94% across severities (6-15% non-response in non-erosive reflux disease; 40-50% in erosive esophagitis) [16]. This shortcomings have spurred alternative and adjunctive therapies for PPI non-responders [19], alongside research targeting non-acid mechanisms like lower esophageal sphincter dysfunction and transient LES relaxations, which are central to GERD pathogenesis [20][21]. Moreover, despite the substantial benefits of PPIs in controlling acid secretion, challenges remain in addressing the non-acidic components of reflux, such as bile and pepsin, which can independently contribute to esophageal mucosal injury and symptoms [31].

Histamine-2 Receptor Antagonists (H2RAs)

Histamine-2 receptor antagonists (H2RAs) are another class of pharmacological agents used in the management of GERD. They act by competitively inhibiting histamine binding to H₂ receptors on parietal cells, thereby reducing acid production [3]. Their development in the mid-1970s marked a significant advancement in GERD treatment, preceding the more potent PPIs [18]. Although less potent than PPIs, H2RAs are valuable for on-demand symptom relief or as adjunct therapy, particularly for nocturnal acid breakthrough in patients with partial PPI response [2][22]. However, their efficacy is limited by a short duration of action and tachyphylaxis-a rapid diminution of acid-suppressing effects with continuous use due to upregulation of histamine receptors or adaptive changes in the acid secretory pathway-which renders them unsuitable for long-term monotherapy in severe GERD [18][23]. Consequently, along with PPIs' superior acid suppression, these

limitations have shifted H2RAs' role primarily to adjunctive therapy for nocturnal symptoms, where PPIs may be less effective due to their pharmacokinetic profile [2]. This historical perspective underscores the ongoing evolution of pharmacological strategies toward more sophisticated acid suppressants, such as potassium-competitive acid blockers [18].

Potassium-Competitive Acid Blockers (P-CABs)

Potassium-competitive acid blockers represent a novel class of antisecretory drugs that reversibly inhibit the H⁺/K⁺ ATPase pump, providing an alternative mechanism to PPIs [1]. Unlike PPIs, which require activation in an acidic environment and irreversible binding, P-CABs directly and competitively bind to the potassium-binding site of the proton pump. This results in rapid, potent, and prolonged acid suppression independent of pump activity or pH [18], enabling faster and more consistent therapeutic effects—even in non-acidic conditions—and offering advantages for patients with nocturnal acid breakthrough or poor PPI metabolism [24]. From the first dose, P-CABs deliver immediate onset and sustained inhibition of gastric acid secretion, more effectively controlling both daytime and nighttime production than PPIs [1]. This enhanced profile yields superior symptom control and healing rates for erosive esophagitis, particularly in those with incomplete responses to conventional PPI therapy [14][24]. For example, P-CABs like vonoprazan maintain intragastric pH above 4 for longer periods than standard PPIs, addressing critical unmet needs in GERD management [17]. Overall, their development marks a major advance in acid-suppressive therapy by overcoming PPI limitations like delayed onset, variable bioavailability, and drug interactions through more rapid, potent, and durable suppression that accelerates symptom relief [16] [25].

Antacids and Alginates

Antacids neutralize existing gastric acid to provide rapid yet short-lived symptom relief. In contrast, alginates form a protective raft atop the gastric contents, creating a mechanical barrier that physically impedes reflux episodes. Primarily used for mild, infrequent symptoms or as adjunctive therapy for breakthrough symptoms in patients on more potent acid suppressants [26], these agents play a supportive role by alleviating acute discomfort rather than addressing the underlying pathophysiology of chronic GERD [2]. Despite their immediate effects, neither antacids nor alginates offer mucosal healing or sustained acid suppression, rendering them less suitable for long-term management of moderate-to-severe GERD [2]. Consequently, more advanced pharmacological interventions are needed to provide durable acid suppression and promote esophageal healing, particularly for patients with persistent symptoms or complications.

Prokinetic agents

Prokinetic agents aim to enhance gastrointestinal motility by increasing lower esophageal sphincter tone, accelerating gastric emptying, and improving esophageal peristalsis, thereby reducing refluxate exposure time and preventing reflux episodes [1]. Nevertheless, their clinical utility in GERD management remains limited by inconsistent efficacy, potential side effects, and the availability of more potent acid-suppressing therapies. Consequently, prokinetics are generally reserved for select patient subsets—such as those with documented delayed gastric emptying or refractory cases where motility disorders contribute to persistent symptoms—particularly when other strategies prove insufficient. Still, concerns over adverse events and limited evidence of broad benefits temper their widespread adoption. Future research into novel prokinetic mechanisms and compounds with improved efficacy and safety is essential to better address motility-related GERD [1].

Other Novel Therapeutic Targets

Persistent challenges such as nocturnal acid breakthrough and PPI nonresponsiveness highlight the need for new therapeutic targets and optimized management strategies [16]. Extending beyond traditional acid suppression, investigational approaches now focus on mechanisms such as esophageal hypersensitivity, impaired mucosal barrier integrity, and inflammatory processes [2]. For example, gamma-aminobutyric acid-B (GABA-B) receptor agonists and metabotropic glutamate receptor-5 (mGluR5) antagonists aim to reduce transient lower esophageal sphincter relaxations—the predominant mechanism of reflux episodes regardless of refluxate pH [2]. Baclofen, a GABA-B agonist, effectively decreases TLESRs and thereby reduces both acidic and weakly acidic reflux, yet its clinical use is limited by central nervous system depression and gastrointestinal intolerance, necessitating careful patient selection [1][2]. These safety concerns have driven interest in peripherally acting GABA-B agonist such as lesogaberan, designed to minimize central adverse effects while

preserving efficacy [28]. mGluR5 antagonists, including mavoglurant, represent another promising option with potentially fewer systemic side effects, although their development has been intermittently halted [2].

Additional therapeutic avenues target symptoms related to hypersensitivity and non-acid reflux. Transient receptor potential vanilloid 1 channel antagonists address esophageal hypersensitivity, a major contributor to refractory symptoms [2]. Mucosal protectants such as sucralfate and alginates show benefit in managing persistent non-acidic or weakly acidic reflux and are sometimes combined with GABA-B agonists like baclofen, despite their side-effect profiles [2][27]. Another notable example is IW-3718, a gastric-retentive bile acid sequestrant shown in phase IIb trials to improve refractory heartburn by binding intragastric bile acids [26].

Other agents under investigation include selective 5-HT₄ agonists such as prucalopride, which may reduce esophageal acid exposure and enhance gastric emptying, though further studies are needed to confirm their role in refractory GERD [2]. Neuromodulators- such as tricyclic antidepressants and selective serotonin reuptake inhibitors-also demonstrate efficacy in reducing heartburn and esophageal pain by modulating visceral perception and central pain-processing pathways, particularly in patients with esophageal hypersensitivity or functional heartburn [1][29]. This multimodal therapeutic approach underscores an evolving understanding of GERD as a complex disorder often driven by visceral hypersensitivity and altered central nervous system processing [8]. Finally, newer acid-suppressive therapies, such as potassium-competitive acid blockers, offer faster onset, more potent acid suppression, and more stable pH control compared to proton pump inhibitors, providing a valuable option for patients with refractory symptoms [24].

Comparative Efficacy of PPIs vs. P-CABs

Recent comparative studies have increasingly focused on evaluating the efficacy of potassium-competitive acid blockers compared with proton pump inhibitors, particularly in the context of persistent symptoms and difficult-to-treat gastroesophageal reflux disease, with evidence suggesting potential advantages of P-CABs, including faster onset and more consistent acid suppression [27]. For example, vonoprazan has demonstrated non-inferiority to lansoprazole in healing erosive esophagitis and superior acid suppression in initial and maintenance phases of GERD treatment [8][28]. However, evidence supporting P-CAB superiority over PPIs for non-erosive reflux disease remains limited, with some studies showing no significant difference between vonoprazan and placebo in achieving primary efficacy outcomes [29]. Nevertheless, P-CABs such as vonoprazan, tegoprazan, and fexuprazan have demonstrated non-inferiority or superiority to PPIs in both symptom relief and mucosal healing, with tegoprazan showing remarkably rapid syndrome control [30]. Specifically, tegoprazan has demonstrated a superior, more sustained acid-suppressive effect compared to esomeprazole and vonoprazan, maintaining intragastric pH above 4 for significantly longer [14]. This prolonged and potent acid suppression translates into improved healing rates for severe EE. It provides superior nocturnal acid control compared to PPIs, addressing a key limitation-and common issue of nocturnal acid breakthrough even with twice-daily dosing- that affects a significant percentage of patients [31][34]. These benefits are particularly pronounced in patients with severe EE, where P-CABs have demonstrated superior efficacy over PPIs, although the therapeutic gain in mild EE may be less significant [14][18]. Beyond their potent acid suppression, P-CABs also circumvent the pharmacokinetic limitations of PPIs, such as the requirement for acid activation and susceptibility to CYP2C19 polymorphisms, offering a more predictable and consistent therapeutic effect, particularly in populations with varied metabolic profiles [32].

Long-term Safety Concerns and Adverse Effects

While P-CABs offer enhanced efficacy, their recent introduction means long-term safety data are still emerging, with potential risks similar to PPIs, such as altered gut microbiota, enteric infections, and nutritional deficiencies [30][33]. Early trials show a favorable short-term profile with low serious adverse events [33], but continuous pharmacovigilance is needed [8]. For example, keverprazan has a high rate of serious events after 24 weeks [8], and vonoprazan raises hypergastrinemia concerns, especially in duodenal ulcer patients [34], potentially leading to enterochromaffin-like cell hyperplasia or carcinoid tumors [7][34]. P-CABs like vonoprazan are mainly metabolized by CYP3A4, reducing CYP2C19-related variability compared to PPIs [35]. Other risks include dysbiosis, infections [14][36], hyperuricemia, liver dysfunction, dizziness (e.g., with fexuprazan)[8], and higher hemorrhagic enterocolitis risk [34]. Overall adverse event rates are comparable to PPIs, though some reports suggest increased serious events [35]; causality for infections like *Clostridioides difficile*, pneumonia, or fractures remains unproven [14]. Long-term studies are essential to assess these risks [8][14][26][32][34][36].

Management of Refractory GERD

Effective management of refractory GERD, defined as persistent symptoms despite optimal PPI therapy, remains a significant clinical challenge that often necessitates alternative pharmacological strategies or surgical interventions. In this context, P-CABs have emerged as a promising therapeutic option, offering a superior acid-suppressing effect that may overcome the limitations of PPIs in a subset of these challenging patients [37]. Their potent, rapid, and sustained acid inhibition provides a rationale for their use in patients who continue to experience symptoms despite high-dose PPIs, particularly those with nocturnal acid breakthrough or partial response to PPIs [18]. Clinical trials have demonstrated that P-CABs, such as vonoprazan, fexuprazan, and tegoprazan, are non-inferior or even superior to PPIs in achieving symptom relief and mucosal healing in patients with GERD, including those with refractory forms [14][30].

Emerging Trends and Future Directions in GERD Pharmacotherapy Drug Repurposing and Novel Formulations

Promising developments include the repurposing of non-GERD drugs with acid-suppressive or mucosal-protective properties for refractory cases, alongside novel formulations such as sustained-release capsules or mucoadhesive patches. These innovations enhance stability, bioavailability, release profiles, patient compliance, and efficacy [38]. New chemical entities targeting acid secretion or hypersensitivity pathways also hold promise for personalized therapies [39].

Vonoprazan exemplifies this progress, delivering potent, sustained acid suppression with rapid onset-making it ideal for refractory GERD and nocturnal symptom control-and showing efficacy at least comparable to PPIs for symptom relief and esophagitis healing in Asian studies [16][38][40][41]. Nevertheless, robust clinical trials are needed to confirm its efficacy and safety in Western populations, where GERD manifestations may vary [1]. Vonoprazan's development highlights the potential of next-generation acid suppressants, which offer advantages over traditional PPIs, particularly for patients inadequately responsive to conventional therapy [16][42].

Despite P-CABs advantages like faster onset and more prolonged acid suppression compared to PPIs, treatment persist in 6-15% of patients with non-erosive reflux disease and 40-50% with erosive esophagitis [16]. This underscores the need for innovative strategies beyond acid suppression alone [18]. Non-acid-centric approaches-such as neuromodulators and transient receptor potential channel modulators-target visceral hypersensitivity and esophageal dysmotility underlying refractory symptoms. Biomarkers and advanced diagnostic tools for stratifying patients by pathophysiology will be crucial for personalized treatment and improved outcomes [1]. For instance, bioadhesive formulations of hyaluronic acid and chondroitin sulfate as add-on therapy to PPIs have improved symptoms and quality of life in non-erosive reflux disease by addressing additional mechanisms [2]. Beyond these, neuromodulators offer promise for patients unresponsive to acid suppression, particularly by modulating esophageal nociception and motility in functional heartburn or reflux hypersensitivity [44].

Non-Pharmacological Interventions as Adjuncts

Non-pharmacological strategies- such as dietary changes, lifestyle modifications, and behavioral therapies-serve as vital adjuncts to pharmacotherapy, enhancing treatment efficacy by targeting symptom triggers, particularly in partial responders or those seeking to minimize drug use [3]. Cognitive-behavioral approaches, including diaphragmatic breathing and hypnotherapy, effectively manage supragastric belching and functional pain [2], while herbal remedies and psychological intervention benefit patients with GERD-dyspepsia overlap, especially amid concerns over PPI side effects [43]. This holistic integration promotes personalized, sustainable care amid GERD's multifactorial pathophysiology [11][12]. By combining advanced pharmacology-such as superior P-CABs for erosive esophagitis healing-with these strategies, GERD management is evolving toward optimized, patient-tailored outcomes [1][3]. Emerging evidence increasingly recognizes neuromodulators and psychological interventions as primary options for reflux hypersensitivity and functional esophageal disorders [44]. These approaches, including diaphragmatic breathing and esophageal-directed hypnotherapy, modulate visceral perception and bolster the anti-reflux barrier by influencing lower esophageal sphincter pressure [2][26]. Moreover, these non-pharmacological interventions often address the psychological and behavioral comorbidities frequently observed in GERD patients, which can significantly contribute to symptom perception and overall quality of life [45].

Therapeutic Strategies for Extraesophageal GERD

The atypical presentations of extraesophageal GERD necessitate a distinct diagnostic and therapeutic approach, often involving a multidisciplinary team [46]. This involves rigorous investigation to differentiate reflux-related symptoms from those caused by other etiologies, often requiring specialized diagnostic modalities such as multichannel intraluminal impedance-pH monitoring to confirm acid or non-acid reflux as the causative factor. Consequently, treatment strategies often extend beyond conventional acid suppression, incorporating therapies aimed at improving esophageal clearance, reducing reflux episodes, or modulating visceral sensitivity [12][47]. For instance, the application of alginates has demonstrated efficacy in forming a protective raft barrier that physically impedes refluxate from ascending into the esophagus, thereby reducing the frequency and severity of extraesophageal symptoms [1]. Furthermore, pharmacological interventions focusing on mucosal integrity and tissue protection, such as hyaluronic acid and chondroitin sulfate, are gaining traction for their potential to alleviate irritation in the upper airways caused by refluxate, thereby mitigating extraesophageal manifestations [48]. This nuanced approach acknowledges the complex interplay between reflux and systemic symptoms, fostering more effective management strategies for conditions like chronic cough, laryngitis, and asthma exacerbated by GERD. However, despite these advances, a significant proportion of patients, particularly those with non-erosive reflux disease or refractory GERD (rGERD), do not achieve complete symptom resolution with current pharmacological approaches [8].

Conclusions

From 2015 to 2025, substantial advancements in elucidating the pathophysiology of gastroesophageal reflux disease have illuminated its multifactorial etiology, thereby endorsing a paradigm shift toward personalized, mechanism-targeted therapies. Although proton pump inhibitors persist as the cornerstone of management, emerging agents-including P-CABs, prokinetics, alginate formulations, neuromodulators, and mucosal protectants-confer targeted benefits for distinct patient phenotypes. Safety considerations underscore the necessity for prudent long-term utilization, periodic therapeutic reevaluation, and risk profile-guided regimen selection. In prospect, precision diagnostics, enhanced phenotyping, and innovative therapeutic targets promise more efficacious, individualized GERD management strategies.

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