



# **Role of Levosulpiride + Rabeprazole in the Management of GERD Associated with Functional Dyspepsia and Gastroparesis**

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## **Abstract**

Gastroesophageal reflux disease (GERD), functional dyspepsia (FD), and gastroparesis frequently coexist, sharing overlapping pathophysiological mechanisms such as impaired gastric motility, delayed gastric emptying, visceral hypersensitivity, and acid-related mucosal injury. Conventional proton pump inhibitor (PPI) monotherapy often provides suboptimal symptom relief in such overlap syndromes. The combination of rabeprazole, a potent PPI, with levosulpiride, a prokinetic and dopamine D2 receptor antagonist, offers a rational therapeutic approach by simultaneously addressing acid suppression and disordered gastrointestinal motility. This review evaluates the pharmacological basis, clinical evidence, and practical role of the levosulpiride-rabeprazole combination in the management of GERD associated with functional dyspepsia and gastroparesis.

**Keywords:** GERD, functional dyspepsia, gastroparesis, levosulpiride, rabeprazole, prokinetic therapy

## **1. Introduction**

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders worldwide and represents a major cause of impaired quality of life and healthcare utilisation [1,7,9]. It is characterised by troublesome symptoms such as heartburn, regurgitation, and chest discomfort, as well as extraoesophageal

manifestations resulting from the reflux of gastric contents into the oesophagus. In routine clinical practice, GERD rarely exists as an isolated entity. A substantial proportion of patients also experience symptoms of functional dyspepsia (FD) and, in selected populations, gastroparesis, creating a complex clinical overlap syndrome.

Functional dyspepsia is defined by chronic or recurrent upper abdominal symptoms, including postprandial fullness, early satiety, epigastric pain, and epigastric burning, in the absence of structural disease [2,3,25]. Gastroparesis, on the other hand, is characterised by delayed gastric emptying without mechanical obstruction and presents with nausea, vomiting, bloating, early satiety, and abdominal discomfort [4,5,10]. These disorders share several common pathophysiological mechanisms with GERD, such as impaired gastric accommodation, delayed gastric emptying, visceral hypersensitivity, and altered gut–brain interaction.

Proton pump inhibitors (PPIs) are the cornerstone of GERD management and are highly effective in suppressing gastric acid secretion and healing erosive esophagitis [7,9,18]. However, up to 30–40% of patients report persistent symptoms despite adequate PPI therapy [21,22]. This partial or non-response is frequently attributed to coexisting motility disorders, non-acid reflux, and functional gastrointestinal disturbances. In such patients, escalation of acid suppression alone may not provide satisfactory symptom control.

Prokinetic agents have therefore gained renewed interest as adjuncts to PPIs, particularly in patients with GERD associated with FD and gastroparesis. Levosulpiride, a selective dopamine D2 receptor antagonist with prokinetic and antiemetic properties, has demonstrated beneficial effects on gastric motility, gastric emptying, and lower esophageal sphincter (LES) tone. Rabeprazole, a newer-generation PPI, offers rapid and consistent acid suppression with relatively low interindividual variability.

The fixed-dose combination of levosulpiride and rabeprazole represents a rational therapeutic approach that targets both acid-related and motility-related components of the overlap syndrome. This review aims to comprehensively evaluate the pathophysiological basis, pharmacological rationale, clinical evidence, safety considerations, and practical role of levosulpiride plus rabeprazole in the management of GERD associated with functional dyspepsia and gastroparesis.

## **2. Pathophysiological Link Between GERD, Functional Dyspepsia, and Gastroparesis**

### **2.1 Impaired Gastric Motility**

Delayed gastric emptying is a key mechanism linking FD and gastroparesis to GERD [11,19,20]. Gastric distension increases transient LES relaxations, promoting reflux. Prolonged gastric retention also exacerbates postprandial symptoms.

### **2.2 Visceral Hypersensitivity**

Patients with FD often exhibit heightened sensitivity to gastric distension and acid exposure, leading to symptom perception disproportionate to objective findings. This explains persistent symptoms despite mucosal healing with PPIs.

### **2.3 Acid and Non-acid Reflux**

While acid reflux is central to GERD, non-acid reflux and weakly acidic reflux also contribute to symptoms, especially in PPI-refractory patients. Improving gastric motility reduces both acid and non-acid reflux episodes.

## **3. Pharmacological Profile of Rabeprazole**

Rabeprazole is a benzimidazole PPI that irreversibly inhibits the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme in gastric parietal cells, resulting in profound and sustained suppression of gastric acid secretion [8,17]. Compared with other PPIs, rabeprazole has:

- Rapid onset of action
- Less dependence on CYP2C19 metabolism
- Consistent acid suppression across different patient populations

These properties make rabeprazole particularly useful in patients with severe or persistent GERD symptoms.

## 4. Pharmacological Profile of Levosulpiride

Levosulpiride is the levo-enantiomer of sulpiride and acts primarily as a selective dopamine D2 receptor antagonist [12,16]. Its gastrointestinal effects include:

- Enhancement of acetylcholine release in the enteric nervous system
- Improved gastric and duodenal motility
- Accelerated gastric emptying
- Increased LES pressure

In addition, levosulpiride has antiemetic properties and beneficial effects on dyspeptic symptoms such as bloating, nausea, and early satiety.

## 5. Rationale for the Levosulpiride–Rabeprazole Combination

The combination therapy targets both major components of the overlap syndrome:

- **Rabeprazole** controls acid-mediated mucosal injury and heartburn.
- **Levosulpiride** corrects motility dysfunction, reduces gastric stasis, and minimizes reflux events.

This dual mechanism provides superior symptom control compared with PPI monotherapy in patients with GERD associated with FD and gastroparesis.

## 6. Clinical Evidence

### 6.1 Evidence in Functional Dyspepsia

Multiple randomised and observational studies have evaluated the role of prokinetic agents in functional dyspepsia. Meta-analyses have consistently shown that prokinetics provide superior symptom relief compared with placebo, particularly for postprandial distress syndrome. Levosulpiride has been shown to significantly improve symptoms such as early satiety, postprandial fullness, nausea, and bloating.

Its efficacy is attributed to the enhancement of gastric emptying and improved coordination of antroduodenal motility.

Clinical trials comparing levosulpiride with placebo or other prokinetics have demonstrated significant improvements in global dyspepsia scores and patient-reported outcomes. Importantly, levosulpiride has also been shown to improve gastric accommodation, a key mechanism implicated in functional dyspepsia.

### 6.2 Evidence in Gastroparesis

Gastroparesis is particularly challenging to manage, and available therapeutic options are limited. Dopamine D2 receptor antagonists have traditionally been used to enhance gastric motility and relieve symptoms. Levosulpiride has demonstrated efficacy in improving gastric emptying times and reducing symptoms such as nausea, vomiting, and early satiety. Although most data are derived from small clinical studies, the overall evidence supports its role as a useful prokinetic option, especially in mild to moderate gastroparesis.

### 6.3 Evidence in GERD and Overlap Syndromes

In patients with GERD, delayed gastric emptying and impaired esophageal clearance contribute to increased reflux episodes. Studies have shown that combining a PPI with a prokinetic agent results in better symptom control than PPI monotherapy, particularly in patients with persistent postprandial symptoms. Levosulpiride has been shown to increase LES pressure and reduce the frequency of transient LES relaxations, thereby decreasing both acid and non-acid reflux events.

Clinical studies evaluating PPI–prokinetic combinations have reported faster onset of symptom relief, greater reduction in regurgitation and bloating, and improved quality of life scores compared with PPIs alone. These benefits are most pronounced in patients with documented motility abnormalities or dyspeptic symptoms.

## 7. Safety and Tolerability

Rabeprazole is generally well tolerated, with a safety profile similar to other PPIs. Levosulpiride, at therapeutic doses, is associated with mild and reversible adverse effects such as somnolence and dizziness. Long-term or high-dose use may lead to hyperprolactinemia; therefore, appropriate patient selection and duration of therapy are important.

## 8. Place in Clinical Practice

The levosulpiride–rabeprazole combination is particularly useful in:

- GERD patients with persistent dyspeptic symptoms
- GERD associated with delayed gastric emptying or gastroparesis
- Patients inadequately controlled on PPI monotherapy

Short- to medium-term combination therapy followed by step-down to maintenance PPI therapy may be an effective strategy.

## 9. Conclusion

GERD associated with functional dyspepsia and gastroparesis represents a common yet under-recognized overlap syndrome that poses significant therapeutic challenges in routine clinical practice [1–5,26]. Acid suppression alone, although effective for mucosal healing, is often insufficient to address the full spectrum of symptoms experienced by these patients [7,9,21,22]. Disordered gastric motility, delayed gastric emptying, visceral hypersensitivity, and non-acid reflux play crucial roles in symptom persistence and treatment failure [11,14,19,20,26,27].

The combination of levosulpiride and rabeprazole offers a comprehensive and mechanistically sound therapeutic strategy for this overlap population [8,12,16,17]. Rabeprazole provides potent and consistent acid suppression, while levosulpiride addresses underlying motility disturbances by

enhancing gastric emptying, improving gastric accommodation, and increasing lower esophageal sphincter tone [8,12,16,20]. Clinical evidence supports the superiority of this combination over PPI monotherapy in selected patient populations, particularly those with prominent dyspeptic symptoms and features suggestive of gastroparesis [16,21,22,26].

When used judiciously, with appropriate patient selection and duration of therapy, the levosulpiride–rabeprazole combination can significantly improve symptom control, patient satisfaction, and quality of life [3,12,16,27]. Future well-designed randomized controlled trials are warranted to further define its role, optimal dosing strategies, and long-term safety in the management of GERD-associated overlap syndromes [9,18,25,30].

## Abbreviations

GERD – Gastroesophageal Reflux Disease  
FD – Functional Dyspepsia  
PPI – Proton Pump Inhibitor  
LES – Lower Esophageal Sphincter  
GI – Gastrointestinal  
D2 – Dopamine D2 Receptor  
RCT – Randomized Controlled Trial  
NERD – Non-Erosive Reflux Disease  
AGA – American Gastroenterological Association  
ACG – American College of Gastroenterology  
CAG – Canadian Association of Gastroenterology  
WGO – World Gastroenterology Organisation

## Conflict of Interest

The author declares no conflict of interest related to the preparation, authorship, or publication of this manuscript. No financial or personal relationships influenced the content of this review.

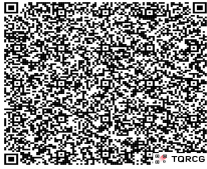
## Funding

This research received no specific grant or funding from any public, commercial, or not-for-profit organizations

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**How to cite this article:**

Hashmuk Vora, Anshuman Pandey, Vishal Seth. (2026). Role of Levosulpiride + Rabeprazole in the Management of GERD Associated with Functional Dyspepsia and Gastroparesis. *Int. J. Curr. Res. Med. Sci.* 12(6): 8-13.

DOI: <http://dx.doi.org/10.22192/ijcrms.2026.12.06.002>