REVIEW ARTICLE

# High Dose Pantoprazole for Gastroesophageal Reflux Disease: Need, Evidence, Guidelines and Our Experience

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## Abstract

Gastroesophageal reflux disease (GERD) has a pooled prevalence of 15.2% in India with varying presentation in different subset of patients. The approach towards the management of GERD includes use of monotherapy or a combination of OTCs like antacids and/or prescription drugs like H2 receptor antagonists and proton pump inhibitors (PPI). Better efficacy and safety profile of PPIs have contributed to its wide spread use as compared with other drugs for the same indication. Among PPIs, most of the healthcare professionals prefer to prescribe pantoprazole in India. Standard dose of Pantoprazole (40 mg) is unable to meet the needs in case of extraesophageal symptoms, partial responders, patients with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), or severe presentation in cases of overweight/obese patients. Multiple guidelines recommend doubling the dose of PPI in such cases. Twice daily dosing of PPI may reduce compliance. Thus, there is a need for a higher dose of Pantoprazole (80 mg) to be prescribed once daily in these cases so that improved compliance leads to better outcomes. The use of dual release Pantoprazole 80 mg may help to improve compliance and also enhance the time for which acid suppression takes place. In this review, we discuss the use of higher dose PPI based on scientific evidence and experience of clinicians for the same.

**Keywords:** Dual-drug release, Gastroesophageal reflux disease, High dose, Pantoprazole, Proton pump inhibitors.

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## Introduction

Gastrointestinal problems affect almost one-fifth of the Indian adult population (18%) with increasing prevalence with age.[1] The prevalence is even higher worldwide with almost 40% of the population reporting these problems.[2] This contributes to an enormous burden on the healthcare system and also affects the patients' quality of life. Commonest gastrointestinal complaints are indigestion, constipation, gastroesophageal reflux disease (GERD), peptic ulcer disease and piles. Out of these, GERD has a varied prevalence worldwide. In the Middle East, the prevalence ranges are from 8.7 to 33.1%. In western world, 23% in South America, 18.1–27.8% in North America and 8.8–25.9% in Europe. In East Asia, the prevalence is 2.5–7.8% and in Australia it is 11.6%.[3] A community-based study from India reported GERD prevalence to be 8.2%.[4] In an Indian meta-analysis of nine studies, 20,614 subjects were included, the prevalence of GERD in India was found to be ranging from 5 to 28.5%, with the pooled prevalence of 15.6% (95% CI, 11.046–20.714).[5] Refractory GERD was reported in almost 40% patients, which is defined as symptoms (retrosternal heartburn and/or regurgitation) present at least 3 times per week not responding to a double dose of PPIs for 8–12 weeks.[6]

The burden of GERD draws our attention to the measures required for its effective management. The GERD has a heterogeneous presentation in patients due to underlying pathophysiology but the management of this chronic disorder has always been done in a standard manner which leads to incomplete recovery.[7] Thus, there is a need to shift a more personalized approach based on patients' compliance and response to therapy.

### Gastroesophageal Reflux Disease

Definition of GERD mentioned by American College of Gastroenterology (ACG) is the condition in which reflux of gastric contents into the esophagus results into symptoms and/or complications, and objectively as the presence of characteristic mucosal injury seen at endoscopy and/or abnormal esophageal acid exposure demonstrated on a reflux monitoring study.[8] Figure 1 describes the multifactorial pathophysiology of GERD briefly.

The GERD is majorly represented by two symptoms; heartburn and regurgitation. However, the patient may present other

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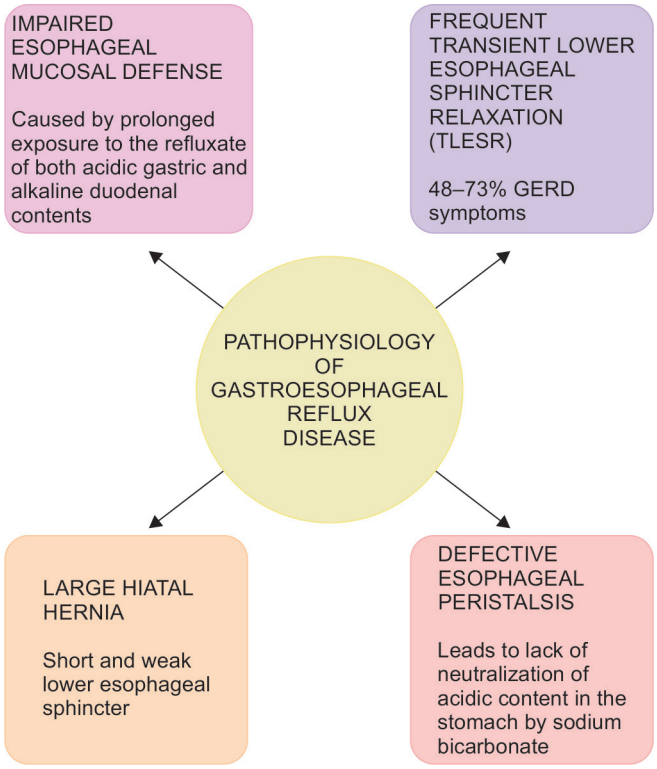


**Fig. 1:** Pathophysiology of gastroesophageal reflux disease (GERD)[9]

symptoms such as chest pain, epigastric pain, water brash, belching, dysphagia, nausea and bloating. In addition, patients may also complain about extra-esophageal symptoms like cough, throat clearing, hoarseness of voice, burning sensation or pain in throat, wheezing and sleep disturbances. The symptoms of GERD may usually be confused with other disorders leading to misdiagnosis which adds up to the overall burden of this disease. Erosive esophagitis (EE), nonerosive reflux disease (NERD), and Barrett's esophagus are the phenotypes of GERD and generally patients represent with their respective phenotype throughout their lifetime.[9,10] The risk of GERD increases with age, higher body mass index (BMI), smoking, anxiety/depression and physical inactivity. The presence of GERD is almost constant with chronic metabolic/lifestyle disorders. Apart from these, even iatrogenic factors like use of non-steroidal anti-inflammatory drugs (NSAID's), disease modifying agents for arthritis, long term steroid therapy for pulmonary and vascular causes contribute to increasing the overall risk of this disease.[11]

## Management of GERD

The initial approach to managing GERD when alarm symptoms are absent consistently involves lifestyle modifications. These modifications encompass abstaining from foods known to trigger reflux episodes (such as coffee, alcohol, carbonated drinks, chocolate, and spicy foods), achieving weight loss, quitting smoking, elevating the head while sleeping, refraining from consuming large meals, and avoiding eating right before bedtime.[12] A randomized controlled trial by Gu et al. also showed that the slight reduction in the intake of sugars improved symptoms of GERD and pH monitoring outcomes.[13]

The algorithm for the management of GERD given by the Association of Physicians of India – Indian Society of Gastroenterology is summarized in Figure 2.

Proton pump inhibitors (PPIs) have remained the cornerstone of GERD treatment because of their significant and reliable ability to suppress acid.[10] The PPIs function by irreversibly inhibiting the $H^+$–$K^+$ ATPase (proton pump) found in the gastric parietal cells. As compared with H2 receptor antagonists (H2RA), PPIs provide significantly faster healing rates (12%/week vs 6%/week) and faster and more complete relief from heartburn (11.5%/week vs 6.4%/week).[14,15] The PPIs are also able to maintain an intragastric pH of >4 for 15–21 hours daily whereas H2RAs maintain the same for only 8 hours.[16] Out of all the PPIs available in the Indian market, Pantoprazole is the most prescribed drug owing to its efficacy and least interaction with other drugs.[17] When taken orally, pantoprazole is swiftly absorbed with an absolute oral bioavailability of 77%. The presence of antacids does not affect its absorption, although food can delay it. However, neither food nor antacids alter the extent of pantoprazole absorption. Furthermore, increasing the dose results in a proportional increase in both the peak plasma concentration and the area under the plasma concentration–time curve (AUC).[18] Pantoprazole also exhibits difference in properties as compared with other PPIs. It binds only to cysteine residues 813 and 822 and these residues are believed to be specific for inhibition of acid secretion by the proton pump. It is also much slowly activated at a moderately acidic pH thus, preventing unwanted effect on other tissues or cell organelles that express proton pumps.[19]

Despite this, there are numerable causes for failure of PPI therapy including noncompliance, incorrect dose timing, rapid PPI metabolism, hypersecretory state in patients, hiatus hernia, visceral hypersensitivity and non-reflux esophageal causes like dysmotility, eosinophilic esophagitis, pill-induced esophagitis and infectious esophagitis.[20] Noncompliance or lack of adherence to PPI is frequent in GERD patients as shown by two meta-analyses, wherein adherence was found in only 55% of patients at one month and in 30% at six months of therapy. Moreover, fewer than 46% of patients experiencing persistent GERD symptoms despite prolonged PPI treatment were prescribed PPIs in the fasting state, before breakfast.[21]

The upper GI endoscopy is performed on patients not responding to PPI therapy. In cases where signs of esophagitis are seen, the patients are prescribed double dose of PPI for 8 weeks, as per the guidelines given by Indian Society of Gastroenterology and Association of Physicians in India (Fig. 2). Patients who do not respond to an 8-week course of double-dose PPI therapy, this condition is termed as refractory GERD. In such cases, impedance pH testing is conducted to gain additional insights into the underlying mechanisms of damage and to determine the subsequent treatment course.[14]

## Guideline Recommendations for Double Dose PPI

The Indian Society of Gastroenterology (ISG) and Association of Physicians of India (API) recommend two potential courses of action in cases of partial response to once-daily PPI therapy for GERD. One option is to increase the dose of the same PPI to twice daily. Alternatively, switching to another PPI that can be administered once daily is suggested.

The NICE guidelines from UK recommends 8 weeks of the standard dose of PPI for the healing reflux esophagitis. If initial treatment proves ineffective, patients may be transitioned to several alternative strategies like escalating the dose of the initial PPI to double the initial amount or patients can switch to a different PPI at a full therapeutic dose, or opt for a different PPI at a higher dose level.[22]

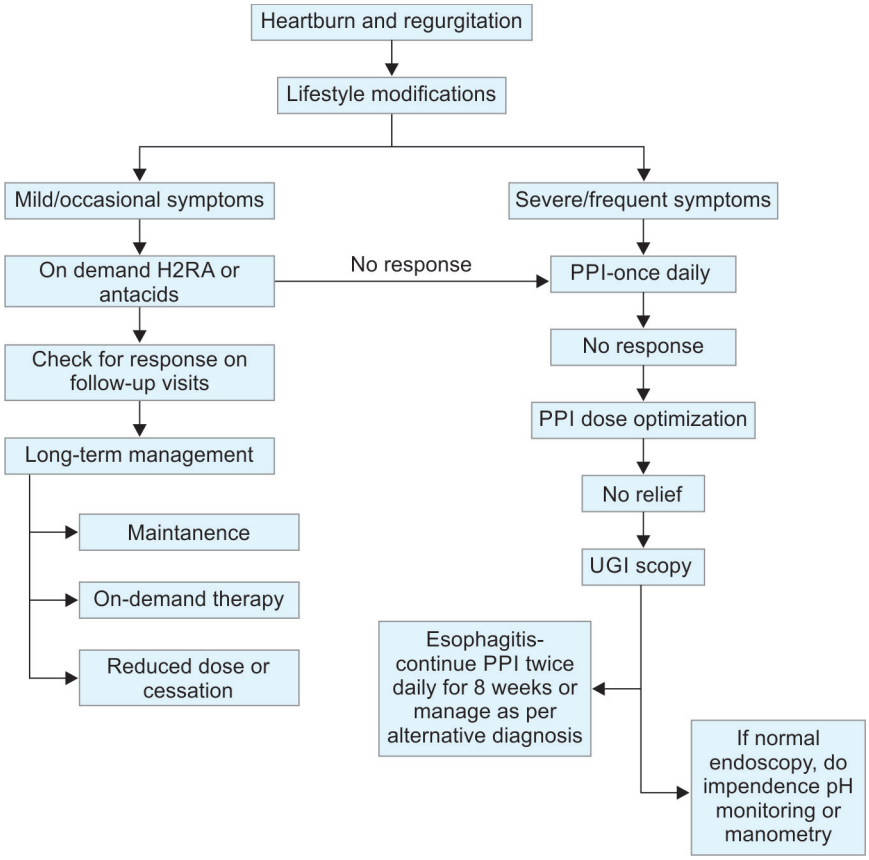


**Fig. 2:** Algorithm for management of GERD by Association of Physicians of India-Indian Society of Gastroenterology[14]

The American College of Gastroenterology Clinical guidelines for the diagnosis and management of GERD also suggest that in patients with both extra-esophageal and typical symptoms of GERD, a trial of b.d. dose of PPI should be given for 8–12 weeks. It also recommends the use of PPI over H2RA for healing as well as maintenance of healed EE.[8]

## Evidence for High-dose Pantoprazole (80 mg)

In a study investigating the response to conventional high-dose PPI therapy in patients with uncomplicated GERD and duodeno-gastro esophageal reflux (DGER), 30 patients received pantoprazole at a dosage of 80 mg/day for 6–8 weeks. Patients were having uncomplicated GERD and concurrent pathological bile and acid reflux. During the treatment period, acid reflux normalized in 93% of the patients. Additionally, the mean percentage of DGER decreased from 19.6 (±13.7) to 5.7% (±7.7, $p < 0.05$). Moreover, the median quality of life index showed improvement, rising from 4.78 (±0.86) before therapy to 8.04 (±1.84) under treatment.[23]

In overweight or obese patients with reflux esophagitis of Los Angeles Grade A and B, a total of 200 participants were evenly randomized into two groups: One group receiving pantoprazole 40 mg twice daily, and the other getting pantoprazole 40 mg in the morning and one placebo at night. On the basis of intent-to-treat (ITT) and per protocol (PP) analysis, the sustained systematic response was significantly higher in the double dose group than in the single dose group from week 4 (ITT: 62 vs 41%, $p = 0.005$; PP: 63.9 vs 42.3%, $p = 0.004$) until week 8 (ITT: 86 vs 70%, $p = 0.01$; PP: 90.5 vs 72.9%, $p = 0.01$). On the basis of PP analysis, when the absolute risk reduction of no sustained symptomatic response was calculated, it came out to be 21.6% on week 4 and 17.6% on week 8.[24]

In another study, 35 patients with hypersecretory states like Zollinger-Ellison syndrome and idiopathic hypersecretion were enrolled to three different groups such as pantoprazole 40 mg ($n = 25$), pantoprazole 80 mg ($n = 8$) and pantoprazole 120 mg ($n = 2$). At 6 months, 94% of the patients had controlled acid output. From months 12 to 36, the rate of acid output control ranged from 93 to 100%. It was concluded that maintenance oral pantoprazole therapy, administered at dosages ranging from 80 to 240 mg per day, proved effective and generally well tolerated for patients with pathological hypersecretory conditions, with treatment extending for up to 36 months.[25]

In a patient level survey conducted in Hungary, 29.4–36.9% of the inpatients used pantoprazole 80 mg per day and nearly 20% of them have been taking this drug for more than 5 years.[26]

Table 1 describes briefly the current scientific evidence available for pantoprazole 80 mg.

## Challenges in Management of GERD

The usual dose of PPI that is most frequently used in clinical practice is not able to meet the need in cases of partial responders, patients with extra-esophageal symptoms of GERD, cases with breakthrough symptoms, GERD with severe esophageal dysmotility, and in Barrett's esophagus.[20,27] Double dose of PPI is given in these patients to check for improvement in symptoms. These disorders are chronic so the patients have to take PPIs twice daily for longer periods of time. Multiple studies have shown that in such cases once daily regimen provides more benefit to the patients as there

**Table 1:** Current evidence for high-dose pantoprazole (80 mg)

| *Author* | *Population* | *Key findings* |
|---|---|---|
| Matuz et al.[26] | Patient surveys in non-gastroenterological inpatient hospital departments in Hungary to reveal characteristics of proton pump inhibitor use – dose, duration, and indication. | A total of 71.5–80% of the patients were prescribed pantoprazole for prophylaxis 29.4–36.9% of the patients used 80 mg pantoprazole per day. |
| Kunsch et al.[23] | Patients with uncomplicated GERD and DGER who were given pantoprazole 80 mg for 6–8 weeks. | Acid reflux normalized in 93% of the patients.<br>Mean percentage of DGER reduced from 19.6 to 5.7%. |
| Chen et al.[24] | Total of 200 of overweight or obese patients with reflux esophagitis (Los Angeles Grade A and B).<br>2 groups:<br>Pantoprazole 40 mg twice daily.<br>Pantoprazole 40 mg once daily and placebo. | Sustained symptomatic response was higher in the double dose group from week 4 to 8.<br>Absolute risk reduction of no sustained symptomatic response was also higher in the double dose group. |
| Metz et al.[25] | A total of 35 patients with hypersecretory states like Zollinger-Ellison syndrome and Idiopathic hypersecretion were divided into three groups receiving pantoprazole 40, 80 and 120 mg. | The rate of control of acid output ranged from 93 to 100%, from months 12 to 36.<br>Maintenance dose of 80 mg is well-tolerated in these patients. |

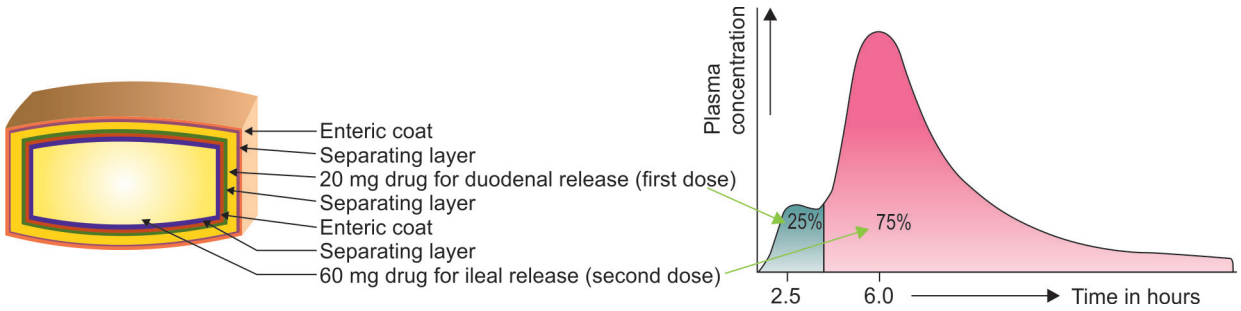


**Fig. 3:** Illustration of pantoprazole 80 mg dual release gastro-resistant tablets and its plasma profile

is improvement in compliance.[28–31] A meta-analysis conducted with the objective of studying the impact of dosing frequencies on adherence to oral therapy showed that reducing the dosage frequency from multiple dosing to single dosing may help in improving adherence of patients.[31]

The PPIs reach a peak plasma concentration in 2 hours after oral administration but due to its hepatic metabolism, the amount of drug available in the plasma for acid suppression is reduced during the late hours of the 24-hour dosing period. This can lead to recovery of acid secretion in the stomach by uninhibited, restored, or new proton pumps.[32]

All these factors show that there is a need of higher dose of PPI that can be taken once daily and produces effect for a longer duration so that its clinical efficacy is obtained by the patients along with improved compliance.

## Pantoprazole 80 mg: Dual Delayed Release Technology

To ensure that the effect of higher dose of PPI lasts for a longer duration, the formulation with pantoprazole 80 mg is modified as dual release. This technology is based on separating the drug dose into two discrete fractions – 25% dose (i.e., 20 mg) is designed to release the drug immediately after the tablets reach the proximal duodenum (at pH > 5.0), while the second dose fraction which is remaining 75% of the drug (i.e., 60 mg) is tailored to transit farther down in the distal portion of the small bowel and release the medicament (at pH > 6.5). When pantoprazole 80 mg dual-release gastro-resistant tablets are administered, they induce a dual-peak time–concentration profile, unlike the single peak observed with conventional delayed-release PPIs. This unique profile leads to a significantly prolonged plasma exposure following oral intake of pantoprazole 80 mg dual-release tablets. Consequently, this prolonged exposure potentially enables the inhibition of newly activated proton pumps that become active following the initial PPI effect (Fig. 3).

## Clinical Usage and Our Experience – Patient Subsets in Clinical Practice

In clinical practice, there is a specific set of patients who have been treated with pantoprazole 80 mg. To start with, patients who have severe symptoms of GERD and they are not getting relief on a dose of 40 mg despite 4 weeks of treatment need to be shifted to a higher dose. Patients who have been taking NSAID's for pain (in cases of polyarthralgia and arthritis) and come with symptoms of GERD also are started on a higher dose owing to the increase risk of progression of symptoms. Patients coming to the out-patient clinic with atypical symptoms of GERD apart from heartburn and waterbrash, like laryngitis, pharyngitis, non-cardiac chest pain and chronic cough need to be started on a higher dose. Overweight/obese patients also tend to report better symptomatic relief when a higher dose of PPI is given to them. Higher dose of PPI is also used in patients who show signs of esophagitis on endoscopy. A single dose of pantoprazole 80 mg has shown better compliance in patients than a twice daily dose of pantoprazole 40 mg with the latter being reserved for cases when patients report night time symptoms.

## Duration of Clinical Treatment

A higher dose of 80 mg pantoprazole is usually given for duration of 2–4 weeks. If there is a positive response in the symptoms,

**Table 2:** Indications for high-dose pantoprazole (clinical experience)

- Severe symptoms of GERD with no relief at standard dose.
- Overweight/obese patients with GERD.
- Atypical symptoms of GERD like laryngitis, chronic cough, non cardiac chest pain.
- Erosive esophagitis with signs on endoscopy.
- Polyarthralgia and arthritis patients with use of NSAID.

the dose is usually lowered down for maintenance at 40 mg pantoprazole. In case of no relief even after 8 weeks, it is labeled as refractory GERD. In such cases, further investigation like endoscopy and pH monitoring needs to be done to rule out cases of reflux esophagitis, hypersensitive esophagus, alkaline reflux, or eosinophilic esophagitis.

### Adverse Events Seen in Clinical Practice

Patients have not reported any specific unexpected adverse effect that comes with taking a higher dose of PPI for 4 weeks. Although the long-term effects of taking high doses especially on renal function has to be studied.

Therapy for GERD has to be modified based on the symptomatology and the response of the patients. It is vital to give the appropriate dose at the appropriate time to get maximum positive outcome. Table 2 summarizes the indications for which high-dose pantoprazole is being used by physicians in clinical practice.

## Conclusion

Higher dose of pantoprazole is used in patients of GERD with severe symptoms, EE, co-morbidities where NSAID is used, obesity, or in cases of atypical symptoms of GERD like laryngitis, chronic cough, and non-cardiac chest pain. It has shown positive response in terms of symptomatic relief and better quality of life. Dual release formulation of pantoprazole 80 mg ensures that the drug is present in the plasma for longer duration thus, improving the acid suppression and the patient compliance. Additional studies are warranted to comprehensively grasp the long-term impacts and potential adverse effects associated with its usage.

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