Review Article on Functional Dyspepsia: New England Journal of Medicine

Presented by Dr. Alireza Khafaf
DYSEPSIA IS A CONSTELLATION OF SYMPTOMS REFERABLE TO THE GASTRODUODENAL REGION OF THE UPPER GASTROINTESTINAL TRACT. FUNCTIONAL DYSEPSIA, A RELAPSING AND REMITTING DISORDER, IS THE MOST COMMON CAUSE OF THESE SYMPTOMS. THE CURRENT STANDARD FOR THE DIAGNOSIS OF FUNCTIONAL DYSEPSIA IS THE ROME III CRITERIA, DEVELOPED BY THE ROME III COMMITTEES, A MULTINATIONAL GROUP OF EXPERTS IN THE FIELD, FIRST CONVENED IN 1990, THAT MEETS REGULARLY TO REVIEW AND REVISE THE DIAGNOSTIC CRITERIA FOR ALL FUNCTIONAL GASTROINTESTINAL DISORDERS.

THE ROME III CRITERIA FOR FUNCTIONAL DYSEPSIA CONSIST OF A SENSATION OF PAIN OR UNCOMFORT IN THE MIDDLE OR LOWER ABDOMEN, FREQUENTLY OCCURRING AFTER EATING OR WITH BREATHE.

From the Faculty of Health, University of Newcastle, Australia (N.J.T); and Leeds Institute of Biomedical Research in Digestive and Clinical Sciences, University of Leeds, Leeds, United Kingdom. Address reprint requests to Dr. Nicholas J. Talley, Department of Medicine, the Hunter Medical Research Institute, University of Newcastle, N.S.W. 2308, Australia.
Functional dyspepsia is a constellation of symptoms referable to the gastroduodenal region of the upper gastrointestinal tract. Functional dyspepsia, a relapsing and remitting disorder is the most common cause of these symptoms.

The current standard for the diagnosis of functional dyspepsia is the Rome III criteria.

The Rome III criteria for functional dyspepsia consist of a sensation of pain or burning in the epigastrium, early satiety (inability to finish a normal-sized meal), fullness during or after a meal or a combination of these.
Symptoms must be chronic, occurring at least weekly and over a period of at least 6 months, in the absence of an organic explanation.

The global prevalence of functional dyspepsia is between 5% and 11%.

Up to 40% of persons who have functional dyspepsia consult a physician, and the condition negatively affects attendance and productivity in the workplace.
Diagnosis of Functional Dyspepsia:

Symptoms do not reliably distinguish between organic and functional forms of the disease, so the challenge for the physician evaluating a patient with dyspepsia is important. (table 1)

In most cases, the cause can be clarified by means of upper GI endoscopy, a test that generally shows that less than 10% of patients with dyspepsia have a peptic ulcer, less than 1% have gastro esophageal cancer, and more than 70% have functional dyspepsia.
Guidelines recommend that patients with dyspepsia who report so-called alarm symptoms (table 2) be referred urgently for upper gastrointestinal endoscopy; however, only a small percentage of these patients have such a cancer, which indicates that alarm symptoms have only modest predictive capability.

In populations in which the prevalence of H. pylori infection is at least 10%, non-invasive testing is recommended.

It is reasonable to use one of non-invasive testing as a first-line strategy.

Functional dyspepsia may be confused with other GI conditions outside the gastroduodenal region.
### Table 1. Possible Underlying Causes of Symptoms of Dyspepsia.

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Functional dyspepsia</td>
</tr>
<tr>
<td>Peptic ulcer disease and infection with <em>Helicobacter pylori</em></td>
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<tr>
<td>Gastroesophageal cancer</td>
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<tr>
<td>Gastroparesis</td>
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<tr>
<td>Gallstones, sphincter of Oddi dysfunction, biliary dyskinesia, or gallbladder cancer</td>
</tr>
<tr>
<td>Drugs (e.g., nonsteroidal antiinflammatory drugs, iron, calcium antagonists, angiotensin-converting–enzyme inhibitors, methylxanthines, and glucocorticoids)</td>
</tr>
<tr>
<td>Chronic pancreatitis or pancreatic cancer</td>
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<tr>
<td>Parasites (e.g., <em>Giardia lamblia</em>, strongyloides, and anisakis)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Chronic mesenteric ischemia</td>
</tr>
<tr>
<td>Crohn’s disease</td>
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<tr>
<td>Infiltrative diseases (e.g., eosinophilic gastroenteritis and sarcoidosis)</td>
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</table>

### Table 2. Alarm Symptoms of an Underlying Upper Gastrointestinal Cancer.

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Age &gt;55 yr with new-onset dyspepsia*</td>
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<tr>
<td>Evidence of overt gastrointestinal bleeding including melena or hematemesis</td>
</tr>
<tr>
<td>Dysphagia, especially if progressive, or odynophagia</td>
</tr>
<tr>
<td>Persistent vomiting</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
</tr>
<tr>
<td>Family history of gastric or esophageal cancer</td>
</tr>
<tr>
<td>Palpable abdominal or epigastric mass or abnormal adenopathy</td>
</tr>
<tr>
<td>Evidence of iron-deficiency anemia after blood testing</td>
</tr>
</tbody>
</table>

* In regions with a high background prevalence rate of gastric cancer, such as Southeast Asia, a lower age threshold should be considered.
<table>
<thead>
<tr>
<th>Alarm features in dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age older than 55 years with new-onset dyspepsia</td>
</tr>
<tr>
<td>Family history of upper gastrointestinal cancer</td>
</tr>
<tr>
<td>Unintended weight loss</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Progressive dysphagia</td>
</tr>
<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Unexplained iron deficiency anemia</td>
</tr>
<tr>
<td>Persistent vomiting</td>
</tr>
<tr>
<td>Palpable mass or lymphadenopathy</td>
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<tr>
<td>Jaundice</td>
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</table>

In the past 20 years, there has been a concerted effort to standardize the definitions of functional dyspepsia.

For the most part, this goal has been achieved by excluding from the definition of functional dyspepsia.

Common underlying mechanisms such as failure of the gastric fundus to relax properly, may account for such symptoms in patients with overlapping functional dyspepsia and heartburn.

The presence of lower gastrointestinal symptoms, such as diarrhea and constipation, increased the ability of physicians to discriminate between people with functional dyspepsia and those without it.
Functional dyspepsia

- There is also overlap between symptoms of functional dyspepsia and those of gastroparesis.

More than one in four patients with functional dyspepsia have evidence of delayed gastric emptying, and in one study 86% of the patients with gastroparesis met the criteria for functional dyspepsia.

The capacity of diagnostic tests such as gastric scintigraphy to discriminate between functional dyspepsia and gastroparesis is limited.
Functional dyspepsia

- **Classification of functional dyspepsia:**

  In the past 10 years, the terminology used to describe functional dyspepsia has changed, which describing them as having one of two newly defined syndromes, the Epigastric pain syndrome and the Post prandial distress syndrome.

  The Epigastric pain syndrome consists of intermittent pain or burning in the epigastrium, occurring at least once per week, and post prandial distress syndrome is marked by the occurrence at least several times per week of bothersome postprandial fullness.
### Diagnostic criteria for functional dyspepsia*

**One or more of:**

1. Bothersome postprandial fullness
2. Early satiation
3. Epigastric pain
4. Epigastric burning

**AND**

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

### Diagnostic criteria for postprandial distress syndrome*

**Must include one or both of the following:**

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times a week

**Supportive criteria**

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. Epigastric pain syndrome may coexist

### Diagnostic criteria for epigastric pain syndrome*

**Must include all of the following:**

1. Pain or burning localized to other abdominal or chest regions
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

**Supportive criteria**

1. The pain may be of a burning quality but without a retrosternal component
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
3. Postprandial distress syndrome may coexist
Functional dyspepsia

- These two syndromes were proposed because as many as 80% of persons with dyspepsia report that their symptoms are aggravated by the ingestion of a meal.

- The definitions were also based on factor analysis that showed the grouping of dyspeptic symptoms into three or four clusters, with the epigastric pain syndrome and the postprandial distress syndrome appearing consistently in several different studies.

Subsequent community-based cross-sectional surveys, which showed good separation between these two subgroups, support this approach.
Functional dyspepsia

• Studies in referral populations are less convincing, however, with a greater degree of overlap evident between the epigastric pain syndrome and the postprandial distress syndrome (Fig. 1).

• The rationale for assigning patients into these two syndrome subtypes in the clinic is that the classification may help guide therapy.
Figure 1. Overlap between Subcategories of Functional Dyspepsia in Community-Based and Referral Populations.

The Venn diagrams show the degree of overlap between patients with functional dyspepsia who present with the postprandial distress syndrome and those who present with the epigastric pain syndrome. A total of 114 patients with functional dyspepsia were included in a community-based study\(^\text{25}\) (Panel A), and 482 were included in a study conducted in a referral population\(^\text{7}\) (Panel B).
Functional dyspepsia

- Pathophysiological features of functional dyspepsia:

  Psychological distress, particularly anxiety, is associated with functional dyspepsia and may precede the onset of the disorder in some persons.

  Central pain processing may be abnormal in persons with functional dyspepsia.

  Genetic factors have also been implicated in functional dyspepsia, but the associations remain weak.
Functional dyspepsia

- Functional dyspepsia has conventionally been attributed to a disturbance of gastric physiologic factors, such as slow gastric emptying, failure of the gastric fundus to relax after a meal or gastric hypersensitivity with distension of the stomach.

Some patients with functional dyspepsia have none of these abnormalities.

Gastric accommodation failure is also linked to transient relaxations of the LES that occur in GERD and may, in part explain the overlap of GERD with functional dyspepsia.
Functional dyspepsia

- Duodenal hypersensitivity to acid or distention has also been reported in patients with functional dyspepsia.

Infections may cause functional dyspepsia.

The occurrence of a post infectious IBS is well established, however gastroenteritis can also lead to functional dyspepsia and symptoms of IBS.

Salmonella, Escherichia coli O157, Campylobacter jejuni, Giardia Lamblia, and Norovirus with risk factors as genetic and smoking.
It is conceivable that functional dyspepsia arises when the proximal small intestine or stomach becomes inflamed after an enteric infection, whereas the IBS may arise from involvement of the distal small intestine or colon.

If both the proximal and distal small intestine are inflamed an overlap may be likely.

Duodenal inflammation has been observed in up to 40% of patients with functional dyspepsia.

Duodenal eosinophilia has been linked to smoking and to symptoms of early satiety and pain.
In some cases mast cells that can recruit eosinophils have also been observed in functional dyspepsia, but the patient population that was studied included patients with both functional dyspepsia and the IBS.

Further evidence linking intestinal inflammation to functional dyspepsia is provided by the finding of enhanced small-bowel T lymphocytes that are positive for some Integrin and Chemokine that has been associated with a greater severity of symptoms and delayed gastric emptying.

Together these findings suggest that some patients with functional dyspepsia may have an organic mechanism for their symptoms.
Another likely infectious cause is H.pylori.

In a small subgroup of patients with functional dyspepsia the eradication of infection leads to the long-term resolution of symptoms.

Functional dyspepsia is most often a meal-induced syndrome.

Food intolerance or allergy may play direct role in functional dyspepsia, but this is poorly studied.
Functional dyspepsia

- An overarching disease model postulates that, an allergen or infection leads to antigen presentation, barrier disruption, immune activation, and a type 2 helper T-cell response in functional dyspepsia.

- This process can lead to tissue injury and symptoms, whereas in others, eosinophils may be protective and promote healing.

- An inflamed duodenum may alter gastroduodenal function and result in meal-related symptoms, if this hypothesis is correct then some patients may have a response to immune activation targeted therapy.
Figure 2. An Overarching Disease Model of Functional Dyspepsia.

In the presence of a background genetic disposition, a type 2 helper T (Th2)–cell response may be activated in the duodenum, possibly by allergens or pathogens, which cross through the gut epithelium. Resident and recruited eosinophils may be activated by eotaxin, which is expressed constitutively in the lamina propria, and act as antigen-presenting cells to Th2 lymphocytes, which in turn express interleukin-5. This process can lead to eosinophil degranulation that impinges on nerve fibers, which may then fire, inducing muscle contraction or pain. Duodenal feedback to the stomach by means of interleukin-4 and interleukin-13, also expressed by Th2 cells, may promote immunoglobulin class switching to proallergic IgE antibody expression by B cells, further recruiting eosinophils and leading to degranulation with increased epithelial permeability. The cytokines tumor necrosis factor α (TNF-α), interleukin-10, and interleukin-1β can then be released into the blood and invoke an anxiety or stress response, which in turn may lead to disordered motility and visceral hypersensitivity in the stomach and duodenum. Gut-homing T cells may also increase in number and produce excess inflammatory cytokines that could then delay gastric emptying. APC denotes antigen-presenting cell.
Functional dyspepsia

- Treatment of Functional Dyspepsia:

Placebo or Reassurance?

The rate of response to placebo in trials involving patients with functional dyspepsia is 30% to 40%.

A randomized clinical trial that compared placebo with no treatment in patients with the IBS showed a significantly greater likelihood of adequate relief of symptoms with placebo.
There have also been no randomized trials of reassurance as a treatment strategy in patients with functional dyspepsia.

H. Pylori eradication therapy

Although 5% of the cases of dyspepsia in the community are attributable to infection with H. pylori, the effect of eradication therapy on the symptoms of functional dyspepsia is modest.

Economic modelling suggests that eradication therapy is a cost-effective strategy for managing functional dyspepsia.
A trial assessing the effect of eradication therapy according to individual symptoms reported by the patient showed a significant effect on epigastric pain and burning but not on early satiety or postprandial fullness.

These data suggest that the benefit of eradication therapy may be more pronounced in patients with the epigastric pain syndrome than in others.
Acid-suppression therapy:

Despite evidence of impaired duodenal clearance of gastric acid and duodenal hypersensitivity to infused gastric acid in persons with functional dyspepsia, the efficacy of acid-suppressive drugs such as PPI or histamine H2-receptor antagonists is modest.

A Cochrane meta-analysis of 10 randomized trials of PPIs, involving 3347 patients, reported a relative risk of persistent symptoms of 0.87 (95% CI, 0.80 to 0.96) and a number needed to treat of 10.

For histamine H2-receptor antagonists, the effect was more pronounced than with PPIs (relative risk, 0.77; 95% CI, 0.65 to 0.92; number needed to treat, 7), but the quality of the trials was lower.
The majority of these trials were completed before the Rome III classification of functional dyspepsia, and subgroup analyses were therefore conducted according to the predominant symptoms reported by the patients rather than according to whether the patients had the epigastric pain syndrome or the postprandial distress syndrome.
The meta-analysis showed that PPI were effective in patients reporting reflux-like or ulcer-like functional dyspepsia.

A trial of acid suppression seems to be a worthwhile strategy in most patients with functional dyspepsia, particularly in those who have negative result on H.pylori testing or in those with positive results on H.pylori testing in whom eradication therapy has not improved symptoms.

Antacid, Bismuth, and Sucralfate are not efficacious in functional dyspepsia.
Functional dyspepsia

- **Prokinetic Agents:**
  
  Existing prokinetic agents, including cisapride, domperidone, and itopride, have all been tested in functional dyspepsia.

  Cisapride was withdrawn because of its increased adverse cardiac events, including sudden death due to a prolonged QT interval and itopride was no more effective than placebo.

  Metoclopramide is not recommended routinely because of its uncertain efficacy and side effects.
Partly as a result of the lack of efficacy of these drugs, new agents have been developed and tested in recent years.

Acotinomide is an acetylcholiesterase inhibitor that accelerates gastric emptying and enhances gastric accommodation which was demonstrated in Japanese study.

The effect of Acotinomide on individual dyspeptic symptoms was noted: significant improvement were identified in postprandial fullness, upper abdominal bloating, and early satiety but not in upper abdominal pain or discomfort, the drug has now been approved for the treatment of the postprandial distress syndrome in Japan.
Buspiron and tandospirone, which act on the 5-hydroxytryptane1-A receptor, have also been tested in functional dyspepsia.

A randomized crossover trial of buspirone in 17 patients with functional dyspepsia showed that the drug was effective in relaxing the gastric fundus and reduced bloating and postprandial fullness.

In a double-blind, placebo-controlled study involving 144 patients, the response rate after 4 weeks of treatment with tandospirone was 31.5%, as compared with 12.7% with placebo (P = 0.002).
Antidepressants have been suggested as a second-line or third-line therapy for many years, because of the potential role of the brain-gut axis and abnormal central pain processing in functional dyspepsia. In one trial, venlafaxin showed no benefit after 8 weeks of treatment, 37% vs 39%. Mirtazapine has also been assessed in 34 patients with functional dyspepsia and weight loss; significant improvements were seen in early satiety and quality of life at 8 weeks in these patients vs placebo group.
In a large North American multicenter trial, 292 patients with functional dyspepsia were assigned to amitriptyline, escitalopram, or placebo.

The rate of response after 10 weeks was 53% with amitriptyline, 38% with escitalopram, and 40% with placebo.

These data suggest that TCA such as amitriptyline, should be preferred over selective serotonin–norepinephrine reuptake inhibitors for the treatment of functional dyspepsia.
• Psychological therapy:

The use of psychological therapy in functional dyspepsia remains an understudied area and more studies will be required.

There were significant improvement in dyspepsia-related quality-of-life and symptom score at 10 weeks with psychotherapy and these effects persisted for as long as 6 months after the end of treatment, although more studies are required.

Such treatment should probably be considered for patients who have not had any improvement in their symptoms with conventional medical therapy.
Functional dyspepsia

- Complementary and Alternative Therapy:
  It is not surprising that up to 50% of patients with functional dyspepsia seek out other forms of treatment.

  In one study, nearly 50% of the patients were willing to accept a 12.7% risk of sudden death with a drug affected a 99% chance of cure, in the hope of better life.

  Some patients may find herbal supplements, such as the nine-herb combination product Iberogast, beneficial and has been observed to relax the gastric fundus.
Capsaicin, a component of red pepper, was superior to placebo in terms of the reduction in symptom scores in one small trial.

Sleep disorder is more common in patients with functional dyspepsia than in healthy controls without functional dyspepsia.
Management of functional dyspepsia:

- Attention to stress reduction and lowering of anxiety is important, and dietary advice should be provided (e.g., ingestion of small, regular, low-fat meals and avoidance of foods that precipitate symptoms, if possible).

- However, there is no evidence to support the screening of all patients with functional dyspepsia for anxiety or for treating them.
Figure 3. Recommended Treatment Algorithm for Patients with a Provisional Diagnosis of Functional Dyspepsia.

This treatment algorithm can be applied in patients who present with epigastric pain or burning, early satiety, or postprandial fullness. In the case of treatment failure, the clinician should reevaluate and reconsider the diagnosis at each step by means of further investigations, such as upper gastrointestinal endoscopy if the procedure has not been performed within the past 5 years; ultrasonography of the abdomen, particularly if the patient has severe, intermittent episodes of pain; serologic testing for celiac disease; and gastric scintigraphy or carbon-13–labeled octanoic or spirulina (Arthospira platensis) breath test to assess gastric emptying if the symptoms are severe or resistant to treatment or if the patient has vomiting and prominent weight loss. There are no data from randomized trials in support of using metoclopramide to treat patients with the postprandial distress syndrome; we suggest starting the drug at a low dose owing to the potential for cardiac and neurologic toxic effects. PPI denotes proton-pump inhibitor.
Management of refractory functional dyspepsia:

Treatment is empirical. Histamine H2-receptor antagonists may help even if PPIs have failed. The combination of acid suppression with a prokinetic agent appears to benefit some other patients.

The combination of peripheral drug therapy with psychological treatment is promising.
Functional dyspepsia

If pain is the predominant symptom despite these strategies, the physician should consider other options, although these are empirical and not evidence-based.

Approaches that may be helpful include adjusting the dose of a tricyclic antidepressant to the full antidepressant level, prescribing an antipsychotic drug such as levosulpiride, or adding anxiolytic (e.g., buspirone) to a tricyclic antidepressant.
The combination of an antidepressant with pregabalin or gabapentin is yet another option that appears to relieve pain. Opioids have no therapeutic role in the management of functional dyspepsia and should be avoided because of the risk of dependence, the frequent failure of analgesia, and possibility of the narcotic bowel syndrome.
Prognosis in functional dyspepsia:

In most patients with functional dyspepsia, the natural history is chronic and fluctuating, with periods of time when the patient is asymptomatic followed by episodes of symptom relapse.

Data from population-based studies suggest that, during extended follow-up, approximately 15 to 20% of people with functional dyspepsia have persistent symptoms and 50% have resolution of in the remaining 30 to 35% of patients symptoms will fluctuate and meet the criteria for another functional gastrointestinal disorder.

Despite the chronic nature of functional dyspepsia, there is no evidence to suggest that it is associated with decreased survival.
Figure 4. Management of functional dyspepsia

H. pylori negative functional dyspepsia (normal endoscopy) and failed and adequate trial of PPI

1. Re-evaluate the symptoms and diagnosis
2. Consider other sources of abdominal pain: pancreas, colon, biliary tract
3. Does the patient have symptoms of delayed gastric emptying?
4. Does the patient have IBS?
5. Does the patient have panic disorder or other psychological issues?

Persistent symptoms
No other cause established

Consider: Antidepressants, hypnotherapy, behavior therapy, prokinetic agents

_H. pylori_ : *Helicobacter pylori* ; PPI: proton pump inhibitor;  IBS: irritable bowel syndrome.

## Recommendations for PPI doses in the treatment of acid-related disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (adult) oral</th>
</tr>
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<tbody>
<tr>
<td><strong>Active and maintenance therapy of gastroduodenal ulcers</strong></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30 to 60 mg</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 to 40 mg</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>15 to 30 mg</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 to 40 mg</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20 to 40 mg</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg</td>
</tr>
<tr>
<td>All administered daily before breakfast</td>
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</table>

**Primary and secondary prevention of NSAID-induced ulcers**

All PPIs as above

**Treatment of erosive or nonerosive gastroesophageal reflux disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (adult) oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>30 mg daily or 30 mg twice daily</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 or 40 mg daily</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg daily or 30 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 to 40 mg daily or 20 mg twice daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg daily or 40 mg twice daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg daily or 20 mg twice daily</td>
</tr>
<tr>
<td>All administered daily before breakfast, second dose if necessary should be given before evening meal</td>
<td></td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor; NSAID: nonsteroidal antiinflammatory drug.

* As a general rule, active duodenal ulcers should be treated for four weeks and gastric ulcers for eight weeks.
* Meals should ideally contain protein to enhance parietal cell stimulation.