Chapter 1

APPROACH TO THE ADULT WITH DYSPEPSIA

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DEFINITION

Dyspepsia is derived from the Greek words “dys” and “pepse” and, in medical parlance, means “difficult digestion.” The differential diagnosis and etiology of dyspepsia are diverse. Although it affects approximately 20% of the population, it has little impact on survival(1, 2). Nonetheless, it has a substantial impact on the quality of life and increases the expense of health care (3-6)

Dyspepsia is commonly defined as pain or discomfort in the upper abdomen, and its symptoms may include epigastric pain, postprandial fullness, anorexia, early satiation, upper abdominal bloating, heartburn, regurgitation, nausea, and vomiting(7). Throughout time, dyspepsia definition has gotten increasingly detailed, concentrating on symptoms considered to originate in the gastroduodenal region as opposed to the esophagus (8, 9).

The most successful consensus classification for dyspepsia and functional dyspepsia was created by the Roma Consensus Committees. The Roma-3 Consensus Committee defined dyspepsia as the presence of symptoms originating from the gastroduodenal region; the Roma-4 Consensus Committee endorsed this restriction. The symptoms of postprandial fullness, early satiation, and epigastric discomfort or epigastric burning are accepted as being of gastroduodenal origin, whereas many additional symptoms not included in the categories of dyspepsia are acknowledged as non-specific symptoms (7, 8, 10). Twenty to twenty-five percent of patients with dyspepsia have an underlying organic disorder. 75% to 80% of people with dyspepsia had functional dyspepsia and no underlying illness, as determined by diagnostic testing (11).

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Organic Dyspepsia

There are various organic causes for dyspepsia, with peptic ulcer disease, gastroesophageal reflux, Helicobacter pylori (hp), medications (nonsteroidal anti-inflammatory agents being the most common), and gastric malignancy (Table 1).

Peptic Ulcer Disease

In patients with peptic ulcers, pain or discomfort in the upper abdomen is the most important symptom. Although ulcer-related pain is typically centered in the epigastrium, it can sometimes radiate to the upper right or left quadrants. Classic duodenal ulcer symptoms are triggered by an increase in acid secretion when the stomach is empty, whereas peptic ulcer symptoms may be triggered by meals. Peptic ulcers can also be related to epigastric fullness, early satiation, belching, nausea, vomiting, and fatty food intolerance. (12).

Table 1. Differantial Diagnosis of Dyspepsia
Diagnosis
Functional dyspepsia
Dyspepsia caused by structural or biochemical disease
Peptic ulcer disease
Helicobacter pylori gastritis
Gastroesophageal reflux disease
Billiary pain
Chronic abdominal wall pain
Gastric or esophageal cancer
Gastroparesis
Pancreatitis
Carbonhydrate malabsorption
Medications
İnfiltrative disease of the stomach (eg, Crohn ,sarcoidosis)
Metabolic Disturbances (hypercalcemia,hyperkalemi)
Hepatocellular carcinoma
İschemic bowel disease, celiac artery compression syndrome, superior mesenteric artery. syndrome
Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease
İntestinal parasites (Giardia, strongyloides)
Abdominal cancer, especially pancreatic cancer

Gastroesophageal Malignancy

Malignancy of the gastroesophageal tract is a rare cause of chronic dyspepsia. Those with hp infection, a family history of gastric cancer, gastric surgery, and those who migrated to places with a high risk of gastric cancer had an increased risk of developing the disease. Higher esophageal cancer risk is associated with male gender, excessive alcohol use, smoking, and long-term heartburn(13).

Biliary Pain

Classic biliary pain is episodic, intense pain that can spread to the back and occurs in the right upper quadrant, epigastrium, or rarely the substernum (especially the right shoulder blade). Typically, the pain is accompanied by sweating, vomiting, and nause. The pain is not similar to colic. It is neither aggravated nor increased by movement, nor is it ameliorated by bowel movements or flatus passage. The pain lasts for at least 30 minutes and typically subsides within six hours(13).

Drug-Induced

The most common drugs that induce dyspepsia without peptic ulcer are NSAIDs and COX-2 inhibitors(14). Other drugs that can cause dyspepsia are listed in Table 2.

Other Disease

Rarely, chronic pancreatitis and celiac disease can occur with only dyspeptic symptoms. Other uncommon causes of dyspepsia include stomach infiltrative diseases (e.g., eosinophilic gastroenteritis, sarcoidosis, amyloidosis, Crohn's disease, and lymphoma(15-17), diabetic radiculopathy, hepatoma, steatohepatitis, metabolic disturbances (e.g., hypercalcemia, hypercalemia), superior mesenteric artery syndrome, intestinal angina, and wall pain (18). Other diseases are shown in Table -1.

Table 2. Medications Cause of Dyspepsia
Oral antibiotic particularly ampicillin and erytromycin
Nonsteroidal antiinflamatory drugs and glucocorticoids
Potassium supplement,digitalis, iron, theophyline
Niacin, gemfibrozil,narcotics,colchicine, quinidine,estrogens,levodopa

Initial Evaluation

History, physical examination, and laboratory evaluation are the initial steps in assessing a patient with newly developed dyspeptic symptoms. The initial evaluation aims to determine the presence of gastroesophageal cancer, which will direct the diagnostic strategy (Table-3)(13).

History

A comprehensive medical history is necessary for determining the underlying cause and identifying patients with alarm symptoms. When pyrosis and heartburn are the predominant symptoms, gastroesophageal reflux is primarily suspected, but functional dyspepsia may also be present(19, 20).

Aspirin and other NSAIDs increase the risk of dyspepsia and peptic ulcer disease associated with NSAID use. Significant dysphagia, odynophagia, weight loss, anorexia, vomiting, anemia, and a family history of gastrointestinal cancers are suggestive of gastroesophageal cancer (13).

The development of severe epigastric or right upper quadrant abdominal discomfort that lasts at least 30 minutes and is frequently accompanied by nausea or vomiting is diagnostic of symptomatic cholelithiasis (21). With persistent upper abdominal pain, nausea and vomiting, with or without weight loss, increase the likelihood of gastroparesis, particularly in patients with risk factors.

However, gastroparesis and functional dyspepsia share similar symptoms and pathophysiology (22). An analysis of patients in multicenter gastroparesis studies revealed that gastroparesis and functional dyspepsia symptoms overlap significantly (23).

Physical Examination

The physical examination of dyspepsia patients is generally normal, with the exception of epigastric pain. The presence of epigastric tenderness cannot distinguish between pathological and functional dyspepsia. It is essential to evaluate Cornett's sign during a physical examination to determine whether abdominal pain comes from the abdominal wall. After ascertaining where the pain is felt most prominently during the abdominal examination, the worsening of discomfort by the patient's contraction of abdominal muscles typically indicates a condition that causes abdominal wall pain. The lack of change in pain, however, suggests visceral pain.

The physical examination may also reveal abdominal mass, lymphadenopathy, jaundice, pallor, and ascites. Due to weight loss, patients with an underlying cancer may exhibit subcutaneous fat loss, muscular wasting, and peripheral edema.

Laboratory Tests

Blood chemistry and blood counts, including liver function tests, serum lipase, and amylase, should be performed routinely to identify patients with dyspepsia-causing alarm features and underlying metabolic diseases (e.g., diabetes, hypercalcemia, hyperkalemia)

DIAGNOSTIC STRATEGIES AND INITIAL MANAGEMENT

The diagnostic evaluation of a patient with dyspepsia is guided by the patient's clinical presentation, age, and the presence or absence of alarm symptoms (Table 3). The ideal age cutoff for endoscopic examination of dyspepsia patients is controversial. Guidelines also recommend that the minimum age for endoscopic assessment may vary from country to country based on the incidence of gastric cancer. The algorithm describes a method for evaluating a patient with dyspepsia (Figure-1) (24).

According to the Canadian Association of Gastroenterology (CAG) and the American College of Gastroenterology (ACG) guidelines, it may be permissible to offer endoscopy to all newly diagnosed dyspeptic patients at the age of 60 or 65. In addition, a cutoff age of 45 or 50 years may be more appropriate in populations with a high prevalence of gastric cancer among young people(24).

British Society of Gastroenterology guidelines suggest that if no additional upper gastrointestinal alarm symptoms or signs are revealed, urgent endoscopy is only required in patients aged 55 years with dyspepsia with weight loss or those aged >40 years from a zone with an elevated risk of gastric cancer or with a family history of gastroesophageal cancer(25). A European consensus statement recommends endoscopy for persons over 45 with chronic dyspepsia (26). Due to symptoms, age, family history, ethnic background, nationality, and regional incidence of gastric cancer, the diagnostic evaluation of a patient with dyspepsia must be individualized, as demonstrated by these recommendations

Evaluation of dyspepsia in adults 60 years of age should include upper endoscopy (24). To rule out H. pylori, gastric biopsies should be obtained. In addition to treatment for the underlying diagnosis, H. pylori eradication therapy should be administered to patients with the infection (eg, peptic ulcer disease). And after treatment H. pylori, eradication should be evaluated.

The majority of individuals with a normal upper endoscopy and normal laboratory tests suffer from functional dyspepsia. On occasion, further evaluation may be required based on the symptoms.

H. pylori should be diagnosed and treated in patients aged 60, and selective upper endoscopy should be performed.

Endoscopy is performed on younger than 60-year-old patients who exhibit one of the following typical:

- Clinically serious weight loss (>5 percent normal body weight lost over 6 to 12 months).
- Gastrointestinal hemorrhage.
- >1 additional alarm characteristic (Table-3)

Within two to four weeks, upper endoscopy should be performed on patients with alarm symptoms. To rule out H. pylori, stomach biopsies should be performed, and individuals with evidence of infection should get eradication treatment.

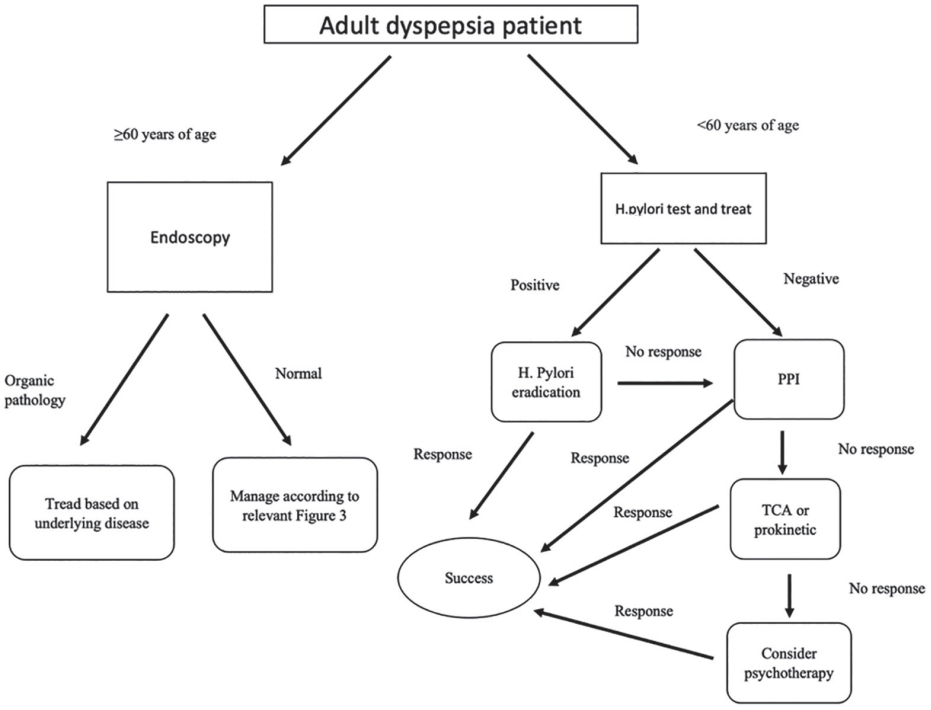

Figure 1. Approach to Patient with Uninvestigated Dyspepsi

Table 3. Alarm Features in Dyspepsia
Undetermined weight lose,
Dysphagia, odynophagia, persistent vomiting
Palpable mass or lymphadenopathy
Unexplained iron deficiency anemia
Family History of upper gastrointestinale cancer

Test and Treat for Helicobacter Pylori

In patients whose upper endoscopy is not biopsied or do not require upper endoscopy, the h.pylori test should be performed with tests showing active infection. The tests showing active infection are the urea breath test and stool antigen assay. Due to its low positive predictive value, serologic testing should be avoided (27).

Patients who test positive for Helicobacter pylori should undergo eradication therapy. Patients with H. pylori positivity who receive effective antibiotic treatment for their dyspepsia typically continue to experience persistent dyspepsia even after the antibiotics have cleared up the infection. Nonetheless, research has shown that one-seventh of patients treated with antibiotics experience improvement in dyspeptic symptoms. Patients with H. pylori infection who were experiencing dyspepsia were randomly assigned to receive either eradication therapy or a placebo, and the results of the meta-analysis showed that the patients who received eradication therapy had a significant improvement in their symptoms(28).

Antisecretory Therapy

Antisecretory therapy with proton pump inhibitors(PPIs) may relieve dyspepsia symptoms (13). However, the meta-analysis of six randomized controlled trials has shown that dyspepsia symptoms in the PPI group were lower than in the control group (24). Some studies illustrated that PPIs are more effective at relieving dyspepsia symptoms than H2 receptor antagonists (H2RA)(29). İn addition, studies have shown that a twice-daily PPI is not more efficient than a once-daily PPI at relaxing dyspeptic symptoms (30).

Tricyclic Antidepressants

Patients who test negative for H. pylori or sustain symptomatic after its eradication and have insufficient response to a PPI can be thought for treatment with a tricyclic medication (Figure-1).

Prokinetics

Evaluations of prokinetic therapy for undiagnosed dyspepsia are limited. Prokinetics may cause side effects; however, they should be administered at the lowest effective dose consistent with country-specific safety guidelines(24).

FUNCTIONAL DYSPEPSIA

Functional dyspepsia is presented with a clinical history of epigastric pain, epigastric burning or postprandial fullness, early satiety. Diagnosis of functional dyspepsia occurs by administering symptom-based diagnostic criteria and excluding organic/structural disease to explain the symptoms. Symptom-based criteria have been recommended to standardize the diagnosis of functional dyspepsia. Roma -4 criteria was occurred to standardize functional dyspepsia diagnosis (Figure-2)(31).

The onset of symptoms is required 6 months before diagnosis and symptoms should be active within the past 3 months. Two subtypes of functional dyspepsia are defined based on the predominant symptoms.

Postprandial distress syndrome is characterized by unsettling early satiety and/or postprandial fullness (Figure-2). Epigastric pain syndrome is characterized by bothersome, postprandial epigastric burning or pain. (Figure-2).

Epidemiology and Pathophysiology

The prevalence of functional dyspepsia odds from 5 to 11 percent worldwide (1, 32). The pathophysiology of functional dyspepsia is unexplained completely.

Gastric Emptying, Accommodation, and Vagal Function

Various motility disorders have been linked to functional dyspepsia. Abdominal vagal dysfunction, gastric dysrhythmias, and mild delays in gastric emptying are all included in this category, as are hypomotility, abnormal duodenal motility, impaired gastric accommodation in response to a meal, and gastric dysrhythmias (33, 34). However, these results vary from patient to patient.

Diagnostic criteria for functional dyspepsia

One or more of the following:

- ► Bothersome epigastric pain.
- ► Bothersome epigastric burning.
- ► Bothersome postprandial fullness.
- ► Bothersome early satiation.
- ► Symptom onset at least 6 months prior to diagnosis.
- ► Symptoms should be active within the past 3 months.
- ► And, no evidence of structural disease (including at upper endoscopy) likely to explain the symptoms.

Diagnostic criteria for epigastric pain syndrome (EPS)

Must include *one* or *both* of the following symptoms at least 1 day a week.

1. Bothersome epigastric pain (ie, severe enough to impact on usual activities).
2. Bothersome epigastric burning (ie, severe enough to impact on usual activities).

Supportive criteria:

1. Pain may be induced by ingestion of a meal, relieved by ingestion of meal or may occur while fasting.
2. Postprandial epigastric bloating, belching and nausea can also be present.
3. Persistent vomiting likely suggests another disorder;.
4. Heartburn is not a dyspeptic symptom, but may often coexist.
5. The pain does not fulfil biliary pain criteria.
6. Symptoms that are relieved by evacuation of faeces or gas generally should not be considered as part of dyspepsia.
7. Other digestive symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with the EPS.

Diagnostic criteria for postprandial distress syndrome (PDS)

Must include one or both of the following symptoms at least 3 days a week:

1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities).
2. Bothersome early satiation (ie, severe enough to prevent finishing a regular sized meal).

Supportive criteria:

1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present.
2. Vomiting warrants consideration of another disorder.
3. Heartburn is not a dyspeptic symptom, but may often coexist.
4. Symptoms that are relieved by evacuation of faeces or gas should generally not be considered as part of dyspepsia.
5. Other individual digestive symptoms or groups of symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with PDS.

Figure 2. Diagnostic criteria of functional dyspepsia

Visceral Hypersensitivity:

Both mechanical and chemical hypersensitivity have been demonstrated in subtypes of fasted patients with FD(35-37). After eating, the hypersensitivity of the stomach to balloon distension increases (38) and causes symptoms such as postprandial pain, fullness, belching, and bloating((33, 38, 39).

Chemical sensitivity has been shown in some patients due to exposure to endogenous and exogenous acids (40-42). It has been shown that excessive duodenal acid exposure worsens dyspeptic symptoms, especially nausea, by decreasing duodenal acid clearance and duodenal motility(40, 41). Studies showed that due to duodenal dysmotility, certain patients experience dyspeptic symptoms despite having normal gastric acid secretion(43, 44). It has been shown that duodenal acid infusion inhibits gastric accommodation and increases visceral sensitivity as a cause of gastric distension (45).

There are studies showing that duodenal lipid infusion (45), but not carbohydrates and proteins (46, 47) rises visceral sensitivity to gastric distension. This effect is reduced by antagonism of the cholecystokinin -A receptor (45).

Although some studies have shown that capsaicin in red pepper increases the feeling of pain, warmth and nausea in the stomach, it has been shown that this symptom is more common especially in patients with functional dyspepsia(48). Transient receptor potential cation channel subfamily V member 1 (TRPV1) substance causes increased visceral sensitivity by increasing the release of neurotransmitters likewise P and calcitonin gene-related peptide(49). Recent studies have shown that TRPV1 receptors are increased in patients with functional dyspepsia (50), and may be activated by prostaglandin, acid, inflammatory mediators, mechanical stimulation, nerve growth factors, and harmful temperatures(51).

Helicobacter Pylori Infection

Uncertainty persists regarding the involvement of H. pylori infection in the development of functional dyspepsia. In addition, only a minority of individuals with functional dyspepsia see symptom improvement after H. pylori eradication therapy(52).

The Microbiome

There is growing evidence that gastric, esophageal, and duodenal dysbiosis are associated with FD, and that similar alterations in the microbiome may contribute to abnormal visceral sensitivity and motility via alterations in neuronal activity, immunity, and mucosal integrity(53-56).

The Hypothalamic-Pituitary-Adrenal (HPA) Axis and Stress

Mentally stressed patients with functional gastrointestinal issues may have increased amygdala activity and dysregulation of the HPA axis (57).

Acute stress increases intestinal permeability and salivary cortisol levels in healthy people (58). In patients with functional dyspepsia, particularly those with the epigastric pain subtype, functional abnormalities in areas that process afferent signals were detected using magnetic resonance imaging(59).

Duodenal Inflammation and Immune Activation

Raised mast cells, eosinophils, and changed lymphocyte populations containing "gut-homing" lymphocytes have been declared in the duodenum of patients with functional dyspepsia(60-64).

Functional and structural variation in duodenal submucosal ganglia between patients with functional dyspepsia and volunteers have also been defined(65). The proton pump inhibitor pantoprazole decreased duodenal mast cells, eosinophils, mucosal permeability, and symptoms in patients with functional dyspepsia (66). These findings showed that luminal variables, including acid and bile acids, triggered low-grade inflammation that compromises mucosal integrity, leading to aberrant gastrointestinal neuroregulation and symptoms (67).

Psychology

Although depression and anxiety are associated with functional dyspepsia, it has not been fully proven(68). Stress can activate corticotropin-releasing hormone (CRH) from the hypothalamic-pituitary-adrenal axis. CRH activation stimulates local inflammation that affects microbiota, intestinal function, immune function and epithelial permeability(69). Anxiety has been shown to be associated with dudodenal eosinophilia in patients with functional dyspepsia. Stress causes the release of corticotropin-releasing hormone and P substance from eosinophils, but it also increases epithelial permeability by activating mast cells(70). This peripheral may alter afferent signaling to the brain, so enhancing bidirectional interaction between the gut and brain and maybe the neuroplasticity of the brain.

Genetics

The role of familial and genetic predisposition in functional dyspepsia is controversial. The findings of the studies are uncertain(71, 72).

Management of Functional Dyspesia

The management of patients with functional dyspepsia is controversial and relieves symptoms in only a small group of patients.

Initial Approach

Patients with functional dyspepsia should be tested and treated for Helicobacter pylori. Treat patients with functional dyspepsia who test negative for H. pylori with a proton pump inhibitor (PPI). Also, patients with persistent symptoms four weeks after eradication of H. pylori should be treated with proton pompa inhibitors (Figure-3). H. pylori eradication can heal dyspeptic symptoms by varying acid secretion or variety of intestinal microbiota(73, 74).

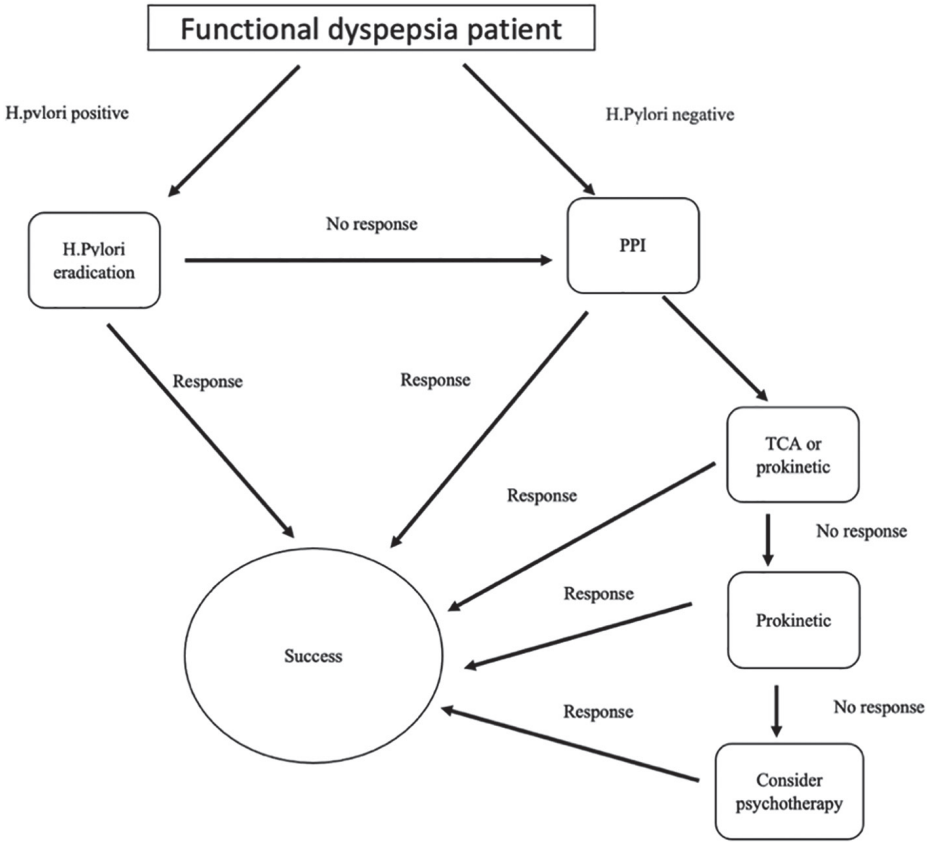

Figure 3. Algorithm for the treatment of functional dyspepsia

Proton Pump Inhibitors

For effective therapy of FD, use proton pump inhibitors (PPIs). In functional dyspepsia, PPI medications are administered for 4-8 weeks. If symptoms do not improve during this time, the PPI therapy should be discontinued. To minimize the long-term risk of treatment, patients with functional dyspepsia who respond to PPI therapy should discontinue PPI therapy every 6-12 months. The lowest effective dose should be administered. This medication is well tolerated(25)

H2-Receptor Antagonists

Antagonists of the histamine-2 receptor can be an effective therapy for FD. These medications are tolerated well (25)

Antidepressants

If patients with functional dyspepsia don't feel better after eight weeks of proton pump inhibitor treatment, we can begin a TCA trial. In cases where a PPI has only had a moderate effect, a TCA can be added to the treatment plan. Patients who don't feel better while taking a PPI should switch to a TCA (25).

Starting out, we use a low dose of TCA (eg, amitriptyline 10 mg or desipramine 25 mg at night). As needed, the dosage can be increased every two weeks. Many patients only need a dose of 20–30 mg, and we rarely give more than 75 mg to anyone. There is no benefit to taking a higher dose, and doing so may cause unpleasant side effects, such as drowsiness during the day and other anticholinergic symptoms. If the TCA is not working after 8–12 weeks, we usually stop giving it. If the patient improves while taking the drug, we typically keep them on it for six months before thinking about tapering them off. If dyspepsia returns, treatment with TCA can be restarted.

Antipsychotics such as sulpiride (100 mg, four times a day) or levosulpiride may be used as second-line treatment options for FD (25 mg, three times daily). Patients should be informed thoroughly of the benefits and risks of their use (25).

When it comes to treating global symptoms associated with FD, there is no evidence to support the use of SSRIs as gut-brain neuromodulators as a second-line treatment (25).

Second-line SNRIs as gut-brain neuromodulators for global symptoms of FD have not been shown to be effective(25).

A 10-milligram dose of tandospirone three times daily may be an effective second-line treatment for FD, but the same cannot be said for other 5-hydroxytryptamine-1A agonists, including buspirone. The need for additional drug trials cannot be overstated(25).

Although there are studies suggesting 25 mg of pregabalin once a day, randomized controlled studies are needed on this subject. (25).

İn addition, there are insufficient data for the use of mirtazapine 15 mg once a day in FD patients with early satiety and weight loss, randomized controlled studies are needed on this subject(25).

Procinetics

For patients in whom other treatments have been unsuccessful, the use of prokinetics is indicated (for example, metoclopramide 5 to 10 mg three times daily one-half hour before meals and at night for four weeks). The use of prokinetics for longer than four weeks is not recommended(25).

And therefore, medications that improve the motility of the gastroduodenal junction and the capacity of the fundus of the stomach to adapt to the contents of a meal could be a potentially useful treatment. However, there are no randomized controlled studies with prokinetic drugs such as domperidone and metoclopramide in FD, and therefore their efficacy in treatment is controversial. There are safety concerns with these drugs due to extrapyramidal and cardiac side effects (25).

Gut–Brain Behavioural Therapies in FD

Interpersonal psychodynamically informed psychotherapy can be an effective treatment for global symptoms associated with FD(25).Cognitive–behavioural therapy (CBT) and metacognitive therapy may be an appropriate cure for global FD symptoms (25).

Global symptoms of FD may be successfully treated with stress management techniques (25). Hypnotherapy may be a treatment option for FD's global symptoms (25).

Diet

There is inadequate evidence to suggest dietary therapie(25)

Additional Evaluation of Persistent Symptoms

Those patients with functional dyspepsia who continue to experience dyspepsia symptoms can undergo additional testing to determine an alternative diagnosis. In select patients with refractory functional dyspepsia who have persistent nausea and vomiting or risk factors for delayed gastric emptying, we conduct a gastric emptying study to assess for gastroparesis (eg, diabetes mellitus). Importantly, however, there is a significant overlap between dyspepsia and gastroparesis(75, 76), and treatment aimed at accelerating delayed gastric emptying may not alleviate symptoms in these patients.

Conclusion

Most patients with FD are seen and cared for in primary care settings, but it is a complex, multifactorial disease with a high prevalence in the community and one of the most common situations seen in the internal medicine outpatient clinic. Therefore, it is crucial for patients, society, and healthcare systems to have an effective method for managing and diagnosing FD.

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