# Functional Dyspepsia….An Update.

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## Introduction

Dyspepsia is a common symptom with an extensive differential diagnosis and a heterogeneous pathophysiology (1). A systematic review (2) reported that ~20% of the population has symptoms of dyspepsia globally. Dyspepsia is more common in women, smokers, and those taking non-steroidal anti-inflammatory drugs (2). Patients with dyspepsia have a normal life expectancy (3), however, symptoms negatively impact on quality of life (4, 5) and there is a significant economic impact to the health service and society (6). Approximately 25 percent of patients with dyspepsia have an underlying organic cause. However, up to 75 percent of patients have functional (idiopathic or non-ulcer) dyspepsia with no underlying cause on diagnostic evaluation (7- 9).

**Definitions**

The Rome committee has developed iterative definitions of dyspepsia that have become more specific culminating in Rome IV (10). These definitions have attempted to minimize the inclusion of gastro-esophageal reflux disease in those with dyspepsia by excluding patients with heartburn and acid regurgitation (11). Rome definitions have been helpful in better-standardizing patients that are included in studies of dyspepsia but are less relevant to clinical practice as there is considerable overlap in symptom presentation (12) making classification difficult in many patients presenting in primary and secondary care.

Rome IV criteria define FD as one or more of the following four symptoms during the last 3 months with onset at least the 6 months before diagnosis (10): (i) Bothersome postprandial fullness, (ii) bothersome early satiety, (iii) bothersome epigastric pain and (iv) bothersome epigastric burning, and no evidence of structural disease (Esophagogastroduodenoscopy) to explain the symptoms. The Rome IV criteria labels patients with bothersome (i.e. severe enough to affect usual activities) epigastric pain and/or burning at least once/ week as epigastric pain syndrome (EPS), while those with bothersome postprandial fullness, and/or early satiety at least 3 days/week as postprandial distress syndrome (PDS).

**Epidemiology and Pathophysiology**

The prevalence of functional dyspepsia ranges from 5 to 11 percent worldwide (2). The pathophysiology of functional dyspepsia is not well understood. However, several potential mechanisms have been suggested. These mechanisms may differ between subtypes of functional dyspepsia (postprandial distress syndrome and epigastric pain syndrome) (13).

Gastric motility and compliance – Functional dyspepsia has been associated with several motility disorders. These include mild delays in gastric emptying, rapid gastric emptying, antral hypomotility, gastric

dysrhythmias, and impaired gastric accommodation in response to a meal (13-16). However, these findings are noted in only a subset of patients with dyspepsia. As examples, delayed gastric emptying and antral hypomotility are found in approximately 25 to 35 percent of patients with dyspepsia while up to 10 percent of patients with dyspepsia have rapid gastric emptying (8, 17-19).

Visceral hypersensitivity – Visceral hypersensitivity is characterized by a lowered threshold for induction of pain in the presence of normal gastric compliance. Several studies have demonstrated visceral hypersensitivity in patients with functional dyspepsia that occurs independently of delayed gastric emptying (20-23). Both mechanoreceptor dysfunction and aberrant processing of afferent input in the spinal cord or brain may play a role in the pathophysiology of visceral hypersensitivity (24, 25).

**Diagnosis and differential diagnosis**

The diagnosis of FD is based on clinical assessment and exclusion of organic disease. Thus, before the diagnosis of FD is made, laboratory tests and upper GI endoscopy with biopsies are normally performed to exclude infection (in particular, H. pylori), peptic ulceration, celiac disease, and neoplasia (10). Physiological investigations are normally not required at this stage (10).

Gastro-oesophageal reflux disease (GERD) is a potential cause of "dyspeptic symptoms" that is highly prevalent in the community. GERD is present when the reflux of stomach contents causes symptoms or mucosal disease (or both) and is characterized by the presence of heartburn and regurgitation. Formally, if heartburn is present, then this excludes the diagnosis of FD in the Rome IV classification (26). However, studies show that reflux and dyspeptic symptoms co-exist in up to 40% of cases, which is much more often than expected by chance (27–29). This overlap between GERD and FD is not surprising given the immediate proximity and shared innervation of the oesophagus and proximal stomach.

IBS is a frequent functional disorder with a prevalence of about 10% in the general population. Rome IV defines the condition in terms of the presence of chronic recurrence of pain in association with defecation and/or an altered bowel habit in terms of either stool frequency or stool consistency (30). An important overlap is present between FD and IBS with both occurring in 30% and 60% of patients, respectively (31). Overlap may be more common in patients with severe symptoms than in patients with mild symptoms and in PDS than in EPS, especially in patients with postprandial fullness (31,32,33). Moreover, longitudinal studies demonstrate that the risk of a patient with FD developing IBS is increased by up to eightfold compared with the general population (34). Indeed, the pathophysiological mechanisms shared by PDS and IBS are very similar and include anxiety, altered motility, and visceral hypersensitivity. Low-grade inflammation with activation of the innate mucosal immune system and increased mucosal permeability has also been documented in both conditions (35).

**Management**

The management of patients with FD should start with reassurance and education about the possible pathophysiological and risk factors associated with FD appropriate for the

PDS or EPS subgroup or both (10). Lifestyle and dietary recommendations may be helpful (10, 36).

The next step recommended by the Rome committee is to exclude iatrogenic causes of dyspeptic symptoms and to recognize and treat overlapping disease. Identification of H. pylori infection is appropriate, as prospective trials indicate that eradication therapy is curative in approximately 1 in 10 infected patients (10). If the patient is not infected, then an empirical trial of acid suppression is justified to suppress symptoms related to an atypical presentation with GERD (10).

Pharmacological treatments for FD that are more effective than placebo in randomized controlled trials and are available in the market are limited (10, 36).These include acid suppression (PPIs), H2 receptor antagonists (H2RAs), prokinetics, herbal preparations, and antidepressants (10, 36). Dietary interventions and medications that modulate digestive function may be more likely to be effective in PDS patients in whom abnormal gastric function is present (10). Conversely, pain modulators and, if appropriate, antidepressants may be most appropriate in EPS (10).

**Acid and reflux suppression**

A just-published Cochrane systematic review has concluded that PPIs are effective for the treatment of FD, independent of the dose and duration of treatment compared with placebo. PPIs may be slightly more effective than H2RAs for the treatment of FD, even if the evidence is scarce (37). A recent randomized, placebo-controlled trial with an alginate-antacid preparation that controls both acid and non-acid reflux has also shown a significant benefit not only in typical reflux but also in dyspeptic (epigastric pain) symptoms (38, 39).

**Prokinetics**

Historical studies with cisapride, a mixed 5-HT4 agonist and 5-HT3 antagonist with procholinergic effects, indicate that selected prokinetics can be more effective than placebo in treating FD (36). Unfortunately, this medication is now restricted in most countries because of increased risk of tachyarrhythmia in patients with heart disease (36). Only limited data are present for the dopamine-2 antagonists, domperidone and metoclopramide although they are prescribed extensively (36). One phase IIb randomized, placebo-controlled study reported that itopride, a dopamine D2 antagonist and acetyl cholinesterase inhibitor, is effective in FD, in particular for the management of pain and fullness (36). However, two subsequent phase III trials were negative (36). More recent data have demonstrated that acotiamide at a dose of 100 mg three times daily was efficacious and safe in the treatment of PDS (40–42). The drug has been commercially available in Japan since 2013, and trials in Europe and the USA are in progress (40). Interestingly, a higher percentage of patients with PDS have been reported to respond to the treatments with acotiamide. It may be that this is related to effects on gastric motility and gastric emptying documented in animal models (40). Data have also recently appeared about the possible effect of prucalopride, a 5-HT4 agonist licensed in Europe and Canada for the treatment of refractory constipation, in treating FD. This drug increases oesophageal and gastric motility in healthy subjects (43), and

recent data, still in abstract form, have also reported a benefit in treating symptoms of patients with FD and gastroparesis (44). Iberogast (STW5), a nine-herb combination, has been shown in studies to relax the gastric fundus, promote gastric emptying, and reduce visceral sensitivity through multiple putative mechanisms (10). Some clinical data also support its use, and it is a popular over-the-counter remedy for FD in several European countries. However, a recent report of severe hepatotoxicity leading to liver transplantation potentially associated with the use of Iberogast suggests some caution in prescribing this medication (45). Finally, rikkunshito, another herbal medicine, which is thought to accelerate gastric emptying, has been shown to improve symptoms of epigastric pain and postprandial fullness in patients with FD in a randomized clinical trial (46).

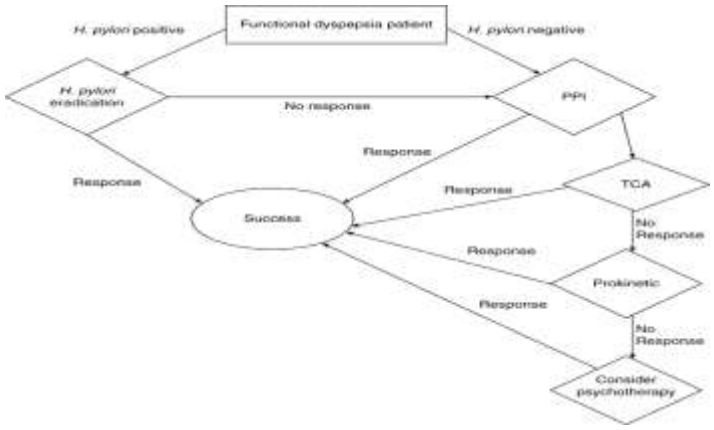
**Centrally acting drugs**

A substantial body of work supports the use of low-dose antidepressants in the management of FD and other functional GI disorders and chronic pain syndromes (47). Talley et al. (48), recently conducted an important randomized controlled trial that compared the effects of two classes of antidepressant in FD: (i) the tricyclic amitriptyline (50 mg) and (ii) the selective serotonin reuptake inhibitor (SSRI), escitalopram (10 mg). A large number (n = 292) of patients with Rome II dysmotility-like (similar to PDS) or ulcer-like (similar to EPS) FD were studied. Solid gastric emptying was documented by gastric scintigraphy, and the maximally tolerated ingestion of liquid nutrient was documented to estimate gastric accommodation and sensation (48). Significant treatment effects were observed over 12 weeks. Amitriptyline, but not escitalopram, appeared to benefit patients with FD, particularly those with ulcer-like FD (EPS-like) (48). Importantly, the trial by Talley et al. found that, although adverse events were commonly reported, there was no difference in side effects among the placebo, amitriptyline, and escitalopram, except in neurological symptoms with the SSRI (48). These findings support the use of amitriptyline in FD patients without delayed gastric emptying.

**Psychological and other interventions**

Controlled trials suggest clinical benefit of psychological interventions from several, small randomized controlled studies (49); however, the quality of evidence is still suboptimal. A recent systematic review concluded that acupuncture therapy achieves a statistically significant effect for FD in comparison with sham acupuncture and is superior to medication (prokinetic agents) in improving the symptoms and quality of life of patients with FD (50). Nonetheless, despite stringent methodological analyses, there is still need for additional randomized controlled studies of higher quality (50).

**Figure 1;** Algorithm for the treatment of functional dyspepsia (51).




**Abbreviations**

CHS, cannabinoid hyperemesis syndrome; CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; EPS, epigastric pain syndrome; ERD, erosive reflux disease; FD, functional dyspepsia; FH, functional heartburn; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome; PPI, proton pump inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor inhibitor.

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