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## Subtypes of functional dyspepsia

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### Abstract

Functional dyspepsia is a common clinical condition characterised by chronic or recurrent upper abdominal pain or discomfort commonly associated with a variety of associated gastrointestinal symptoms and a normal endoscopy. To standardise research-based approaches, an initial categorisation of into sub groups was agreed to, based on clusters of symptoms. However the early expectation that these subgroups would be associated with distinct pathophysiologies amenable to specific therapy has not been realised. A classification based on the most troublesome symptom has been suggested but the utility of this is also unclear. More recent data suggest that some of the pathophysiologic dysfunctions may be associated with specific symptoms and so provide a better tool for grouping patients. But this approach remains incomplete as current insights into the pathogenesis are still too limited for this to be satisfactory. In conclusion, no classification provides for an adequate treatment-based approach to the syndrome of functional dyspepsia. As a consequence treatment remains largely empiric.

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**Key words:** Functional dyspepsia; Classification; Subtypes; Symptoms; Pathophysiology; Management

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### INTRODUCTION

Dyspepsia is broadly defined by predominantly midline pain or discomfort located in the upper abdomen<sup>[1]</sup>.

Although the term often implies a relationship with food ingestion and majority of patients have symptoms worsened by food<sup>[2]</sup> this is no longer essential. Dyspeptic symptoms occur commonly in the general community<sup>[3]</sup> and constitute one of the most frequent reasons for referral to gastroenterologists<sup>[4]</sup>. Surveys suggest as many as 15%-20% of the population in Western countries experience dyspepsia over the course of one year<sup>[5]</sup>. During investigation of dyspepsia, three major structural causes are readily identifiable: peptic ulcer disease (10%), gastroesophageal reflux (20%)(with or without oesophagitis), and malignancy (2%)<sup>[6]</sup>. It is apparent that most (50%-70%) patients with chronic dyspepsia do not have a significant focal or structural lesion found at endoscopy. When symptoms are chronic or recurrent, but without an identifiable structural cause using standard diagnostic tests (usually endoscopy), the condition is usually labelled functional (or non-ulcer) dyspepsia<sup>[7]</sup>. Hence functional dyspepsia is a diagnosis of exclusion that implies that symptoms have been investigated without the demonstration of an organic or anatomical cause.

### INITIAL APPROACHES TO CLASSIFICATION INTO SUBTYPES

To standardise research studies amongst this heterogenous population of patients, a definition of functional dyspepsia was developed by consensus amongst a group of international experts. In addition to describing the nature of reported symptoms a temporal component of persistent or recurrent for 4 wk in a 3 mo period was included<sup>[11]</sup>. This was subsequently modified to include more than 12 wk in one year<sup>[8]</sup>. As many patients with a final diagnosis of functional dyspepsia presented with symptoms suggestive of specific diseases initial efforts to subcategorise the syndrome, proposed subdividing dyspepsia into symptom-based subgroups namely reflux-like, ulcer-like, dysmotility like and non-specified<sup>[11]</sup>. The underlying expectation was that such subgroups would share common pathophysiology and might also respond to specific therapy. However, as is typical of a chronic condition, the manifestations of dyspepsia can be complex. Patients with upper abdominal discomfort frequently complain of a multiple of related symptoms. (Table 1)<sup>[9]</sup>. Indeed population-based studies indicate that patients presenting with uninvestigated dyspepsia, have at least three dyspepsia symptoms; more than 80% have at least six and approximately half have eight or more<sup>[10]</sup>.

Table 1 Definitions of dyspeptic symptoms

Symptom	Description
Pain centred in the upper abdomen	A subjective unpleasant, patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome A subjective unpleasant without being interpreted as pain.
Discomfort centred in the upper abdomen	A subjective unpleasant sensation that is not interpreted as pain, which may include any of the symptoms below.
Early satiety	A feeling the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal.
Fullness	An unpleasant sensation of the persistence of food in the stomach (may or may not occur post prandially).
Bloating in the upper abdomen	A tightness in the upper abdomen, this should be distinguished from true abdominal distension.
Nausea	A feeling of the need to vomit.
Retching	Heaving as if to vomit but no gastric contents are forced up.

Furthermore, symptoms often vary over time. The initial classifications were expanded to include cluster analysis of these associated symptoms.

With further intensive investigation, it has become apparent that dividing patients with uninvestigated dyspepsia empirically according to clusters of symptoms has not assisted in identifying specific gastrointestinal mechanisms for different symptom types<sup>[11]</sup>. This may well reflect the extensive overlap of symptoms within the empirically derived groupings<sup>[12]</sup> the frequent association with irritable bowel syndrome<sup>[13]</sup> and the temporal variation in symptoms<sup>[9, 12, 13]</sup>. It also became apparent that the symptom sub classification was a poor predictor of underlying structural abnormality.<sup>[14]</sup>

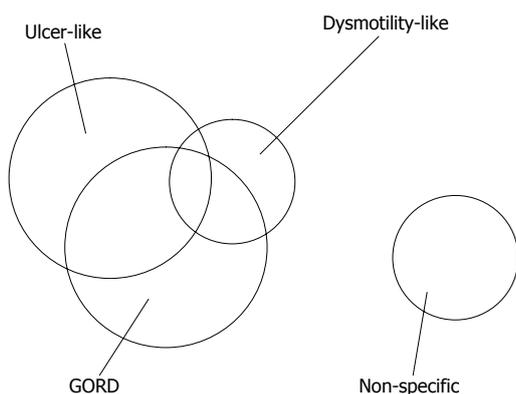
## SUB-TYPES IN FUNCTIONAL DYSPESIA POST ROME II (TABLE 2)

Concerns about the lack of progress in understanding the syndrome and the overlap between various symptom clusters resulted in a refinement of these in a subsequent consensus agreement<sup>[8]</sup>. In particular the inclusion of patients with predominant symptoms of GORD was considered unwarranted as this entity should be distinguished in its own right. Thus the ROME II assessment of Functional Gastrointestinal Disorders recognised three subtypes of functional dyspepsia<sup>[8]</sup>. (1) Ulcer-like: Characterised by predominantly epigastric pain or discomfort which may worsen with hunger and improve with food or antacids. As with ulcer disease, symptoms may remit and relapse spontaneously. (2) Dysmotility-like: Contained clinical features suggestive of disturbed upper gastrointestinal motility. Thus upper abdominal discomfort aggravated by food commonly associated with nausea, vomiting, bloating and upper satiety together. Anorexia also occurred in part because of the consequences of food ingestion was also a feature and often associated with significant weight loss. (3) Unspecified: Patients with symptoms which did not fit either of the categories above.

Table 2 Categorisation of Adult Functional Gastroenterological disorders as per Rome II<sup>[11]</sup>

A: Oesophageal disorders
Globus
Rumination syndrome
Functional chest pain of presumed oesophageal origin
Functional heartburn
Functional dysphagia
Unexplained functional oesophageal disorder
B: Gastroduodenal disorders
Functional dyspepsia
Ulcer-like dyspepsia
Dysmotility-like dyspepsia
Unspecified (non-specific dyspepsia)
Aerophagia
Functional vomiting
C: Bowel Disorders
Irritable bowel syndrome
Functional abdominal bloating
Functional constipation
Functional diarrhoea
Unspecified functional disorder
D: Functional abdominal pain
Functional abdominal pain syndrome
Unspecified abdominal pain syndrome
E: Biliary Disorders
Gall bladder dysfunction
Sphincter of Oddi dysfunction
F: Anorectal disorders
Functional faecal incontinence
Functional ano-rectal pain
Levator ani syndrome
Proctalgia fugax
Pelvic floor dyssynergia

As noted previously, patients with functional dyspepsia often do not fit neatly into symptom cluster classifications, in part because of the wide overlap of symptoms<sup>[13]</sup>. The attempts to subgroup patients using the Rome II modification has also not been particularly helpful in either clinical practice or research studies<sup>[11]</sup>. In addition the substantial overlap between dyspeptic groups, those with GORD and other functional gastrointestinal disorders has limited the utility of this approach (Figure 1)<sup>[15]</sup> although it has been suggested that functional dyspepsia can usually be separated from symptoms related to the lower gut (ie Irritable Bowel Syndrome) by the presence of bowel disturbance despite the fact that many patients had both dyspepsia and IBS<sup>[16]</sup>. In the light of the extensive symptom overlap and poor discriminatory value in individual patients, the value of the cluster-based symptom classification has been questioned and possibly replaced by a subcategorisation based on the most troublesome symptom. The value of this approach remains unproven<sup>[17]</sup>. Notwithstanding these restrictions, some recent data suggest that symptom clusters based around specific pathophysiologic disturbances may provide insights into the mechanisms of the functional dyspepsia<sup>[2]</sup>. These appear to have predictive value and could possibly direct approaches to the development of novel strategies.



**Figure 1** Schema of overlap of dyspepsia subtypes (according to Rome II) and gastro-oesophageal reflux disease<sup>[15]</sup>.

### **GORD and functional dyspepsia**

It has become obvious that it is important to discriminate between symptoms related to GORD and functional dyspepsia. A sensation of retrosternal or epigastric burning that characteristically radiates towards the throat, is precipitated by meals or the supine posture and is relieved at least temporarily by antacids, is strongly suggestive of GORD<sup>[15]</sup>. Frequent heartburn increases the likelihood of GORD as the cause of symptoms<sup>[6]</sup> although pyrosis may be much less obvious in the older patient<sup>[18]</sup>. It is likely that the majority of dyspeptic patients with predominantly reflux symptoms have GORD, although only 50% of these patients have oesophagitis at endoscopy. As noted above, the revised criteria in ROME II did not include reflux-like dyspepsia as a sub-grouping of functional dyspepsia, and patients with heartburn as their major symptom are now generally excluded from dyspepsia studies. However it needs to be recognized that many patients with GORD have multiple symptoms<sup>[10]</sup> and a substantial number of patients with GORD also have functional dyspepsia which may be unmasked by successful treatment of GORD with PPI. A number of patients with functional dyspepsia may have heartburn as an extra symptom and the prevalence of GORD in patients with epigastric pain alone is unknown. It is also unclear whether this could represent undiagnosed or non-erosive reflux disease.

### **Pathophysiologically based sub-groups**

The pathophysiology of functional dyspepsia is unclear and a large number of mechanisms proposed as causative<sup>[19]</sup>. These include delayed gastric emptying<sup>[20,21]</sup>, visceral hypersensitivity<sup>[22]</sup>, impaired gastric accommodation to meals<sup>[23]</sup>, abnormal motility<sup>[24]</sup>, infection with *Helicobacter pylori* (*H pylori*)<sup>[25]</sup> and CNS dysfunction. In addition, childhood abuse<sup>[26]</sup> and prior gastrointestinal infection<sup>[27]</sup> have been described as precursors to later dyspepsia. However, an association between the majority of these mechanisms and specific symptoms is lacking.

## **CLASSIFICATION ACCORDING TO SPECIFIC PATHOPHYSIOLOGIES ASSOCIATED WITH FUNCTIONAL DYSPEPSIA**

### **Gastric motor and sensory dysfunction**

Although it has long been recognized that gastric emptying

is delayed in approximately 1/3 of patients with functional dyspepsia<sup>[20]</sup>, this does not reliably predict individual patient symptoms, with the exception that there is some association with fullness and bloating<sup>[28, 29]</sup>. Gastric antral hypomotility measured by manometry is well described<sup>[24]</sup>, but may well reflect the limitations of pressure recordings with non-lumen occlusive contractions. More promising are recent descriptions of the proximal gastric function, which may permit better discrimination of some symptoms related to meal ingestion<sup>[2]</sup>. Thus intolerance to gastric distension suggesting impaired visceral sensitivity has been associated with epigastric pain, and belching<sup>[22]</sup>. Similarly, impaired proximal gastric accommodation has been associated with pain, early satiety and weight loss particularly in young women<sup>[23]</sup>. Of particular interest to clinicians, are reports that these abnormalities can be evaluated with a high calorie drink test<sup>[30]</sup>. This technique potentially allows an office-based approach to address at least some symptoms in these patients, without resorting to invasive gastric barostat techniques, or expensive technology with limited availability<sup>[31-33]</sup>.

### **Helicobacter pylori Infection**

Depending on the population under study, between 30%-65% of patients diagnosed with functional dyspepsia have *H pylori*-induced gastritis<sup>[25,34]</sup>. However, a consistent causal link between *H pylori* infection and specific symptom profiles has not reliably been established<sup>[35]</sup>. *H pylori* positive individuals are as likely to have symptoms of bloating and early satiety as symptoms suggestive of peptic ulcer<sup>[17]</sup>. Suggestions that *H pylori* infection has a significant impact on gastric motility have also not been confirmed<sup>[36]</sup>. It is feasible that some of these patients could have undiagnosed peptic ulcer disease. At present, the aetiology of symptoms in *H pylori* patients without peptic ulceration is unclear<sup>[37]</sup>.

### **Intestinal hypersensitivity**

Dyspeptic symptoms are frequently worsened by food especially those rich in fat. A heightened sensitivity to both lipids<sup>[38]</sup> and acid<sup>[39]</sup> have been reported to be possible mechanisms underlying symptoms. High fat meals slow gastric emptying and hence may accentuate bloating and fullness. A similar effect may be seen with high fibre meals. These studies involved small numbers of patients and their general applicability at this stage remains uncertain.

## **CLASSIFICATION ACCORDING TO POSSIBLE PATHOGENESIS**

The pathogenesis of functional dyspepsia is unknown and probably multi-factorial. Only a minority of patients report previous gastrointestinal infection<sup>[27]</sup> or an acute onset compatible with a post-infective aetiology. Psychological factors especially stress<sup>[40]</sup> and previous abuse<sup>[26]</sup> have been suggested to be important but direct evidence for a causative role is yet to be established. A recent description of an association between dyspeptic symptoms and a functional polymorphism of a G-protein subunit<sup>[41]</sup> has demonstrated that patients who are homozygous for the GNB3 825C subunit have a higher incidence of abdominal symptoms. The full implications of this is currently under

investigation. In the light of these uncertainties, further data are required before a meaningful classification based on potential pathogenesis can be undertaken.

## THERAPEUTIC IMPLICATIONS

Given the limited understanding of the pathophysiological basis for symptoms in functional dyspepsia, there are limited options for rational treatment. It appears however unlikely that a single therapy will effectively manage all or even most patients with the condition<sup>[42]</sup>. In addition to general measures such as reassurance and avoiding obvious precipitants, the most commonly available options are: (1) Eradication of *H pylori* infection; (2) Acid reducing therapy; (3) Gastrokinetic agents

### Eradication of helicobacter pylori infection

In patients where abdominal pain is the most bothersome symptom especially if ulcer-like in character, current practice frequently involves eradication of *H pylori* particularly in regions where *H pylori* infection is endemic<sup>[42]</sup>. This has the advantage of treating patients where the diagnosis of peptic ulcer has been missed as well as reducing the risk of subsequent malignancy. These patients may well be cured, although it must be recognised that the overall direct therapeutic gain from this approach in dyspeptic patients in general is small<sup>[43]</sup>.

### Acid-reducing therapy

Although ulcer-like symptoms would be expected to benefit from acid suppression with simple antacids, H<sub>2</sub> receptor antagonists or more recently proton pump inhibitors, the therapeutic benefit is small<sup>[42,44]</sup>. Some of this may derive from successful management of hidden GORD and peptic ulcer disease.

### Gastrokinetic drugs

Data indicating that patients who have predominant pain are associated with hypersensitivity to gastric distension suggests that targeting modulation of gastric accommodation (such as 5HT<sub>1</sub> antagonists) may have a role in the future management<sup>[2]</sup> although such approaches are at present in limited use. In patients with dysmotility-like symptoms prokinetic therapy is a rational approach especially if supported by objective evidence of delayed gastric emptying or a positive response to a satiety drinking test. Cisapride, a substituted benzamide with activity as a 5HT<sub>4</sub> agonist, was arguably the most effective prokinetic agent although the evidence for an effect on symptoms is controversial<sup>[42]</sup>. The drug has been withdrawn in many countries due to rare but life-threatening cardiac toxicity. Another 5-HT<sub>4</sub> agonist with prokinetic activity, mosapride<sup>[45]</sup>, has not been widely released. Newer agents such as tegaserod<sup>[46]</sup> and itopride<sup>[47]</sup> are currently undergoing evaluation. In patients with *H pylori* gastritis there is the theoretical possibility that gastritis-induced hypersensitivity may be ameliorated by treating the infection<sup>[35]</sup>.

In conclusion, the sub-classification of functional dyspepsia is currently in transition. The early spec-

tation that particular subtypes based on dominant symptom clusters would be associated with specific pathophysiological disturbances has not been realised, although these descriptive terms remain entrenched in clinical practice. More recent data support a division into pathophysiologically-based patient groupings. In particular there appears to be an association between slow gastric emptying and dysmotility-like symptoms whilst hypersensitivity to gastric distension is more common in patients with post prandial pain. Eradication of *H pylori* gastritis has limited direct therapeutic gain. Patients with predominantly reflux symptoms need exclusion of GORD. Until further data are available it seems rationale to base initial therapy on the suspected pathophysiological abnormalities rather than symptoms, although well evaluated therapeutic options are limited. Further research is required to clarify the relationship between symptoms and motor and sensory dysfunction to provide an evidence-based management strategy.

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