Belgian consensus on the management of patients with functional dyspepsia

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Abstract

Background: **Functional dyspepsia (FD) is a disorder of gut-brain interaction characterised by epigastric pain, epigastric burning, early satiation or postprandial fullness. Despite its high prevalence, clinicians struggle with the diagnosis and management of these patients.**

Methods: **A Delphi consensus was conducted by 20 experts from Belgium, and consisted of a literature review, summarising the existing evidence, and a voting process on 119 statements. Grading of recommendations, assessment, development and evaluation criteria were applied to evaluate the quality of evidence. Consensus was defined as > 80 % agreement.**

Results: **Consensus was reached for 64 statements. The Belgian consensus underlines the multifactorial aetiology of FD. In addition to the cardinal symptoms, bloating and weight loss are also observed in FD. Functional dyspepsia co-exists with other DGBIs, including IBS. Subtyping based on the postprandial nature of symptoms is recommended. Patients should receive a positive diagnosis. Additional testing is not routinely required before initiating therapy, except in the presence of alarm features or treatment-refractory symptoms, and can consist of upper GI endoscopy, abdominal imaging and gastric emptying testing. The consensus refuted the role of carbohydrate malabsorption testing, pyloric impedance planimetry, pH/impedance monitoring, food allergy testing and permeability testing in FD. Explanation and reassurance, also addressing lifestyle factors, represent the cornerstone of the management. Proton Pump Inhibitors are considered the first-line pharmacological treatment. With the exception of specific neuromodulators, the panel did not achieve consensus for other therapeutic options. This consensus recommends against restrictive diets, invasive endoscopic or surgical treatment, parenteral nutrition, antibiotics, spasmolytics and opioids in the management of FD.**

Conclusion: **A panel of Belgian experts summarised the existing evidence on the aetiology, presentation, diagnosis and treatment of FD with attention to the availability within the Belgian healthcare system. Areas of future research are identified. (**Acta gastroenterol belg., **2025**, 88, **157-178**).

Keywords: Functional dyspepsia, Delphi consensus, diagnosis, treatment, aetiology.

Introduction

According to the Rome IV consensus, functional dyspepsia (FD) is defined as the presence of postprandial fulness or early satiation for at least three days per week, and/or epigastric pain or epigastric burning for at least one day per week for 3 months with onset at least 6 months earlier, in the absence of an identifiable organic, systemic or metabolic cause (1). It includes 2 subcategories: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). According to the Rome global epidemiology study, 7.0-7.4% of the world population suffers from FD (2), with a prevalence of 5.2-7.4% in Belgium (3). Interestingly, the prevalence appears higher in the French-speaking participants. Despite this high prevalence, the exact aetiology and pathophysiology remain elusive. Nevertheless, several treatment approaches are available, including lifestyle advice, medical therapy targeting pain or motility, dietary, endoscopic and non-pharmaceutical approaches. However, there is a lack of consensus beyond proton-pump inhibitors (PPIs) as demonstrated by the European consensus (4).

The aim of this project was to develop consensus on the definition of FD, its clinical characteristics, underlying pathophysiology and therapeutic options

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Submission date: 29/01/2025
Acceptance date: 10/03/2025

at a national level, taking into account local availability and experience with different therapeutic options. The results provide guidance to improve the management of these patients.

Methods

A steering group of Belgian gastroenterologists involved in the care of patients with disorders of gut-brain interaction (DGBI) initiated a Delphi process to develop statements on different aspects of FD, with Belgian healthcare professionals as target audience. The principles of the Delphi process have been published elsewhere (5). The primary purpose of the Delphi technique is to generate a reliable consensus opinion of a group of experts by an iterative process of questionnaires interspersed with controlled feedback (6). Its goal is to provide answers to complex medical problems insufficiently backed by evidence from controlled trials. The process involved multiple steps: 1/ selection of a steering committee of 3 Belgian gastro-enterologists involved in the care of patients with FD and/or the Delphi process, 2/ selection of a consensus group from Belgian gastro-enterologists involved in the care of patients with FD, 3/ drafting of statements pertaining to the current knowledge on FD with focus on the Belgian situation, 4/ systematic literature review to identify the existing evidence for each statement, 5/ group discussion of the available evidence and voting with discussion to establish a stable level of consensus, and 6/ grading of the strength of evidence using accepted criteria.

The Belgian consensus group was established by contacting Belgian gastroenterology specialists with a specific interest in FD identified by their clinical or scientific activity. A total of 20 experts agreed to participate, including one dietitian. The steering committee drafted a list of 59 statements covering different aspects of FD. This list was evaluated during the initiatory meeting. The steering group adjusted the statements list based on the comments formulated during this meeting, including variations of the same statement, generating a total of 119 statements. The consensus group was divided into 12 working groups consisting of 3 to 5 panellists each. Each working group was allocated statements, conducted a systematic literature search, and provided a narrative summary of the identified evidence. Summaries and references were made available to each member of the Belgian consensus group using cloud computing.

The consensus group met in March 2024 for the initiatory meeting. Based on these discussions, statements were reformulated. The collected summaries with reference list were provided to all participants by October 2024, followed by an online voting round during which 18 members indicated their degree of agreement for each statement using a 6-point Likert scale. The dietitian only voted for statements related to nutrition. One expert contributed to the summaries but could not vote due to prolonged unavailability. The voting outcomes were discussed during an online meeting in November 2024. Participants remained blinded to the votes of other panellists throughout the process. The consensus group received support from the Belgian Society of Neurogastroenterology and Motility (BSNM).

In accordance with the requisites of the Delphi process, consensus was defined as agreement (A+ or A) of at least 80% on a statement (Table 1). The strength of evidence for each statement was scored using the GRADE system by the members of the Steering Committee (Table 2) (7). Following the last voting round, a draft of the manuscript was circulated to all members for approval. The references presented with the statements in this manuscript only represent a selection of the articles reviewed during the Delphi process chosen to clarify the discussion.

An overview of the statements with voting results, GRADE of evidence and associated references is provided in Table 3. Evidence underlying the answer to the different statements is discussed further in the next topics.

Results

A. Definitions and symptoms

Statements on definitions and statements are summarised in Table 3.

According to the Rome IV consensus, dyspepsia refers to symptoms thought to originate from the gastroduodenal region and consists of 4 key symptoms: early satiation, postprandial fullness, epigastric burning and epigastric pain (1). Postprandial fullness and/or early satiation should be present at least 3 days per week, whereas epigastric pain and/or epigastric burning should be present at least 1 day per week. Furthermore, to fulfil the Rome IV criteria of FD the symptoms should be present for the last three months with onset at least six months ago, in the absence of a readily identifiable organic, systemic or metabolic cause. Symptoms of FD persist long-term. Several studies investigated the natural evolution of symptoms, demonstrating persistent symptoms in 41% of patients after ten years (7), or conversely, symptom resolution or improvement over five years in only 17% and 38%, respectively (8).

Table 1. — **6-point Likert scale.**

Point	Description
A+	Agree strongly
A	Agree with minor reservation
A-	Agree with major reservation
D-	Disagree with minor reservation
D	Disagree with major reservation
D+	Strongly disagree

Table 2. — **Grading of recommendations assessment, development and evaluation system (Balshem 2011).**

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect · Several high-quality studies with consistent results · In special cases: one large, high-quality multicentre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate · One high-quality study · Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate · One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain · Expert opinion · No direct research evidence · One or more studies with very severe limitations

Table 3. — **An overview of statements on definitions and symptoms with endorsement and grading of evidence.**

Statements on definitions and symptoms	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Dyspepsia refers to any of the following epigastric symptoms: early satiety, postprandial fullness, epigastric burning, epigastric pain.	100%, Yes	B	A+ 100%, A 0%, A- 0%, D- 0%, D 0%, D+ 0%
Functional dyspepsia is characterised by chronic dyspeptic symptoms in the absence of a readily identifiable organic cause.	100%, Yes	A	A+ 94%, A 6%, A- 0%, D- 0%, D 0%, D+ 0%
FD symptoms persist long-term in the majority of FD patients.	88%, Yes	B	A+ 66%, A 22%, A- 6%, D- 6%, D 0%, D+ 0%
The use of pictograms is useful to clarify dyspeptic symptoms.	89%, Yes	C	A+ 61%, A 28%, A- 11%, D- 0%, D 0%, D+ 0%
Functional dyspepsia should be divided into the epigastric pain syndrome and postprandial distress syndrome.	94%, Yes	C	A+ 66%, A 28%, A- 6%, D- 0%, D 0%, D+ 0%
In functional dyspepsia, symptom relationship to a meal enables the identification of subgroups	88%, Yes	C	A+ 66%, A 22%, A- 6%, D- 6%, D 0%, D+ 0%
Postprandial distress syndrome is characterised by any dyspeptic symptom occurring within 120 minutes after a meal.	88%, Yes	C	A+ 33%, A 55%, A- 6%, D- 0%, D 0%, D+ 6%
Epigastric pain or epigastric burning unrelated to meal intake characterize the epigastric pain syndrome.	94%, Yes	C	A+ 61%, A 33%, A- 6%, D- 0%, D 0%, D+ 0%
Epigastric pain or epigastric burning in the absence of PDS symptoms characterize the epigastric pain syndrome.	78%, No	C	A+ 72%, A 6%, A- 16%, D- 0%, D 6%, D+ 0%

Appropriate understanding of symptom definitions used in clinical practice, requires patients to possess adequate levels of literacy, abstract thinking capacity and comprehension of nuances (9). To overcome this issue, the Leuven group developed and validated a set of pictograms illustrating upper gastro-intestinal symptoms to supplement verbal descriptors used in questionnaires (9). In tertiary care FD patients, the addition of pictograms to a Rome questionnaire significantly enhanced the agreement with the physician's interpretation of the symptom pattern. Although not validated in daily practice, pictograms could ensure that patients and physicians refer to the same symptoms.

FD is subdivided into epigastric pain syndrome (EPS) and/or postprandial distress syndrome (PDS). Meal-related symptoms of early satiation or postprandial fullness characterise PDS. A time-lapse of 120 minutes after a meal covers the time needed for the gastric assimilation and emptying of food (10). Also, the peak intensity of typical meal-related FD symptoms is reached within this interval (11). In EPS patients, the

dyspepsia symptoms consist of epigastric pain and/or burning unrelated to meal ingestion. By emphasizing the postprandial occurrence of symptoms in PDS, the Rome IV criteria significantly reduced the overlap between PDS and EPS (12) as compared to Rome III (13). However, recent research identified a subgroup of patients reporting epigastric pain after a meal, insufficiently captured by the current Rome definition (14) .

B. Associated symptoms

Statements on associated symptoms are summarised in Table 4.

Apart from the four cardinal symptoms, FD is often associated with other symptoms, such as bloating, belching, heartburn, nausea and vomiting, or weight loss (1). The severity of primary and associated symptoms varies between patients. A factor analysis of dyspeptic symptoms identified a 4-factor model, comprising nausea/vomiting/early satiation/weight loss, bloating/fullness, pain/burning, and belching, with cluster analysis revealing the varied distribution of these factors within a tertiary care population of FD patients (15).

Patients describe upper abdominal bloating as a sensation of gassiness, fullness of tightness in the upper abdomen, frequently after meals (1, 16). According to a study from 2019, 17% of patients reported bloating as the most bothersome symptom (17). FD patients also report belching. In 2003, a study reported excessive or distressing belching in up to 80% of patients with FD (18). However, patients with Gastro-oesophageal Reflux Disease (GORD) also frequently report belching, which appears more severe and correlated to reflux episodes (18).

Previous Rome definitions excluded patients with predominant heartburn from the definition of FD because they were considered to have GORD. Heartburn is defined as a burning sensation beneath the breastbone (19), contrasting with the epigastric localisation of FD symptoms. Nevertheless, typical reflux symptoms (heartburn, regurgitations) often co-exist with dyspeptic symptoms in the general population, especially with EPS (20, 21), potentially confounding the differential diagnosis between GORD and FD.

One study found a prevalence of vomiting in 29% of FD patients (15). Another study from 1996 reported that, respectively, 72% and 90% of FD patients reported no or only mild vomiting symptoms and that the presence of vomiting was significantly correlated with severely delayed gastric emptying (22), which is more in keeping with a diagnosis of gastroparesis instead of FD (23).

Therefore, in the absence of an organic cause, when associated symptoms predominate the clinical presentation rather than the cardinal symptoms of FD, one should consider other DGBI. The European guidelines recommend to use nausea and/or vomiting as key indicators to differentiate gastroparesis from FD (23). Similarly, when nausea is predominant or unrelated to meal intake, or when nausea presents in the absence of bothersome PDS symptoms, chronic nausea and vomiting syndrome or gastroparesis should be considered (1).

Because of self-imposed dietary restrictions or

Table 4. — **An overview of statements on associated symptoms with endorsement and grading of evidence.**

Statements on definitions and symptoms	Overall agreement, Endorsement	Grade of evidence	Voting distribution
There is a high intra- and inter-individual variation in FD severity.	94%, Yes	B	A+ 77%, A 17%, A- 6%, D- 0%, D 0%, D+ 0%
Upper abdominal bloating is part of the spectrum of functional dyspepsia.	94%, Yes	C	A+ 28%, A 66%, A- 6%, D- 0%, D 0%, D+ 0%
Belching is part of the spectrum of functional dyspepsia.	50%, No	C	A+ 11%, A 39%, A- 11%, D- 11%, D 22%, D+ 6%
Heartburn is part of the spectrum of functional dyspepsia.	33%, No	C	A+ 11%, A 22%, A- 17%, D- 11%, D 11%, D+ 28%
Heartburn is distinguishable from epigastric burning.	72%, No	C	A+ 22%, A 50%, A- 28%, D- 0%, D 0%, D+ 0%
Nausea is part of the spectrum of functional dyspepsia.	77%, No	C	A+ 11%, A 66%, A- 11%, D- 6%, D 0%, D+ 6%
Vomiting is part of the spectrum of functional dyspepsia.	28%, No	C	A+ 6%, A 22%, A- 17%, D- 17%, D 17%, D+ 22%
Nausea and vomiting are more prominent in gastroparesis as compared to FD.	100%, Yes	B	A+ 72%, A 28%, A- 0%, D- 0%, D 0%, D+ 0%
FD can result in significant weight loss.	95%, Yes	B	A+ 47%, A 47%, A- 5%, D- 0%, D 0%, D+ 0%

as a result of dietary recommendations, weight loss can become alarming in some FD patients. Clinically significant weight loss is defined as a reduction of more than 5% in body weight within 6 to 12 months (24). In FD, weight loss was reported to be present in 34- 40% of tertiary care patients (15, 25). Both impaired gastric accommodation and hypersensitivity to distention, two of the pathophysiological mechanisms described in FD, have been associated with weight loss (25, 26).

C. Aetiology and pathophysiology

Statements on aetiology and pathophysiology are summarised in Table 5.

No single aetiological factor or pathophysiological mechanism explains the symptoms experienced by FD patients. Past research extensively focused on disturbances in gastric physiology, identifying associations between delayed gastric emptying, gastric hypersensitivity to distension and impaired gastric accommodation in at least a subset of patients (27, 28).

More recently, the role of the duodenum gained attention. Pathogenic microbes may cause immune activation, with persisting duodenal changes after the initial event and systemic immune activation in acute post-infection, compared to unspecified-onset FD (29-32). In a recent systematic review and meta-analysis, 12.7% of subjects developed FD after acute gastroenteritis, corresponding to threefold increased odds (33). Moreover, prevalence of PI-FD was 10.0% following SARS-CoV-2 and 19.4% after Enterobacteriaceae infection. Duodenal eosinophil infiltration has been demonstrated in FD patients (34, 35), which was associated with postprandial symptoms, possibly as a result of altered duodeno-gastric reflexes in response to a meal (36, 37). However standardised protocols for eosinophil counting and evaluation of duodenal mucosal permeability in clinical practice are lacking (38). Inflammatory changes are hypothesised to alter gut mucosal permeability (39). Interestingly, results from Ussing chamber studies (40), confocal laser endomicroscopy (41), and mucosal impedance analysis (39) demonstrated mucosal barrier disruption.

Although these findings harbour a potential for future therapeutic interventions, additional research should further investigate the underlying mechanisms. A potential central role of the microbiome has been hypothesized. Indeed, randomized controlled studies with the probiotic combination of Bacillus coagulans MY01 and Bacillus subtilis MY02 strains on the one hand (42), and rifaximin on the other hand (43),

Table 5. — **An overview of statements on aetiology and pathophysiology with endorsement and grading of evidence.**

Statements on aetiology and pathophysiology	Overall agreement, Endorsement	Grade of evidence	Voting distribution
The origin of symptoms in FD is multifactorial.	100%, Yes	B	A+ 89%, A 11%, A- 0%, D- 0%, D 0%, D+ 0%
Delayed gastric emptying contributes to FD in some patients.	78%, No	C	A+ 44%, A 33%, A- 22%, D- 0%, D 0%, D+ 0%
Gastric hypersensitivity contributes to FD in some patients.	89%, Yes	C	A+ 50%, A 39%, A- 11%, D- 0%, D 0%, D+ 0%
Impaired gastric accommodation contributes to FD in some patients.	89%, Yes	C	A+ 44%, A 44%, A- 11%, D- 0%, D 0%, D+ 0%
Acute GI infection is a risk factor for development of FD.	94%, Yes	B	A+ 61%, A 33%, A- 0%, D- 0%, D 0%, D+ 6%
Duodenal immune activation contributes to FD in some patients.	55%, No	C	A+ 11%, A 44%, A- 39%, D- 0%, D 6%, D+ 0%
Impaired gut mucosal permeability contributes to FD in some patients.	50%, No	C	A+ 0%, A 50%, A- 39%, D- 0%, D 11%, D+ 0%
Altered microbiota composition contributes to FD in some patients.	28%, No	C	A+ 0%, A 28%, A- 44%, D- 11%, D 6%, D+ 11%
HP contributes to dyspeptic symptoms in some patients.	94%, Yes	B	A+ 61%, A 33%, A- 0.%, D- 6%, D 0%, D+ 0%
Altered central processing contributes to FD in some patients.	78%, No	C	A+ 44%, A 34%, A- 22%, D- 0%, D 0%, D+ 0%
Stress, anxiety and depressive mood are risk factors for FD.	83%, Yes	B	A+ 61%, A 22%, A- 6%, D- 6%, D 6%, D+ 0%
Genetic factors determine susceptibility to FD.	50%, No	C	A+ 11%, A 39%, A- 39%, D- 6%, D 0%, D+ 6%
Duodenogastric (bile) reflux contributes to FD in some patients.	22%, No	C	A+ 6%, A 17%, A- 17%, D- 17%, D 28%, D+ 17%
Dietary composition contributes to FD in some patients.	61%, No	C	A+ 22%, A 39%, A- 22%, D- 11%, D 0%, D+ 6%

provided symptomatic improvement. However, evidence for altered microbiota composition in FD remains poor. Most studies investigating microbiota composition were hampered by methodological issues such as risk of sample contamination from oral genera such as Streptococci (44), or confounding factors such as PPI intake (45). Nevertheless, a large body of evidence is in favour of the association of Helicobacter pylori and dyspeptic symptoms, as summarised in a systematic review (46). Eradication also provides a small therapeutical advantage long-term, albeit limited (46).

Visceral hypersensitivity can be due to peripheral gastroduodenal mechanisms, including neuronal sensitization by low-grade immune activation, but can also relate to altered brain processing of incoming signals. Functional brain imaging studies using fMRI and PET have shown alterations in visceral sensation perception, pain modulation, emotion regulation, salience and homeostatic processing networks in two meta-analyses (47, 48). Noteworthy, psychological factors such as depression and anxiety seem to play a larger role than gastric sensorimotor function in FD (49), the so-called gut-brain interaction. In the 10-year longitudinal Kalixanda study, anxiety at baseline – but not depression – resulted in a 7.6-fold increase in the risk of developing FD (50). However, in an Australian longitudinal study, psychological symptoms developed after the onset of gastrointestinal symptoms in the majority of patients and not vice versa (51).

Other mechanisms have been postulated. As summarised by Kourikou et al., many studies investigated a possible role of genetic polymorphisms, with variable evidence for their association with FD (52). A comparison of FD patients with or without cholecystectomy and healthy volunteers did not demonstrate an increase in severity or frequency of dyspeptic symptoms in relation to fasting duodeno-gastric bile reflux (53).

Finally, patients with FD frequently attribute that intake of specific food or beverages provokes or exacerbates their symptoms (54). However, it is more likely that this represents an adaptive behaviour related to symptoms, rather than a factor causing or maintaining the symptoms. Currently, there is no congruent evidence to attribute symptoms in functional dyspepsia to one or more specific food items, even if dietary patterns in general (e.g. large, fatty and spicy meals) can contribute to symptom generation (55).

D. Associated disorders

Statements on associated disorders are summarised in Table 6.

Disorders of gut-brain interaction frequently overlap. IBS is the most commonly reported comorbidity in FD (56). A meta-analysis indicated that the prevalence of IBS among subjects with FD was 37%, compared to 7% among those without (57). Other DGBI overlap less frequently with FD. Patients with FD, recruited from a population consulting for a health check-up, had clinically significant belching in 14.4% of cases (58). Cyclic vomiting syndrome was reported by 6.9% and rumination syndrome by 3.4% of FD patients in a Japanese secondary care setting (59). An overlap with rumination syndrome is observed in 16.0% of FD patients (60).

Apart from DGBI, an overlap between FD and GORD symptoms is frequent, with 31.3% of subjects diagnosed with FD complaining of heartburn and/or acid regurgitation in a meta-analysis (20). Similarly, in a population-based study, overlapping reflux symptoms were present in 33.8% of subjects with dyspeptic symptoms (54).

Functional dyspepsia is associated with delayed gastric emptying in about one-third of patients (22, 61), possibly complicating the differential diagnosis with idiopathic gastroparesis, especially in the PDS subtype. According to the European consensus, gastroparesis can be differentiated from FD based on the predominant symptoms (23). However, at least in tertiary care, both entities are indistinguishable based on clinical and pathophysiologic features or gastric emptying testing (62), suggesting that they are part of the same spectrum.

E. Initial diagnostic workup

Statements on initial diagnostic work-up are summarised in Table 7.

The definition of FD according to Rome IV implies ruling out an underlying organic cause that likely explains dyspepsia, at least with endoscopy (1). In

Table 6. — **An overview of statements on associated disorders with endorsement and grading of evidence.**

Statements on associated disorders	Overall agreement, Endorsement	Grade of evidence	Voting distribution
IBS and other DGBI often co-exists with FD.	100%, Yes	A	A+ 83%, A 17%, A- 0%, D- 0%, D 0%, D+ 0%
GERD often co-exists with FD.	100%, Yes	A	A+ 78%, A 22%, A- 0%, D- 0%, D 0%, D+ 0%
There is an overlap between FD and idiopathic gastroparesis.	72%, No	B	A+ 50%, A 22%, A- 22%, D- 0%, D 6%, D+ 0%

Table 7. — **An overview of statements on initial diagnostic work-up with endorsement and grading of evidence.**

Statements on initial diagnostic work-up	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Limited laboratory testing is mandatory in all patients presenting with dyspepsia	67%, No	C	A+ 28%, A 39%, A- 16%, D- 6%, D 6%, D+ 6%
Testing for and treating H pylori is mandatory in all patients presenting with dyspepsia.	100%, Yes	A	A+ 89%, A 11%, A- 0%, D- 0%, D 0%, D+ 0%
In the absence of alarm symptoms or risk factors in dyspeptic patients < 50 years, upper g.i. endoscopy is not mandatory for initial management.	100%, Yes	A	A+ 61%, A 39%, A- 0%, D- 0%, D 0%, D+ 0%
In the presence of vomiting at least once a week and/or unintentional weight loss of > 5%, other causes need to be excluded before diagnosing FD.	94%, Yes	D	A+ 83%, A 11%, A- 6%, D- 0%, D 0%, D+ 0%
When performing upper g.i. endoscopy in patients with dyspepsia, gastric biopsies are mandatory.	100%, Yes	B	A+ 72%, A 28%, A- 0%, D- 0%, D 0%, D+ 0%
When performing upper g.i. endoscopy in patients with dyspepsia, duodenal biopsies are mandatory.	22%, No	C	A+ 11%, A 11%, A- 22%, D- 22%, D 11%, D+ 22%
Abdominal imaging is not mandatory in all patients presenting with dyspepsia.	83%, Yes	D	A+ 72%, A 11%, A- 6%, D- 0%, D 6%, D+ 6%
Abdominal Imaging is mandatory in dyspeptic patients with significant weight loss.	83%, Yes	D	A+ 11%, A 72%, A- 17%, D- 0%, D 0%, D+ 0%
Imaging findings suggesting Wilkie/Dunbar are unlikely to explain dyspepsia symptoms.	100%, Yes	C	A+ 50%, A 50%, A- 0%, D- 0%, D 0%, D+ 0%
Gastric emptying testing has no place in the initial workup.	89%, Yes	B	A+ 72%, A 17%, A- 11%, D- 0%, D 0%, D+ 0%
There is no place for carbohydrate malabsorption testing in FD.	100%, Yes	C	A+ 83%, A 17%, A- 0%, D- 0%, D 0%, D+ 0%

clinical practice, FD patients are subjected to more elaborate investigations, consisting of laboratory testing, upper GI endoscopy with biopsies, abdominal imaging, testing of gastric emptying or even carbohydrate malabsorption testing. However, there is insufficient data to support this practice. Evidence for the role of routine laboratory testing in uninvestigated dyspepsia is lacking. Earlier research assessing the usefulness of blood sampling focused primarily on risk stratification for upper gastrointestinal malignancy, including screening for anaemia and low albumin levels (63). However, malignancy is rarely found below 60 years in subjects without alarm symptoms, and the incidence of gastric cancer has decreased in Western Europe during the last decades (64, 65). Standard screening for coeliac disease is also not recommended, as the prevalence is not increased compared with the healthy population (66). In contrast, as Helicobacter pylori is a potentially curable cause of dyspepsia, guidelines recommend non-invasive testing for H. pylori in FD (4).

British and European guidelines recommend against systematic endoscopy, while reserving it for patients with alarm symptoms or risk factors for gastric cancer, including weight loss, evidence of GI bleeding, vomiting, subjects from an area at increased risk of gastric cancer or with a family history of gastro-oesophageal cancer (4, 67). Nevertheless, alarm features do not perform well as indicators of underlying upper GI malignancy which endoscopy will reveal (68). Additionally, performing upper GI endoscopy in patients with FD, however, does not improve psychological well-being or health-related quality of life (69). Finally, repeat endoscopy within 2 years of a normal endoscopy does not yield additional information (65).

Nevertheless, gastric biopsies are recommended when a patient undergoes an endoscopy because of alarm symptoms, to allow the staging of gastritis and H. pylori detection (70, 71). This does not apply to the duodenum, as American and European guidelines do not advocate biopsies of the normal-appearing mucosa in the absence of signs or symptoms potentially associated with coeliac disease or Giardiasis in this population (70, 72, 73). Although activated eosinophils and mast cells are more frequently found in duodenal biopsies of dyspeptic patients, so far this does not impact subsequent management (74).

Since symptoms do not allow to distinguish between functional and organic dyspepsia (75), abdominal imaging, such as abdominal ultrasound or abdominal Computed Tomography, can be ordered upon suspicion of a secondary cause of dyspeptic symptoms and especially in the presence of alarm symptoms.

However, weight loss is also observed in FD, and even significant weight loss(10 kg or more) was reported in approximately 15% of patients (25). Upon imaging superior mesenteric artery syndrome (Wilkie syndrome) or median arcuate ligament syndrome (Dunbar syndrome) are sometimes reported. These represent rare but controversial disorders based on anatomical alterations on imaging, potentially associated with postprandial epigastric pain. However, there are no systematic reports on the characteristic imaging of these disorders in patients suffering from FD. Moreover, the high prevalence of the characteristic signs of these disorders in even asymptomatic subjects (76) makes these an unlikely explanation of the symptoms in most patients. Systematic evaluation of patients with FD by imaging in search of these rare syndromes is therefore not recommended.

The link between gastric emptying and dyspeptic symptoms remains a matter of debate (77, 78). The relation between improvement of gastric emptying and the improvement of symptoms has been questioned (79). Furthermore, presence of delayed gastric emptying does not predict the predominant symptom (80). Therefore, the panellists recommend against gastric emptying testing during initial work-up.

Concerning carbohydrate malabsorption, there is insufficient evidence for testing in FD. Studies investigating the role of small intestinal bacterial overgrowth by breath testing are hampered by a low quality of evidence (81), while suffering from poor reproducibility and lack of therapeutic implications (82). There is no indication that lactose or even fructose malabsorption are implicated in symptom generation - such as pain or bloating - in FD.

F. Diagnostic work-up in patients with refractory symptoms

Statements on diagnostic work-up in patients with refractory symptoms are summarised in Table 8.

In refractory patients, or for research purposes, the panel favours an endoscopic examination to refute an organic cause of the symptoms. A similar strategy is proposed in the Japanese clinical practice guideline, with the committee indicating that endoscopy should

Table 8. — **An overview of statements on diagnostic work-up in patients with refractory symptoms with endorsement and grading of evidence.**

Statements on diagnostic work-up in patients with refractory symptoms	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Absence of explanatory findings on upper g.i. endoscopy is mandatory to confirm a diagnosis of functional dyspepsia for research purposes or in treatment-refractory patients.	89%, Yes	C	A+ 56%, A 33%, A- 6%, D- 6%, D 0%, D+ 0%
In the absence of improvement by initial treatment, additional testing to rule out other (organic) disease is not routinely required	56%, No	C	A+ 17%, A 39%, A- 17%, D- 17%, D 6%, D+ 6%
Assessment of delayed gastric emptying should be considered in FD patients with refractory symptoms.	72%, No	C	A+ 22%, A 50%, A- 22%, D- 0%, D 6%, D+ 0%
Assessment of delayed gastric emptying should be considered in refractory dyspeptic patients with prominent nausea and/or vomiting.	94%, Yes	B	A+ 61%, A 33%, A- 0%, D- 6%, D 0%, D+ 0%
Assessment of delayed gastric emptying should be considered in refractory dyspeptic patients with weight loss.	83%, Yes	B	A+ 17%, A 67%, A- 17%, D- 0%, D 0%, D+ 0%
There is no place for pyloric endoflip testing in FD patients with delayed gastric emptying.	94%, Yes	C	A+ 78%, A 17%, A- 6%, D- 0%, D 0%, D+ 0%
There is no place for routine pH/imp monitoring in FD patients in the absence of reflux symptoms.	89%, Yes	C	A+ 78%, A 11%, A- 11%, D- 0%, D 0%, D+ 0%
There is no place for food allergy testing in FD patients.	100%, Yes	C	A+ 83%, A 17%, A- 0%, D- 0%, D 0%, D+ 0%
There is no place for gut permeability testing in FD patients.	94%, Yes	C	A+ 78%, A 17%, A- 0%, D- 0%, D 0%, D+ 6%
Psychological evaluation should be considered in treatment-refractory FD.	83%, Yes	C	A+ 56%, A 28%, A- 17%, D- 0%, D 0%, D+ 0%
Psychiatric evaluation to exclude eating disorders is mandatory in FD patients with major weight loss.	78%, Yes	C	A+ 22%, A 56%, A- 22%, D- 0%, D 0%, D+ 0%

be performed only in the presence of alarm symptoms, or in case of refractory FD (after failure of second-line treatment) (83). While a negative endoscopy does not reassure the patient, it should increase the healthcare provider's confidence in the diagnosis. On the other hand, routine motility testing of patients with FD is not recommended (84). Indeed, testing for other pathophysiological mechanisms is not readily available or expensive, invasive and uncomfortable, and the results do not predict treatment response. Although gastric emptying testing is not initially required, certain patients failing initial therapy might benefit from testing. Certainly, gastroparesis should be excluded in patients with prominent nausea and vomiting (4, 23), and possibly also in patients with weight loss (85). However, the panellists do not advocate gastric emptying testing in all refractory patients.

Similarly, there is insufficient evidence to routinely recommend pyloric impedance planimetry or pH/impedance monitoring in FD patients. Pyloric distensibility is reduced in delayed gastric emptying and inversely correlates with gastric emptying (86-88). However, no pyloric physiological parameter assessed by impedance planimetry predicts the response to gastric per oral endoscopic myotomy(G-POEM). Moreover, the procedure is invasive; the catheters are single-use, expensive and not reimbursed in Belgium. Further assessment of its role as a screening procedure in patients with FD, delayed gastric emptying and refractory symptoms, to identify patients who might benefit from G-POEM is warranted (89).

Dyspepsia and GORD symptoms overlap in over 25% of patients (20, 21). In addition, prospectively collected data from a large group of off-PPI non-erosive reflux disease patients, revealed clinically significant dyspeptic symptoms in 44% of them (90). It is, therefore, not surprising that pH monitoring does not reliably distinguish between FD and erosive and non-erosive GORD (91, 92). Moreover, there is no proof that oesophageal pH or impedance monitoring identifies patients with FD who may benefit from acid-suppressant therapy.

The exact mechanisms by which food triggers FD symptoms remain incertain. However, evidence indicates that food allergy testing such as food-specific IgE's or skin prick tests do not predict food sensitivity at all. While a small study found that patients with FD had increased IgG antibody titres to certain common foods, symptom severity did not correlate with food antigen-specific IgG levels (93). Additionally, according to the same study, the percentage of patients with FD with detectable food IgE antibody titres did not differ from the healthy controls. Although evidence about altered duodenal mucosal permeability exists, standardised methods for its assessment are needed as results differ between studies (39-41). In addition, causality remains uncertain necessitating further research and up to now there is no treatment option targeting intestinal permeability (38).

Apart from the above-mentioned physiological testing, psychological evaluation and intervention are worth considering in FD patients refractory to first-line interventions. FD patients demonstrate higher anxiety and depression scores, which drive symptom severity more than gastric sensorimotor function (8, 49, 94, 95). Psychological interventions, and especially psychotherapy, improved both symptoms of FD as well as the anxiety and depression levels (96). A multidisciplinary approach, involving a psychologist or psychiatrist, provided more symptomatic relief than the standard of care (97, 98).

FD is frequently observed in patients with eating disorders (99). Conversely, feeding/eating disorders are frequently encountered in FD (100). Additionally, depression was identified as the main determinant of weight loss in FD patients, an effect mediated by somatisation (49). Therefore, when suspecting an underlying eating disorder, one might consider referral for further evaluation.

G. General management considerations

Statements on general management considerations are summarised in Table 9.

In most patients, history and clinical examination enable a positive diagnosis of FD, without the need for upper GI endoscopy, allowing treatment initiation. A recent European Delphi consensus agreed that in the absence of alarm symptoms or risk factors, functional dyspepsia can be managed without upper endoscopy in primary care (4). Communication and explanation are primordial aspects of management. This includes counselling about positive long-term evolution, as up to two-thirds of DGBI patients report symptom improvement following reassurance (101). It reduces the stigma associated with the diagnosis and improves treatment adherence (102). Communication strategies should focus on the role of gut-brain interactions and the psychological mechanisms of FD (103, 104).

FD significantly impacts on multiple aspects of quality of life (QOL). Patients with FD often experience psychological distress and are susceptible to mental illnesses like anxiety and depression, which negatively influence symptom frequency and intensity, resulting in a vicious cycle (105, 106). FD symptoms are chronic and often unpredictable in nature, causing discomfort and embarrassment when interacting with other people,

Table 9. — **An overview of general management considerations with endorsement and grading of evidence.**

Statements on general management considerations	Overall agreement, Endorsement	Grade of evidence	Voting distribution
A positive diagnosis can be established in most patients based on symptom pattern, absence of alarm symptoms and selected additional tests.	100%, Yes	C	A+ 78%, A 22%, A- 0%, D- 0%, D 0%, D+ 0%
In the absence of alarm symptoms, treatment can be initiated without the immediate need for further investigation.	89%, Yes	D	A+ 56%, A 33%, A- 6%, D- 6%, D 0%, D+ 0%
Explanation and communication of the diagnosis of FD is a crucial part of the management.	94%, Yes	C	A+ 83%, A 11%, A- 6%, D- 0%, D 0%, D+ 0%
Patient should be reassured about long-term evolution.	89%, Yes	C	A+ 50%, A 39%, A- 6%, D- 6%, D 0%, D+ 0%
Different aspects of QOL are impaired in FD	100%, Yes	B	A+ 89%, A 11%, A- 0%, D- 0%, D 0%, D+ 0%
The management of FD includes the assessment of co-existing IBS symptoms.	89%, Yes	D	A+ 50%, A 39%, A- 6%, D- 0%, D 0%, D+ 6%
Treatment of FD patients should address lifestyle factors.	89%, Yes	C	A+ 61%, A 28%, A- 11%, D- 0%, D 0%, D+ 0%
The initial management of patients with FD should address stress, anxiety and depressive symptoms.	72%, No	C	A+ 22%, A 50%, A- 22%, D- 0%, D 6%, D+ 0%

resulting in a decreased quality of life or even social isolation (107). FD is also associated with significant direct and indirect costs. Direct costs include costs of visits with a variety of health care professionals, costs of investigations and costs of therapy. Indirect costs include work absenteeism and productivity losses (presenteeism) (108, 109).

History taking should consider assessing concurrent DGBIs such as IBS. Many studies highlighted the co-existence of symptoms from both the gastroduodenal and bowel disorder group (110-112). Moreover, there is concurring evidence that with increasing numbers of overlapping DGBIs, there is a more severe symptom profile and decreased quality of life (2). Available data suggest that overlap of DGBI is also linked with increased somatisation as well as higher depression and anxiety rates.

Before initiating medical treatment, management should address lifestyle factors. According to patients, wheat and specifically gluten, fermentable oligo-, di-, monosaccharides and polyols (FODMAPs), fat, and naturally occurring food chemicals play an important role in developing symptoms (55). Therefore, general dietary advice for FD consists of eating smaller but more frequent meals and limiting fatty foods, carbonated drinks, and caffeine (113). Regular physical activity is recommended as it improves symptoms of FD by promoting motility and reducing stress (113, 114). A study showed that smoking increases the odds of developing PDS but not EPS (115). Poor sleep, including insomnia, is associated with a lower quality of life, higher symptom severity, and higher anxiety and depression scores (116). A regular sleep schedule and comfortable sleep environment are therefore paramount.

Despite the lack of high-level evidence, there is indirect data favouring the management of stress, anxiety and depression in FD. This includes associations of psychological comorbidity with symptom severity (117) or with distinct pathophysiological mechanisms (118, 119), anxiety and depression preceding FD (50, 120), and results of latent-class analysis (121) among others.

H. First-line treatment

Statements on first-line treatment are summarised in Table 10.

The use of acid-suppressing therapy, including standard dose PPI, is advocated in the management of FD by different guidelines (4, 67, 84). This recommendation is substantiated by a Cochrane review (122) and a meta-analysis of the British guidelines (67). Both EPS and PDS patients might benefit from PPI. There is no evidence to favour higher doses. Because of this extensive evidence, PPI represent the preferred first-line treatment for FD.

The postprandial presentation of symptoms as well as the association with delayed gastric emptying make drugs with gastric prokinetic properties an attractive treatment option. However, studies failed to confirm this assumption. Concerning dopamine-2 receptor antagonists (D2RA), only several small and older trials, comparing the efficacy of metoclopramide with placebo or other drug therapies in FD, showed a significant improvement of dyspepsia symptoms. Studies evaluating the effect of domperidone in FD suffer from insufficient rigour concerning the evaluation of FD (123-129).

Table 10. — **An overview of statements on first-line treatment with endorsement and grading of evidence.**

Statements on diagnostic work-up in patients with refractory symptoms	Overall agreement, Endorsement	Grade of evidence	Voting distribution
PPI are effective in the management of FD.	89%, Yes	A	A+ 72%, A 17%, A- 6%, D- 0%, D 0%, D+ 6%
PPI are the preferred first-line treatment for FD.	83%, Yes	C	A+ 50%, A 33%, A- 6%, D- 6%, D 0%, D+ 6%
Dopamine-2 receptor antagonists are effective in the management of FD.	39%, No	C	A+ 11%, A 28%, A- 44%, D- 6%, D 6%, D+ 6%
Dopamine-2 receptor antagonists/ acetylcholinesterase inhibitors are effective in the management of FD.	83%, Yes	C	A+ 11%, A 72%, A- 17%, D- 0%, D 0%, D+ 0%
Motilin receptor agonists are effective in the management of FD.	39%, No	C	A+ 11%, A 28%, A- 6%, D- 33%, D 17%, D+ 6%
Serotinine-4 receptor agonists are effective in the management of FD.	56%, No	C	A+ 6%, A 50%, A- 22%, D- 17%, D 6%, D+ 0%
Management of constipation may improve dyspeptic symptoms.	56%, No	C	A+ 39%, A 17%, A- 39%, D- 6%, D 0%, D+ 0%
Spasmolytics are not effective in the management of FD (in the absence of IBS symptoms).	89%, Yes	C	A+ 61%, A 28%, A- 6%, D- 6%, D 0%, D+ 0%
Ginger extract is effective in the management of FD.	56%, No	C	A+ 11%, A 44%, A- 33%, D- 6%, D 6%, D+ 0%
Peppermint oil/Caraway oil combination is effective in the management of FD	61%, No	C	A+ 11%, A 50%, A- 22%, D- 11%, D 0%, D+ 6%
Artichoke extract is effective in the management of FD.	39%, No	C	A+ 11%, A 28%, A- 39%, D- 17%, D 6%, D+ 0%
Selected probiotics are effective in the management of FD.	39%, No	C	A+ 6%, A 33%, A- 44%, D- 6%, D 11%, D+ 0%
Antihistaminics (H1) are effective in the management of FD.	12%, No	C	A+ 6%, A 6%, A- 17%, D- 44%, D 28%, D+ 0%
Antibiotics are not recommended in the management of FD.	94%, Yes	C	A+ 56%, A 39%, A- 0%, D- 6%, D 0%, D+ 0%
Opioids are not recommended in the management of FD	100%, Yes	C	A+ 100%, A 0%, A- 0%, D- 0%, D 0%, D+ 0%

Moreover, the risk of the extrapyramidal syndrome with metoclopramide and QTc prolongation with domperidon, preclude the prolonged use of these drugs.

More recently, itopride, a mixed D2RA and cholinesterase inhibitor, became available in Belgium. Results from phase 2 and phase 3 trials provided contradictory results (130, 131). Nevertheless, a recent study in FD defined according to Rome IV, demonstrated its potential in patients with postprandial symptoms during an 8-week treatment phase (132). Despite these inconsistent results, this panel favours the use of itopride. Results from studies on long-term efficacy are expected.

Motilin, a GI peptide synthesised and released by enterochromaffin cells in the proximal small intestine, stimulates interdigestive antral contractions. The most well-known motilin agonist is erythromycin. It accelerates gastric emptying in healthy volunteers and patients with diabetic gastroparesis or post-vagotomy (133, 134). However, despite the prokinetic properties, studies with motilin agonists failed to improve symptoms (135, 136).

Likewise, 5-HT4 receptor agonists have been evaluated for treating gastrointestinal motility disorders because of their prokinetic properties, most of which are unavailable in Belgium. Furthermore, cisapride and tegaserod have been withdrawn due to severe cardiac side effects. On the other hand, prucalopride, a highly selective 5-HT4 agonist with demonstrated efficacy in treating constipation, offers an improved safety profile, with no reported significant cardiac adverse events. In a placebo-controlled crossover trial, a daily dose of 2 mg provided symptomatic relief, particularly in patients with idiopathic gastroparesis (137). Interestingly, there was no correlation between symptom improvement and changes in gastric emptying rate, suggesting involvement of other mechanisms. However, the lack of reimbursement precludes its use in Belgium. In line with the use of prucalopride in FD, a study observed that the prevalence of FD increased with worsening constipation (138), while correction of dyssynergic defaecation resulted in a reduction of dyspeptic symptoms (139). Therefore, further research should determine whether treatment of concurrent constipation can directly impact FD severity.

A multitude of other pharmacological options were studied in FD. Evidence remains limited for

the use of antispasmodics (140), ginger extract (141, 142), artichoke extract (143), or the combination of peppermint oil and caraway oil (144). More recently, randomised controlled studies pointed at the potential of probiotic therapy in FD vs. placebo or PPI (42, 145, 146). The exact mechanism of action remains unclear. Like in IBS increased intestinal permeability and mast cells have been implicated in at least a subset of FD patients.

In IBS, encouraging data with the H1-receptor antagonist ebastine have recently been published. Interestingly, cyproheptadine - another H1-receptor antagonist - provided symptom relief in children with FD (147). Finally, symptomatic improvement following treatment with antibiotics (such as Rifaximin) provides evidence that altered microbial composition may play a role in the pathogenesis of at least a subgroup of patients with FD (43). However, these encouraging results need further corroboration.

In some patients with FD, pain severely impacts daily life. Prescription of opioids for the treatment of DGBI-related pain has been reported (148). However, chronic use for non-cancerous pain results in opioid-induced constipation, narcotic bowel syndrome, nausea, worsening psychopathology and addiction (149) as well as more GI symptoms (148). Therefore, the panel unanimously advocates against this practice in FD.

I. Invasive management

Statements on invasive management are summarised in Table 11.

Invasive management in FD usually targets delayed gastric emptying. Gastric electrical stimulation (GES) was approved by the FDA in 2000 for gastroparesis associated with nausea and vomiting refractory to medication. Studies demonstrated the efficacy of GES in treating gastroparesis symptoms (150-152). However, there is only spurious data on the impact on dyspeptic symptoms. Other endoscopic approaches directly targeting the pylorus have been researched. Despite several open-label studies reporting initial short-term benefice, two controlled studies failed to show any improvement in patients treated with intrapyloric botulinum toxin (153, 154). Only one pilot randomised sham-controlled study in 41 patients showed superiority of G-POEM in improving symptoms and gastric emptying 6 months after the procedure (155). It remains unknown which patients are the best candidates for this procedure, since no pyloric physiological parameter and no clinical parameter predict the clinical outcome (156). Other techniques, such as endoscopic pylorus balloon dilation, trans-pyloric stenting and laparoscopic pyloromyotomy, were evaluated on their effectiveness in gastroparesis with, in general, non-convincing evidence for this indication (157-159). Therefore, the panel complies with recent guidelines recommending against endoscopic treatment targeting delayed gastric emptying outside of a research trial (23, 160, 161).

When imaging suggests Wilkie or Dunbar syndrome, patients or healthcare professionals might feel tempted to refer for surgical correction. However, the outcome of surgery remains uncertain in this population. Available studies in both disorders are hampered by poor definition of FD, and only a short-term follow-up. Moreover, results from one single-centre retrospective case series of Wilkie syndrome question the specificity of the radiographic signs as outcome predictors of surgery, as 11% of women diagnosed with FD met the (radiographic) criteria (162). Concerning the Dunbar syndrome, recruitment is ongoing for a study investigating the effects of coeliac artery release or sham operation (163). Until further data is available,

Table 11. — **An overview of statements on invasive management with endorsement and grading of evidence.**

Statements on invasive management	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Gastric electrical stimulation should not be proposed for the management of FD.	94%, Yes	C	A+ 83%, A 11%, A- 0%, D- 6%, D 0%, D+ 0%
Intrapyloric botulinum injection should not be proposed for the management of FD with delayed gastric emptying.	89%, Yes	C	A+ 83%, A 6%, A- 6%, D- 6%, D 0%, D+ 0%
G-POEM should not be proposed for the management of refractory FD with delayed gastric emptying.	83%, Yes	C	A+ 50%, A 33%, A- 0%, D- 11%, D 6%, D+ 0%
Endoscopic or surgical procedures targeting the pylorus and the stomach should not be proposed to patients with FD.	94%, Yes	C	A+ 67%, A 28%, A- 6%, D- 0%, D 0%, D+ 0%
Surgical correction of Wilkie/Dunbar should not be proposed for the management of FD.	100%, Yes	C	A+ 61%, A 39%, A- 0%, D- 6%, D 0%, D+ 0%

this consensus group recommends against surgical correction based on radiological signs of Wilkie or Dunbar syndrome only.

J. Pharmacological management targeting the brain-gut axis

Statements on pharmacological management targeting the brain-gut axis are summarised in Table 12.

Researchers investigated different drugs targeting the brain-gut axis in FD. Most evidence exists for tricyclic antidepressants (TCA), as well as for the antipsychotic drug sulpiride and its derivatives. According to a meta-analysis, TCA provide global improvement in FD symptoms compared to placebo (164, 165), especially in the EPS subtype (166-168). Sulpiride, mostly by its active form levosulpiride, also demonstrated greater efficacy than placebo in FD patients in secondary or tertiary care (169, 170). Notwithstanding their efficacy, one should remain aware of the potential side effects of these drugs. There is reasonable data on the role of mirtazapine in the management of FD, especially in patients with weight loss. According to different studies, mirtazapine improved symptoms, QoL, and provided a significant weight gain (171, 172). Contrasting with previous observations, selective serotonin reuptake inhibitors (SSRI) and the selective serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine were not superior to placebo for overall relief of FD symptoms (168, 173).

Only one prospective study investigated the role of gabapentin in FD (174). Similarly, only one randomised study evaluated the potential of pregabalin in patients failing PPI therapy (175). While both studies harboured positive results on symptom management, further studies should corroborate these results.

Two randomised controlled studies demonstrated significant improvement in global symptom relief and quality of life in FD patients treated with melitracen/flupentixol (176, 177), a combination of an antipsychotic and TCA. However, the short treatment duration and sample size of the studies, together with the concerns about neurological and cardiovascular side effects (Belgian Center for Pharmacotherapeutic information), question its value in FD for long-term management.

No studies investigated the best timing of follow-up after start of treatment. In addition, treatment duration is highly variable between studies, as indicated by a meta-analysis assessing a group of neuromodulating agents (164).

K. Nutritional considerations

Statements on nutritional considerations are summarised in Table 13.

Patients relate their symptoms to the intake of certain foods. Also, evidence exists that meal intake induces FD symptoms, especially postprandial fullness (178). Therefore, dietary optimisation has the potential to manage these patients (55). Both a gluten-free and low FODMAP diet have been explored in FD. Wheat-based products are often reported as cause of symptoms (55, 179), prompting the exploration of the effects of gluten-free diets in FD patients (180). However, a randomised, double-blind, placebo-controlled crossover study in individuals with self-reported non-coeliac gluten sensitivity demonstrated that fructans, rather than gluten, induced gastrointestinal symptoms (181). Expanding on this and taking into account its well-established efficacy in patients with IBS (182), the low FODMAP diet showed promising efficacy in FD (183,

Table 12. — **An overview of statements on pharmacological treatment targeting the brain-gut axis with endorsement and grading of evidence.**

Statements on pharmacological treatment targeting the brain-gut axis	Overall agreement, Endorsement	Grade of evidence	Voting distribution
TCA are effective in the management of PDS.	28%, No	C	A+ 17%, A 11%, A- 33%, D- 6%, D 22%, D+ 11%
TCA are effective in the management of EPS.	100%, Yes	B	A+ 83%, A 17%, A- 0%, D- 0%, D 0%, D+ 0%
Antipsychotics (e.g. Sulpiride) are effective in the management of FD.	83%, Yes	C	A+ 22%, A 61%, A- 17%, D- 0%, D 0%, D+ 0%
SSRI are effective in the management of FD.	11%, No	C	A+ 6%, A 6%, A- 0%, D- 11%, D 39%, D+ 39%
SNRI are effective in the management of FD.	23%, No	C	A+ 6%, A 17%, A- 17%, D- 17%, D 22%, D+ 22%
Tetracyclic antidepressants (e.g. Mirtazapine) are effective in the management of FD.	83%, Yes	C	A+ 28%, A 56%, A- 11%, D- 0%, D 0%, D+ 6%
A2d ligand agents (pregabalin) are effective in the management of FD.	12%, No	C	A+ 6%, A 6%, A- 33%, D- 6%, D 28%, D+ 22%
Melitracen /flupentixol (Deanxit) is effective in the management of FD	12%, No	C	A+ 6%, A 6%, A- 44%, D- 22%, D 6%, D+ 17%
Treatment success evaluation should be timed in accordance with study protocol/ results.	50%, No	D	A+ 22%, A 28%, A- 17%, D- 6%, D 6%, D+ 22%

Table 13. — **An overview of statements on nutritional considerations and grading of evidence.**

Statements on nutritional considerations	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Dietary advice should be provided to all FD patients.	47%, No	D	A+ 26%, A 21%, A- 32%, D- 5%, D 5%, D+ 11%
A gluten free diet is not recommended in FD in the absence of coeliac disease	84%, Yes	C	A+ 74%, A 11%, A- 5%, D- 5%, D 0%, D+ 5%
A low FODMAP diet is effective in FD.	32%, No	C	A+ 5%, A 26%, A- 42%, D- 16%, D 11%, D+ 0%
In FD patients with severe weight loss, oral nutritional supplements should be considered.	79%, No	D	A+ 53%, A 26%, A- 21%, D- 0%, D 0%, D+ 0%
In FD patients with insufficient improvement on oral nutritional supplements, enteral nutrition can be considered.	79%, No	D	A+ 37%, A 42%, A- 21%, D- 0%, D 0%, D+ 0%
Parenteral nutrition should be avoided in FD patients.	100%, Yes	D	A+ 89%, A 11%, A- 0%, D- 0%, D 0%, D+ 0%
In underweight FD patients, or FD patients with severe weight loss, eating disorders should be excluded.	84%, Yes	C	A+ 47%, A 37%, A- 11%, D- 0%, D 5%, D+ 0%
ARFID can be a consequence of FD.	74%, No	C	A+ 37%, A 37%, A- 16%, D- 5%, D 5%, D+ 0%

184). However, further confirmation by randomised controlled trials involving a larger number of patients is needed.

The NICE guidelines propose oral nutritional support in cases of unintentional weight loss greater than 10% over the last 3 to 6 months or greater than 5% if the BMI is less than 20kg/m² (170). Conversely, the same guidelines recommend enteral tube feeding for malnourished patients with inadequate oral intake and an accessible digestive tract (170). Both methods of nutritional support are frequently proposed to manage involuntary weight loss in FD patients, but no studies evaluated their impact on symptoms and weight gain, possibly explaining the borderline agreement of this consensus group. On the other hand, according to the recent position statement of the European Society of Clinical Nutrition and Metabolism (ESPEN), the European Society of Neurogastroenterology and Motility (ESNM) and the Rome Foundation for Disorders of Gut-Brain Interaction, parenteral nutrition should not be prescribed for patients without intestinal failure, including FD (185).

Differentiating between FD and eating disorders might prove difficult in some patients. Postprandial discomfort is reported in over 90% of eating disorder patients (186), and nausea in 21% (187). Whether the risk of having an eating disorder is elevated in patients with FD and severe weight loss is unclear, especially because weight loss can be a consequence of isolated FD even in the absence of underlying psychiatric comorbidity. However, symptoms compatible with FD occur more frequently in patients with eating disorders (such as bulimia and anorexia nervosa) and tend to improve after psychiatric treatment (188, 189).

Avoidant/restrictive food intake disorder (ARFID) is an eating disorder previously reserved for children, but now also recognized in adults. ARFID is defined according to the DSM-5 criteria as an eating or feeding disturbance, causing subsequent nutritional deficiencies that are associated with one (or more) of the following: weight loss, nutritional deficiency, dependence on enteral feeding or oral nutritional supplements or marked interference with psychosocial functioning (American psychiatric association, 5th edition, 2013). There is an overlap between ARFID and disorders of gut-brain interactions, such as FD. In particular, 39.9% of patients presenting gastroparesis/dyspepsia symptoms meet the criteria for ARFID (100). Patients often avoid food to manage post-prandial symptoms (190). Conversely, patients with ARFID frequently report fear of gastrointestinal symptoms, especially dyspepsia, nausea and vomiting, which could drive avoidant or restrictive eating behaviours (190).

L. Non-pharmacological management

Statements on non-pharmacological management are summarised in Table 14.

The value of non-dietary and non-pharmacological interventions such as cognitive behavioural therapy (CBT), hypnotherapy and mindfulness in the treatment of FD were the object of several studies. According to a recent meta-analysis, these psychotherapeutic approaches have a beneficial effect on GI symptoms in FD, despite the absence of an effect on quality of life (191). Different systematic reviews drew similar conclusions concerning CBT (192) and hypnotherapy (193) but pointed at the large heterogeneity and risk of bias. Overall, mindfulness-based therapies may provide

Table 14. — **An overview of statements on non-pharmacological management with endorsement and grading of evidence.**

Statements on non-pharmacological management	Overall agreement, Endorsement	Grade of evidence	Voting distribution
Cognitive behavioural therapy is effective in the management of FD.	61%, No	C	A+ 17%, A 44%, A- 39%, D- 0%, D 0%, D+ 0%
Medical hypnotherapy is effective in the management of FD.	61%, No	C	A+ 6%, A 56%, A- 39%, D- 0%, D 0%, D+ 0%
Mindfulness is not recommended in the management of FD.	55%, No	C	A+ 22%, A 33%, A- 17%, D- 6%, D 17%, D+ 6%
Yoga is not recommended in the management of FD.	55%, No	D	A+ 28%, A 28%, A- 28%, D- 0%, D 17%, D+ 0%
Acupuncture is not recommended in the management of FD	78%, No	C	A+ 50%, A 28%, A- 0%, D- 22%, D 0%, D+ 0%
Osteopathy is not recommended in the management of FD.	94%, Yes	D	A+ 61%, A 33%, A- 6%, D- 0%, D 0%, D+ 0%

a benefit to DGBI as a group (194). Specifically in a randomised trial comparing 8 weeks of mindfulness-based cognitive therapy vs. rabeprazole and mosapride for FD, psychotherapy resulted in better sleep and lower GI symptoms, anxiety and depression levels (195). Notwithstanding their demonstrated beneficial effect in FD, the poor availability of therapists proficient in CBT, hypnotherapy and mindfulness for DGBI hamper the application of these treatment modalities in Belgium. The limited experience with these options could also explain the lack of agreement from our panel. Internet-based CBT might represent an interesting future alternative (196).

Other non-pharmacological treatments are sometimes offered to patients with FD. Yoga lowers anxiety and stress levels (197). According to a narrative review, only one study evaluated the potential of yoga in abdominal pain in DGBI in children (198). This review concludes that yoga might provide symptom relief, but additional research is required. A meta-analysis from the Cochrane Collaboration concluded that it remains unknown whether acupuncture is more effective than other treatments (199), contrasting with the conclusion of two subsequent large meta-analyses (200, 201). However, the interpretation of these studies remains hampered by a lack of standardized inclusion criteria, the absence of a proper control group, validated outcome measures, short follow-up and a cultural bias since most studies originated from Asia. In the absence of studies evaluating its role, the panel does not recommend osteopathy in FD.

Discussion

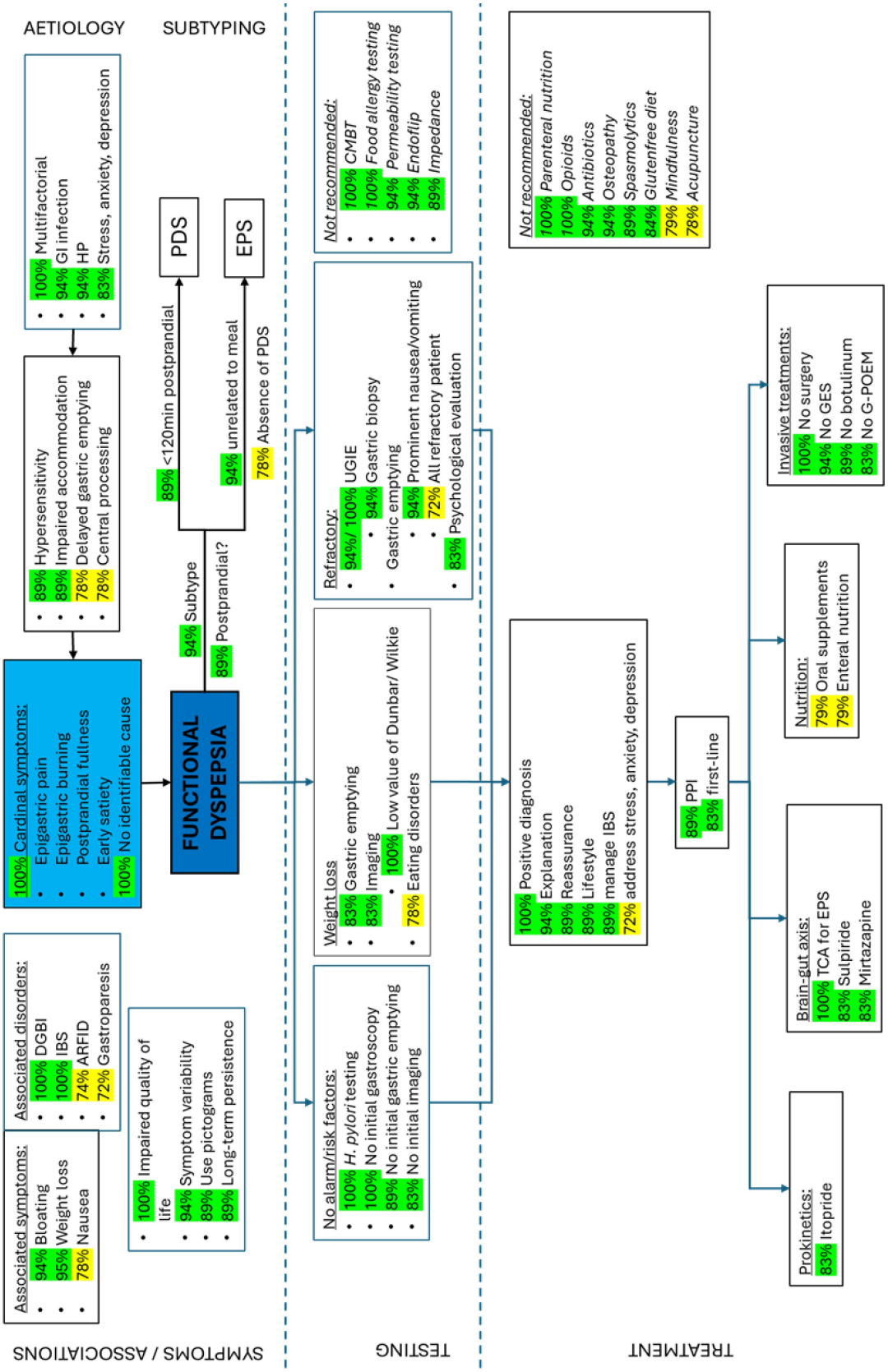
The statements achieving consensus provide guidance in the clinical practice on how to approach a patient with dyspeptic symptoms, as summarised in Fig. 1. A large agreement was obtained concerning the presentation of FD patients. The Rome IV criteria of FD were confirmed, while recognising that patients may experience bloating and weight loss. Further on, this group agreed upon possible aetiologic and pathophysiological mechanisms, while highlighting the implication of psychological factors and the impact on the quality of life. This consensus recommends subtyping patients, based on symptom occurrence within 120 minutes after a meal.

In the absence of alarm symptoms or risk factors, and after non-invasive testing for H pylori, additional testing is not a prerequisite for treatment initiation. In case of alarm features or treatment failure, upper GI endoscopy is required, while imaging, gastric emptying testing and psychological evaluation should be considered on a case-by-case manner. When performing upper GI endoscopy, gastric biopsies should be obtained. This consensus points out that Wilkie syndrome and Dunbar syndrome identified by imaging remain unlikely causes of the symptoms and, therefore, recommend against invasive management of such radiological abnormalities.

Patients should receive a positive diagnosis, clearly mentioning FD, accompanied by explanation, reassurance and lifestyle measures. PPI represent the first-line treatment irrespective of the subtype. However, as previously emphasised in the European guidelines (4), it remains uncertain how to manage patients with FD failing PPI. The panellists concurred best on the role played by TCA in EPS, and sulpiride and mirtazapine in both PDS and EPS. In contrast, strong evidence in favour of prokinetics is missing. Similarly, there is a lack of evidence for treatments avoiding neuromodulators. Concerning nutritional support, only borderline agreement was reached for the role of oral nutritional supplements and enteral feeding.

Notwithstanding the existing evidence, non-pharmaceutical interventions targeting the brain-gut axis were not favoured in this consensus. This is explained by the very limited availability of trained therapists providing cognitive behavioural therapy, hypnotherapy or gut-directed mindfulness in Belgium. The development of internet-based CBT could overcome this issue.

Figure 1. — Schematic representation of the outcome of the consensus on the management of functional dyspepsia. The percentage of agreement is depicted by coloured sqaures, with green representing > 80% consensus and yellow 70 - 80% agreement. 5HT4R serotonin-4 receptor, ARFID avoidant/restrictive food intake disorder, CBT cognitive behavioural therapy, D2RA dopamine 2 receptor antagonist, DGBI disorders of gut-brain interaction, EPS epigastric pain syndrome, FODMAP fermentable oligo-, di-, polysaccharides and polyols, G-POEM gastric peroral endoscopic myotomy, GES gastric electrical stimulation, GI gastrointestinal, H1 histamine-1, IBS irritable bowel syndrome, PDS postprandial distress syndrome, PN parenteral nutrition, SSRI selective serotonin reuptake inhibitor, SNRI serotonin and noradrenaline reuptake inhibitors, TCA tricylic antidepressant, UGIE upper gastrointestinal endoscopy.



Furthermore, the panel recommends strongly against ordering specific tests in FD patients, because of the lack of evidence or therapeutic implications. Similarly, invasive management, being endoscopic or surgical in nature, is not advocated. Finally, this consensus group discourage exclusion diets, parenteral nutrition, as well as the use of opioids, antibiotics, spasmolytics and osteopathy in FD patients.

In summary, based on this consensus, it becomes apparent that a clinical diagnosis of FD is achievable. Testing is only recommended in the presence of alarm features or when failing treatment (repetitively) and should at least consist of upper GI endoscopy. Explanation remains paramount in the management of these patients. While PPI are advocated as first-line treatment, only some neuromodulators provide a therapeutic benefit. Non-pharmaceutical management by a trained therapist with expertise in FD can be considered when available. There is an unmet need for high-quality research to identify other therapeutic options.

Conclusions

FD is a highly prevalent disorder impacting the quality of life of the patients. Following a Delphi process, a group of Belgian FD experts voted on the evidence concerning the definition, aetiology, pathophysiology, required testing and treatment options, taking into account the availability of different options within the Belgian healthcare system. Areas requiring further research are identified. This consensus aims to increase the confidence of clinicians in recognising, diagnosing and treating FD patients in their practice.

Declarations

Conflict of interest:

Sébastien Kindt: Speaker's fee from Truvion Healthcare and Schwabe, Consultancy for Truvion Healthcare, Advisory for Truvion Healthcare.
Joris Arts: No conflicts of interest.
Philip Caenepeel: No conflicts of interests.
Frederik de Clerck: Speaker's fee from Truvion healthcare, Advisory for Truvion Healthcare.
Heiko De Schepper: Speaker's fee from Truvion Healthcare, Menarini, Mayoli, Dr. Falk. Consultancy for Truvion Healthcare, Takeda.
Hubert Louis: Speaker's fee from Takeda, Advisory for Truvion Healthcare.
Pascale Latour: Speaker's fee from Mayoly and advisory for Truvion Healthcare.
Tania Mahler: Author's fee and speaker's fee from Biocodex.
Sara Nullens: Speakers fees and/or on advisory board of Truvion Healthcare, Falk, Ipsen Nv.
Hubert Piessevaux: Advisory board for Truvion Healthcare.
Karen Routhiaux: No conflicts of interests.
Jolien Schol: Speaker's fee from Dr. Falk Pharma.
Magali Surmont: Speaker's fee from Dr. Falk Pharma and MSD, grant from MSD.
Haydeh Vafa: No conflicts of interests.
Kathleen Van Malderen: No conflicts of interests.
Cedric Van de Bruaene: Speaker's fee from Mayoly and the Rome Foundation.
Tim Vanuytsel: Lecturing fees from Abbott, Biocodex, BMS, Dr. Falk Pharma, Ipsen, Menarini, Microbiotica, MyHealth, Schwabe, Takeda, Truvion. Consultant for Baxter, Biocodex, BMS, Dr. Falk Pharma, Promed, Ipsen, Norgine, Takeda, Truvion. Research grants from Danone, Dr. Falk Pharma, MyHealth, Takeda.
Lucas Wauters: Lecturing fees from Biocodex, Dr. Falk Pharma, Ipsen, Menarini, MyHealth, Takeda, Truvion. Consultant for Biocodex, Dr. Falk Pharma. Research grants from Biocodex, Dr. Falk Pharma.
Fabien Wuestenberghs: Consulting and/or lecturing fees from Biocodex Belfium, Biocodex France, Grünenthal, Menarini Belgium, Sanofi, Viatris.
Jan Tack: Scientific advice to Aclipse, Adare, AlfaSigma, Clasado, Danone, Falk, FitForMe, Ironwood, Kyowa Kirin, Menarini, Promed, Ricordati, Takeda, Truvion, Tsumura, Zealand Pharmaceuticals; research support from Biohit, Kiowa Kirin, ProMed, Sofar and Takeda; Speaker bureau for Abbott, Bio-Codex, Mayoly, Menarini, ProMed, Reckitt-Benckiser, Schwabe, Takeda, Thai Meiji and Truvion Pharmaceuticals.

Abbreviations

5HT	5-hydroxytryptamine, serotonin
ARFID	Avoidant/restrictive food intake disorder
CBT	Cognitive behavioural therapy
CI	Confidence interval
D2RA	Dopamine-2 receptor antagonist
DGBI	Disorder of gut-brain interaction
EPS	Epigastric pain syndrome
FD	Functional dyspepsia
FODMAP	Fermentable oligo-, di-, and monosaccharides and polyols
GORD	Gastro-oesophageal reflux disease
GES	Gastric electrical stimulation
GI	Gastrointestinal
G-POEM	Gastric peroral endoscopic myotomy
IBS	Irritable bowel syndrome
PDS	Postprandial distress syndrome
PPI	Proton pump inhibitors
QoL	Quality of Life
RCT	Randomized controlled trial
SSRI	Selective Serotonin Re-uptake Inhibitor
SNRI	Serotonin and noradrenaline re-uptake inhibitor
TCA	Tricyclic antidepressants

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