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Guidelines

Italian guidelines for the diagnosis and treatment of functional dyspepsia – joint consensus from the Italian societies of gastroenterology and endoscopy (SIGE), Neurogastroenterology and motility (SINGEM), hospital gastroenterologists and endoscopists (AIGO), digestive endoscopy (SIED) and general medicine (SIMG)

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ABSTRACT

Functional dyspepsia (FD) is one of the most prevalent disorders of the upper gastrointestinal tract. Despite its broad prevalence, FD diagnosis and treatment are still not well standardized. The aim of this project was to outline an Italian Guideline to define a standardized approach in terms of diagnostic and therapeutic work-up to support both general practitioners and specialists in Gastroenterology. To address this issue, experts from 5 Italian Societies conducted a Delphi consensus process, which included a review of the current literature and voting process on 24 key statements. Recommendations and quality of evidence were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria. Consensus for each statement was defined as $\geq$ 80 % agreement.

Diagnostic Approach: The panel reached consensus on defining FD and its main symptoms and dividing this entity into two different subgroups: the epigastric pain syndrome (EPS) and the post-

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prandial distress syndrome (PDS). Consensus was reached on defining FD as a diagnosis of exclusion and on the need of performing an esophagogastroduodenoscopy with biopsies to exclude organic causes in patients 45 or older, in presence of alarm symptoms and/or in case of refractoriness to treatment. It was agreed that all patients should be screened for H. pylori infection (by invasive or non-invasive means) and that all HP-positive patients should receive eradication therapy. Routine blood tests were recommended to exclude underlying systemic diseases that could present with dyspeptic symptoms. On the other hand, the panel recommended against the routine use of additional testing, including abdominal ultrasound, celiac disease screening and motility studies in FD patients.

Treatment Approach: Consensus was not reached regarding the dietary regimen to adopt in FD patients. Healthy general lifestyle advice was deemed as reasonable to pursue in FD patients, while the use of exclusion diets was discouraged by the panel. The consensus supports a short course of PPIs at standard dose as a first line treatment in FD patients, regardless of the prevalent symptom pattern, while higher PPI doses should not be pursued as an effective strategy in improving patient's response. Consensus was not reached regarding the routine use of H2RA, antacids and alginate-containing products and/or mucosal protectants in the management of FD. The panel recommended against the use of prokinetics as first line treatment in FD patients and advised on preferentially using a short course of prokinetics in PDS-subtype patients. The panel recommends the use of tricyclic antidepressants to treat EPS and supports the use of mirtazapine for FD patients, particularly for those patients with weight loss, while no sufficient evidence was available to recommend SSRIs. The panel recommends the use of cognitive and behavioral therapy for dyspepsia patients who do not respond to medical therapies. Finally, although the panel recognizes the usefulness of complementary and alternative (CAM) treatments in the management of FD patients, no sufficient evidence was available to recommend its use in FD patients, owing to the poor methodology of most published studies involving CAM.

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1. Introduction

Functional dyspepsia (FD) is one of the most prevalent gastrointestinal conditions encountered in general practice and it is defined by the presence of recurrent/chronic symptoms originating from the gastro-duodenal region in the absence of any organic disease likely to explain them [1,2]. In Western countries, the prevalence of dyspepsia is approximately 1 in 4 patients in the general population and the condition accounts for 2–5 % of all consultations in primary care [3].

Despite its broad prevalence, FD still represents a major clinical conundrum, as its definition, pathophysiological mechanisms and clinical spectrum have sensibly evolved over time [4]. Furthermore, it poses major challenges in differential diagnosis since many conditions may mimic its clinical presentation, resulting in a poorly defined diagnostic work-up across primary, secondary, and tertiary care settings. Finally, given the still-uncertain contribution of the underlying pathophysiological mechanisms [5–9], there is still ambiguity regarding the optimal pharmacological management with disappointing results in terms of treatment response [10]. The above-mentioned uncertainties in FD management and treatment translate into an inconsistency in the clinical approach and treatments' choice in this group of patients, also owing to the lack of updated Italian guidelines supporting clinicians' decision -making.

Based on these unmet needs, a joint consensus comprising a group of experts from the Italian Societies of Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED) and General Medicine (SIMG) aimed at developing an Italian consensus defining the diagnostic criteria, diagnosis and treatment of functional dyspepsia.

The aim of this consensus is to guide clinicians in the management of FD in order to optimize patients' treatment outcomes and standardize the optimal clinical management, adapting the most updated evidence from Literature to the specificity of the Italian setting, when applicable.

2. Methods

The Italian Society of Gastroenterology and Digestive Endoscopy (SIGE) initiated a Delphi process to develop a national guideline in order to obtain consensus statements on different aspects of FD including in the process members of all the major Italian societies. A total of 24 representatives' members from the Italian Society of Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG) participated to the Delphi process.

The Delphi process involves developing consensus statements through a voting process based on the best available evidence from a systematic search of the literature, in order to reach consensus where scientific evidence is lacking (e.g., when evidence is not supported by results from randomized controlled trials and/or conflicting evidence has been produced) [11]. Each statement reports the quality of available evidence and the strength of the recommendation according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [12].

After completion of the Delphi process and finalization of the consensus statements, an independent external review was performed. Three external experts (VS, CS, and VS), who were not involved in the Delphi panel or in the initial statement development or voting phases, critically evaluated the finalized consensus document. Their review focused on ensuring clarity, coherence, and clinical applicability of the statements. Minor editorial adjustments based on their feedback were incorporated to enhance the overall readability and precision of the guidelines. No substantial changes were made to the content or strength of recommendations following this review.

The Core Working Group was composed of 4 panel members (EVS, GS, BB and MP) with expertise in Delphi consensus processes and/or guidelines [13–15] which identified 24 clinical questions regarding FD diagnosis and treatment to answer using the patient, intervention, control, and outcome (PICO) process (Table 1). The Italian Consensus Group was recruited within the SIGE and other Italian societies in the field of Gastroenterology and included ex-

Table 1
Six-point Likert scale.

Point	Description
A+	agree strongly
A	agree with minor reservation
A-	agree with major reservation
D-	disagree with major reservation
D	disagree with minor reservation
D+	disagree strongly

perts in FD/GERD. All members submitted a conflict-of-interest statement by April 2023. All panel members performed a systematic literature review of the literature to answer each PICO and drafted statements with a summary of the evidence. The strength of recommendation was graded using accepted criteria and finally, one to two rounds of repeated voting of the statements were performed for reaching consensus. The literature search was performed using MEDLINE, EMBASE, Web of Science and the Cochrane Database of Systematic Reviews until June 30th 2023, without time and/or language restrictions. References were available on an online shared folder accessible to all members. Researchers prioritized data from systematic reviews and meta-analyses of randomized controlled trials (RCTs) and data regarding the specific Italian population in order to identify evidence related to that specific subgroup, when available. The strength of recommendation (GR) was assessed using the GRADE methodology (https://www.gradeworkinggroup.org/) and the recommendations for the different clinical scenarios were classified into three categories: strong (desirable effects outweigh undesirable effects), conditional (trade-offs are less certain) or consensus (the expert opinion supports the guideline recommendation even though the available scientific evidence did not present consistent results, or controlled trials were lacking). To evaluate the quality of evidence (LE), the following definitions were used: high (further research is unlikely to change confidence in the estimate), moderate (further research is likely to change confidence in the estimate), low (further research is very likely to change confidence in the estimate), or very low (the estimate of the effect is very uncertain). The quality of the evidence could be downgraded or upgraded according to different factors such as limitations or implementations in the study design, imprecision of estimates, variability in the results, indirectness of the evidence, publication bias, large magnitude of effects, dose-response gradient, or if all the plausible biases would reduce an apparent treatment effect. In addition, the recommendations also considered other factors such alternative management strategies, variability in values and preferences and the costs. The finalized list of statements with the summary of evidence was edited and discussed in a 3-day telematic session. Thereafter, all members were asked to participate in a first blinded voting round in September 2023 to give their agreement with the statements using a 6-point Likert scale (Table 2) and to provide feedback on their clarity. When at least 80 % of the members agreed with a given statement (*A+* or A), this was defined as a consensus. Since the agreement on all statements was reached after the first voting round, the manuscript was drafted and reviewed by participants for final approval.

3. Results

3.1. SECTION 1: diagnosis (see Fig. 1)

Is dyspepsia an umbrella-term referred to a set of symptoms originating from the gastroduodenal region?

3.1.1. ***Statement 1.1: the panel agrees on defining dyspepsia as "a syndrome that is considered to originate from the gastroduodenal region"***

Statement endorsed. Agreement: 91.3 % [*D* + (0 %); D (0 %); d- (4.3 %); A- (4.3 %); A (26.1 %); *A* + (65.2 %)]

Level of evidence: Moderate Quality Evidence

Level of recommendation: Consensus Recommendation - unable to assess using GRADE methodology

The definition of dyspepsia has been substantially refined over the years. The most recent revision of the Rome criteria, in its 4th iteration, defines dyspepsia as an umbrella term referring to a set of troublesome symptoms in which gastric and/or duodenal dysfunction are key players [1].

The term "uninvestigated dyspepsia" refers to patients in whom a specific cause explaining the symptoms has not been evaluated yet. In dyspepsia patients, additional investigations may identify underlying organic disease (organic dyspepsia); whilst when no organic abnormality is found, patients are deemed to have Functional Dyspepsia [1].

Both Rome III and IV criteria identify four cardinal FD symptoms; namely postprandial fullness, early satiation, epigastric pain and epigastric burning [1,5]. Nonetheless, a number of other digestive symptoms such as upper abdominal bloating, belching and nausea can also coexist in dyspeptic patients, likely reflecting common pathophysiological mechanisms, such as visceral hypersensitivity.

Ever since its third iteration, the Rome Consensus Committee has stressed the concept that dyspepsia symptoms should arise from the gastroduodenal region, significantly narrowing the symptoms profile and thus excluding heartburn from the dyspepsia spectrum. However, nearly one in three dyspepsia patients also complain of typical GERD symptoms; hence the presence of coexisting heartburn should not exclude the diagnosis of FD.

This definition and its implications have been accepted by the most recent international guidelines (ACG, ESNM) [16,17] allowing to minimize the inclusion of GERD and other disorders of gut-brain interaction (DGBI), such as irritable bowel syndrome (IBS), whose symptoms often overlap with FD.

*Should dyspepsia patients be categorized, according to the prevalent symptom pattern, in two different subtypes which may overlap? [*i.e.*, the postprandial distress syndrome (PDS) characterized by meal - induced symptoms (early satiation, postprandial fullness) and the epigastric pain syndrome (EPS), with epigastric pain and/or epigastric burning not necessarily associated to the meal]*

3.1.2. *Statement 1.2: the panel recommends classifying dyspepsia patients into the meal-induced postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS) in which symptoms are not necessarily associated with meals, based on the prevalent symptom pattern*

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (0 %); d- (8.7 %); A- (8.7 %); A (30.4 %); *A* + (52.2 %)]

Level of evidence: Moderate Quality of Evidence

Level of recommendation: Consensus Recommendation - unable to assess using GRADE methodology

All the most recent guidelines (ACG and ESNM) support the identification of two different FD subtypes, the epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) based on two elements: the predominant symptom pattern and the correlation with meals [16,17]. PDS patients report post-prandial fullness and early satiation with loss of appetite, most frequently triggered by ingestion of food; while EPS patients complain of epigastric burning or epigastric pain that are not necessarily meal related. In the EPS subset of patients, symptoms may actually be relieved by meals, or they can also occur while fasting [18]. These symptoms can be acute or chronic and can also be associated with oth-

Table 2
All statements with endorsement, level of evidence, grade of recommendation and agreement.

PICO N	PICO	PICO statement	Endor sement	Degree of recommendation	Quality of Evidence	Agreement
	Diagnosis					
1.1	**Is dyspepsia an umbrella-term referred to a set of symptoms originating from the gastroduodenal region?**	**The panel AGREES on defining dyspepsia as "a syndrome that is considered to originate from the gastroduodenal region"**	**Yes**	**Consensus-unable to assess using GRADE methodology**	**Moderate**	**91.3 %**
1.2	**Should dyspepsia patients be categorized, according to the prevalent symptom pattern, in two different subtypes which may overlap? [i.e., the postprandial distress syndrome (PDS) characterized by meal - induced symptoms (early satiation, postprandial fullness) and the epigastric pain syndrome (EPS), with epigastric pain and/or epigastric burning not necessarily associated to the meal]**	**The panel recommends FOR classifying dyspepsia patients into the meal-induced postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS) in which symptoms are not necessarily associated with meals, based on the prevalent symptom pattern.**	**Yes**	**Consensus-unable to assess using GRADE methodology**	**Moderate**	**82.6 %**
1.3	**Is there an overlap between dyspepsia and other disorders of gut-brain-axis interaction?**	**The panel AGREES on a substantial overlap between dyspepsia and other conditions including gastroesophageal reflux disease and disorders of gut-brain-axis interaction**	**Yes**	**Strong**	**High**	**95.6 %**
1.4	**Is functional dyspepsia a diagnosis of exclusion?**	**The panel recommends FOR defining functional dyspepsia as a diagnosis of exclusion.**	**Yes**	**Strong**	**High**	**82.6 %**
1.5	**Is an upper gastrointestinal endoscopy required for a positive diagnosis of functional dyspepsia?**	**The panel AGREES that an upper gastrointestinal endoscopy is mandatory for establishing a positive diagnosis of functional dyspepsia.**	**Yes**	**Strong**	**High**	**82.6 %**
1.6	**Should dyspeptic patients younger than 45 years of age without alarm signs/symptoms undergo upper gastrointestinal endoscopy?**	**The panel recognizes that dyspeptic patients <45 years might undergo a first upper gastrointestinal endoscopy even in the absence of signs or symptoms of alarm, on a case-by-case basis, if refractory to appropriate first line treatments.**	**Yes**	**Conditional**	**Very low**	**91.3 %**
1.7	**Should routine gastric biopsies be performed to diagnose dyspepsia in patients requiring an early endoscopy?**	**The panel recommends FOR obtaining routine gastric biopsies to document H. pylori status, in dyspepsia patients requiring an early endoscopy.**	**Yes**	**Strong**	**High**	**86.9 %**
1.8	**Should uninvestigated dyspepsia patients routinely be screened for H. pylori infection?**	**The panel recommends FOR testing H. pylori status in dyspepsia patients.**	**Yes**	**Strong**	**High**	**86.9 %**
1.9	**Should H. pylori positive dyspepsia patients receive eradication therapy?**	**The panel recommends FOR treating H. pylori positive- dyspepsia patients.**	**Yes**	**Strong**	**High**	**91.3 %**
1.10	**Should dyspepsia patients routinely be tested for celiac disease?**	**The panel recommends AGAINST routine testing for celiac disease in dyspepsia patients, in the absence of bowel symptoms.**	**Yes**	**Conditional**	**Low**	**91.3 %**
1.11	**Are routine blood tests useful in the diagnostic algorithm of dyspepsia patients?**	**The panel recommends FOR routine blood tests in dyspepsia patients.**	**Yes**	**Conditional**	**Low**	**86.9 %**
1.12	**Should an abdominal ultrasound be performed in patients with dyspepsia to rule out other causes for the symptoms?**	**The panel recommends AGAINST routine abdominal ultrasound in dyspepsia patients, in absence of abdominal pain or symptoms suggestive of biliary disease.**	**Yes**	**Conditional**	**Low**	**82.6 %**
1.13	**Should functional and motility tests be performed in dyspepsia patients?**	**The panel recommends AGAINST routine motility studies in dyspepsia patients.**	**Yes**	**Moderate**	**Moderate**	**91.3 %**
	Treatment					
2.1	**Should dietary interventions be the first-line management strategy in dyspepsia patients?**	**The panel recognizes that while restrictive exclusion diets are not recommended as first-line therapy, general healthy dietary advice may represent a reasonable supportive measure in the management of dyspeptic patients.**	**Yes**	**Conditional**	**Very low**	**91.4 %**

(*continued on next page*)

Table 2 (*continued*)

PICO N	PICO	PICO statement	Endor sement	Degree of recommendation	Quality of Evidence	Agreement
2.2	**Are exclusion diets (low FODMAP diet and gluten-free diet) effective in relieving dyspepsia symptoms?**	**The panel recommends AGAINST exclusion diets (low FODMAP diet and gluten-free diet) in dyspepsia patients.**	**Yes**	**Conditional**	**Low**	**86.9 %**
2.3	**Should PPIs be used as a first line treatment in patients with EPS-subtype of functional dyspepsia?**	**The panel recommends FOR PPIs as a first-line treatment in patients with EPS-subtype of functional dyspepsia.**	**Yes**	**Moderate**	**Strong**	**95.6 %**
2.4	**Should standard-dose PPI therapy be used as a first line treatment in dyspepsia patients, regardless of their subtype (EPS vs PDS)?**	**The panel recommends FOR a short-course of PPIs at standard dose as a first line treatment in dyspepsia patients, regardless of the prevalent symptom pattern.**	**Yes**	**Moderate**	**Strong**	**82.6 %**
2.5	**Can H2-receptor antagonists be used in dyspepsia patients?**	**The panel recommends AGAINST the routine use of H2RA in dyspepsia patients.**	**Yes**	**Conditional**	**Low**	**91.3 %**
2.6	**Can antacids, alginate-containing products and/or mucosal protectants be used in dyspepsia patients?**	**The panel recommends AGAINST the routine use of antacids, alginate-containing products and/or mucosal protectants in dyspepsia patients.**	**Yes**	**Conditional**	**Low**	**82.6 %**
2.7 **2.8**	**Should prokinetics be used as a first-line therapy in dyspepsia patients?***	**Statement 2.7: The panel recommends AGAINST prokinetics as a first-line therapy in dyspepsia patients [1]. Statement 2.8: When indicated, the panel recommends FOR the preferential use of prokinetics in PDS-subtype dyspepsia patients [2]**	**Yes**	**1.Moderate** **2.Consensus**	**1.Moderate** **2.Low**	**95.6 %**
2.9	**Should antidepressants (TCAs, SSRIs, mirtazapine) be used to treat refractory dyspepsia symptoms?**	**The panel recommends FOR TCAs to treat EPS dyspepsia patients refractory to standard treatments, while there is insufficient evidence to support the use of SSRIs in these patients. Mirtazapine could be useful in patients with weight loss.**	**Yes**	**Consensus**	**Moderate**	**82.6 %**
2.10	**Can psychological therapies be useful in managing dyspepsia symptoms?**	**The panel recommends FOR cognitive and behavioral therapy for dyspepsia patients not responding to medical therapies**	**Yes**	**Consensus**	**Low**	**82.6 %**
2.11	**Should complementary and alternative (CAM) treatments be considered in managing dyspepsia symptoms?**	**The panel recognizes that CAM therapy might be useful in dyspepsia patients, however, most studies involving CAM treatments have poor methodology.**	**Yes**	**Consensus**	**Low**	**82.6 %**

* Statements 2.7 and 2.8 were derived from a single voting session concerning the role of prokinetics in functional dyspepsia. The reported agreement percentage applies to both statements.

ers such as nausea, bloating or belching. The two subtypes can be present in the same patient (overlap EPS-PDS), but improvement in defining patient symptoms reduces the possibility of overlapping between two subtypes.

These diagnostic categories were first recognized by the Rome III criteria; however, data from epidemiological studies showed that with those criteria a substantial percentage of FD patients would be identified in the overlap group. The Rome IV criteria further refined this distinction, by introducing minimal thresholds for frequency and severity of individual symptoms and introducing the concept of 'bothersome' symptoms (which should be clinically defined as "severe enough to impact on usual activities), thus overcoming the substantial overlap between EPS and PDS syndrome [1]. Compared to Rome III, according to a recent study [18], Rome IV could better distinguish PDS from EPS, significantly reducing the overlap of Rome III (67 %). However, using Rome IV, a clinical overlap remains in more than a third of cases (35 %). The overlap of PDS and EPS obviously complicates further targeted diagnostic and therapeutic choices. In addition, EPS is extremely less frequent than PDS (8 % vs 57 %) from epidemiological point of view [18].

The suggestion of distinguishing among the two main symptom patterns was based on the assumption that each subtype would be more homogenous in terms of underlying pathophysiological mechanisms, thus potentially influencing therapeutic choices compared with FD as a whole [1,18,19]. Indeed, preliminary reports showed a different contribution of gastric dysmotility (i.e. impaired gastric accommodation and delayed gastric emptying) and/or duodenal subtle abnormalities (low-grade inflammatory change and duodenal hypersensitivity to chemical stimuli) between the two subgroups, with a higher rate of delayed gastric emptying in the PDS as compared to EPS subtype [5].

However, further studies questioned whether the prevalent symptom pattern pointed at a different pathophysiological mechanism(s), with several studies demonstrating no significant difference in gastric or duodenal abnormalities between the EPS and PDS subgroups, according to Rome III criteria [6,20]. Overall, available data shows conflicting results in terms of treatment response rates and contribution of pathophysiological mechanisms in EPS and PDS syndrome and to date, no studies have systematically assessed differences in treatment responses between EPS and PDS, according to the Rome IV criteria.

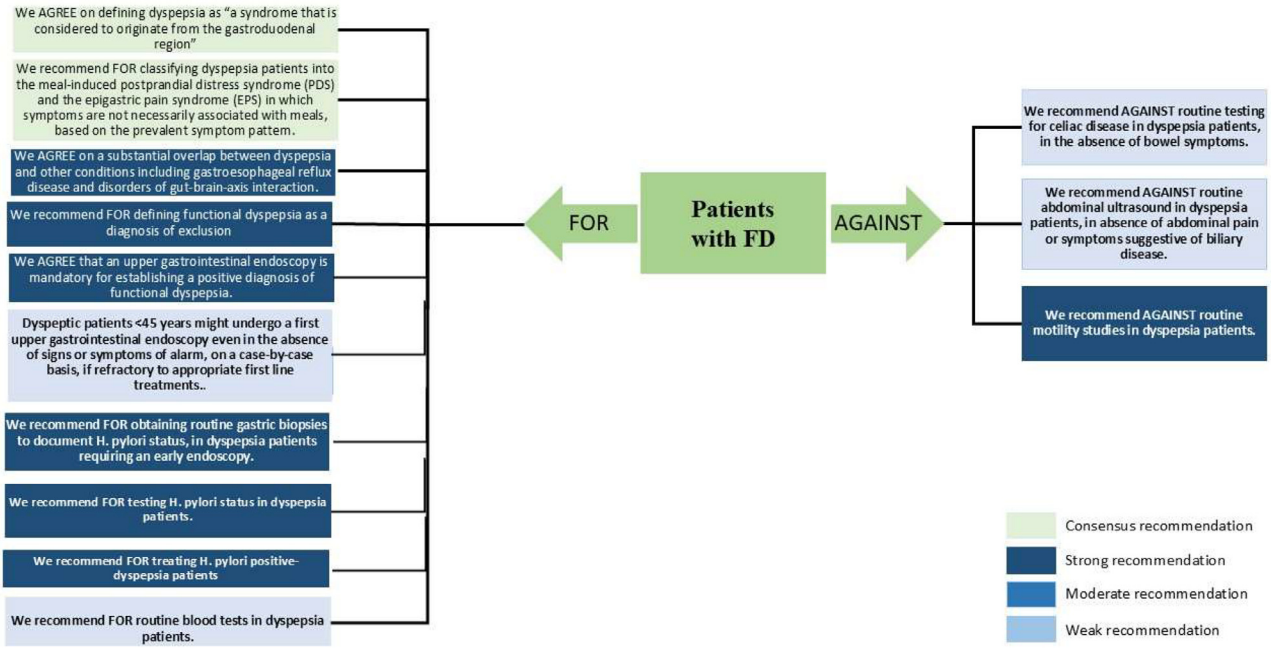


Fig. 1. Summary of the diagnostic strategies for the workup of FD patients with strength of recommendations indicated.

Is there an overlap between dyspepsia and other disorders of gut-brain-axis interaction?

3.1.3. Statement 1.3: the panel agrees on a substantial overlap between dyspepsia and other conditions including gastroesophageal reflux disease and other disorders of gut-brain interaction

Statement endorsed. Agreement: 95.6 % [*D* + (0 %); D (0 %); d- (0 %); A- (4.3 %); A (0 %); *A* + (95.6 %)]

Level of evidence: High Quality Evidence

Level of recommendation: Strong Recommendation

FD and other DGBI show a high rate of overlap that could be explained by common etiological risk factors (e.g., acute infectious gastroenteritis and psychological disturbances) and pathophysiological mechanisms (e.g., visceral hypersensitivity and altered motility) [21,22].

IBS is a DGBI which often overlaps with FD, and patients with overlapping conditions are at higher risk of developing more severe symptoms [2,22]. In a large observational study, it was reported that an overlap with FD occurred in 55.3 % of subjects who met Rome IV criteria for IBS [23].

GERD is another symptomatic condition which often overlaps with FD: typical GERD symptoms have been reported by one-third of FD patients [21]. In patients with GERD, a poor response to proton pump inhibitors (PPIs) has been associated with co-existing FD [24]. In addition, non-acid-related conditions, such as functional heartburn, frequently overlap with FD [21,22]. At least 30 % of patients presenting dyspeptic symptoms without heartburn as a predominant symptom show abnormal esophageal acid exposure in pH monitoring, and up to 50 % in the subgroup of patients suffering from epigastric burning show the same symptoms [21].

Rumination syndrome is another functional gastroduodenal disorder characterized by effortless regurgitation of ingested food. According to recent reports, rumination syndrome overlaps with FD with a shared risk factor profile [25].

A delayed gastric emptying, which is a hallmark of gastroparesis, has been reported in 20–50 % of FD patients, but inconsistent results have been reported by its association with symptoms and response to therapy [26,27]. Although generally considered different, there is substantial overlap in these two disorders, and they likely represent part of a range of gastric sensorimotor disorders.

Is functional dyspepsia a diagnosis of exclusion?

3.1.4. Statement 1.4: the panel recommends FOR defining functional dyspepsia as a diagnosis of exclusion

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (4.3 %); d- (0 %); A- (13 %); A (21.7 %); *A* + (60.9 %)]

Level of evidence: High Quality Evidence

Level of recommendation: Strong Recommendation

FD is considered a diagnosis of exclusion, with no signs of organic disease [1,28]. According to guidelines, an upper GI endoscopy is recommended in dyspeptic patients aged over 45 years, in order to exclude the presence of neoplasia and to assess the presence of *Helicobacter pylori* (HP) infection [1,5,16,17,29]. Endoscopy is also mandatory in younger patients presenting with alarm features [1,5]. According to Rome IV criteria, heartburn is not a dyspeptic symptom, yet it may coexist with FD, and the presence of heartburn should not exclude the diagnosis of FD [1,17]. While considering the actual diagnosis of FD, an upper GI endoscopy is mandatory to exclude benign organic disorders which may justify symptoms such as peptic ulcers (prevalence 8 %), esophagitis (20 %), or HP-associated gastritis [30].

Microscopic HP infection has been considered a factor potentially involved in generating symptoms, when dealing with FD patients with otherwise normal macroscopic findings in the endoscopy. The Kyoto and the Rome IV consensus stated that HP infection is strictly connected with dyspepsia in a subset of patients, with a strong grade of recommendation and high evidence level [1,31]. However, an intermittent peptic ulcer disease is also plausible if missed during a prior endoscopy for dyspeptic symptoms [31]. No evidence are available to confirm whether the presence of chronic superficial gastritis (with or without atrophy) could be responsible for FD symptoms [1,31,32]. As a result, if HP infection cannot be demonstrated, a patient with dyspeptic symptoms and normal endoscopy should be considered to have FD even if gastritis is present, whatever its severity [1].

A meta-analysis of 21 controlled studies on the association between gallstones and dyspeptic symptoms was performed by Kraag

et al. and no reasonable association between gallstones and "classical" dyspeptic symptoms was found [33] As a result, upper abdominal ultrasound is not routinely recommended for the exclusion of biliary pathology in the diagnosis of FD [1,34].

Is an upper gastrointestinal endoscopy required for a positive diagnosis of functional dyspepsia?

3.1.5. Statement 1.5: the panel agrees that an upper gastrointestinal endoscopy is required for establishing a positive diagnosis of functional dyspepsia

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (4.3 %); d- (0 %); A- (13 %); A (39.1 %); *A* + (43.5 %)]

Level of evidence: High Quality Evidence

Level of recommendation: Strong recommendation

FD is a diagnosis of exclusion, thus requiring the identification and treatment of underlying organic diseases (such as peptic ulcer disease and gastric cancer) that could potentially present with dyspeptic symptoms [1].

Although many attempts have been made to categorize patients into pathophysiologically meaningful subgroups, it is apparent that the prevalent symptom pattern at presentation is not able to discriminate whether patients with uninvestigated dyspepsia have an underlying organic disease causing the symptoms. Indeed, in a large prospective study involving 820 patients with uninvestigated dyspepsia, the prevalent dyspepsia subgroup (i.e. dysmotility-like vs ulcer-like) showed a very low sensitivity in discriminating functional vs organic dyspepsia and was a poor predictor of the diagnosis as compared to other variables; such as younger age, female gender, frequent upper abdominal pain, no pain relief with antacid use, and infrequent vomiting [35]. Furthermore, a large meta-analysis involving 11 366 patients referred to endoscopy for dyspepsia symptoms concluded that neither clinical patterns nor models computing several patients' characteristics (including demographics, risk factors, history items, and symptoms) was adequately reliable in distinguishing between organic and functional disease in patients with uninvestigated dyspepsia [36].

For these reasons, an upper gastrointestinal endoscopy is deemed mandatory to establish a positive diagnosis of FD, according to the most recent international guidelines and meta-analyses [1,5,16,17,29,35–37].

According to the European guidelines, in patients with warning signs an upper gastrointestinal endoscopy should be performed regardless of age [17]. ACG and CAG guidelines suggest upper gastrointestinal endoscopy in patients with symptoms or warning signs only over the age of 60 [16].

However, the initial management of younger patients without alarm symptoms remains a conundrum, particularly in primary care settings. According to both European and American guidelines, in a primary care setting, endoscopy should not be performed in younger patients without warning symptoms [17]. This choice is justified by the very low probability of a missed diagnosis of underlying malignancy in patients aged < 45 years old. In this group of patients, non-invasive testing for HP infection should represent the initial management of choice due to the non-invasiveness, cost-effectiveness and similar efficacy in terms of symptoms relief and improvement in quality of life as compared to early endoscopy.

Should dyspeptic patients younger than 45 years of age without alarm signs/symptoms undergo upper gastrointestinal endoscopy?

3.1.6. Statement 1.6: the panel recognizes that dyspeptic patients <45 years might undergo a first upper gastrointestinal endoscopy even in the absence of signs or symptoms of alarm, on a case-by-case basis, if refractory to appropriate first line treatments

Statement endorsed. Agreement: 91.3 % [*D* + (0 %); D (0 %); d- (0 %); A- (8.7 %); A (43.5 %); *A* + (47.8 %)]

Level of evidence: Very low-quality Evidence

Recommendation: Conditional recommendation.

The most recent guidelines consider an upper digestive endoscopy as mandatory for a conclusive diagnosis of functional dyspepsia and in the presence of warning signs or symptoms [16], [17]. While endoscopy remains mandatory to establish a definitive diagnosis of functional dyspepsia in all age groups, current guidelines recognize that, particularly in younger patients without alarm features, initial management without endoscopy is appropriate in primary care settings. The ACG/CAG guidelines specifically recommend endoscopy for patients older than 60 years [16].

In the latest UEG/ESNM guideline [17] it is generically stated that "in younger patients" without warning symptoms, gastroscopy is not necessary to detect malignancy considering the low prevalence of cancer in this population. However, this threshold should be defined locally: for instance, in Tuscany, the incidence of gastric cancer (GC) is approximately three-fold higher than in southern Italy. In patients <45 years, according to published Italian data, the incidence rate of GC is 1.4/100.000 (105 cases in the years examined between 2013 and 2017) [38]. The criteria of appropriateness established by the ASGE guidelines [39] in order to reduce examinations with low cost-benefit outcomes should always been considered in the selection of patients for upper GI endoscopy. A recent systematic review reported 21.7 % of inappropriate upper GI endoscopies [40]. Similar data have been published in an Italian survey [41]. Moreover, an Italian study [42] analyzed 602 dyspeptic patients including 30 % of patients aged <45 years (age range 19–87). The overall inappropriateness was 27.3 % without significant differences between the age group < to 45 (25.1 %) and the age group > 45, (28.2 %). This study [42] reported significantly greater inappropriateness in the repeated endoscopies compared to the 1st endoscopy (47 % vs 6 %). This is confirmed by a large American study [43] on 86,000 patients reporting inappropriateness of 43 % for the repeated endoscopies.

Furthermore, an early endoscopy could provide reassurance to both the physician and the patient and enables a positive diagnosis of FD. In patients with FD resistant to empirical medical therapy, an early endoscopy could lead to a proper differential diagnosis and at the same time could provide reassurance and refer patients to appropriate second or third-line treatments (such as behavioral therapy, psychotherapy, antidepressants). Based on these data, in young anxious patients, an initial gastroscopy might be considered, even without warning signs, to investigate refractory dyspepsia, particularly in specialist settings. In this particular subset of patients, the exclusion of a malignant disease might reduce the number of future visits and significantly improve the quality of life and could increase appropriateness and compliance to medical therapy, although conflicting data have been published in this regard [44,45].

Based on these data, a baseline endoscopy might be considered in young patients, on a case-by-case basis, particularly if refractory to adequate medical therapy. In conclusion, more studies are needed to evaluate the indication for endoscopy in subjects <45 years considering appropriateness and the potential reassuring effect.

Should routine gastric biopsies be performed to diagnose dyspepsia in patients requiring an early endoscopy?

3.1.7. Statement 1.7: the panel recommends FOR obtaining routine gastric biopsies to document H. pylori *status, in dyspeptic patients requiring an early endoscopy*

Statement endorsed. Agreement: 86.9 % [*D* + (4.3 %); D (8.7 %); d- (0 %); A- (0 %); A (13 %); *A* + (73.9 %)]

Level of evidence: High Quality Evidence

Recommendation: Strong Recommendation

According to the European guidelines, an upper GI endoscopy is mandatory in patients with dyspeptic symptoms aged 45 years or

older to rule out GC and/or other organic underlying causes for the symptoms. In fact, the incidence rate of GC rises progressively with age; with a median age at diagnosis of 70 years [46]. However, approximately 10 % of gastric carcinomas are detected at the age of 45 or younger. An upper GI endoscopy is, therefore, also mandatory in younger patients with alarm features, although alarm symptoms have limited value in predicting an organic disease [36]. Endoscopy can rule out not only malignancies but also diagnose benign organic disorders which may explain the symptoms such as peptic ulcer (prevalence 8 %), esophagitis (20 %), or HP-associated gastritis [16,29].

In patients requiring an early endoscopy, all current guidelines agree on obtaining routine gastric biopsies to document the HP status [17]. The endoscopy-based tests to assess HP status include the rapid urease test and the histopathological evaluation.

In the absence of risk or alarm factors (e.g., family history of dysplasia or gastric cancer) and in patients with a normal endoscopic examination without pathological endoscopic features, current guidelines recommend for using the rapid urease test (one biopsy taken in the corpus and one in the antrum) as opposed to routine histological evaluation, since it is faster and cheaper, with high sensitivity and specificity (> 90–95 %) [47,48]. However, in the context of active bleeding and/or in patients with previous therapy with PPI, bismuth or antibiotics, the sensitivity of the rapid urease test significantly drops [49].

Hence, in this group of patients or in the presence of family history and in patients with documented HP infection; histopathological examination, obtaining multiple biopsies according to the Sidney protocol (two biopsies from the antrum, at the lesser and greater curvature, two from the body, at the lesser and greater curvature, and one from the incisura), is currently deemed necessary, as it provides useful information that should guide management and follow-up of dyspeptic patients [48]. Indeed, histopathology can discriminate patients with a higher likelihood of developing peptic ulcer disease, chronic atrophic gastritis and gastric neoplasia based on the grade, extent, and topography of inflammatory and atrophy-related lesions [50].

At the same time, a normal histopathological evaluation indicates a very low likelihood of future peptic ulcer disease and GC; thus, providing reassurance and avoiding unnecessary rescoping of dyspeptic patients [48].

Should uninvestigated dyspeptic patients routinely be screened for H. pylori infection?

3.1.8. Statement 1.8: the panel recommends FOR testing H. pylori *status in dyspeptic patients*

Statement endorsed. Agreement: **86.9 %** [*D* + (0 %); D (8.7 %); d- (4.3 %); A- (0 %); A (8.7 %); *A* + (78.2 %)]

Level of evidence: High Quality Evidence

Recommendation: Strong Recommendation

HP infection can cause dyspeptic symptoms [40]; therefore, HP infection should be excluded in all dyspeptic patients at the first evaluation [51].

Testing of HP status can be performed by non-invasive means in younger patients without alarm features. However, the non-invasive test of choice needs to have a high negative predictive value since it needs to provide reassurance of the effective negativity of the HP status in patients who will not be referred for further invasive tests [3]. Hence, the test of choice for HP infection in primary care should either be a 13C urea breath test or a stool antigen test, given their high accuracy in detecting HP infection. It is important to note that proton pump inhibitors should ideally be discontinued at least two weeks before performing urea breath tests or stool antigen tests, to minimize the risk of false-negative results. On the other hand, if endoscopy is performed, biopsies should be obtained to test for HP status. The HP search should be done independently by the local prevalence of the infection [16].

Several trials compared the HP test and treat with prompt upper GI endoscopy in uninvestigated dyspeptic patients, showing no difference in terms of global dyspeptic symptoms at the end of one year follow up between H. pylori test and treat and prompt endoscopy [51–56]. For these reasons, all current guidelines agree on a test and treat approach as a first-line management in patients with uninvestigated dyspepsia without alarm features.

A possible concern raising from the test and treat strategy as opposed to early endoscopy is to miss underlying organic causes, such as GC. Western European countries, including Italy, have however, a low incidence of GC, despite some regional differences. For instance, in Tuscany, the incidence of GC is approximately threefold higher than in southern Italy [57]. However, by using an appropriate age threshold and promptly scoping patients with alarm symptoms, the probability of under-recognizing gastric cancer will be extremely low. Furthermore, the eradication of HP removes a key risk factor for gastric cancer and can be viewed as preventative medicine, as it is likely to reduce the risk of future organic gastroduodenal disease.

Should H. pylori positive dyspeptic patients receive eradication therapy?

3.1.9. Statement 1.9: the panel recommends FOR treating H. pylori *positive- dyspeptic patients*

Statement endorsed. Agreement: **91.3 %** [*D* + (0 %); D (0 %); d- (4.3 %); A- (4.3 %); A (4.3 %); *A* + (87 %)]

Level of evidence: High Quality Evidence

Recommendation: Strong Recommendation

All the most recent international guidelines (ACG, Nice and European) agree on pursuing a test and treat strategy for HP infection in dyspeptic patients.

HP eradication may improve symptoms in a subset of patients with investigated dyspepsia. However, this subgroup of patients is relatively small; a meta-analysis showed a 10 % relative risk reduction of persisting symptoms in the HP eradication group compared to placebo, with a number needed to treat (NNT) of 12.5 to cure one case of dyspepsia [16]. Moreover, the clinical benefit, when present, may be observed only after 6–12 months after eradication [31].

Both EPS and PDS-like dyspeptic patients could potentially benefit from HP eradication in terms of symptoms improvement; however, several studies demonstrated a preferential improvement of predominant EPS symptoms [58,59].

Although there is a modest benefit in terms of improvement of symptoms, HP eradication has to be preferred since it reduces future risk of gastric cancer and peptic ulcer disease.

Hence, based on the available data, clinicians must be aware that a substantial number of FD patients will not benefit from HP eradication from a symptomatic standpoint, at least in the short-term follow-up. Nevertheless, HP eradication is necessary as it can be regarded as preventative medicine, since it is likely to impact on the risk of developing future organic gastroduodenal disease, including gastric cancer [31,60].

Should dyspeptic patients routinely be tested for celiac disease?

3.1.10. Statement 1.10: the panel recommends against routine testing for celiac disease in dyspeptic patients, in the absence of bowel symptoms

Statement endorsed. Agreement: 91.3 % [*D* + (8.6 %); D (0 %); d- (0 %); A- (0 %); A (30.4 %); *A* + (60.8 %)]

Level of evidence: Low quality of evidence

Recommendation: Conditional recommendation

The dyspepsia spectrum includes symptoms of post-prandial fullness, bloating, early satiation and epigastric pain that may also

be the presenting clinical symptom of celiac disease (CeD). FD patients often report food as a main trigger for their symptoms and develop eating-avoidant behaviors, excluding groups of ailments from their diet, including gluten [61]. In patients with refractory dyspepsia, the gluten-free diet has been shown to relieve symptoms and improve the quality of life in a placebo-controlled trial [62]. Hence, given the positive symptomatic response to gluten-free regimens, an accurate diagnosis of CeD in dyspeptic patients can have key therapeutic and prognostic implications. However, conflicting data on the prevalence of CeD in patients with uninvestigated dyspepsia have been produced. In a 2009 systematic review, patients with dyspepsia were reported to have a nearly doubled risk of having a positive celiac serology compared to controls. However, when comparing the prevalence of biopsy-proven CeD, the Authors found no significant differences compared to controls [63]. These results were biased by the unclear definition of biopsy-proven CeD and a lack of formal bias assessment of the included studies.

In a more recent systematic review and metanalysis including 21 studies (10,275 FD patients), the Authors observed a 4.8 % prevalence of positive anti-tissue transglutaminase and/or anti-endomysial antibodies and a 1.5 % prevalence of biopsy-proven CeD in dyspepsia patients [64]. They concluded that the pooled prevalence of CeD in dyspeptic patients was not significantly higher than that of the general population. Although the authors reported a considerable heterogeneity in the pooled results, explained by the heterogeneity in the dyspepsia diagnostic criteria, screening strategy, and the study settings; they stated that there was insufficient evidence to support for the routine CeD screening in patients with dyspepsia [64].

Given these results, we recommend against routine testing for CeD in dyspeptic patients, particularly in the absence of bowel symptoms and/or other risk factors (such as familial history of CeD and/or presence of other autoimmune conditions).

Are routine blood tests useful in the diagnostic algorithm of dyspeptic patients?

3.1.11. Statement 1.11: the panel recommends FOR routine blood tests in dyspeptic patients

Statement endorsed. Agreement: 86.9 % [*D* + (4.3 %); D (0 %); d- (0 %); A- (8.7 %); A (21.7 %); *A* + (65.2 %)]

Level of evidence: Low quality of evidence

Recommendation: Conditional recommendation

The dyspepsia symptom complex can be caused by a variety of organic gastro-duodenal, biliary-pancreatic and metabolic disorders that can present with bothersome upper gastrointestinal symptoms. The presence of iron deficiency anemia is included in the "red flags" that should impose a prompt endoscopy to address patients' symptoms [16,17].

Hence, routine blood tests comprising full blood count and routine biochemistry including glycaemia, iron, ferritin, liver function tests, serum lipase, and amylase, might be useful as an initial approach to identify patients with alarm features (e.g. iron deficiency anemia) and/or underlying metabolic diseases that can cause dyspepsia (e.g. diabetes).

Furthermore, particularly in patients presenting with vomiting and weight loss, routine blood test could identify secondary metabolic alterations, such as electrolyte imbalance or nutrient deficiencies.

Nonetheless, current guidelines do not address the usefulness of laboratory testing in the diagnostic algorithm of dyspepsia patients. The most recent European guidelines by UEG/ESNM failed to endorse a statement that screening blood tests are useful in FD patients with an overall agreement of 46 % [17]. They state that there is substantial lack of evidence to support the cost-benefit advantage of routine blood tests in these patients, with a single study from India [65] showing that hemoglobin and albumin levels could be useful to discriminate between functional and organic dyspepsia, when computed in a complex risk model with other variables (i.e. demographics, symptoms onset and other alarm features). However, these results were not replicated in western populations, so far.

Overall, despite the lack of evidence, routine blood tests could stratify the population of dyspeptic patients, helping to identify those with underlying organic disorders and/or exclude secondary metabolic alterations in case of severe symptoms.

Should an abdominal ultrasound be performed in patients with dyspepsia to rule out other causes for the symptoms?

3.1.12. Statement 1.12: the panel recommends against routine abdominal ultrasound in dyspeptic patients, in absence of abdominal pain or symptoms suggestive of biliary disease

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (4.3 %); d- (0 %); A- (13 %); A (39.1 %); *A* + (43.5 %)]

Level of evidence: Low quality of evidence

Recommendation: Conditional recommendation

Dyspepsia symptoms include, among the others, epigastric pain that could mimic pancreato-biliary pathologies. However, contrary to earlier convictions, it has been well established that no dyspeptic symptom, other than upper abdominal pain, have a clear correlation with the presence of gallstones.

Indeed, a meta-analysis of 21 studies reasonably excluded a positive association between the presence of gallstones and dyspeptic symptoms other than upper abdominal pain, while they reported a weak association for nausea and vomiting [33].

Furthermore, in a subsequent systematic review comprising 24 studies, the authors found that biliary colic, described as 'an episodic, severe steady pain, lasting >15 min', was the only symptom consistently associated with gallstones [66]. However, up to 5 % of patients can report food-related biliary pain in the absence of ultrasonographic evidence of gallstone disease or bile duct dilatation. This condition has been referred to as "biliary dyspepsia" [67].

Based on these results, the most recent UEG/ESNM guidelines did not endorse to investigate each patient presenting with dyspeptic symptoms with an upper abdominal ultrasound (US) [17].

Hence, the decision to perform a US examination should be undertaken on an individual basis based on symptoms characteristics, refractoriness to appropriate first-line treatments and/or other features suggestive of biliary pathology.

Should functional and motility tests be performed in dyspeptic patients?

3.1.13. Statement 1.13: the panel recommends against routine motility studies in dyspeptic patients

Statement endorsed. Agreement: 91.3 % [*D* + (0 %); D (0 %); d- (0 %); A- (8.7 %); A (34.8 %); *A* + (56.5 %)]

Level of evidence: moderate quality of evidence

Recommendation: Moderate recommendation

A number of subtle abnormalities in gastroduodenal motility and sensitivity have been described in FD patients [1]. Abnormal gastric accommodation may be present in up to 40–50 % of patients with FD [30]. However, gastric accommodation can only be accurately assessed using sophisticated techniques, such as gastric barostat, single-photon emission computed tomography (SPECT) scanning, or gastric emptying scintigraphy [68], hindering their role in the routine diagnostic workup of FD patients. Similarly, although usually mild, a delay in gastric emptying rates can occur in up to one-third-of FD patients [4]. A recent systematic review and meta-analysis of observational studies supported an associa-

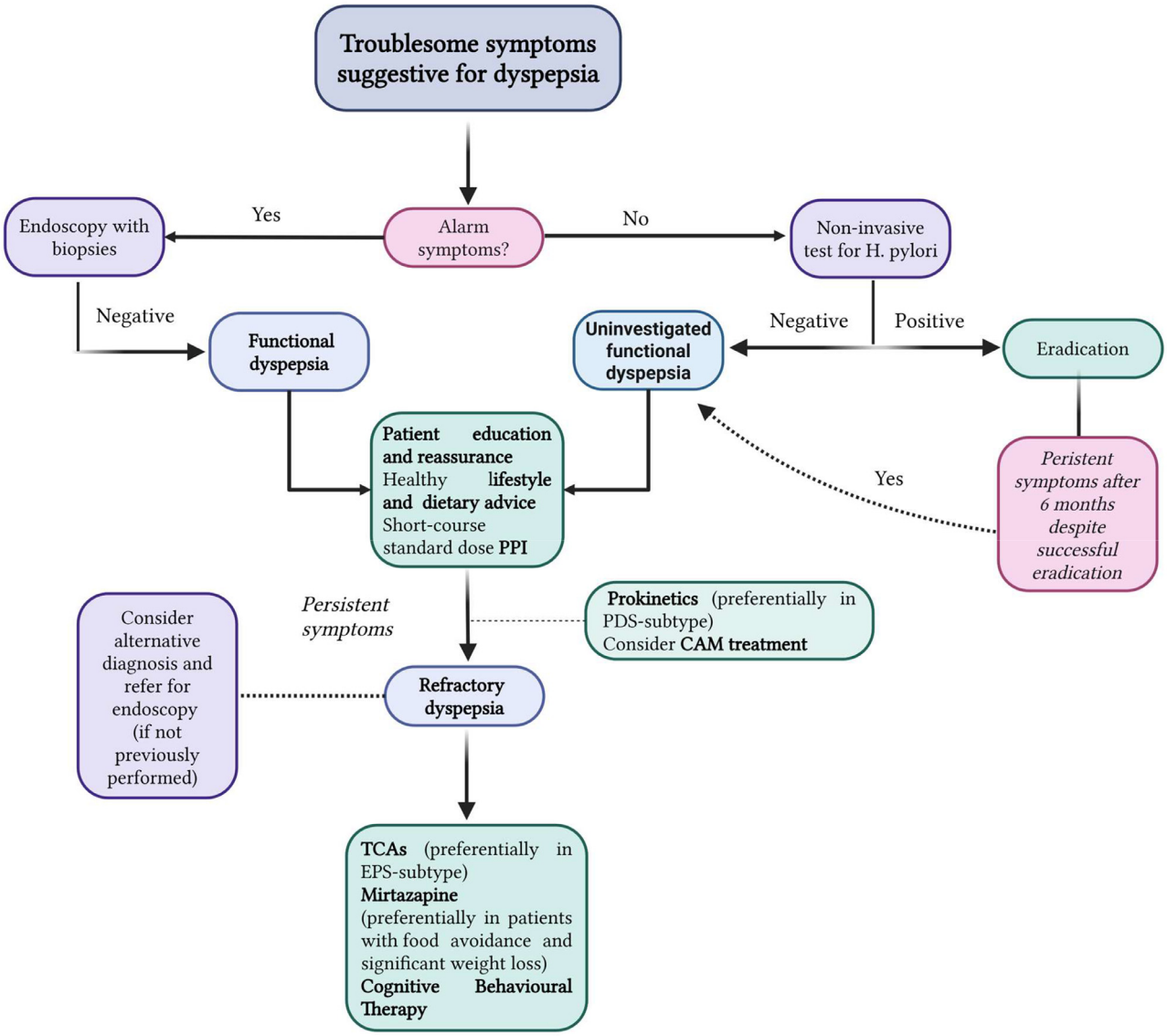


Fig. 2. Diagnostic and therapeutic algorithm for FD, including lifestyle, pharmacologic and complementary approaches.

tion between optimally measured gastric emptying testing (using breath test or scintigraphy) and upper gastrointestinal symptoms (namely: nausea, vomiting, abdominal pain, bloating and early satiation/fullness). However, the magnitude of the association is not robust, and different results were reported depending on the protocol used (optimal or suboptimal method) and/or the methodology applied (breath test or scintigraphy) [26]. Another recent systematic review and meta-analysis evaluated the association between gastric emptying rates and dyspeptic symptoms after using promotility agents [27]. The meta-regression failed to show a significant correlation between improved gastric emptying rates and upper GI symptoms [27,69]. However, when 5 studies using a "suboptimal" methodology to evaluate gastric emptying rates were excluded from the analysis, a significant correlation emerged [27]. Yet, it should be noted that all prokinetics included in the analysis could exploit different mechanisms other than accelerating gastric emptying time [69]. Evidence is therefore not consistent [17]. For these reasons, and also considering their limited availability, costs and invasiveness (e.g., gastric barostat), routine motility tests for FD patients should not be routinely recommended [1,16,17].

3.2. Section 2: treatment (see Fig. 2)

The management of functional dyspepsia requires a comprehensive and patient-centered approach. Before initiating specific interventions, it is essential to establish a strong therapeutic relationship, provide clear patient education, and offer reassurance regarding the benign nature of the condition. These initial steps, together with encouragement of healthy lifestyle habits and regular physical activity, can significantly enhance the overall therapeutic response.

Should dietary interventions be the first-line management strategy in dyspeptic patients?

3.2.1. Statement 2.1: the panel recognizes that while restrictive exclusion diets are not recommended as first-line therapy, general healthy dietary advice may represent a reasonable supportive measure in the management of dyspeptic patients

Statement endorsed. Agreement: 91.4 % [*D*+ (0 %); D (0 %); d - (4.3 %); A- (4.3 %); A (42.9 %); *A*+ (48.5 %)]

Level of evidence: Very low evidence

Recommendation: Conditional recommendation

Among current guidelines (ACG, NICE and European) only the European document has included a specific statement (albeit not endorsed) about the presumed role of dietary interventions in the therapeutic management of FD.

As frequently reported by dyspeptic patients, food is considered a common trigger for FD symptoms [61,70–73], with gluten, wheat, FODMAPs and fat-containing foods being the most frequently implicated [74]. It is reasonable that FD patients take frequent small-size meals and avoid high-fat food, but the supporting evidence for this strategy is nonetheless limited.

There is not enough data to confirm that dietary habits or specific foods might induce symptoms in FD patients and that dietary manipulations may be effective as a first line management of FD. Nonetheless, healthy lifestyle and dietary measures, including small frequent meals and avoidance of high-fat foods, represent reasonable supportive advice**.**

Given the high prevalence of lactose intolerance in the Italian adult population, many patients could report an association between gastrointestinal symptoms and lactose ingestion. However, according to a recent study, both dyspeptic and GERD-related symptoms were significantly more prevalent in patients with negative lactose breath test as compared to lactose intolerant patients, thus the Authors concluded that most frequently patients erroneously attribute to lactose ingestion the occurrence of dyspeptic- and reflux-related symptoms [74,75].

Larger randomized studies are needed to evaluate the impact of dietary factors on symptoms of FD and the role of diet as an effective therapeutic strategy. Therefore, we recommend against using dietary interventions, particularly restrictive exclusion diets, when managing FD patients. Nonetheless, healthy lifestyle advice including frequent small-size meals and balanced meals avoiding high-fat food represent reasonable general advice to pursue in FD patients. Therefore, while restrictive exclusion diets are not recommended as a first-line treatment, healthy lifestyle and general dietary advice should be considered as part of an integrated management approach for FD patients.

Are exclusion diets (low FODMAP diet and gluten-free diet) effective in relieving dyspeptic symptoms?

3.2.2. Statement 2.2: the panel recommends against exclusion diets (low fodmap diet and gluten-free diet) in dyspeptic patients

Statement endorsed. Agreement: 86.9 % [*D* + (0 %); D (4.3 %); d- (0 %); A- (8.7 %); A (21.7 %); *A* + (65.2 %)]

Level of evidence: low quality of evidence

Recommendation: conditional recommendation

No specific mention to exclusion diets in FD is present in current international guidelines. On the other hand, randomized controlled studies evaluating efficacy of specific dietary restrictions in FD are scarce. Nonetheless, most patients spontaneously limit the intake of selected food(s) triggering symptoms.

It has been demonstrated that high fat-meals can induce greater nausea, pain and fullness compared to a low-calorie meal and an equicaloric high-carbohydrates meal and that intraduodenal lipid infusion can increase the sensitivity of the proximal stomach to distention. Fatty foods could exacerbate FD symptoms by delaying gastric emptying rates and increasing sensitivity to gastrointestinal hormones. However, to date the long-term effects of a low-fat diet on dyspepsia symptoms has not been tested in interventional studies [61,76].

In a RCT [77], a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet (LFD) led to significant symptomatic and quality of life improvement in patients with FD. Patients with PDS or bloating responded significantly better to a LFD. Besides, in a pilot double-blind randomized placebo-controlled trial [62] a gluten free and a LFD led to a modest overall reduction in dyspeptic symptoms although a specific food trigger could not be identified. Also, a gluten free diet improved symptoms in 35 % of refractory dyspeptic patients during another randomized placebo-controlled trial [78].

Regarding food allergy, only a dated case control study [79] showed that the prevalence of FD was 2–4 % higher in allergic patients but no significant studies have been published on the usefulness of an allergic exclusion diet in FD [80]. Moreover, the excessive promotion of restrictive exclusion diets in this group of patients may increase the risk of developing Avoidant/Restrictive Food Intake Disorder (ARFID), a condition increasingly recognized in association with disorders of gut-brain interaction, including FD [81,82]

Despite promising data on potential results in a part of dyspeptic patients, no sufficient evidence is available to recommend a particular exclusion diet in FD. Common sense dietary recommendations, including eating slowly with small frequent meals and avoiding high-fat meals, rather than exclusion diets could be advised in FD patients.

Should PPIs be used as a first line treatment in patients with EPS-subtype of functional dyspepsia?

3.2.3. Statement 2.3: the panel recommends FOR PPIs as a first-line treatment in patients with EPS-subtype of functional dyspepsia

Statement endorsed. Agreement: 95.6 % [*D* + (0 %); D (0 %); d- (0 %); A- (4.3 %); A (17.4 %); *A* + (78.2 %)]

Level of evidence: Moderate Quality Evidence

Recommendation: strong Recommendation

The efficacy of PPIs in FD without considering the sub-groups is quite evident. A recent systematic review and network meta-analysis of randomized controlled trials (RCTs) found that PPIs were more effective than placebo in achieving an improvement of symptoms when PPIs were used with standard doses (RR for symptoms not improving: 0.84; 95 % CI: 0.77–0.91), with low-doses (RR: 0.86; 95 % CI: 0.79–0.94), but not with high doses (RR: 0.89; 95 % CI: 0.79–1.01), likely because high doses does affect gastric motility by delay gastric emptying [10,83]. PPIs were also more effective than placebo in achieving a resolution of symptoms when used with standard doses (RR of symptoms not resolving: 0.86; 95 % CI: 0.80–0.93), low-doses (RR: 0.89; 95 % CI: 0.83–0.96), and were barely superior to placebo when used with high doses (RR: 0.88; 95 % CI: 0.77–0.99) [10]. Nevertheless, when subgroups of dyspepsia are considered, the efficacy becomes less clear. A Cochrane systematic review and meta-analysis published in 2017 identified only 2 RCTs providing data on the efficacy of PPI therapy in patients with FD sub-grouped according to Rome III criteria, and it found that there was no significant difference in achieving an improvement in symptoms between PPIs and placebo in patients with EPS (RR of remaining dyspeptic: 0.99; 95 % CI: 0.76 to 1.28) or PDS (RR: 0.89; 95 % CI: 0.77 to 1.03) [84]. Recently, a sub-group analysis of a network meta-analysis found that in patients with EPS, standard doses of PPIs were more effective than placebo in achieving an improvement in symptoms, even if the magnitude of the effect was modest (RR: 0.84; 95 % CI: 0.76–0.94), whilst the efficacy of high doses (RR: 0.91; 95 % CI: 0.76–1.08) and low doses (RR: 0.89; 95 % CI: 0.80–1.00) were not significant different from placebo (although in the case of the low doses, the efficacy was barely not significant) [10]. It should be mentioned that among the RCTs included in the network meta-analysis, very few trials recruited patients only with EPS or only with PDS [10]. For this reason, the sub-group analysis according to FD subtype was performed by the Authors on trials that mandated only the presence of epigastric pain or burning, or only the presence of early satiation and/or postprandial fullness for trial entry but allowed coexistence of other symptoms [2]. As a consequence, the analyses were based on patients with EPS or overlap, or patients with PDS or overlap, rather than EPS alone or

PDS alone [10]. This, of course, represents a limitation in the interpretation of the data.

In conclusion, PPIs may be effective in FD patients as first line treatment, even if the magnitude of the expected effect is modest. More robust and well performed RCTs comparing PPI to placebo performed in patients only with EPS are therefore needed.

Should standard-dose PPI therapy be used as a first line treatment in dyspeptic patients, regardless of their subtype (EPS vs PDS)?

3.2.4. Statement 2.4: the panel recommends FOR a short course of PPIs at standard dose as a first line treatment in dyspeptic patients, regardless of the prevalent symptom pattern

Statement endorsed. Agreement: 82.6 % [*D* + (4.35 %); D (4.35 %); d- (4.35 %); A- (4.35 %); A (21.7 %); *A* + (60.9 %)]

Level of evidence: Moderate Quality Evidence

Recommendation: Strong Recommendation

Current Literature is still divided on distinguishing between PDS and EPS subgroups for guiding therapeutic choices. According to Rome IV, acid suppressive therapies, particularly with PPIs, would be more effective in EPS than in PDS patients. However, later studies substantiated that this difference in terms of treatment response was not observed [59,85].

Increased esophageal acid exposure at pH-impedance monitoring is often found in FD patients, even when heartburn is not the predominant complaint, and can reach a percentage as high as 50 % of patients in the EPS subgroup. Furthermore, recent studies have shown the contribution of duodenal hypersensitivity to acid in triggering dyspeptic symptoms, thus providing the rationale for the usefulness of acid suppressive therapies in these patients [86,87].

Several RCTs and a most recent network meta-analysis of RCTs (including four RCTs comparing standard-dose and low-dose PPIs both with each other and with placebo, four trials comparing high-dose PPIs with placebo, three RCTs comparing standard-dose PPIs with placebo and three trials comparing low-dose PPIs with placebo) have shown that PPI therapy may have a significant, albeit small benefit in FD patients [84].

Based on this, standard dose of PPIs once daily represents the first line treatment in dyspeptic patients without any organic disease (HP negative patients or patients who remain symptomatic after a successful HP eradication therapy without alarm symptoms) according to both the European and American guidelines [16,17]. PPIs are more effective than both placebo and H_2RA therapy in dyspeptic patients [16,88,89], regardless of the subtype (EPS or PDS) [16].

A recent systematic review showed that PPIs were more effective in obtaining symptom relief at low or standard dose, but failed to achieve symptom improvement at high doses, probably by delaying gastric emptying rates [84]. Therefore, increasing dose or changing should not be pursued as an effective strategy in improving patient's response [16,84,90].

Can H2-receptor antagonists be used in dyspeptic patients?

3.2.5. Statement 2.5: the panel recommends against the routine use of H_2RA in dyspeptic patients

Statement endorsed. Agreement: **91.3 %** [*D* + (0 %); D (4.35 %); d- (4.35 %); A- (0 %); A (17.4 %); *A* + (73.9 %)]

Level of evidence: Low Quality of Evidence

Recommendation: Conditional recommendation

PPIs are more effective than both placebo and H_2RA therapy in dyspeptic patients [16,88,89]. The effects of H_2RAs have been reported in several RCTs. However, these studies with inconsistent methodologies or results did not provide sufficient evidence to reach definitive conclusions on their efficacy or otherwise in controlling the disorder [91].

H_2RA are a group of drugs that reduce gastric acid secretion by competitive inhibition of histamine H_2 receptors expressed by parietal cells [92]. Over the years, H_2RAs have played an important role in treating acid-related disorders such as GERD and peptic ulcer [93]. Regarding their use in FD, the effects of H_2RAs have been reported in several RCTs. From 2000 to 2009, 2 meta-analyses of RCTs were published suggesting that H_2RAs were superior to placebo in improving FD symptoms [94,95]. Unfortunately, the results obtained were limited due to serious methodological flaws such as the inclusion of cross-studies, short duration of treatment and no subgroup analysis for dose of H_2RA or given H_2RA. Since then, a previous Cochrane Review has been withdrawn from publication [94] and new RCTs have been developed. Despite this, no more up-to-date systematic reviews have been produced.

These methodological problems are associated with a clinical difficulty in treating FD, which can be extremely complicated as there is a considerable overlap of symptoms and there are multiple mechanisms such as disturbed gastroduodenal motility, gastric acid secretion and visceral hypersensitivity [96] which strongly play a confounding role in the symptomatology and therapeutic response of dyspepsia. Some evidence has suggested that a subgroup of patients with FD respond well to acid suppression with H_2RA therapy or PPIs, even though these patients have normal gastric acid secretion [97]. An early meta-analysis of few studies showed that there was no significant difference between these two classes of antisecretory compounds [98].

Unlike PPIs, H_2RAs including cimetidine, ranitidine, famotidine, and nizatidine are not recommended as first-line treatments for FD. However, these drugs are widely used in clinical practice [16]. Some patients also find them helpful if PPIs fail. An underlying reason could be that - in some patients – PPIs delay gastric emptying and can actually make symptoms worse. H_2RAs (especially ranitidine and nizatidine) possess a cholinergic-like action and show a prokinetic activity [99,100]. However, the effectiveness of H_2RAs in FD remains controversial, and their use remains very much in the option of choice dictated by the control of one or more individual symptoms presented by the individual subject, based on the objective analysis of the response by the gastroenterologist.

Therefore, based on available evidence, although H_2RA therapy could have an effect on FD symptoms, we recommend AGAINST the routine use of H_2RA in dyspeptic patients.

Can antacids, alginate-containing products and/or mucosal protectants be used in dyspeptic patients?

3.2.6. Statement 2.6: the panel recommends against the routine use of antacids, alginate-containing products and/or mucosal protectants in dyspeptic patients

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (0 %); d- (4.3 %); A- (13 %); A (21.7 %); *A* + (60.9 %)]

Level of evidence: Low Quality of Evidence

Recommendation: Conditional recommendation

Antacids are routinely used in FD patients despite the lack of strong evidence for their effectiveness [101]. sucralfate (Carafate) and alginate can, at least in theory, improve symptoms in some patients with FD.

Treatment with sucralfate (Carafate), in particular, has somehow beneficial effects in the control of dyspeptic symptoms, despite conflicting reported results.

However, it should be remembered that the mechanisms by which mucosal protective agents relieve FD symptoms are unclear. Yet, it is believed that the symptoms related to hypersensitivity to acid insult can, at least partially, benefit from these drugs [102,103].

Some trials demonstrated that sucralfate (Carafate) improved FD symptoms. sucralfate (Carafate) has been studied in two randomized studies over placebo that comprised a total of 246 FD

patients. Both studies reported a reduced severity in dyspeptic symptoms, although this difference failed to reach statistical significance.

A subsequent small trial by Kumar et al. reported no difference of sucralfate (Carafate) therapy over placebo in improving the dyspepsia global symptoms score [104].

Based on this evidence, a Cochrane meta-analysis evaluating the effectiveness of pharmacological interventions for non-ulcer dyspepsia concluded that both antacids and sucralfate (Carafate) were not significantly superior to placebo in relieving dyspeptic symptoms [94].

However, a recent RCT assessing the efficacy and safety of a novel mucosal protective agent, Poliprotect, showed a non-inferiority to omeprazole in the relief of epigastric pain/burning and heartburn [105]. In this study, 275 endoscopy-negative outpatients were given a 4-week treatment with omeprazole (20 mg q.d.) or Poliprotect (5 times a day for the initial 2 weeks, followed by on-demand use) showing similar efficacy in alleviating both GERD and EPS-like symptoms [105].

Overall, despite their widespread use as over-the-counter medications for upper abdominal symptoms, there is lack of evidence supporting the efficacy of antacids in the management of FD patients without concomitant GER symptoms and larger, randomized controlled trials are essential to validate their use in the subset of FD patients.

Should prokinetics be used as a first-line therapy in dyspeptic patients?

3.2.7. Statement 2.7: the panel recommends against prokinetics as a first-line therapy in dyspeptic patients

3.2.7.1. Statement 2.8: when indicated, we recommend FOR the preferential use of prokinetics in PDS-subtype patients. **Agreement: 95.6 %** [*D* + (0 %); D (0 %); d- (4 %); A- (0 %); A (31 %); *A* + (65 %)]

Level of evidence: Moderate Quality Evidence

Recommendation: Moderate Recommendation

Clarification: Statements 2.7 and 2.8 were both derived from a single voting session addressing the role of prokinetics in functional dyspepsia. The panel first voted against the routine use of prokinetics as first-line therapy and subsequently voted for their preferential use in patients with PDS subtype when clinically indicated. The agreement percentage reported refers to the overall voting session.

Regardless of PDS or EPS subtypes, all FD patients who remain symptomatic after HP eradication or who are HP-negative should be given once-daily PPI therapy for 4–8 weeks as a first-line treatment. This still represents the recommended treatment of choice by several recent guidelines (UEG/ESNM, ACG/CAG) [16,17]. The long-term use of first-generation prokinetics, particularly dopamine-2 (D2) receptor antagonists, has been associated with severe adverse effects, such as extrapyramidal symptoms and QTc prolongation, which strongly limit their chronic use in FD. However, newer prokinetic agents, such as itopride and acotiamide, demonstrate a more favorable safety profile, although their availability is limited in some regions [106,107].

Finally, FD is frequent among young child-bearing women and hyperprolactinemia represents a commonly reported side-effect during chronic therapy with D2-recetptor antagonists. Altogether, the unfavorable safety profile of these drugs for long-term use, has led the ACG/CAG guideline to recommend treatment with antidepressants in patients refractory to PPI treatment, even before considering prokinetic drugs.

According to Rome IV guidelines, prokinetics could be useful in PDS patients, while they should not be used as drugs of choice in the EPS subgroup, in whom acid suppressive therapies would be more beneficial. A recent meta-analysis of 29 studies involving 10,044 patients with FD demonstrated a significant benefit of prokinetics in improving all dyspeptic symptoms (RR 0.81; 95 % CI 0.74 to 0.89; NNT=7) [108]. However, publication and heterogeneity bias were noted and the removal of cisapride from the market, due to its cardiac adverse effects, led to an overall less convincing effect with a NNT increased up to 12 [108]. A 2021 meta-analysis of 58 RCTs (15,629 participants) comparing the rank and efficacy of 21 different pharmacological treatments showed that in terms of efficacy, cisapride, domperidone, itopride and levosulpiride were superior to placebo in improving FD symptoms (OR ranging between 0.05 and 0.38) especially short term (<4 weeks). Furthermore, levosulpiride was more effective than 15 other drugs and placebo (ORs ranging between 0.05 and 0.15) and most likely to be ranked 1 (77 %) [109]. Another unconventional prokinetic agent is acotiamide, with a low affinity for serotonin receptors (5-HT2, 5-HT3 and 5HT-4) and D2 receptors, affinity for muscarinic receptors and inhibitor of AChE. Its efficacy was studied in a recent RCT of 86 enrolled patients classified in PDS and EPS, investigating the potential association of its benefits with gastric acid secretion (estimated by measuring the serum pepsinogen and Hp infection status) in a 4-week course at a dose of 100 mg TID. This study showed no significant differences between the PDS and EPS groups in terms of estimated gastric acid secretions, while acotiamide was effective for treating EPS as well as PDS symptoms using symptom-based severity scores (response rates: 66 % for PDS and 73.1 % for EPS). Its efficacy was reduced only in EPS patients displaying gastric acid hypersecretion, suggesting that this subgroup of patients would benefit more from PPI treatment [110].

Another used prokinetic in FD is mosapride citrate conventional release (Gasmotin^{TM}) which has been recently compared with his sustained release formulation (DWJ1252) in a 4-week RCT, double-blind study of 119 patients with FD showing the same efficacy on symptoms for both formulations and a similar safety profile [111]. In Italy and Europe, however, unconventional prokinetics, such as mosapride and acotiamide are not currently marketed.

Should antidepressants (TCAs, SSRIs, mirtazapine) be used to treat refractory dyspeptic symptoms?

3.2.8. Statement 2.9: the panel recommends FOR using TCAs to treat EPS dyspeptic patients refractory to standard treatments, while there is insufficient evidence to support the use of SSRIs in these patients. mirtazapine could be useful in patients with weight loss

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (0 %); d- (4.3 %); A- (13 %); A (21.7 %); *A* + (60.9 %)]

Level of evidence: Moderate Quality Evidence

Recommendation: Consensus Recommendation

Neuromodulators, including antidepressants and certain prokinetics such as levosulpiride, have been progressively introduced in the management of different DGBIs, including functional dyspepsia (FD) [109].A systematic review and meta-analysis evaluating psychotropic drugs in FD and including 1241 patients form 13 RCTs, showed that these molecules are effective with an NNT of 6, although benefits resulted limited to TCAs and antipsychotics [112]. The ACG and CAG clinical guidelines on FD suggest to consider TCA treatment before prokinetics in patients no responders to PPI and *H. pylori* eradication therapy, basing on an higher quality of evidence [16]. No consideration was given regarding FD subtypes [16]. The UEG and ESNM consensus on FD tried to deal with FD subcategorization in EPS and PDS [17]. Eight statements regarding antidepressants have been set up, but none of them reached the cut-off value of agreement to be endorsed. Anyway, TCAs were considered an effective drug for EPS, with a 78 % of agreement [17]. In a RCT published in 2015, almost 300 FD patients were allocated to receive placebo, amitriptyline or escitalopram for 12 weeks. Subjects with “ulcer-like” FD (∼ EPS) treated with amitriptyline showed more adequate improvement of symptoms than those receiving placebo or escitalopram (p = 0.06) [113]. Another systematic re-

view and network meta-analysis evaluating drugs for FD has been published in 202,0[10]. Two hundred twenty-eight patients treated with TCAs from 5 RCTs, were included. TCAs were ranked second for efficacy following antipsychotics, and first when only low risk of bias trials were included, showing a RR of remaining symptomatic of 0.71 (95 % CI=0.58–0.87). TCAs were also ranked first in studies of ≥8 weeks duration, and in those including patients with EPS. To be noted, most RCTs that used TCAs recruited patients who were refractory to other drugs. Anyway, TCAs were the only drugs included in the network meta-analysis that were more likely to cause adverse events than placebo (RR = 1.56; 95 % CI 1.07–2.26), although there was no increased risk of adverse events leading to withdrawal [10].

Considering other antidepressants, data from three studies including 525 patients treated with SSRIs showed similar rates to placebo for failure to achieve an improvement in dyspeptic symptoms (RR=0.99; CI=0.81–1.21). Similar considerations can be made for SNRIs with data coming from one trial that evaluated 160pts (RR=1.02; 95 % CI=0.81–1.43).

Keeping in mind that weight loss affects up to 40 % of patients with FD, also mirtazapine has been considered for their management. Pooled data from 2 small trials with only 37 patients treated with mirtazapine, showed an interesting relative risk of 0.73 of remaining dyspeptic, although the 95 % CIs crossed 1 (0.48–1.13) [10]. In parallel, a significant weight gain has been reported in both studies [114,115].

Given this evidence, TCAs can be used with a moderate confidence in patients with EPS predominant FD, although particular attention should be paid to adverse events related to these drugs and to stigma and concerns of patients of being treated with antidepressants. Mirtazapine could be considered in patients with food avoidance and significant weight loss, although further studies are needed to strengthen these findings [114].

Can psychological therapies be useful in managing dyspepsia symptoms?

3.2.9. Statement 2.10: the panel recommends FOR cognitive and behavioral therapy for dyspepsia patients not responding to medical therapies

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (0 %); d- (13 %); A- (4.3 %); A (26.1 %); *A* + (56.5 %)]

Level of evidence: Low Quality Evidence

Recommendation: Consensus Recommendation

A proportion of FD patients continue to experience symptoms after medical therapies [10]. Management of these patients is challenging and frequently complicated by the coexistence of psychiatric comorbidities [116]. Psychological treatments should be considered for a comprehensive management of FD, as for other DGBIs [117]. A revision of the literature published in 2017 identified 12 controlled trials of psychological therapies involving 1563 FD patients [16]. The most common classes of treatments evaluated were cognitive behavior therapy and hypnotherapy. Data showed that there was a significant reduction of dyspeptic symptoms in patients treated with psychological interventions (RR=0.53; 95 % CI=0.44–0.65), with an interesting NNT of 3 (95 % CI=3–4) [16]. Subsequently, in 2020 a systematic review and meta-analysis which was focused on psychological interventions in FD, included 814 patients from 9 randomized clinical trials [118]. A random-effects meta-analysis of standardized mean differences (SMD) indicated a significant improvement of symptoms after psychotherapy, compared to control (SMD - 1.33, 95 % CI from −1.97 to −0.68). Significant heterogeneity concerning the type and method of psychological intervention, treatment course, and modality of symptoms assessment, has been observed. Moreover, a high risk of bias has been found in most of the studies, especially considering that patients were not blinded to their treatment group.

In conclusion, the available evidence suggests that psychological treatments have a positive impact on FD symptoms and, indeed, should be offered for comprehensive management. Data should be considered with caution as it is based on very low-quality studies. Anyway, these therapies are typically well-tolerated without significant side effects. In contrast, these interventions may be expensive, time-consuming and require high motivation from patients. Therefore, large, well-designed, randomized controlled trials are needed to increase the level of evidence of this recommendation.

Should complementary and alternative (CAM) treatments be considered in managing dyspeptic symptoms?

3.2.10. Statement 2.11: the panel recognizes that CAM therapy might be useful in dyspeptic patients, however, most studies involving CAM treatments have poor methodology

Statement endorsed. Agreement: 82.6 % [*D* + (0 %); D (0 %); d- (8.7 %); A- (8.7 %); A (30.4 %); *A* + (52.2 %)]

Level of evidence: Low Quality Evidence

Recommendation: Consensus Recommendation

A significant share of FD patients seeks complementary and alternative medicines (CAM) as an alternative treatment strategy, given the still disappointing results in terms of symptomatic relief by conventional pharmacotherapy. CAM therapies comprises both herbal remedies, commonly administered as dietary supplements, and mind-body medicine which includes procedures overseen by a practitioner or performed autonomously by patients such as acupuncture, hypnosis or meditation [119].

Several herbal formulations have been tested in FD patients, with Ginger (Zingiber officinale), Peppermint (Mentha piperita) and Caraway (Carum carvi) being the most extensively studied preparations to relieve dyspeptic symptoms. Overall, even though all these preparations have been proven beneficial in a number RCTs studies over placebo, the quality of evidence is considered low owing to the small number of patients included in the studies or the poor methodology employed [97,119–121]. Several trials also demonstrated the superiority of Iberogast STW5 (an herbal preparation containing extracts of bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm) over placebo, but again results were marginal, because the methodological quality of the studies was poor [122].

Rikkunshito, a Japanese herbal medicine, is thought to improve functional gastrointestinal disorders, by accelerating gastric emptying rates and ameliorating dyspepsia-related anxiety. This beneficial effect in FD is acknowledged by the most recent guidelines by the Japanese Society of Gastroenterology (JSGE), stating that Rikkunshito should represent a first-line treatment in FD patients [Recommendation Strong (92 %), evidence level A] [89]. However, it must be underlined that published studies derive almost exclusively from far east Asian countries and that the formulation is not available in Italy. Furthermore, a meta-analysis including 2175 FD patients (24 RCTs) found no significant benefit when evaluating upper gastrointestinal symptoms based on the Gastrointestinal Symptom Rating Scale, whilst the superiority of Rikkunshito to placebo was proven in improving appetite and FD symptoms based on a five-point scale [123].

Another CAM modality evaluated in dyspepsia is acupuncture. According to a recent study, among patients with PDS, acupuncture resulted in increased response and elimination rate of all 3 cardinal symptoms (postprandial fullness, upper abdominal bloating, and early satiation) compared with sham acupuncture, with sustained efficacy over 12 weeks in patients who received thrice-weekly acupuncture for 4 weeks [124]. Nonetheless, a Cochrane systematic review comprising 7 RCTs (542 FD patients) concluded that manual and electroacupuncture is not known to be more effective than other treatments [125].

Overall, most studies are biased due to the methodology used and the risk of publication bias. To date, there is no unquestionable evidence about the real usefulness of CAM in dyspeptic patients and new adequate trials are needed.

4. Research priorities AND future directions

The panel identified several key areas where further research is essential to advance the diagnosis and management of FD. Improving early diagnostic accuracy through the development of reliable biomarkers and better stratification of FD subtypes, such as postprandial distress syndrome and epigastric pain syndrome, remains a priority. The role of dietary interventions, including exclusion diets and personalized dietary regimen also warrants further investigation through high-quality randomized controlled trials. Additional research should focus on the long-term safety and efficacy of neuromodulators, with attention to patient selection and treatment duration. The gut microbiota's influence on FD pathophysiology and the potential for microbiota-targeted therapies represent promising areas for exploration. Non-pharmacological strategies, such as cognitive-behavioral therapy, gut-directed hypnotherapy, and mindfulness-based interventions, should also be more extensively evaluated. Finally, the development of integrated, multidisciplinary care models that combine dietary counseling, pharmacological treatment, neuromodulation, and psychological support is needed to optimize patient-centered outcomes and improve long-term quality of life. Advancing these research areas will be crucial for the development of more effective, personalized, and holistic approaches to FD management.

5. Conclusions

A panel of experts, comprising general practitioners and gastroenterologists supported by the major scientific Italian societies of Gastroenterology and General Medicine, has defined for the first time a National Guideline to standardize the approach to the diagnosis and treatment of FD in primary, secondary**,** and tertiary care settings. This national, multidisciplinary group of Italian experts used a Delphi process to summarize and grade the current consensus on the diagnosis and treatment of this condition. The Consensus Group reviewed and voted on various statements to guide hospital physicians and general practitioners in the management of FD in clinical practice. It is acknowledged that the literature search was finalized in June 2023, and future updates will be necessary to incorporate newly emerging evidence.

Specific author contributions

All the authors contributed with data collection and analysis, writing of the manuscript, approving final version. EVS, BB, MP, GS edited the final version of the manuscript.

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