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eISSN 2450-3118 · Open Access · Peer-reviewed

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BEDNARZ, Hubert, MORTKA, Magdalena, PIOTROWSKA, Gabriela, GACZOŁ, Agnieszka Anna, KOPYTO, Maja, KOPCIŃSKA, Paulina, KAWA, Michał, IDZIK, Kamil, GRZYBOWSKA, Dominika, URBAŚ, Aleksander, KILIAN, Tomasz, KURNIK, Michał and GRZYB-KURNIK, Weronika. Functional Dyspepsia in Clinical Practice Current Recommendations and Future Perspectives. *Quality in Sport*. 2026;71:74783. <https://doi.org/10.12775/QS.2026.71.74783>

ARTICLE TIMELINE

Received: 31.07.2026. Revised: 05.08.2026. Accepted: 07.09.2026. Published: 10.09.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Functional Dyspepsia in Clinical Practice: Current Recommendations and Future Perspectives

Authors:

Hubert Bednarz, <https://orcid.org/0009-0003-1639-0699>

hubertb7809@gmail.com

Medical University of Lublin, Lublin, Poland

Magdalena Mortka, <https://orcid.org/0009-0009-0403-0008>

magdalenamortka2@gmail.com

Medical University of Lublin, Lublin, Poland

Gabriela Piotrowska, <https://orcid.org/0009-0009-1283-7135>

piotrowskagabi24@gmail.com

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Maja Kopyto, <https://orcid.org/0009-0002-0261-5781>

maja.kopyto@gmail.com

Medical University of Lublin, Lublin, Poland

Agnieszka Anna Gaczol, <https://orcid.org/0009-0008-9020-7123>

agnieszkagaczol1@gmail.com

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Paulina Kopcińska, <https://orcid.org/0009-0006-1495-1968>

pjkopcinska@gmail.com

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Michał Kawa, <https://orcid.org/0009-0001-8083-291X>

michal.kawa2000@gmail.com

Murcki Hospital in Katowice, Poland

Kamil Idzik, <https://orcid.org/0009-0000-7532-9255>

kamilidzik99@gmail.com

Murcki Hospital in Katowice, Poland

Dominika Grzybowska, <https://orcid.org/0009-0002-0599-8896>

dominika.grzybowska996@gmail.com

St. Luke's Provincial Hospital in Tarnow, Poland

Aleksander Urbaś, <https://orcid.org/0009-0004-5347-7192>

urbas41@gmail.com

Murcki Hospital in Katowice, Poland

Tomasz Kilian, <https://orcid.org/0009-0000-3161-6914>

kilianowskipl@gmail.com

Murcki Hospital in Katowice, Poland

Michał Kurnik, <https://orcid.org/0009-0008-4791-0630>

michalkurnik95@gmail.com

Megrez Provincial Multi-Specialist Hospital in Tychy, Poland

Weronika Grzyb-Kurnik, <https://orcid.org/0009-0001-7622-281X>

wgrzyb@gmail.com

Megrez Provincial Multi-Specialist Hospital in Tychy, Poland

Corresponding Author

Hubert Bednarz, hubertb7809@gmail.com

Background:

Functional dyspepsia (FD) is a common disorder of gut–brain interaction and a major cause of chronic upper gastrointestinal symptoms and impaired quality of life. Current evidence challenges the traditional view of FD as solely a gastric motility disorder and indicates a multifactorial pathophysiology involving motor dysfunction, visceral hypersensitivity, duodenal immune activation, epithelial barrier impairment, gut microbiota alterations, and dysregulated gut–brain communication.

Aim:

To review current knowledge of the pathophysiology, clinical presentation, diagnosis, and evidence-based management of FD, with emphasis on emerging therapeutic targets and precision medicine.

Material and methods:

A narrative review was conducted using international clinical guidelines, systematic reviews, meta-analyses, randomized controlled trials, and translational studies concerning FD diagnosis, treatment, and recent advances in disease mechanisms.

Results:

FD is a heterogeneous disorder in which several overlapping biological mechanisms contribute to symptom generation. Diagnosis is primarily based on the Rome IV criteria after exclusion of structural disease. Established management includes lifestyle modification, *Helicobacter pylori* eradication, proton pump inhibitors, prokinetics, neuromodulators, and psychological therapies. Emerging approaches targeting the duodenal microenvironment, epithelial barrier, gut microbiota, and gut–brain axis are promising. Nevertheless, treatment efficacy remains modest because of biological heterogeneity and the lack of validated biomarkers for patient stratification.

Conclusions:

The evolving understanding of FD supports a shift from empirical symptom-based treatment toward individualized, mechanism-informed care. Future research should focus on clinically

applicable biomarkers, improved phenotyping, and high-quality clinical trials to enable precision medicine and improve long-term outcomes.

Key words:

functional dyspepsia; disorders of gut–brain interaction; gut–brain axis; duodenal microenvironment; visceral hypersensitivity; gut microbiota; helicobacter pylori;

1. Introduction

Functional dyspepsia (FD) is a chronic disorder of gut–brain interaction (DGBI) characterized by bothersome upper gastrointestinal symptoms in the absence of structural, systemic, or metabolic abnormalities that could explain their occurrence. According to the Rome diagnostic criteria, the cardinal symptoms of FD include bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning. Based on the predominant symptom profile, patients are classified as having postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), or overlapping PDS and EPS [1–3,7]. Despite the absence of an identifiable organic cause, FD is associated with considerable impairment in quality of life, increased healthcare utilization, and a substantial socioeconomic burden, making it one of the most frequently encountered disorders in gastroenterological practice [1,4].

Globally, functional dyspepsia represents a major health problem, affecting millions of individuals and imposing a substantial burden on both patients and healthcare systems. Although the disorder is not associated with increased mortality, it significantly compromises health-related quality of life, negatively impacts daily functioning and work productivity, and contributes to frequent healthcare utilization and rising socioeconomic costs [1,2,4]. The considerable heterogeneity of clinical presentation, together with the lack of disease-specific biomarkers and the multifactorial nature of symptom generation, continues to pose significant diagnostic and therapeutic challenges. Consequently, growing research efforts have focused on elucidating the complex pathophysiological mechanisms underlying FD, with the aim of

improving diagnostic accuracy and developing more effective, targeted therapeutic strategies [2,3,6].

Current evidence indicates that functional dyspepsia is a heterogeneous and multifactorial disorder in which symptoms arise from complex interactions between gastrointestinal and central nervous system mechanisms rather than a single underlying abnormality. Several interacting mechanisms have been implicated, including impaired gastric accommodation, delayed gastric emptying, visceral hypersensitivity, disturbances in gut–brain signalling, and abnormalities within the duodenal environment [2,3,7]. In recent years, increasing attention has also been directed towards the potential role of the intestinal microbiota and low-grade mucosal inflammation. These discoveries have substantially expanded the current understanding of FD and may facilitate the development of more targeted therapeutic approaches [2,3,6].

Despite considerable advances in understanding its pathophysiology, the diagnosis of functional dyspepsia remains challenging because no disease-specific biochemical, endoscopic, or histopathological biomarkers are currently available. Diagnosis therefore relies on symptom-based Rome criteria supported by a thorough clinical assessment aimed at excluding structural, systemic, or metabolic disorders that could account for the patient's symptoms [1,5,7]. Patients presenting with alarm features or clinical suspicion of organic disease require further diagnostic evaluation. Consequently, careful differential diagnosis remains essential to establish an accurate diagnosis and guide appropriate clinical management [1,5].

Current management of functional dyspepsia relies on a personalized and multidisciplinary approach tailored to the patient's predominant symptoms and underlying pathophysiological mechanisms. Contemporary management includes dietary and lifestyle modifications, *Helicobacter pylori* eradication when indicated, acid-suppressive therapy, prokinetic agents, neuromodulators, and psychological interventions in selected patients [1,2,5]. However, therapeutic responses remain highly variable, reflecting the heterogeneous nature of the disorder and underscoring the need for more effective, mechanism-based, and individualized treatment strategies [1,2,5–7].

The aim of this review is to provide a comprehensive and up-to-date overview of functional dyspepsia, focusing on its epidemiology, pathophysiology, clinical presentation, diagnosis, and evidence-based management. Furthermore, this review highlights recent advances in the understanding of disease mechanisms, emerging therapeutic approaches, and future perspectives that may contribute to improving patient outcomes and optimizing clinical practice.

2. Materials and methods

2.1 Research materials and methods

This study is a narrative literature review focusing on functional dyspepsia. A literature search was conducted using the PubMed and Google Scholar databases to identify relevant publications published between January 2020 and June 2026. The search strategy included combinations of the following keywords: "functional dyspepsia", "disorders of gut-brain interaction", "Rome IV", "Rome V", "epidemiology", "pathophysiology", "diagnosis", and "management". Current clinical guidelines, systematic reviews, meta-analyses, and original studies published in English were included. The analysis focused on publications addressing the epidemiology, pathophysiology, diagnosis, and management of functional dyspepsia in adult patients.

2.2 Research results

The literature search identified original studies, systematic reviews, meta-analyses, clinical practice guidelines, and consensus statements relevant to functional dyspepsia. The selected publications addressed the epidemiology, pathophysiology, clinical presentation, diagnosis, and management of functional dyspepsia and constitute the basis of the present review.

3. Results

3.1 Epidemiology

Functional dyspepsia (FD) is one of the most common disorders of gut–brain interaction worldwide. However, its reported prevalence varies considerably depending on the diagnostic criteria applied, study methodology, and characteristics of the study population. A recent systematic review and meta-analysis of studies published between 1990 and 2020 estimated the global prevalence of FD at approximately 8.4%. Notably, studies using the more restrictive Rome IV criteria consistently reported lower prevalence estimates than those based on earlier Rome definitions, highlighting the substantial influence of diagnostic criteria on epidemiological findings [4].

The largest multinational epidemiological study based on the Rome IV criteria included 54,127 adults from 26 countries and reported an overall prevalence of functional dyspepsia of 7.2% [8]. Considerable geographical variation was observed, with prevalence ranging from approximately 2.4% in Japan to 12.3% in Egypt, while the prevalence in Poland was estimated at 8.3% [8]. Women were affected more frequently than men, and disease prevalence gradually decreased with advancing age. Among the clinical subtypes, postprandial distress syndrome (PDS) represented the predominant phenotype, accounting for approximately two-thirds of all FD cases [8].

The development of functional dyspepsia is considered multifactorial and is influenced by the interaction of biological, psychological, and environmental factors. Female sex and younger age have consistently been identified as demographic factors associated with a higher prevalence of FD [4,8]. In addition, psychological comorbidities, particularly anxiety and depression, occur significantly more frequently in patients with FD and are believed to contribute to symptom development through disturbances of the gut–brain axis [9]. Lifestyle and dietary habits may also influence disease occurrence. A recent systematic review and meta-analysis demonstrated that spicy food consumption was associated with an increased risk of FD, whereas more frequent meal consumption appeared to exert a protective effect [10].

Beyond its high prevalence, functional dyspepsia imposes a considerable burden on both patients and healthcare systems. Individuals with FD report significantly impaired health-related quality

of life, reduced work productivity, and more frequent healthcare utilization than the general population [4,8]. The Rome IV Global Epidemiology Study also demonstrated that patients with overlapping PDS and EPS experienced the greatest symptom burden and were more likely to seek medical care and use pharmacological treatment than those with isolated symptom subtypes [8]. These findings emphasize that the impact of FD extends well beyond gastrointestinal symptoms and represents an important public health challenge.

3.2 Pathophysiology

The pathophysiology of functional dyspepsia (FD) is complex and heterogeneous, with no single mechanism capable of explaining the entire clinical spectrum of the disorder. Current evidence supports a multifactorial model involving gastric motor dysfunction, visceral hypersensitivity, duodenal microinflammation, epithelial barrier dysfunction, alterations in the gut microbiota, and dysregulation of gut–brain communication. The relative contribution of these mechanisms varies considerably between patients, which may explain the marked heterogeneity in symptom presentation and therapeutic response [2,3,6].

3.2.1 Gastric motor dysfunction

Gastric sensorimotor dysfunction has traditionally been regarded as one of the principal pathophysiological mechanisms underlying FD. Impaired gastric accommodation, defined as inadequate relaxation of the proximal stomach following meal ingestion, reduces the stomach's reservoir capacity and results in an abnormal increase in intragastric pressure. A landmark physiological study demonstrated impaired postprandial gastric accommodation in approximately 40% of patients with FD, with early satiation identified as the symptom most strongly associated with this abnormality. Delayed gastric emptying was observed in approximately one-third of patients and may contribute to postprandial fullness, nausea, and vomiting, although its correlation with symptom severity remains inconsistent [2,3,14].

These findings suggest that abnormalities of gastric motor function alone are insufficient to explain the clinical manifestations of FD. Rather, impaired accommodation and delayed gastric emptying represent only two components of a broader pathophysiological network that interacts with altered visceral sensitivity, duodenal abnormalities, and central nervous system mechanisms to generate symptoms [2,3,6,14].

3.2.2 Visceral hypersensitivity

Visceral hypersensitivity represents another key pathophysiological mechanism in functional dyspepsia (FD). Patients with FD may exhibit an exaggerated perception of physiological gastric distension, chemical stimulation, or nutrient exposure, resulting in epigastric pain, burning, postprandial fullness, or discomfort in response to stimuli that are normally well tolerated. This altered sensory processing is thought to involve peripheral sensitization of gastroduodenal afferent pathways, abnormal spinal transmission, and enhanced central processing of visceral signals [2,3].

Visceral hypersensitivity may occur independently of impaired gastric accommodation or delayed gastric emptying, indicating that symptom generation cannot be explained solely by abnormalities of gastric motor function. Instead, altered sensory processing represents a distinct pathophysiological phenotype that may coexist with other mechanisms in varying combinations among individual patients [2,3].

Experimental studies suggest that hypersensitivity may develop as a consequence of both peripheral and central sensitization. Enhanced responsiveness of gastroduodenal afferent neurons increases the transmission of visceral stimuli to the central nervous system, where altered processing further amplifies symptom perception. Consequently, physiological mechanical or chemical stimuli that are normally innocuous may be perceived as painful or uncomfortable, contributing to the characteristic symptoms of FD [2,3].

Overall, visceral hypersensitivity is increasingly recognized as a fundamental mechanism linking peripheral gastrointestinal dysfunction with symptom perception. Its coexistence with gastric

motor dysfunction and duodenal abnormalities further supports the concept of FD as a heterogeneous disorder of gut–brain interaction rather than a single disease entity [2,3,6]

3.2.3. Duodenal abnormalities

Growing evidence indicates that the duodenum plays a central role in the pathogenesis of FD, shifting the traditional focus from the stomach towards the proximal small intestine. Rather than serving solely as a conduit for gastric contents, the duodenum functions as a highly integrated sensory and immunological organ that regulates gastric motility, nutrient sensing, and gut–brain signalling. Disruption of this finely balanced microenvironment has emerged as a key mechanism contributing to symptom generation [3,11,28].

One of the most consistent findings is the presence of low-grade duodenal inflammation characterized by increased infiltration of eosinophils and mast cells. A systematic review and meta-analysis including 22 case-control studies demonstrated significantly higher numbers of both cell types in patients with FD compared with healthy controls, together with increased eosinophil degranulation, suggesting enhanced immune activation rather than merely increased cellular density. These abnormalities appear particularly pronounced in post-infectious FD, although no consistent differences have been identified between the postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) subtypes. Activated eosinophils and mast cells release cytokines, proteases, histamine, and other inflammatory mediators capable of sensitizing adjacent enteric and vagal afferent nerve endings, thereby promoting visceral hypersensitivity and altered gastroduodenal function. Nevertheless, considerable heterogeneity among studies and the overall low quality of available evidence preclude firm conclusions regarding causality [3,11].

In parallel with immune activation, increasing attention has focused on impairment of the duodenal epithelial barrier. Experimental studies have demonstrated increased mucosal permeability associated with disruption of tight junction proteins, including zonula occludens-1 (ZO-1), occludin, and claudins. Loss of barrier integrity may facilitate the penetration of luminal

antigens, dietary components, microorganisms, and bile acids into the mucosa, thereby perpetuating immune activation and sensory dysfunction. Emerging evidence also suggests that altered epithelial repair mechanisms and dysregulated microRNA expression may further contribute to impaired barrier homeostasis [3,12,28].

Alterations in the duodenal microbiota constitute another important component of the abnormal duodenal microenvironment. Although no reproducible microbial signature has yet been identified, multiple studies have demonstrated reduced bacterial diversity together with compositional shifts involving several bacterial taxa in patients with FD. More recently, third-generation sequencing of duodenal aspirates demonstrated significantly lower microbial diversity than in healthy controls, accompanied by distinct taxonomic alterations and a positive correlation between microbial richness and symptom severity, further supporting a role for duodenal dysbiosis in disease pathogenesis. However, whether these microbial changes represent a primary pathogenic mechanism or develop secondary to altered gastrointestinal physiology remains uncertain [13,17,28].

Taken together, current evidence supports the concept of the duodenal microenvironment as an integrated functional unit in which epithelial barrier integrity, immune activation, microbial composition, luminal factors, and neurosensory signalling interact to regulate gastroduodenal function. Rather than representing isolated abnormalities, these interconnected processes are increasingly considered central drivers of symptom generation in FD and may provide promising targets for future mechanism-based therapies [3,11–13,17,28].

3.2.4 Gut microbiota

Alterations in the gut microbiota have recently emerged as another potential contributor to the pathogenesis of FD. Although no reproducible microbial signature has been identified, a growing body of evidence indicates that patients with FD exhibit reduced microbial diversity together with compositional changes involving several bacterial taxa. A systematic review of available studies demonstrated consistent alterations in microbial composition despite substantial methodological heterogeneity, supporting the concept that dysbiosis may represent a biologically relevant feature of the disorder rather than an incidental finding [3,13].

Most investigations have focused on the duodenal microbiota, reflecting the increasing recognition of the duodenum as a key site of disease pathogenesis. Using third-generation sequencing, Tziatzios et al. demonstrated significantly lower microbial diversity in duodenal aspirates from patients with FD than in healthy controls (Shannon index 3.07 vs. 3.34; $p = 0.022$). The authors also identified significant reductions in the relative abundance of several bacterial phyla, including Chloroflexota, Rhodothermota, and Thermotogota, while symptom severity positively correlated with microbial richness. These findings support a potential association between duodenal dysbiosis and symptom generation, although they do not establish causality [17].

Beyond compositional changes, microbial metabolites are increasingly recognized as important mediators of host–microbiota interactions. Short-chain fatty acids, secondary bile acids, tryptophan metabolites, and other microbial products may influence epithelial barrier integrity, mucosal immune activation, gastroduodenal motility, and visceral sensitivity. However, differences in sampling techniques, sequencing methodologies, patient selection, and diagnostic criteria have resulted in considerable heterogeneity across studies, limiting direct comparison and preventing identification of a disease-specific microbial profile [3,13,28].

Current evidence therefore suggests that microbial alterations are likely to represent one component of the abnormal duodenal microenvironment rather than an isolated pathogenic mechanism. Future studies integrating microbiome profiling with immune, epithelial, and

metabolomic analyses may help identify clinically relevant endotypes and facilitate the development of personalized microbiota-directed therapies for FD [17,28].

3.2.5. Gut–brain axis and psychosocial factors

Functional dyspepsia is increasingly recognized as a disorder of gut–brain interaction in which bidirectional communication between the gastrointestinal tract and the central nervous system plays a fundamental role in symptom generation. The gut–brain axis integrates neural, endocrine, immune, and autonomic pathways, enabling peripheral gastrointestinal signals to influence central sensory processing while psychological factors modulate gastrointestinal motility, secretion, and visceral perception. Consequently, disturbances at either end of this axis may contribute to symptom development even in the absence of structural abnormalities [2,3,6].

Psychological comorbidities, particularly anxiety, depression, chronic stress, and adverse life events, occur more frequently in patients with FD than in the general population and have been associated with greater symptom severity, impaired quality of life, and poorer therapeutic response. Conversely, persistent gastrointestinal symptoms may themselves exacerbate psychological distress, creating a self-perpetuating cycle that reinforces both peripheral and central mechanisms of disease [2,3,6].

Recent neuroimaging studies have provided objective evidence supporting central nervous system involvement in FD. In a multimodal MRI study including 15 patients with FD and 14 healthy controls, patients with FD demonstrated significantly slower antral peristaltic propagation (3.8 ± 0.8 vs. 5.6 ± 1.6 mm/s; $p = 0.001$), accompanied by increased functional connectivity between the nucleus tractus solitarius (NTS) and the anterior insular cortex, anterior cingulate cortex, bilateral ventrolateral prefrontal cortex, and pre-supplementary motor area. Furthermore, NTS connectivity correlated with gastric motility indices, supporting the concept that altered brainstem–cortical communication contributes to symptom generation and reflects maladaptive plasticity within the gut–brain axis [29].

Increasing evidence suggests that peripheral and central mechanisms interact dynamically rather than functioning independently. Signals arising from the abnormal duodenal microenvironment, including immune activation, epithelial barrier dysfunction, and microbial dysbiosis, may influence central neural circuits through neural, immune, and metabolic pathways, while central stress responses further modulate gastrointestinal function. This bidirectional communication provides a mechanistic framework linking gastric motor dysfunction, visceral hypersensitivity, duodenal abnormalities, and microbial alterations into a unified model of FD pathogenesis [3,28,29].

Recognition of FD as a disorder of gut–brain interaction has important therapeutic implications. The clinical benefit observed with neuromodulators and selected psychological interventions supports the concept that modulation of central sensory processing and stress-related pathways may reduce symptom burden in appropriately selected patients, even in the absence of structural gastrointestinal abnormalities [2,3,6].

3.3. Clinical presentation

Functional dyspepsia (FD) is characterized by chronic upper gastrointestinal symptoms that cannot be explained by structural or biochemical abnormalities. According to the Rome IV diagnostic criteria, the cardinal symptoms include bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning. These symptoms often fluctuate over time, vary in severity, and substantially impair daily functioning and health-related quality of life. Although symptom-based classification facilitates diagnosis and clinical decision-making, considerable heterogeneity exists among patients, reflecting the multifactorial nature of the disorder [2,5,7].

Based on the predominant symptom pattern, FD is classified into two clinical subtypes: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS is characterized primarily by bothersome postprandial fullness and early satiation, whereas EPS is characterized by intermittent epigastric pain or burning that is not exclusively related to meals. Despite this classification, symptom overlap is common, with approximately one-third of patients fulfilling

diagnostic criteria for both subtypes. Multinational epidemiological studies indicate that PDS represents the predominant clinical phenotype, while overlap syndrome is associated with greater symptom severity, increased healthcare utilization, and poorer health-related quality of life [5,8].

The clinical course of FD is highly variable and often characterized by alternating periods of symptom exacerbation and remission. Symptom severity may fluctuate over time and is frequently influenced by meal composition, psychological stress, sleep disturbances, and other environmental factors. Importantly, symptom intensity correlates poorly with objective physiological abnormalities, indicating that the clinical presentation cannot be explained by a single pathophysiological mechanism. Consequently, patients with apparently similar symptom profiles may differ substantially in the underlying biological processes responsible for symptom generation, highlighting the heterogeneous nature of FD [2,3,6].

Functional dyspepsia commonly coexists with other disorders of gut–brain interaction and several extraintestinal conditions. Overlap with irritable bowel syndrome and gastroesophageal reflux disease is particularly frequent and has been associated with greater symptom burden and poorer quality of life. In addition, anxiety and depressive disorders occur more commonly in patients with FD than in the general population and may amplify gastrointestinal symptoms through bidirectional interactions within the gut–brain axis. Recognition of these comorbidities is essential, as they may influence both diagnostic evaluation and therapeutic decision-making [2,3,9].

Overall, the clinical presentation of FD extends beyond isolated upper gastrointestinal symptoms and reflects the complex interplay of gastrointestinal, psychological, and environmental factors. Careful assessment of symptom phenotype, associated comorbidities, and factors influencing symptom severity is essential for accurate diagnosis and individualized management. Such an approach may also facilitate identification of the predominant pathophysiological mechanisms underlying symptoms, thereby supporting a more individualized and mechanism-based therapeutic strategy as precision medicine approaches continue to evolve [2,3,5,28].

3.4 Diagnosis

The diagnosis of functional dyspepsia (FD) is primarily based on clinical assessment and symptom-based diagnostic criteria, as no disease-specific biochemical, endoscopic, or histopathological marker is currently available. According to the Rome IV criteria, patients should present with bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning for at least 3 months, with symptom onset at least 6 months before diagnosis, in the absence of structural disease capable of explaining the symptoms. A detailed medical history and physical examination remain fundamental components of the diagnostic process and should be performed in all patients presenting with dyspeptic symptoms [2,5,7].

The initial diagnostic evaluation aims to identify patients who require further investigation and to exclude organic diseases that may mimic FD. Particular attention should be paid to alarm features, including unintentional weight loss, progressive dysphagia, persistent vomiting, gastrointestinal bleeding, iron-deficiency anemia, palpable abdominal masses, or a family history of upper gastrointestinal malignancy. Patients presenting with alarm features, or those above the age threshold recommended by current regional guidelines, should undergo upper gastrointestinal endoscopy to exclude malignancy, peptic ulcer disease, eosinophilic gastrointestinal disorders, and other structural abnormalities. Conversely, in younger patients without alarm features who fulfil the Rome IV criteria, a positive clinical diagnosis can usually be established without routine endoscopy [5,7].

Testing for *Helicobacter pylori* represents an essential component of the diagnostic work-up because eradication therapy may result in symptom resolution in a subset of patients.

Non-invasive methods, including the urea breath test and stool antigen test, are preferred in most clinical settings, whereas biopsy-based testing may be performed during upper gastrointestinal endoscopy when indicated. Additional laboratory investigations should be guided by the clinical

presentation rather than performed routinely and may include a complete blood count, celiac serology, inflammatory markers, thyroid function tests, or other targeted investigations when alternative diagnoses are suspected. The differential diagnosis should also include gastroesophageal reflux disease, peptic ulcer disease, gastroparesis, biliary tract disorders, pancreatic diseases, medication-induced dyspepsia, celiac disease, and upper gastrointestinal malignancies [5,7].

Despite substantial advances in understanding FD pathophysiology, clinically applicable biomarkers remain unavailable. Consequently, current diagnostic algorithms continue to rely predominantly on symptom-based criteria combined with selective exclusion of organic disease. Nevertheless, growing evidence suggests that physiological and molecular assessments—including gastric emptying, gastric accommodation, epithelial barrier integrity, intestinal permeability, and mucosal immune activation—may improve disease phenotyping in selected patients. Emerging biomarkers, such as microRNAs, tight junction proteins, and microbiome-derived signatures, also show promise for identifying biologically distinct FD subgroups, although further validation is required before these approaches can be incorporated into routine clinical practice [16,17,28].

Overall, the diagnosis of FD requires a structured, patient-centered approach that combines careful symptom assessment with selective use of diagnostic investigations. Contemporary guidelines increasingly emphasize a positive symptom-based diagnosis supported by appropriate exclusion of organic disease, rather than extensive testing in all patients. As understanding of the biological mechanisms underlying FD continues to evolve, future diagnostic strategies are expected to shift toward mechanism-based phenotyping, enabling more personalized therapeutic decisions and potentially improving clinical outcomes [5,7,17,28].

3.5 Management

The management of functional dyspepsia (FD) aims to reduce symptom burden, improve quality of life, and address underlying pathophysiological mechanisms where possible. Because FD is a heterogeneous disorder involving multiple mechanisms, including impaired gastric accommodation, delayed gastric emptying, visceral hypersensitivity, duodenal immune activation, and gut–brain axis dysfunction, treatment should be individualized according to the predominant symptom pattern, *Helicobacter pylori* status, associated psychological comorbidities, and patient preferences. Current management follows a stepwise approach beginning with lifestyle and dietary modification, followed by *H. pylori* eradication when indicated, pharmacological therapy, and, in selected patients, neuromodulators or psychological interventions. Despite the availability of several therapeutic options, treatment remains primarily symptom-oriented, highlighting the need for more targeted therapies based on the underlying pathophysiology. [1,2,5]

3.5.1. Lifestyle and dietary modification

Lifestyle modification and dietary counseling are recommended for all patients with FD as the first step in management. Approximately 50–80% of individuals with FD report meal-related symptom exacerbation, particularly following the consumption of large-volume or high-fat meals, supporting the role of individualized dietary modification. Although evidence from interventional studies remains limited and no specific diet has consistently demonstrated superiority, patients are generally advised to consume smaller, more frequent meals, reduce dietary fat intake, and avoid foods that reproducibly trigger symptoms. Additional lifestyle measures, including limiting alcohol and caffeine consumption, smoking cessation, regular physical activity, and adequate sleep, may further contribute to symptom control. Equally important are patient education and reassurance regarding the benign nature of the disorder and its chronic, relapsing course, as these measures improve treatment adherence and help establish realistic therapeutic expectations. [1,10]

3.5.2. Helicobacter pylori eradication

Helicobacter pylori eradication is recommended for all infected patients presenting with dyspeptic symptoms before establishing a diagnosis of FD, as successful eradication may both resolve symptoms in patients with *H. pylori*-associated dyspepsia and provide long-term benefits in those with true FD. Although the therapeutic effect is modest, a Cochrane meta-analysis demonstrated that *H. pylori* eradication was superior to placebo or no treatment for long-term symptom improvement (RR 0.91, 95% CI 0.88–0.94), corresponding to a number needed to treat (NNT) of approximately 14. Beyond symptom relief, eradication also reduces the risk of peptic ulcer disease and gastric cancer, further supporting a universal test-and-treat strategy in appropriate patients. Consequently, current international guidelines recommend *H. pylori* eradication as the first disease-modifying intervention before initiating long-term symptomatic pharmacological treatment. [1,18]

3.5.3. Proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are recommended as the first-line pharmacological treatment for patients with FD, particularly those with epigastric pain syndrome (EPS) or persistent symptoms following *H. pylori* eradication. A 2017 Cochrane systematic review including 25 randomized controlled trials involving 8,453 patients demonstrated that PPIs were significantly more effective than placebo in relieving global dyspeptic symptoms (RR 0.88, 95% CI 0.82–0.94), corresponding to an NNT of 11. Treatment efficacy was independent of PPI dose, duration of therapy, *H. pylori* status, geographical region, and Rome subtype, supporting the use of standard-dose PPIs for 4–8 weeks in most patients. PPIs were also well tolerated, with no significant increase in adverse events compared with placebo, H₂ receptor antagonists, or prokinetics. In patients who fail to respond after an adequate treatment course, prolonged empirical acid suppression is generally not recommended, and alternative therapeutic strategies should be considered. [1,19]

3.5.4. Prokinetics

Prokinetic agents are recommended primarily for patients with postprandial distress syndrome (PDS), in whom impaired gastric accommodation and delayed gastric emptying are considered key pathophysiological mechanisms. An updated Bayesian network meta-analysis published in 2023, including 28 randomized controlled trials involving 5,790 patients, demonstrated that all six evaluated prokinetics—metoclopramide, cinitapride, domperidone, acotiamide, itopride, and mosapride—were more effective than placebo in improving global FD symptoms.

Metoclopramide ranked as the most effective agent, with a 97.9% probability of being the best treatment, followed by cinitapride (82.1%) and domperidone (63.2%). However, efficacy should be interpreted alongside safety considerations. Although no significant differences in drug-related adverse events were observed among the evaluated agents, cinitapride was associated with fewer overall adverse events than domperidone, suggesting a more favorable benefit–risk profile. In contrast, long-term use of metoclopramide remains limited by the risk of extrapyramidal adverse effects, whereas domperidone requires caution because of its association with QT interval prolongation. Consequently, current guidelines recommend individualized, short-term use of prokinetics according to symptom profile, drug availability, and patient characteristics. [1,20]

3.5.5. Neuromodulators

Neuromodulators are recommended for patients with persistent symptoms despite adequate first-line therapy, particularly when visceral hypersensitivity and disturbances of the gut–brain axis are considered major contributors to symptom generation. Their therapeutic benefit is thought to result primarily from modulation of central pain processing rather than from antidepressant effects. A 2025 systematic review and meta-analysis including nine randomized controlled trials involving 924 patients demonstrated that antidepressants significantly improved global dyspeptic symptoms compared with placebo (RR 1.30, 95% CI 1.02–1.67; NNT = 11). This benefit was driven predominantly by tricyclic antidepressants (TCAs), which showed superior efficacy (RR 1.41, 95% CI 1.07–1.85; NNT = 6), whereas selective serotonin reuptake inhibitors (SSRIs) were not superior to placebo (RR 0.97, 95% CI 0.72–1.29). Trial sequential

analysis confirmed sufficient evidence supporting the efficacy of TCAs, with moderate-certainty evidence according to the GRADE framework. Although antidepressants overall were associated with more adverse events than placebo, TCAs alone did not significantly increase adverse events. Consequently, current guidelines recommend low-dose TCAs, such as amitriptyline, as the preferred neuromodulators for refractory FD, whereas SSRIs should generally be reserved for patients with coexisting anxiety or depressive disorders rather than prescribed solely for dyspeptic symptom relief. [1,21]

3.5.6. Psychological therapies

Psychological therapies are recommended for patients with refractory FD, particularly in the presence of coexisting anxiety, depression, or other disorders of gut–brain interaction. A systematic review and meta-analysis published in 2022, including 14 randomized controlled trials involving 1,434 patients, demonstrated that psychological interventions significantly improved overall symptom response compared with control interventions (RR 1.74, 95% CI 1.12–2.72). They also significantly reduced gastrointestinal symptom severity both at the end of treatment (SMD –0.98, 95% CI –1.29 to –0.67) and during follow-up (SMD –1.06, 95% CI –1.55 to –0.57), while improving anxiety (SMD –0.80, 95% CI –1.38 to –0.22) and depression (SMD –1.11, 95% CI –1.62 to –0.61). Subgroup analyses indicated that the greatest benefit was achieved with structured psychotherapy, whereas evidence for cognitive behavioral therapy, hypnotherapy, relaxation therapy, and other psychological interventions remains limited because of the small number of available studies. Current evidence therefore supports integrating psychological therapies into the multidisciplinary management of carefully selected patients with refractory FD, although additional high-quality randomized trials are needed to further define their role. [1,22]

3.5.7. Emerging therapies

Emerging therapies for FD increasingly target the underlying biological mechanisms of disease rather than symptom control alone. Among these, modulation of the intestinal microbiota has emerged as one of the most promising approaches. Experimental and clinical evidence suggests that probiotics may alleviate symptoms by restoring microbial homeostasis, strengthening intestinal barrier integrity, reducing low-grade mucosal inflammation, regulating immune responses, and attenuating visceral hypersensitivity through the gut–brain axis. A systematic review and meta-analysis published in 2020, including five randomized controlled trials involving 409 patients, found that prebiotic and probiotic therapy was associated with a modest improvement in global FD symptoms compared with placebo (RR 1.15, 95% CI 1.01–1.30; $I^2 = 0\%$). However, analysis of probiotic therapy alone, based on four randomized controlled trials including 310 patients, failed to demonstrate a statistically significant benefit (RR 1.13, 95% CI 0.99–1.28), although no increase in adverse events was observed. These findings suggest that therapeutic effects are likely strain-specific and may be enhanced by combining probiotics with prebiotics. Beyond microbiota-directed interventions, therapies targeting duodenal immune activation, epithelial barrier dysfunction, and specific pathophysiological phenotypes are currently under investigation and may further expand future treatment options. Ultimately, advances in mechanism-based phenotyping are expected to facilitate precision medicine approaches, enabling treatment to be tailored to the predominant mechanisms responsible for symptom generation in individual patients. [23,24,28]

4. Discussion

4.1. From pathophysiology to personalized management

The evidence summarized in this review supports a conceptual shift from viewing functional dyspepsia (FD) as a purely functional gastric disorder toward recognizing it as a heterogeneous disorder of gut–brain interaction. Rather than being driven by a single mechanism, FD results from complex interactions among impaired gastric motility, visceral hypersensitivity, duodenal

immune activation, epithelial barrier dysfunction, alterations in the gastrointestinal microbiota, and dysregulated gut–brain communication. Importantly, these mechanisms frequently coexist within the same patient, although their relative contribution varies considerably, contributing to the marked clinical heterogeneity observed in FD [1–4,6,7,13,17,28,29].

This evolving understanding has important clinical implications. The modest efficacy of currently available therapies likely reflects the biological heterogeneity of FD, as patients with distinct pathophysiological mechanisms are still managed according to symptom-based classifications rather than validated biological phenotypes. Although the Rome IV classification into postprandial distress syndrome and epigastric pain syndrome represents an important step toward individualized care, substantial symptom overlap and the absence of clinically applicable biomarkers continue to limit truly mechanism-based treatment.

Taken together, current evidence supports a transition toward personalized management that integrates symptom phenotype with emerging insights into the biological mechanisms underlying FD. As clinically applicable biomarkers become available, improved patient stratification may facilitate more targeted therapeutic strategies, ultimately enhancing treatment efficacy while reducing unnecessary empirical therapies [1–7,17,28,29].

4.2. Translating evidence into clinical practice

Although current international guidelines recommend a stepwise approach to FD management, accumulating evidence suggests that treatment should be guided not only by symptom phenotype but also by the underlying pathophysiological mechanisms whenever possible. The available therapeutic options—including *Helicobacter pylori* eradication, proton pump inhibitors, prokinetics, neuromodulators, and psychological interventions—target different components of FD pathogenesis and should therefore be regarded as complementary rather than competing strategies. Selecting therapy according to the predominant clinical presentation and associated biological mechanisms is likely to improve symptom control and reduce unnecessary treatment escalation [1,18–23].

Nevertheless, treatment outcomes remain modest, and complete symptom resolution is achieved in only a subset of patients. Rather than indicating treatment failure or an incorrect diagnosis, persistent symptoms often reflect the coexistence of multiple pathophysiological mechanisms that are insufficiently addressed by a single intervention. Consequently, patients with refractory FD should undergo systematic reassessment, including evaluation of symptom phenotype, treatment adherence, psychological comorbidities, and potential alternative diagnoses before additional therapies are introduced. This patient-centered approach is consistent with current guideline recommendations and emphasizes the importance of shared decision-making and realistic therapeutic expectations [1,5,7,18–23].

Ultimately, the management of FD should evolve beyond the traditional "trial-and-error" strategy toward mechanism-informed care. Although validated biomarkers are not yet available for routine practice, integrating clinical phenotype with emerging evidence on gastric motor dysfunction, duodenal abnormalities, gut microbiota, and gut–brain interactions represents an important step toward more rational and individualized treatment algorithms [6,13,17,28,29].

4.3. Future perspectives and limitations of current evidence

Despite substantial advances in understanding the pathophysiology of functional dyspepsia (FD), important challenges remain before these discoveries can be translated into routine clinical practice. One of the major limitations of current management is the absence of validated biomarkers capable of reliably identifying the predominant pathophysiological mechanisms responsible for symptom generation in individual patients. Consequently, treatment selection continues to rely largely on symptom-based classifications rather than biological phenotypes, despite growing evidence that FD comprises multiple overlapping disease endotypes [1,6,7,15,17].

Recent advances in the understanding of duodenal immune activation, epithelial barrier dysfunction, alterations in the gastrointestinal microbiota, and gut–brain interactions have identified several promising therapeutic targets. However, most emerging interventions remain supported by limited or heterogeneous evidence, and their long-term efficacy has yet to be established. Furthermore, many randomized controlled trials have enrolled heterogeneous patient populations defined exclusively by symptom-based criteria, without stratification according to underlying biological mechanisms. This lack of biological phenotyping may have diluted treatment effects and contributed to the modest efficacy observed across many therapeutic interventions [6,13,17,25,28,29].

Future research should therefore focus on developing clinically applicable biomarkers that facilitate disease phenotyping and predict treatment response. Integrating molecular profiling, microbiome analyses, physiological testing, and neuroimaging may improve patient stratification and accelerate the transition from empirical symptom-based management toward precision medicine. Well-designed randomized controlled trials incorporating standardized diagnostic criteria, mechanism-based patient selection, and long-term follow-up will be essential to determine whether personalized therapeutic strategies can improve clinical outcomes, quality of life, and healthcare utilization in patients with FD [6,13,15,17,25,28,29].

5. Conclusions

Functional dyspepsia remains one of the most prevalent and clinically challenging disorders of gut–brain interaction. Growing evidence indicates that FD should no longer be regarded as an isolated disorder of gastric function but rather as a heterogeneous condition resulting from complex interactions among gastric motor dysfunction, visceral hypersensitivity, the duodenal microenvironment, immune activation, the gastrointestinal microbiota, and the central nervous system.

This evolving understanding has important clinical implications. Although current management remains largely symptom-based, treatment should be individualized according to symptom

phenotype, *Helicobacter pylori* status, associated comorbidities, and the most likely underlying pathophysiological mechanisms. Established therapies—including *H. pylori* eradication, proton pump inhibitors, prokinetics, neuromodulators, and psychological interventions—remain the cornerstone of management, while emerging mechanism-based therapies offer promising opportunities to further improve patient outcomes.

Future progress in FD will depend on the development of clinically applicable biomarkers, improved disease phenotyping, and well-designed prospective studies evaluating targeted therapeutic strategies. Integrating advances in translational research with clinical practice may facilitate the transition from empirical symptom-based management toward precision medicine, ultimately enabling more effective, individualized care and improving the quality of life of patients with FD.

Disclosure

Author Contributions

Conceptualization: Hubert Bednarz, Magdalena Mortka

Methodology: Hubert Bednarz, Magdalena Mortka, Maja Kopyto, Gabriela Piotrowska

Software: not applicable

Check: Agnieszka Anna Gaczoł, Kamil Idzik

Formal analysis: Hubert Bednarz, Magdalena Mortka, Gabriela Piotrowska, Maja Kopyto

Investigation: Hubert Bednarz, Magdalena Mortka, Gabriela Piotrowska, Zuzanna Lechowska

Resources: Hubert Bednarz, Magdalena Mortka, Gabriela Piotrowska, Agnieszka Anna Gaczoł, Michał Kawa, Kamil Idzik

Data curation: Hubert Bednarz, Magdalena Mortka, Zuzanna Lechowska

Writing - rough preparation: Weronika Grzyb-Kurnik, Michał Kurnik, Tomasz Kilian

Writing - review and editing: Aleksander Urbaś, Paulina Kopcińska

Visualization: Agnieszka Anna Gaczoł, Dominika Grzybowska,

Supervision: Hubert Bednarz, Paulina Kopcińska, Magdalena Mortka

Project administration: Hubert Bednarz, Magdalena Mortka, Maja Kopyto

Receiving funding: not applicable

All authors have read and agreed with the published version of the manuscript.

Funding statement:

This research received no external funding.

Statement of the institutional review board:

Not Applicable.

Statement of informed consent:

Not Applicable.

Statement of data availability:

Not Applicable.

Conflicts of Interest

The authors declare no conflict of interest.

AI Statement

During the preparation of this manuscript, the authors used Perplexity (powered by GPT-5.1) solely to assist with language editing and literature organization. All scientific interpretation, critical appraisal of the literature, and final editorial decisions were performed by the authors. The authors reviewed and approved the final manuscript and accept full responsibility for its content.

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