Accepted for publication 19th August 2020

TITLE PAGE

Title: Functional Gastrointestinal Disorders: Advances in Understanding and Management.

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Keywords: pain; bloating; dyspepsia, diarrhoea; constipation

Word count: 3883

ABSTRACT

Gastrointestinal symptoms are highly prevalent, but many people who experience them will have no organic explanation for their symptoms. The majority of these people will be labelled as having a functional gastrointestinal disorder (FGID), such as irritable bowel syndrome, functional dyspepsia, or functional constipation. These conditions affect up to 40% of people at any one point in time, and two-thirds of these people will have chronic, fluctuating symptoms. The pathophysiology is complex, but involves bidirectional dysregulation of brain-gut interaction, via the brain-gut axis, as well as microbial dysbiosis within the gut, altered mucosal immune function, visceral hypersensitivity, and abnormal gastrointestinal motility. Hence, recent nomenclature refers to them as disorders of gut-brain interaction. Psychological co-morbidity is common, although whether this predates, or is driven by, the symptoms is not clear. Patients with FGIDs can feel stigmatised, and often a diagnosis of an FGID is not communicated effectively by physicians, nor education provided. Prompt identification and treatment of FGIDs is critical, because these conditions have a considerable impact on healthcare systems, and society as a whole, due to repeated consultations, unnecessary investigations and surgeries, prescription and over-the-counter medicine use, impaired health-related quality of life, and negative effects on ability to work. Symptom-based criteria are used to make a diagnosis, with the judicious use of limited investigations required in some patients. The general principles of treatment are based on a biopsychosocial understanding, and involve management of physical symptoms, as well as psychological co-morbidity, if present. In the future, treatment approaches to FGIDs are likely to become more personalised based not only on symptoms, but also underlying pathophysiology and psychology.

INTRODUCTION

The spectrum of symptoms attributable to the gastrointestinal tract includes abdominal pain, diarrhoea, constipation, bloating, fullness, nausea, and vomiting. These symptoms are common to a broad range of organic pathology, including gastrointestinal cancer, inflammatory bowel disease (IBD), coeliac disease, peptic ulcer, and motility disorders, such as gastroparesis. However, it is well-recognised that, for a substantial number of patients, investigation reveals no underlying structural abnormality to explain these symptoms, which in this context are often referred to as "functional". Functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS), functional dyspepsia (FD), or functional constipation, although incompletely understood, and with a complex pathophysiology, account for at least one-third of referrals to gastroenterology clinics. [1] Due to a combination of the pathophysiology involved, as well as the stigma of the term "functional", these conditions have been redefined as disorders of gut-brain interaction, in order to better reflect their scientific basis. [2] FGIDs are diagnosed and classified using standardised criteria, recommended by the Rome Foundation. Current approaches to treatment target predominant gastrointestinal and psychological symptoms, rather than identifying and addressing specific underlying pathophysiological mechanisms. Almost one-in-two people will meet criteria for an FGID at any given time, [3] and these conditions frequently overlap. [4] More than two-thirds of people will have seen a doctor in the preceding 12 months, 40% use regular medication, and one-in-three will have had potentially unnecessary abdominal surgery for their symptoms, such as hysterectomy or cholecystectomy. [4] This, together with the fact that these conditions are costly to manage, with an impact on quality of life of a similar magnitude to that of organic gastrointestinal diseases, [4] highlights their fundamental importance to both healthcare systems and society. Despite this, they are not a priority for research funding. [5] This is the first in a series of three

articles. The two accompanying articles deal with two of the most common FGIDs, IBS and FD, in detail.

A PATIENT PERSPECTIVE

A diagnosis of an FGID has implications for the patient because of the stigma that frequently accompanies it. These disorders lack structural "organic" features, so many physicians view them as "second class" and attach negative attitudes or perceptions toward patients with these conditions, [6] often considering them to have a psychiatric disorder. [7] This can be damaging, both physically and emotionally, to the patient, [8] and lead to a sense of stigma and shame. This, in turn, can inhibit the patient's ability to express their thoughts and feelings adequately to their providers, causing them to minimise the severity of their symptoms and "gloss over" the impact on their quality of life. [8,9] Patients fear being seen as "crazy", and some choose instead to suffer needlessly without any medical interventions, eventually giving up hope of regaining their quality of life or, alternatively, actually increase their utilisation of healthcare in the search for answers. This process can cause patients to reject the diagnosis, instead suspecting that the physician has "given up" rather than continuing to seek the "real cause of the symptoms." Even if they accept the diagnosis, they may develop feelings of guilt and self-blame for having a condition not perceived by physicians as "real." [10] Half of all patients with FGIDs do not even inform their family members and friends about the diagnosis, because of fear of being misunderstood or not believed. [11]

So, what can be done to change the perception of these disorders and these patients, and provide more appropriate messaging and impactful care? We must begin first with the clinicians who are looked upon to diagnose and heal. This is the role that physicians have

played throughout history. The frustration for many physicians is that FGIDs are not easily "healed", and often require constant symptom management, and therefore frequent visits and follow-up. This can lead to frustration when the patient reports no improvement and can contribute to physician burnout.

First, it is key that physicians know how to make a confident diagnosis of an FGID using the symptom-based Rome criteria and communicate this diagnosis effectively, providing rationale for the diagnosis and legitimising the disorder with clear, concise communication. Using qualified language when giving a diagnosis is essential. A physician should refrain from saying to a patient, "We think you have IBS" but instead phrase the diagnosis as "You have IBS". This use of qualified language increases patient acceptance, reduces apprehension, and provides a framework to build upon for treatment recommendations, medication adherence, and a positive patient-provider relationship. [12] Second, patients need to be given the proper education about their condition and have an active role in the decision-making process for treatment. Patients respond better to clear, concise education using images and diagrams to reinforce complex concepts such as the brain-gut axis or pain gate control, preventing them from going to unqualified sources that may contain inaccurate information. Finally, patients need to feel empowered in order to be able to ask questions about anything they are unclear on, speak honestly about the severity of their illness and its impact on their quality of life, and feel validated in their experiences. When all of these elements are provided by a skilled clinician, both the patient and the physician can find mutual satisfaction, positive outcomes, and a long-lasting relationship. [13]

EPIDEMIOLOGY

The ability to appropriately classify patients with FGIDs is key, not only to facilitate diagnosis and treatment, but also for research into their aetiology. Over the last 30 years, the

Rome Foundation, a committee of gastroenterologists and allied academics in the field of gastrointestinal health, has created and updated standardised methods to diagnose and classify FGIDs, based on a consensus of expert opinion, and with reference to current available evidence. First proposed in 1990, the Rome diagnostic criteria define each condition according to a particular cluster of patient-reported symptoms, sometimes with recourse to limited investigations, and have undergone three subsequent revisions. There are 33 adult FGIDs categorised by anatomical location (Table 1), each having validated symptom-based criteria, which have been described in detail elsewhere. [14] The most recent iteration, Rome IV published in 2016, advocate rethinking these conditions as disorders of gut-brain interaction, acknowledging the complex interaction of biological, psychological, and social factors in their pathogenesis. [2] This change also reflects the fact that the term "functional" is non-specific and, as a consequence, patients can feel stigmatised by a diagnostic label which is viewed as less "legitimate", or important, than that of an organic disease, despite often having almost identical symptoms, which are equally genuine and troublesome. [2] However, some diagnostic entities retain the term "functional" to identify those without physiological markers or correlates.

A recent Rome Foundation global internet survey of 54,127 adults in the communities of 26 countries reported that 32,112 (43%) people met criteria for at least one FGID. [3] These individuals demonstrated increased healthcare utilisation, and lower quality of life than those not meeting criteria. In one Swedish study, with 7 years of follow-up, only 232 (42%) of 547 respondents in the general population were symptom-free throughout. [15] Some of the commonest FGIDs, as per Rome IV criteria, their estimated prevalence in the general population in the Rome Foundation global survey, [3] and the confirmatory testing required to make these diagnoses are described in Table 2. [16-21] IBS, FD, and functional constipation are among the most prevalent FGIDs, and are a particular focus for researchers in the field.

161 However, other disorders, which are less well-understood, and lack evidence-based
162 treatments, such as rumination and functional dysphagia, are also more common than was
163 thought previously.

164 Women are generally more likely to suffer from FGIDs than men. [22-24] Indeed, the
165 Rome Foundation global survey demonstrated that 49% of women reported at least one
166 FGID, compared with 37% of men. [3] Recent epidemiological studies have demonstrated an
167 increased risk of both atopic and autoimmune diseases in FGIDs. [25,26] Smoking is also a risk
168 factor, [27] and extra-intestinal symptoms, such as fatigue or other chronic pain syndromes,
169 overlap more than would be expected by chance. [28,29] With respect to geography, studies
170 demonstrate consistently that, although FGIDs are present worldwide, there is variation in
171 prevalence rates between countries. [3,22-24,30,31] This variability may, in part, be due to
172 differences in methodology between studies. [31] It may, however, also reflect contrasts in
173 genetics, culture, lifestyle, and dietary traditions that exist between nations. [32,33]

174

175 **PATHOPHYSIOLOGY**

176 By definition, no structural abnormalities explain FGIDs and, based on the
177 biopsychosocial model developed by Engel, [34] and adapted by Drossman, [35,36] they are
178 characterised as complex bidirectional dysregulation of brain-gut interaction, via the brain-
179 gut axis, rather than diseases (Figure 1). Visceral hypersensitivity, abnormal gastrointestinal
180 motility, and psychological disturbances have been recognised to contribute to the
181 pathogenesis for decades, but more recently low-grade intestinal inflammation, increased
182 intestinal permeability, immune activation, and disturbances in the microbiome have been
183 identified, challenging the idea that structural changes are absent entirely. [37,38]

184 An integrated model for pathogenesis of disease would help explain all of the known
185 phenomena encountered in FGIDs and, importantly, provide testable new insights into their

aetiology (Figure 2). [27,39] Importantly, the biopsychosocial model articulates illness as holistic and multifactorial, and emphasises the existence of an intimate mind-body connection, facilitated by bidirectional communication between the brain and the gut in FGIDs, which is well-accepted. [34,35,40] Whatever the underlying aetiology and pathogenesis of FGIDs, central nervous system processing of pain, and other gut signals, is required for the subjective patient symptom experience. This is supported by data, including evidence that there are several areas of abnormal brain activity associated with visceral hypersensitivity, as well as anxiety and depression, in patients with FGIDs. [41,42] However, cause and effect cannot be disentangled from these studies, and is not relevant when pathophysiology is understood in terms of interacting systems.

Emerging data challenge the concept that brain-gut pathways act similarly in all patients with FGIDs. Independent epidemiological studies suggest that in 50% of cases FGIDs begin with psychological distress, followed later by gastrointestinal symptoms, whereas in the other 50% of cases gut dysfunction occurs first, and psychological distress follows later. [43-45] This has led to the hypothesis that a subset of patients have a disease process that begins in, and is primarily driven by, the gastrointestinal tract, which later induces systemic manifestations, including psychological dysfunction as an integral part of the disease process. Further, likely microbial causes have been identified; *H. pylori* is a recognised cause of FD, as the disorder remits long term in a small minority after successful eradication of infection, [46] and following gastroenteritis new-onset IBS, FD, or both, may occur and persist, [47,48] although gastroenteritis as a precipitant is identified by history in only a minority of cases. [49,50]

In further support of the importance of subtle underlying gastrointestinal pathology in FGIDs, low-grade intestinal inflammation (characterised by eosinophils and/or mast cell infiltration), increased intestinal permeability, an altered microbiome, and immune activation

(characterised by circulating homing small intestinal T-cells and a cytokine response) have been identified in subsets of patients. [51-53] In turn, there is evidence that this low-grade intestinal inflammatory process can alter neuronal structure and function, likely inducing visceral hypersensitivity and gastrointestinal motor dysfunction. [54] Further, intestinal reflex responses may then alter gut function more proximally, potentially inducing delayed gastric emptying, impairing accommodation of the gastric fundus, or increasing transient lower oesophageal sphincter relaxations, which may account for overlap between FGIDs. [55]

Intestinal immune activation would be expected to be more prevalent in females, be associated with a risk of atopic and autoimmune disease, and fluctuate over time, possibly accounting for symptom variability, all of which have been observed in FD and IBS. [27] Most patients with IBS and FD have meal-related symptoms; [56,57] dietary components, possibly in some cases because of an aberrant interaction with the microbiome, may lead to antigen presentation in the upper intestine, initiating immune activation and disease cascade. [58] In other cases, a stress response driven centrally may be the primary disease process altering gut function, via the hypothalamic pituitary adrenal axis, a brain-gut predominant disorder. [59] Adverse events in early life, possibly driving epigenetic changes, may account for symptom chronicity and visceral hypersensitivity in a subgroup. [60]

This gut-brain intestinal disease model is testable, and has treatment implications, because it has the potential to identify casual pathways that can be interrupted. These include removal of dietary antigens, specific manipulation of the microbiome, or targeted immunotherapy and, in the future, may offer hope of cure rather than the use of purely symptom-based therapies.

DIAGNOSIS

FGIDs share definable clinical features but, unlike IBD or other structurally-based diseases, currently have no characteristic morphology or biomarkers that enable diagnosis. Patients defined by these standardised criteria are homologous in their clinical features, thus permitting investigators to enrol similar subjects into research, and clinicians to target patients for a specific treatment.

Diagnosis of an FGID requires fulfilling symptom-based criteria and excluding, in a cost-effective manner, other specific conditions having similar clinical presentations by physical examination (including digital rectal exam), laboratory studies, and imaging (Table 2). For research purposes, it is essential to eliminate well-defined motility disorders, such as chronic intestinal pseudo-obstruction or gastroparesis, or even other FGIDs. Therefore, for a clinical trial in IBS, patients who meet criteria for IBS, but also have FD, would be excluded. However, in clinical practice, it is well-accepted that motility disorders and other FGIDs often co-exist; both diagnoses are recognised and treated.

The value of identifying other diagnoses, such as coeliac disease or IBD, which may present with similar symptoms, is that they benefit from entirely different treatments. Yet, the process of doing so requires good clinical judgment as there is risk in over-investigating. [13] Experienced clinicians can discern which patients need further evaluation. For example, a college student attending a primary care clinic with an episode of abdominal cramps and diarrhoea occurring before final examinations may receive minimal investigation, or no investigations at all; the clinician will follow these symptoms expectantly. Conversely, an older patient with similar symptoms that are increasing in severity over several months, with accompanying weight loss, will require more evaluation and will likely undergo colonoscopy and/or imaging studies. Also, the nature of the assessment will depend on the presenting

clinical features; predominant pain leads to a different set of investigations than chronic diarrhoea or vomiting.

The best way to apply cost-effective and well-targeted diagnostic evaluations is to consider specific clinical parameters initially. Factors that might lead to further assessment include older age (e.g., colonoscopy after age 50), other co-morbidities, a shorter symptom duration or a worsening severity and trajectory, no record of previous investigations, or the presence of alarm symptoms or "red flags." The latter depend, to some degree, on anatomical region, and the diagnosis under consideration, and include weight loss, haematemesis, persistent vomiting, blood in the stool, family history of IBD or cancer, abnormal findings on physical examination, or abnormal laboratory studies, such as anaemia. When the symptoms are chronic, it is the development of new or changing clinical features, or alarm symptoms, rather than increased reporting of symptoms, that determines the need for re-evaluation. One method to address these parameters is through diagnostic algorithmic pathways, available through the Rome Foundation. [61] As an example, Figure 3 demonstrates the recommended evaluation pathway for patients presenting with constipation-type symptoms.

NATURAL HISTORY AND EFFECT

FGIDs are chronic conditions. Although symptoms fluctuate, and are often meal-related, [56,57] prevalence of symptom-reporting tends to remain the same, as the number of people whose symptoms disappear are matched by the number who develop new-onset symptoms. [62-64] The development of new-onset symptoms in those who were previously asymptomatic may reflect bi-directional brain-gut pathways, with higher levels of anxiety and depression associated with development of IBS and FD during follow-up. [44,45,65] However, in longitudinal follow-up studies, among those who remain symptomatic, there is also transition between different FGIDs. [64,66,67] Indeed, a Swedish study found that there was symptom

fluctuation in 40% to 60% of those reporting IBS, dyspepsia, gastro-oesophageal reflux symptoms, or minor symptoms not meeting criteria for an FGID over a 7-year period. [15] Symptom overlap is also frequently observed, such that two or more FGIDs may co-exist, [68-70] as may other medically unexplained conditions, such as chronic fatigue syndrome, [71] or fibromyalgia. [72] The prevalence of anxiety and depression increases with the number of co-existent FGIDs and with the frequency and severity of gastrointestinal symptoms. [73] Impaired sleep is also common, [74,75] and again seems to increase with the number of overlapping FGIDs. [74]

Alarmingly, around one-third of patients with FGIDs will undergo unnecessary surgery for their abdominal symptoms, including cholecystectomy and hysterectomy. [4] In one survey of 51 (23%) of 223 patients with FD reported having surgery specifically to investigate their symptoms, including exploratory operations. [76] A multivariate analysis examining rates of surgery in patients with IBS, and adjusting for multiple confounders, showed that having IBS was independently associated with three-fold higher rates of cholecystectomy, two-fold higher rates of appendicectomy and hysterectomy, and 50% higher rates of back surgery, compared with people without IBS. [77] Such procedures, coupled with the fact that two-thirds of patients have seen a doctor in the preceding 12 months and 40% are taking medication for their symptoms, [4] add to the considerable healthcare costs of managing FGIDs. [76,78-80] Although functional constipation has been associated with an increased mortality risk, [81,82] this does not appear to be the case for other FGIDs. However, morbidity is striking. Patients report negative effects on their ability to work, with high rates of absenteeism and presenteeism, [83] and their ability to socialise. [80] The detrimental impact on health-related quality of life is, therefore, substantial. [3,80]

MANAGEMENT

The general principles of treatment are based on a biopsychosocial understanding, [36] and relate to dysregulation of the brain-gut axis. The FGIDs are defined by any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing. [16] Thus, patients meeting Rome IV criteria for an FGID may have protean symptom features influenced by various combinations of these factors. So for example, a patient meeting IBS criteria may have bloating related to maldigestion of dietary constituents, such as fermentable oligo-, di-, or mono-saccharides, and polyols (FODMAPs), pain and diarrhoea related to visceral hypersensitivity, altered mucosal immune dysregulation following a bacterial infection (post-infection IBS), or anxiety and pain due to central pain dysregulation, and associated with post-traumatic stress disorder following sexual or physical trauma. Since the clinical profile and severity may change over time, the discerning clinician needs to identify which of these factors alone, or in combination, are targets for treatment. There are several principles to consider when initiating treatment, which are considered below.

The Patient-provider Relationship.

It is well-established that an effective patient-provider relationship improves patient and provider satisfaction, adherence to treatment, symptom reduction, and improved clinical outcomes. [13,84,85] Table 3 provides general guidelines to establish and optimise this. [84]

The Symptom Profile

The type of symptoms, their location, and the physiological determinants will all influence treatment. Simple inexpensive treatments, such as laxatives or anti-diarrhoeals, will be sufficient for some patients, although the evidence base for these is limited. Trial-based

and network meta-analyses demonstrate that, for functional constipation or IBS with constipation, drugs like linaclotide or lubiprostone acting as secretagogues, via intestinal ion channels, or prokinetics, such as prucalopride or tegaserod, via 5-hydroxytryptamine (5-HT) receptors, are efficacious, [86-88] whereas for diarrhoea in IBS, rifaximin, a minimally absorbed antibiotic, alosetron or ondansetron, which are $5HT_3$ receptor antagonists, or the mixed opioid receptor drug eluxadoline, are beneficial . [89-91] However, if the accompanying abdominal pain is severe, treatment will include an antidepressant or a CNS targeted medication, termed central neuromodulators, [92,93] and, if localised to the rectum (e.g., levator ani syndrome), may also be treated by biofeedback. [21] The clinician needs to determine which symptom features are dominant, and which treatment(s) are most likely to lead to improvement.

Psychosocial Features

The brain-gut axis is the basis for a bidirectional relationship, where gastrointestinal symptoms influence psychosocial state, and vice versa. Thus, chronic pain, nausea, or vomiting can lead to anxiety or depression, as modified by early experiences, coping, and social and family influences. Conversely, psychosocial difficulties, including co-morbid anxiety, depression, a significant loss, or sexual or physical trauma history, influences pain threshold and gastrointestinal motility. This relationship justifies the use of gastrointestinal behavioural treatments such as cognitive-behavioural therapy or hypnotherapy., [94]

Although psychosocial co-morbidities may determine referral for gastrointestinal behavioural intervention, it is also recognised that it is the patient's awareness of the value of the treatment and the motivation to engage that determines success. [95] The best candidates for gastrointestinal behavioural treatments understand the nature of gut-brain disorders, are open to behavioural change to alleviate symptoms, can make connections between times of stress

and anxiety and symptoms, and have the time to participate in the treatment. Patients with severe psychopathology or personality disorder, who have little insight into the gut-brain interaction, who are fixated on a "cure," or who are unable or unwilling to commit to treatment are unlikely to benefit. [94]

Symptom Severity

Severity is a biopsychosocial composite of patient-reported gastrointestinal and extra-intestinal symptoms, the degree of pain, disability, psychosocial impairments, illness-related perceptions and behaviours, and health-related quality of life. [96] It is operative when making treatment decisions. For example, a patient having infrequent low-grade abdominal pain with no other symptoms, and no psychological distress is unlikely to seek healthcare, and would be classified as mild, and not treated. Conversely, a patient having severe abdominal pain, along with fibromyalgia and migraine headaches, who is unable to work, depressed, and frequently seeks healthcare, or is hospitalised, would be considered severe, and treated with behavioural and multiple medical treatments. Table 4 provides guidelines developed by a Rome Foundation working team to help categorise severity for FGIDs. [96]

In summary, treatment of FGIDs requires an effective patient-provider relationship and a multimodal approach that incorporates the nature of the symptoms, their severity, the presence of psychosocial co-morbidities and, in combination, their impact. The multi-dimensional clinical profile, which has been proposed by the Rome Foundation, takes these factors into consideration, in order to help the clinician provide care that is targeted to the personal needs of the patient. [97,98] The five components of this include:

A. Categorical diagnosis (the symptom-based criteria)

B. Clinical modifier (e.g., IBS with constipation, diarrhoea, or mixed bowel habits, post-infection aetiology, FODMAP sensitivity)

C. Impact (mild, moderate, severe)

D. Psychosocial modifier (e.g., psychological diagnosis, loss, trauma history,)

E. Physiological dysfunction and biomarkers (where available)

Although currently this model has heuristic value and is being promoted in clinical education, [98] future studies are needed to provide evidential support.

CONCLUSIONS

FGIDs are extremely prevalent, affecting almost one-in-two people at some point in their lives. Due to healthcare seeking, excess surgeries, medications, and their effects on quality of life, psychological health, work, and social functioning they have a substantial impact not only on the lives of sufferers, but also society as a whole. The pathophysiology is complex, but the biopsychosocial model provides a framework to articulate this. Novel, testable, models may further improve our understanding. Although treatment remains symptom-based, it is recognised increasingly that there is a need to enhance the patient-provider relationship, and that this should be multimodal, to maximise chances of success. In the future, treatment approaches are likely to become more personalised based not only on symptoms, but also underlying pathophysiology and psychology.

Contributors

CJB, DAD, NJT, JR, and ACF did the literature search, wrote the manuscript, and drafted the figures. ACF and DAD revised the initial manuscript. All authors critically revised subsequent versions of the manuscript and approved the final version of the manuscript.

Declaration of Interests

CJB has no conflicts of interest. DAD is President Emeritus and Chief of Operations of the Rome Foundation. NJT reports grants from Abbott Pharmaceuticals, grants from Commonwealth Diagnostics , non-financial support from HVN National Science Challenge NZ, grants and personal fees from GI therapies, grants from Viscera USA , personal fees from Adelphi values, personal fees from Allergens PLC , personal fees from Takeda, personal fees from Ampligent, personal fees from Progenity Inc , personal fees from Sanofi-aventis, personal fees from IM Health Sciences, personal fees from Napo Pharmaceutical, personal fees from Outpost Medicine, personal fees from Samsung Bioepis, personal fees from Synergy, personal fees from Theravance, personal fees from Yuhan, grants from Prometheus (IBS), grants from Pfizer, grants from Rome Foundation , grants from Salix , personal fees from Aviro Health (Digestive health) , personal fees from ARENA Pharmaceuticals , personal fees from Anatara Life Sciences, personal fees from Allakos, personal fees from Censa, personal fees from Cadila Pharmaceuticals , personal fees from Danone, personal fees from Dr. Reddy's Laboratories , personal fees from Planet Innovation , personal fees from twoXAR, personal fees from Theravance, personal fees from Dr Falk, outside the submitted work. In addition, NJT has a patent Biomarkers of IBS licensed, a patent Licensing Questionnaires Talley Bowel Disease Questionnaire licensed to Mayo/Talley, a patent Nestec European Patent licensed, and a patent Singapore Provisional PatentÐu8220“Microbiota Modulation Of BDNF Tissue Repair Pathway” issued. JR has no conflicts of interest. ACF has no conflicts of interest.

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696

Table 1. Rome IV Adult Functional Gastrointestinal Disorders (Disorders of Gut-Brain

697

Interaction).

A. Oesophageal Disorders

A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	

B. Gastroduodenal Disorders

B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome	B3a. Chronic nausea vomiting syndrome
B1b. Epigastric pain syndrome	B3b. Cyclic vomiting syndrome
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	

C. Bowel Disorders

C1. Irritable bowel syndrome	C2. Functional constipation
C1a. IBS with predominant constipation	C3. Functional diarrhoea
C1b. IBS with predominant diarrhoea	C4. Functional abdominal bloating or distension
C1c. IBS with mixed bowel habits	C5. Unspecified functional bowel disorder
C1d. IBS unclassified	C6. Opioid-induced constipation

D. Centrally Mediated Disorders of Gastrointestinal Pain

D1. Centrally-mediated abdominal pain syndrome	D2. Narcotic bowel syndrome or opioid-induced gastrointestinal hyperalgesia

E. Gallbladder and Sphincter of Oddi Disorders

E1. Biliary pain	E2. Functional pancreatic sphincter of Oddi disorder
E1a. Functional gallbladder disorder	
E1b. Functional biliary sphincter of Oddi disorder	

F. Anorectal Disorders

F1. Faecal incontinence	F3. Functional defaecation disorders
F2. Functional anorectal pain	F3a. Inadequate defaecatory propulsion
F2a. Levator ani syndrome	F3b. Dyssynergic defaecation
F2b. Unspecified functional anorectal pain	
F2c. Proctalgia fugax	

698

Table 2. Definitions of Some of the Commonest Rome IV Adult Functional Gastrointestinal Disorders, Population Prevalence, and Confirmatory Tests Required.

Diagnosis	**Definition**	**Prevalence* (%) [3]**	**Confirmatory tests required† [18-21]**
Functional dysphagia	A sensation of abnormal food bolus transit through the oesophagus in the absence of structural, motor, or mucosal abnormalities	3.2	Endoscopy and biopsies, barium swallow, and high-resolution oesophageal manometry
Functional heartburn	Retrosternal burning, discomfort, or pain, which is refractory to optimal acid suppression therapy, in the absence of gastro-oesophageal reflux, histopathological mucosal abnormalities, major motor disorders, or structural abnormalities	1.1	Endoscopy and biopsies, and 24-hour pH and impedance studies
Functional chest pain	Recurrent, unexplained, retrosternal chest pain of presumed oesophageal origin, which is different from heartburn, and not explained by reflux disease, or mucosal, or motor abnormalities	1.4	Cardiology work-up, endoscopy and biopsies, and 24-hour pH and impedance studies

Functional dyspepsia	Characterised by one or more of the following: postprandial fullness, early satiety, epigastric pain, or epigastric burning, that are unexplained after routine clinical investigation	7.2	Endoscopy and biopsies if alarm symptoms present
Rumination syndrome	Repetitive, effortless regurgitation of recently ingested food into the mouth, followed by either re-chewing and re-swallowing, or expulsion of the food bolus	2.8	High-resolution oesophageal manometry
Cyclic vomiting syndrome	Stereotypical episodes of vomiting, with an acute onset, and lasting less than 1 week, with the absence of vomiting between episodes	1.2	History is usually typical, but if atypical features consider endoscopy, computed tomography of the brain, and porphyria screen
Functional constipation	Symptoms of difficult, infrequent, or incomplete defaecation, not meeting criteria for irritable bowel syndrome and, although abdominal pain/bloating may be present, they are not predominant symptoms	11.7	Full blood count, thyroid functions tests, and serum calcium, with colonoscopy only if >50 years
Irritable bowel syndrome	Recurrent abdominal pain, at least 1 day per week, associated with defaecation or a change in bowel habits	4.1	Full blood count, C-reactive protein, coeliac serology, and faecal calprotectin (if diarrhoea present), with colonoscopy only if >50 years or alarm symptoms or atypical features present

Functional diarrhoea	Recurrent passage of loose or watery stools, not meeting criteria for irritable bowel syndrome and, although abdominal pain/bloating may be present, they are not predominant symptoms	4.7	Full blood count, C-reactive protein, thyroid function tests, coeliac serology, faecal calprotectin and elastase, with colonoscopy only if >50 years or alarm symptoms present
Functional abdominal bloating/distension	Subjective symptoms of abdominal fullness, pressure, or a sensation of trapped gas (bloating); an objective measurable increase in abdominal girth (distension); not meeting criteria for an alternative functional bowel disorder, although mild abdominal pain or minor changes in bowel habit may co-exist	3.5	Full blood count, coeliac serology, and CA-125 (in female patients only)
Functional bowel disorder, unspecified	Bowel symptoms, not attributable to an organic aetiology, and not meeting diagnostic criteria for irritable bowel syndrome, functional constipation, functional diarrhoea, or functional abdominal bloating/distension	11.0	As this is a diagnosis reached in a patient not meeting criteria for functional constipation, IBS, functional diarrhoea, or functional abdominal bloating/distension, investigations are as specified for these disorders
Proctalgia fugax	A sudden, severe pain in the rectal area, lasting for a few seconds to several minutes, and then disappearing completely	5.9	Anorectal manometry and magnetic resonance imaging of the pelvis

***The total proportion of people reporting symptoms compatible with at least one FGID in this Rome Foundation global burden of illness study was 42.7%, [3] but the combined prevalence in the table adds up to >50%, because FGIDs frequently overlap with each other. [4] This increases the negative**

impact on quality of life and psychological health, and increases the likelihood of consultation, need for medical therapy, and potential for unnecessary surgery. [4]

†Many of these investigations are only available in secondary care. The clinician in primary care is more likely to make a diagnosis on clinical grounds and treat or refer if there is diagnostic uncertainty.

Table 3. Guidelines for Establishing an Effective Patient-provider Relationship. [13]

1. Improve patient satisfaction and engagement with the patient.	Satisfaction relates to the patient's perception of the provider's humaneness, technical competence, interest in psychosocial factors, and providing relevant medical information. Engagement relies on nonverbal communication including good eye contact, affirmative nods, gentle tone of voice, close interpersonal distance, and creation of a partner-like interaction.
2. Obtain the history through a non-directive, non-judgmental, patient-centred interview.	This process involves active listening and employing questions based on the patient's thoughts, feelings, and experiences, rather than on using a personal or pre-set list of questions.
3. Determine the immediate reason for the patient's visit and evaluate the patient's verbal and non-verbal communication.	"What led you to see me at this time?" Reasons may include: 1) new or exacerbating factors (dietary change, concurrent medical disorder, side effects of new medication); 2) personal concern about a severe disease (e.g., recent family death); 3) personal or family stressors (e.g., recent or anniversary of a death or other major loss, abuse event or history); 4) worsening or development of psychiatric co-morbidity (e.g., depression or anxiety); 5) impairment in daily function (recent inability to work or socialise), or 6) a "hidden agenda" such as narcotic or laxative abuse, pending litigation, or disability claims.
4. Conduct a careful physical examination and cost-efficient investigation.	A well-conducted physical examination has therapeutic value. [99]
5. Determine the patient's understanding of the illness and concerns.	"What do you think is causing your symptoms?" or "What concerns or worries do you have about your condition?"

6. Elicit the patient's understanding of the symptoms ("illness schema") and provide an explanation that considers the patient's beliefs.	"I understand you believe you have an undiagnosed infection. We understand the infection is gone, but your nerves have been affected by it so that it feels as though the infection is still there, like a 'phantom limb'."
7. Identify and respond realistically to the patient's expectations for improvement.	"How do you feel I can be helpful to you?"
8. When possible, provide a link between stressors and symptoms that are consistent with the patient's beliefs.	Many patients are unable to associate stressors with illness. Still, most will understand the stress of the illness on their emotional state. "I understand you don't see stress as causing your pain, but you've mentioned how severe and disabling your pain is. How much do you think that is causing you emotional distress?"
9. Set consistent limits.	"I appreciate how bad the pain must be, but narcotic medication is not indicated because it can be harmful."
10. Involve the patient in the treatment.	"Let me suggest some treatments for you to consider."
11. Make recommendations consistent with patient interests.	"Neuromodulators can be used for depression, but they also are used to 'turn down' the pain, and pain benefit occurs in doses lower than those used for depression."
12. Help establish an ongoing relationship with you, or in association with a primary care provider.	"Whatever the result of this treatment, I'm prepared to consider other options, and I will continue to work with you through this."

Table 4. Clinical Profile for Severity in Functional Gastrointestinal Disorders. [16,96]

Clinical Feature	**Mild**	**Moderate**	**Severe**
Estimated prevalence	40%	35%	25%
Symptom severity score as a psychometric correlate*	Low	Medium	High
Physiological factors	Primarily gastrointestinal dysfunction	Gastrointestinal dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial difficulties	None or mild psychological distress	Moderate psychological distress	Severe psychological distress, catastrophising, abuse history
Abdominal pain	Mild, intermittent	Moderate, frequent	Severe, very frequent or constant
Number of extra-intestinal symptoms	Low (1–3)	Medium (4–6)	High (7 or more)
Health-related quality of life	Good	Fair	Poor
Healthcare utilisation	0–1 time per year	2–4 times per year	5 or more times per year
Activity restriction	Occasional (0–15 days)	More often (15–50 days)	Frequent or constant (more than 50 days)
Work disability	<5%	6 to 10%	11% or greater

*For example: low, an IBS-symptom severity score (IBS-SSS) of 75-175; medium, an IBS-SSS of 176-300; high, an IBS-SSS of >300.

Figure 1. A Biopsychosocial Model of Functional Gastrointestinal Disorders. Adapted from van Oudenhove *et al.* [35]

Figure 2. Intestinal Immune Activation Model of Functional Gastrointestinal Disorders. It is hypothesised that, in a genetically primed host, environmental factors induce immune activation. Antigen presentation of luminal antigens, such as pathogens or food peptides, to T cells drives maturation of naïve T cells to T-helper 2 cells. The release of associated cytokines (IL-4, IL-5, and IL-13) promotes the activation and recruitment of eosinophils, B cells, and mast cells. In addition to the traditional T-helper 2 pathway, secretion of IL-23 from antigen-presenting cells, such as dendritic cells, B cells, and macrophages, promotes T_h17 helper cell differentiation. The production of GM-CSF from T_h17 helper cells further drives eosinophil recruitment. Degranulation of mast cells and eosinophils results in the release of inflammatory mediators, which can damage the intestinal barrier, and stimulate and damage enteric nerve fibres, to induce visceral hypersensitivity and motility disturbances, resulting in gastrointestinal symptoms. α4β7 gut homing T cells are a marker of intestinal inflammation in both functional dyspepsia and irritable bowel syndrome, and correlate with delayed gastric emptying. Duodenal motor dysfunction may also impair duodenal acid clearance, inducing intestino-gastric reflex responses that impair accommodation of the gastric fundus, and increase transient lower oesophageal sphincter relaxations, leading to gastro-oesophageal reflux. Signalling cascades, leading to further cytokine release, may result in extra-intestinal symptoms, such as anxiety and fatigue. The site and extent of intestinal immune activation may define the phenotype (proximal intestinal involvement functional heartburn or functional dyspepsia; more distal involvement irritable bowel syndrome, functional constipation, or functional diarrhoea). Adapted from Talley and Talley. [39] [27]

Figure 3. Diagnostic Algorithm Pathway for a Patient Presenting with Uninvestigated Constipation-type Symptoms. [61]

***A recent change in bowel habit, unintentional weight loss (>10% of ideal body weight), nocturnal symptoms, a family history of colorectal cancer, rectal bleeding (not caused by haemorrhoids or anal fissures), or age >50 years.**

The pathways have been validated and standardised by the Rome Foundation. Purple represents a clinical state (diagnosis), gold represents a decision box (entry path with "yes" and "no" exit paths), and green represents an action box (diagnostic test or therapeutic action required).