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INTRODUCTION

Rome IV—Functional GI Disorders: Disorders of Gut-Brain Interaction

Douglas A. Drossman *William L. Hasler*

Special Issue Editors

Every May, *Gastroenterology* publishes a supplementary issue devoted to a topic of particular interest to the science and practice of gastroenterology. Through a collaboration between *Gastroenterology* and the Rome Foundation, we are delighted to present to you the launching of Rome IV with this series of reviews on functional gastrointestinal disorders. Rome IV occurs fully 10 years after publication of Rome III in this same journal.[1]

Functional GI Disorders, better defined as *Disorders of Gut-Brain Interaction,* though ever present in human society, have only in the last several decades been studied scientifically, categorized and treated based on well-designed clinical investigative studies. Without a structural basis to explain its clinical features, our understanding of these disorders adhere to a biopsychosocial model[2] which is best represented for these disorders in the growing field of neurogastroenterology.[3] Symptoms are generated based on a complex interaction among factors such as microbial dysbiosis within the gut, altered mucosal immune function, altered gut signaling (visceral hypersensitivity) and central nervous system dysregulation of the modulation of gut signaling and motor function. Since publication of Rome III there has been a marked and exciting expansion in our scientific understanding of these disorders, as detailed in this issue, and this has led to improved treatments.

The process for developing the database of information ultimately leading to this special issue is complex. Each article is produced by a series of 5 to 8 expert international investigators and clinicians who were selected for a multi-year project based on their scientific record as well as diversity criteria to cover the broad range of knowledge needed. We covered a wide range of scientific disciplines; from basic science to physiology, mental health, social science and clinical gastroenterology, and geographic localization spanning six continents. The first stage of this effort began over 6 years ago by selecting working teams to acquire and publish reviews and recommendations of new information in areas needed to help the future Rome IV committees produce their articles and chapters. Working team reports included cross-cultural aspects of research, the concept of severity of functional GI disorders (FGIDs), end points and outcomes in clinical trials, the microbiome, and food and diet.[4–12] Then in 2011 the work began to form the 17 committees charged to review and synthesize information and produce manuscripts with communication over conference call, email and in 2014, a meeting in Rome. There were 5 iterations of the manuscripts, most of which were reviewed and modified based on feedback from the 6 members of the Rome IV editorial board and over 50 outside reviewers. In the end, each committee produced a chapter for the Rome IV book that includes a more detailed online version with graphical illustrations, while the reviews in this special issue of *Gastroenterology* provide condensed articles that cover the essentials of each topic.

This special issue covers the full range of the field of FGIDs. It starts with an overview by Douglas Drossman[13] who provides an operational definition and classification system for FGIDs (Table 1), discusses the process with which the committees created the scientific content through evidence-based review and when needed consensus (Delphi method)[14], the changes that occurred between Rome III and Rome IV, the history, conceptual and scientific understanding of FGIDs as a group via the biopsychosocial model, and it ends with a general approach to the care of patients with disorders ranging from mild to severe.

The overview is followed by a series of reviews by the committees that drill down on the bases for understanding these disorders, and set the stage for the clinical information to follow. Stephen J. Vanner, et al[15] (*Fundamentals of Neurogastroenterolgy: Basic Science; pages 1280–1291*) provide basic information on the enteric nervous system, sensory physiology underlying pain and neuroimmune signaling, intestinal barrier function and the role of the microbiome. Guy Boeckxstaens, et al[16] *(Fundamentals of Neurogastroenterology: Physiology/Motility –Sensation; pages 1292–1304)* carries this information further into the

Most current article

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Table 1. Functional Gastrointestinal Disorders

A. Esophageal Disorders
A1. Functional chest pain
A2. Functional heartburn
A3. Reflux hypersensitivity
A4. Globus
A5. Functional dysphagia
B. Gastroduodenal Disorders
B1. Functional dyspepsia
B1a. Postprandial distress syndrome (PDS)
B1b. Epigastric pain syndrome (EPS)
B2. Belching disorders
B2a. Excessive supragastric belching
B2b. Excessive gastric belching
B3. Nausea and vomiting disorders
B3a. Chronic nausea vomiting syndrome (CNVS)
B3b. Cyclic vomiting syndrome (CVS)
B3c. Cannabinoid hyperemesis syndrome (CHS)
B4. Rumination syndrome
C. Bowel Disorders
C1. Irritable bowel syndrome (IBS)
IBS with predominant constipation (IBS-C)
IBS with predominant diarrhea (IBS-D)
IBS with mixed bowel habits (IBS-M)
IBS unclassified (IBS-U)
C2. Functional constipation
C3. Functional diarrhea
C4. Functional abdominal bloating/distension
C5. Unspecified functional bowel disorder
C6. Opioid-induced constipation
D. Centrally Mediated Disorders of Gastrointestinal Pain
D1. Centrally mediated abdominal pain syndrome (CAPS)
D2. Narcotic bowel syndrome (NBS)/ Opioid-induced GI hyperalgesia
E. Gallbladder and Sphincter of Oddi (SO) Disorders
E1. Biliary pain
E1a. Functional gallbladder disorder
E1b. Functional biliary SO disorder
E2. Functional pancreatic SO disorder
F. Anorectal Disorders
F1. Fecal incontinence
F2. Functional anorectal pain
F2a. Levator ani syndrome
F2b. Unspecified functional anorectal pain
F2c. Proctalgia fugax
F3. Functional defecation disorders
F3a. Inadequate defecatory propulsion
F3b. Dyssynergic defecation
G. Childhood Functional GI Disorders: Neonate/Toddler
G1. Infant regurgitation
G2. Rumination syndrome
G3. Cyclic vomiting syndrome (CVS)
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation
H. Childhood Functional GI Disorders: Child/Adolescent
H1. Functional nausea and vomiting disorders
H1a. Cyclic vomiting syndrome (CVS)
H1b. Functional nausea and functional vomiting
H1b1. Functional nausea
H1b2. Functional vomiting
H1c. Rumination syndrome
H1d. Aerophagia
H2. Functional abdominal pain disorders
H2a. Functional dyspepsia
H2a1. Postprandial distress syndrome
H2a2. Epigastric pain syndrome
H2b. Irritable bowel syndrome (IBS)
H2c. Abdominal migraine
H2d. Functional abdominal pain – NOS
H3. Functional defecation disorders
H3a. Functional constipation
H3b. Nonretentive fecal incontinence

physiological realm discussing the function of anatomic regions of the digestive tract, the abnormalities in physiological processes that lead to symptom generation, and the pathophysiology of enhanced visceral perception, and motor dysfunction. Giovanni Barbara, et al[17] *(The Intestinal Microenvironment and Functional Gastrointestinal Disorders; pages 1305–1318)* discuss the role of luminal factors (diet, the microbial environment, and the epithelial barrier) on regulation and dysregulation of gut function leading to functional GI symptoms. Michael Camilleri, et al[18] *(Pharmacological, Pharmacokinetic and Pharmacogenomic Aspects of Functional Gastrointestinal Disorders; pages 1319–1331)* review preclinical pharmacology, pharmacokinetics and toxicology and the application of pharmacogenomics in understanding medicinal treatments for patients with FGIDs. Lesley A. Houghton, et al[19] *(Age, Gender, and Women's Health and the Patient; pages 1332–1343)* cover the range of societal and sociological factors relevant to the clinical expression of FGIDs (gender, age, culture, and society) and in addition discuss the patient's perspective of illness. Carlos F. Francisconi and Ami D. Sperber, et al[20] *(Multicultural Aspects in Functional Gastrointestinal Disorders (FGIDs); pages 1344–1354)* offer a global perspective on the FGIDs to help us understand how geographical diversities in culture, race, and ethnicity impact the patient's explanatory model of their illness, symptom reporting and behavior, and treatments. Lukas Van Oudenhove, et al[21] *(Biopsychosocial Aspects of Functional Gastrointestinal Disorders: How Central and Environmental Processes Contribute to the Development and Expression of Functional Gastrointestinal Disorders; pages 1355–1367)* offer a comprehensive review on the complex interaction of environmental, psychological and biological factors leading to the genesis, clinical expression and perpetuation of functional GI disorders. They also include a detailed flowchart to help the clinician navigate the evaluation and treatment of psychosocial aspects of the illness.

With this comprehensive introduction to the basic aspects of the field, the subsequent articles cover epidemiology, pathophysiology, psychosocial and clinical features and diagnostic evaluation (including the Rome IV diagnostic criteria) and treatment recommendations for the 33 adult and 17 pediatric FGIDs. As is traditional for the Rome Foundation, the disorders are categorized by anatomic regions in adults and by age in pediatric FGIDs Qasim Aziz, et al[22] *(Esophageal Disorders; pages 1368–1379)* introduce more information on the relationship of visceral hypersensitivity, central hypervigilance and motor disturbance in explaining the variety of esophageal conditions from globus to chest pain, to functional dysphagia and describe the new entity of reflux hypersensitivity, where there is physiologically normal acid reflux but symptoms related to visceral hypersensitivity. Vincenzo Stanghellini, et al[23] (*Gastroduodenal Disorders; pages 1380–1392)* provide additional information and evidence to support the subcategorization of functional dyspepsia into overlapping postprandial distress and epigastric pain syndrome,[24] introduce the cannabinoid hyperemesis syndrome[25] and discuss further our understanding and management of chronic nausea vomiting syndrome and supragastric belching. Brian E. Lacy and Fermín Mearin, et al[26] *(Bowel Disorders; pages 1393–1407)* provide revised definitions for the subcategorization of IBS based on recent normative population data, and introduce opioid induced constipation (OIC).[27] Laurie Keefer, et al[28] *(Centrally Mediated Disorders of Gastrointestinal Pain; pages 1408–1419)* update our knowledge of centrally mediated abdominal pain syndrome (CAPS, formerly known as functional abdominal pain syndrome - FAPS) and introduce the new entity, Narcotic bowel syndrome (Opioid induced GI hyperalgesia).[29] Peter B. Cotton, et al[30] *(Gallbladder and Sphincter of Oddi disorders; pages 1420–1429)* provide compelling evidence and make recommendations to reconsider the Milwaukee classification of the sphincter of oddi (SOD) disorders. Now removed from FGIDs is the previous SOD type I which is due to structural stenosis and SOD type III which falls into the general functional GI pain realm, since there is no benefit for sphincterotomy.[31] Finally, Satish Rao, et al[32] *(Anorectal Disorders; pages 1430–1442)* provide an in depth discussion of the rectal pain and dyssynergic syndromes and the use of physiological testing for diagnostic assessment and treatment application.[33]

There are two pediatric articles that cover the FGIDs in neonate-toddlers and children. Marc A. Benninga and Samuel Nurko, et al[34] *(Childhood Functional Gastrointestinal Disorders: Neonate/Toddler; pages 1443–1455)* offer more neurobiological evidence to support our understanding of GI pain experienced in infants and toddlers and provides the classification system for 7 FGIDs. Finally, Jeffrey Hyams and Carlo Di Lorenzo, et al[35] *(Childhood Functional Gastrointestinal Disorders: Child/Adolescent; pages 1456–1468)* present revised diagnostic criteria to more closely approximate the adult disorders including the postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) subsets of functional dyspepsia. Finally, E. Jan Irvine and Jan Tack, et al[36] provide an update on methodological issues relating to the design of treatment trials in FGIDs (*Design of Treatment Trials for Functional Gastrointestinal Disorders; pages 1469–1480*).

Functional GI disorders are separated from everyday GI symptoms based on frequency data that determines abnormality. By determining abnormal frequencies one can create a diagnostic questionnaire that can be used to identify patients with FGIDs for clinical research. To this end Olafur Palsson, et al[37] *(Development and Validation of the Rome IV Diagnostic Questionnaire for Adults; pages 1481–1491)* report the results of the multicenter validation of the Rome IV questionnaire based on a US population sample of over 1000 subjects.

We do hope that this special issue has something for everyone engaged in the research and care of patients with functional GI Disorders. We have come a long way in the last 10 years and special thanks to the efforts of the 120 investigators involved in Rome IV, we can now provide this information to you. Enjoy!

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