



From Rome to Los Angeles -- The Rome III Criteria for the Functional GI Disorders

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Background and Context

Functional gastrointestinal disorders (FGIDs) have become generally more widely accepted as legitimate diagnostic conditions worthy of clinical attention and scientific investigation.^[1] These conditions are very prevalent throughout the world and remain a challenge for clinicians and research scientists, among others. The Rome Foundation has taken on the challenge of establishing symptom-based diagnostic criteria for these FGIDs because of a current lack of diagnostic biologic markers. The newest modification of the criteria, the Rome III criteria, was recently completed and presented at a symposium at this year's Digestive Diseases Week (DDW) meeting. A series of presentations were given by the Rome Foundation Board members at the symposium and included the foundation and rationale of the Rome III process and a review of the Rome III diagnostic criteria for functional gastroduodenal disorders, functional bowel disorders, and for the group of disorders formerly referred to as functional biliary disorders. Classification and responses of the Rome III process were also discussed and included validation of the criteria and development of a diagnostic questionnaire, generalizability of the criteria for clinicians, and new developments in the design of treatment trials.

Introduction

The road to Rome continued its journey by traveling west to Los Angeles, California, in May 2006 to unveil the newly established Rome III criteria for FGIDs at this year's DDW meeting.^[2] The Rome Foundation comprises over 100 international FGID experts who served on various committees and helped develop standardized diagnostic criteria for 28 adult and 16 pediatric FGIDs. The vision of the Rome Foundation is to enhance the clinical recognition and legitimization of FGIDs and to develop a better scientific understanding of the pathophysiologic mechanisms in order to optimize treatment. Substantial progress has been made over recent years, and thus the diagnostic criteria, the understanding of its pathophysiologic mechanisms, and guidelines for treatment for these FGIDs have been updated. The Rome III criteria have been revised from the Rome II criteria and are largely based on findings from published literature. The criteria will be published in a full-length book version and also in a condensed version in this year's April edition of *Gastroenterology*. This work not only includes the Rome III diagnostic criteria for the various FGIDs, but also contains detailed reviews of the literature on a considerable range of topics pertaining to FGIDs, including epidemiology, pathophysiology, diagnostic testing, and treatment.

The DDW symposium was chaired by Douglas Drossman, MD, who is President of the Rome Foundation. Featured lectures on the Rome III criteria, questionnaire development, applicability to patients, and design of treatment trials were presented by the other Rome Foundation Board members.

The Functional GI Disorders and Rome III Process

Dr. Drossman opened the symposium and laid the foundation for the entire Rome III development process and the rationale for the criteria.^[3] He discussed factors that contribute to the rationale for developing criteria for FGIDs, which include the fact that symptoms are not explained primarily by abnormal motility but are defined by multiple factors such as motility disturbances, visceral hypersensitivity, inflammation and mucosal immune dysfunction, brain-gut dysfunction, and early life and psychosocial factors.^[4] Standardized and widely accepted criteria also provide epidemiologic support by defining symptom-based subgroups and demonstrating similar frequencies across different populations. The Rome criteria have also provided diagnostic standards for both clinical trials and clinical cares and have treatment implications. However, there are issues and limitations that were discussed.

The major changes instituted in the Rome III process include (1) revision of time frame requirement to meet diagnostic criteria, (2) changes in classification criteria (eg, rumination is now one of the functional gastroduodenal disorders, and functional abdominal pain syndrome [FAPS] is now a separate category and not a functional bowel disorder), (3) addition of pediatric categories (ie, Neonatal/Toddler and Child/Adolescent), (4) functional dyspepsia as a single disorder has been de-emphasized for research, (5) IBS bowel habit subgroup use primarily of stool consistency to identify IBS bowel habit subgroups (eg, diarrhea or constipation predominance), and (6) more restrictive criteria for gallbladder and sphincter of Oddi dysfunction.

Future plans for the Rome Foundation include global educational programs, support for validation studies, partnering with regulatory agencies, working team initiatives (eg, guidelines for brain imaging and guidelines for severity in FGID working teams), and diversification of structure.

Criteria Development

A Paradigm Shift for Functional Gastroduodenal Disorders

Nicholas J. Talley, MD, PhD, discussed how dyspepsia was defined as "pain or discomfort centered in the upper abdomen" by the Rome I and II criteria.^[5] This old definition was discarded in Rome III because there is no single symptom present in all patients with functional dyspepsia (FD), because considerable variation in symptom patterns exists between patients, and because despite Rome II recommendations, studies still include heartburn and acid regurgitation as "dyspepsia."^[6-8] Dyspepsia is usually polysymptomatic, with 99% of patients reporting more than 2 symptoms, over 80% reporting more than 5 symptoms, and less than 0.1% reporting 1 symptom. These symptoms include upper abdominal pain, heartburn, and acid regurgitation, among others.^[9]

FD is usually referred to as pain or discomfort centered in the upper abdomen with no evidence of organic disease likely to explain symptoms.^[5] The Rome III committee determined that the Rome II criteria were limited for several reasons: (1) a lack of evidence that subdividing FD by predominant symptom is helpful in identifying pathophysiology because of low sensitivity and specificity^[10]; (2) they were based largely on expert opinion; and (3) a factor analysis on symptoms suggests that there is a meal-related syndrome not accounted for by Rome II.^[11]

Therefore, the Rome III committee recommended the following pragmatic definition: Dyspepsia is defined as the presence of 1 or more dyspepsia symptoms that are considered to originate from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms.^[12] These symptoms are listed in Table 1. Thus, the other symptoms that were listed in Rome II no longer fall under the FD umbrella. The committee concluded that the "umbrella term" FD had limited utility and that on the basis of the available evidence, a meal-related grouping and pain-related grouping appear to represent FD because they are associated with distinct symptom groups and pathophysiologic mechanisms. These subgroups are called epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS).

The Rome III definitions for these 2 syndromes are listed in Tables 2 and 3. These new syndromes were defined but remain to be validated and should be used for research purposes only and not for clinical practice at this time. Clinicians are advised to use the definition of FD because treatment studies have applied this definition (and not those of EPS and PDA) in the trials. Another significant change from the Rome II criteria was that the Rome III committee recognized that patients could meet criteria for FD (and EPS or PDA) and have coexistent heartburn or IBS. On the basis of expert opinion, heartburn does not exclude a diagnosis of FD if dyspepsia persists despite a trial of adequate acid suppression. Coexisting IBS has been shown to have no major impact on symptom pattern or putative pathophysiologic mechanisms in FD.^[13]

Fullness and early satiety represent a clear group distinct from nausea and vomiting. There are 2 distinct conditions that are now recognized syndromes in adults and have been defined with Rome III criteria: cyclic vomiting syndrome (CVS) and chronic idiopathic nausea (CIN) -- these are separate from FD on the basis of factor analysis and clinical opinion (Tables 4 and 5).

The New Rome III Criteria for Functional Bowel Disorders and IBS Subgroups

Next, Robin Spiller, MD, discussed how functional bowel disorders comprise the following conditions: irritable bowel syndrome (IBS), functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder. The main changes instituted from Rome II to Rome III criteria are: (1) introduction of a frequency threshold of symptoms needed to meet criteria (ie, 3 or more days per month in the last 3 months); (2) duration of symptoms (reduced to more than 6 months) before one can make a firm diagnosis; and (3) refining the subtyping of IBS.^[14] The Rome III diagnostic criteria for IBS are shown in Table 6.

The Rome II committee subclassified IBS on the basis of expert opinion and attempted to incorporate stool frequency, stool form, and defecation symptoms. However, due to its complexity and a lack of an evidence-based approach, the subclassification was revised to be based solely on stool consistency, which has been supported by recent studies.^[15,16] Subclassification of IBS is important because it would likely be associated with different treatment choices and pathophysiologic mechanisms. The proposed new subtyping based on stool consistency alone is IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS mixed type (IBS-M), and IBS unsubtyped (IBS-U). Patients with IBS-M have both hard and loose stools over periods of hours or days, whereas IBS patients with alternating bowel habits change subtype over periods of weeks and months. Stool form is based on the Bristol stool scale that categorizes stool form and correlates best with colon transit times.^[17] Stability and association with other features, such as visceral sensitivity and response to treatment, remain to be determined.

Functional Gallbladder and Functional Sphincter of Oddi Disorders

Enrico Corazziari, MD, next discussed that the main change is that this group of disorders is no longer referred to as functional biliary disorders; it has been renamed according to the area where the abnormality actually occurs. This group of conditions has been updated to functional gallbladder disorder, functional biliary sphincter of Oddi disorder, and functional pancreatic sphincter of Oddi disorder.^[18] These conditions are not explained by structural abnormalities (eg, gallstones). The definition of biliary-like pain was developed by consensus: (1) pain located in the epigastrium and/or right upper quadrant; (2) recurrent symptoms occurring at different intervals (not daily); and (3) episodes lasting 30 minutes or more; pain builds up to a steady level, and is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit. There are also supportive symptoms, such as that the pain may present with 1 or more of the following: (a) associated nausea and vomiting; (b) radiating to the back and/or right infrascapular region; and (c) causing one to awaken from sleep in the middle of the night. Consensus-recommended Rome III algorithm for functional gallbladder disorder and functional sphincter of Oddi disorder were also discussed.

Challenges and Responses

Rome III Diagnostic Questionnaire -- Development and Validation

William Whitehead, PhD, discussed the goals of the questionnaire development and validation process which were: (1) to develop a questionnaire that incorporates the Rome III criteria as an aid to diagnosis; (2) insure that questions are understandable; and (3) validate the questionnaire and the criteria by comparing to diagnoses made by clinicians. Novel to the Rome process, a questionnaire was developed and validated through a multistep process using the expertise of the Rome committee, working teams, and multicenter study sites. A major innovation of Rome III is the development of an ordinal scale with individual frequency thresholds. One of the goals was to make sure that frequency thresholds of symptoms had the best sensitivity and specificity for abdominal pain in IBS, which was found to be 2-3 days per month with a sensitivity of 71% and specificity of 88%. The Rome III diagnostic questionnaire's reliability and specificity are excellent and sensitivity is good. However, additional testing is needed for other FGIDs.

Applicability of Rome III Criteria for Clinical Practice

W. Grant Thompson, MD, discussed the issues and questions faced by clinicians associated with trying to apply published trial and survey data to clinical practice, specifically treatment selection for their patients. Questionnaires aid in the diagnosis, and also select subjects for clinical trials and survey populations. Optimally, they should be inclusive so that all patients with this condition are encompassed. However, algorithms and inclusion and exclusion criteria used in a questionnaire study can affect the results. Cutoffs of severity and frequency scales are important and will determine who is included. Exclusions are also important because patients with the symptoms of the condition may be excluded depending on the criteria requirements. When reviewing clinical treatment trial data, it is important that the clinician ask the following questions to determine whether the data are applicable to his/her patient: (1) Was the questionnaire altered? (2) What was the purpose of the study? (3) How was the study population selected? and (4) Can the evidence from that trial or survey apply to my patient?

Update on Design of Treatment Trials

Next, Michel Delvaux, MD PhD, addressed the design of trials to assess the efficacy of new treatments for FGIDs, emphasizing trials in IBS and dyspepsia because most research has been undertaken in these conditions.^[19] Design of treatment trials is extremely important in evaluating the efficacy of therapy and in applying data to clinical care. Optimal design should be placebo-controlled, double-blind, parallel group, and randomized to treatment allocation. However, there are challenges in designing clinical trials in FGIDs. These include high placebo response rate, fluctuating symptoms, heterogeneous and complex mechanisms, avoiding bias, contamination by over-the-counter treatments or drugs for other conditions, and avoiding harm given that FGIDs are not considered life-threatening conditions. The study design must clearly define the FGID to be treated, the subgroups, and inclusion and exclusion criteria (eg, sex, symptom severity, comorbidities, concurrent medications). Some unresolved issues concern the duration of the treatment intervention (eg, 4 vs 12 weeks), frequency of treatment (eg, daily vs on-demand), and difficulty blinding the intervention (eg, psychotherapy, hypnotherapy, sphincterotomy, or treatment with predictable effects or side effects).

There are primary and secondary outcome measures. These will likely depend on the mechanism of action of the therapeutic modality. Secondary outcomes are important for determining the efficacy of the treatment on individual symptoms or nongastrointestinal outcomes, such as health-related quality of life. A definition of a responder is a 2-dimensional outcome, the amplitude of the response of the treatment, and the duration of the response over the treatment period. There is a continuous spectrum of response from complete relief 100% of the time to some relief for a short

duration of time. We currently do not know the threshold for a clinically meaningful treatment effect. In summary, the Rome process has facilitated methodologic advances that have been important over the last 2 decades. However, alternative study designs need further validation, and outcome measures are the critical issue and deserve further research.

Conclusion

The Rome process has been dedicated to providing education, legitimization, and validation for the numerous FGIDs affecting the pediatric and adult populations. The Rome III committees have recently provided updated reviews on the basic science, physiologic mechanisms, psychosocial, epidemiologic, diagnostic, and treatment aspects of these disorders. A new Rome III classification system for FGIDs has been established with the inclusion of symptom-based criteria for clinical investigation and practice. An evidence-based approach was taken; however, in areas where this type of information was lacking, consensus opinion was employed. A number of issues still continue to challenge healthcare providers, research scientists, regulatory agencies, and industry, and these remain a goal of the Rome Foundation to tackle in the future in the evolving process of unraveling the complexities surrounding FGIDs.

Table 1. Rome III Diagnostic Criteria for Functional Dyspepsia

Functional Dyspepsia
At least 3 months, with onset at least 6 months previously, of 1 or more of the following:
<ul style="list-style-type: none">• Bothersome postprandial fullness• Early satiation• Epigastric pain• Epigastric burning
And
<ul style="list-style-type: none">• No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

Table 2. Rome III Diagnostic Criteria for Epigastric Pain Syndrome

Epigastric Pain Syndrome
At least 3 months, with onset at least 6 months previously, with ALL of the following:
Pain and burning that is:
<ul style="list-style-type: none">• intermittent• localized to the epigastrium of at least moderate severity, at least once per week,• and NOT:

1. generalized or localized to other abdominal or chest regions
2. relieved by defecation or flatulence
3. fulfilling criteria for gallbladder or sphincter of Oddi disorders

Table 3. Rome III Diagnostic Criteria for Postprandial Distress Syndrome

Postprandial Distress Syndrome
<p>At least 3 months, with onset at least 6 months previously, of 1 or more of the following:</p> <ul style="list-style-type: none"> • Bothersome postprandial fullness <ol style="list-style-type: none"> 1. occurring after ordinary-sized meals 2. at least several times a week <p>Or</p> <ul style="list-style-type: none"> • Early satiation <ol style="list-style-type: none"> 1. that prevents finishing a regular meal 2. and occurs at least several times a week

Table 4. Rome III Diagnostic Criteria for Cyclic Vomiting Syndrome

Cyclic Vomiting Syndrome
<p>At least 3 months, with onset at least 6 months previously of:</p> <ul style="list-style-type: none"> • Stereotypical episodes of vomiting regarding onset (<i>acute</i>) and duration (<i>less than 1 week</i>) • 3 or more discrete episodes in the prior year • Absence of nausea and vomiting between episodes <p><i>Supportive criteria: History of migraine headaches or a family history of migraine headaches</i></p>

Table 5. Rome III Diagnostic Criteria for Chronic Idiopathic Nausea

Chronic Idiopathic Nausea
<p>At least 3 months, with onset at least 6 months previously, of:</p>

- Bothersome nausea, occurring at least several times per week in the last 3 months
- Not usually associated with vomiting
- Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea

Separate from FD (factor analyses)

Table 6. Rome III Diagnostic Criteria for Irritable Bowel Syndrome

Irritable Bowel Syndrome

At least 3 months, with onset at least 6 months previously of recurrent abdominal pain or discomfort** associated with 2 or more of the following:

- Improvement with defecation; *and/or*
- Onset associated with a change in frequency of stool; *and/or*
- Onset associated with a change in form (appearance) of stool

**Discomfort means an uncomfortable sensation not described as pain.

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