Editorial

The challenges of evolving Rome criteria for functional dyspepsia

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Functional gastrointestinal disorders (FGIDs) are defined by symptom complexes that occur in the absence of organic, systemic, or metabolic diseases that are likely to explain the symptoms. The criteria were first standardized by a group of experts in 1995 forming the Rome I criteria. There have been 3 subsequent iterations with Rome IV being released in 2016. Pain-associated FGIDS are common, with one of the two most prevalent being functional dyspepsia (FD). With Rome III, adult FD criteria were altered significantly to include 4 specific symptoms: early satiety, postprandial fullness, epigastric pain, and epigastric burning. Although some alterations were made in Rome IV FD criteria, the four symptoms remained. These symptoms were first adopted in the pediatric FD criteria with Rome IV. FD has two recognized sub-types—postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS)—which are not mutually exclusive. PDS is defined by bothersome postprandial fullness or bothersome early satiation. EPS is defined by bothersome epigastric pain or bothersome epigastric burning. Defining FD subtypes under the adult Rome III criteria spurred new research linking specific FD symptoms and subtypes differentially with inflammation, mechanical disturbances, and psychosocial functioning.

While evolution in the FD criteria allows for the inclusion of new scientific information, it is not without cost. Specifically, there is a risk that previous study findings utilizing older criteria may be rendered obsolete with regard to prevalence estimates and associated factors for specific FGIDs. The recent study by Aziz and colleagues is the first to systematically assess FD prevalence and associations utilizing Rome IV criteria in a large population (1). Previously, our best knowledge of FD prevalence in adults was provided by two systematic reviews (2,3). The first review analyzed studies published from 1980 to 2002 and determined a prevalence of 11.5–14.7% in the general population (2). Of note, all of the studies included in this review predate the significant alteration in adult FD criteria that was made with Rome III. The second review analyzed the prevalence of uninvestigated dyspepsia in adults in over 100 studies that spanned the time period before and after adoption of the Rome III criteria in adults. For the 312,415 included subjects, an overall prevalence of approximately 21% was found (3). Of note, the 7 studies within this review which specifically utilized Rome III criteria yielded a much lower overall prevalence of 7.6% (3). It seems clear that adjustments in the diagnostic criteria have the potential to substantially alter our understanding of FD prevalence.

The current study by Aziz and colleagues fills an important knowledge gap by systematically evaluating the FD population prevalence across 3 countries (United Kingdom, Canada, and the United States) in a standard fashion utilizing Rome IV criteria for the first time. The authors analyzed 6,300 completed surveys (2,100 from each country) and found a relatively consistent prevalence of around 10% (8% in the UK and Canada, 12% in the US). The 8% prevalence found in the UK and Canada is remarkably close to the 7.6% reported by Ford and colleagues for studies utilizing Rome III criteria (1,3). These data would suggest that changes made in Rome III and carried through to Rome IV have more narrowly defined FD in adults and, consequently, have stabilized prevalence estimates in the general population. In contrast,

transitioning from Rome III to Rome IV FD pediatric criteria, which could be likened to transitioning from Rome II to Rome III in adults, appears to have resulted in an increase in prevalence estimates for FD in children and adolescents (4,5). This difference in impact of criteria on prevalence estimates between adults and youth is interesting and suggests that there may be differences at play in the criteria or condition itself across the lifespan that would benefit from further investigation.

While overlap syndromes (e.g., FD with irritable bowel syndrome; FD/IBS) were recognized utilizing pre-Rome III criteria in adults, the prevalence of FD/IBS overlap did not differ with regard to Rome II FD subtypes (ulcer-like *vs.* dysmotility-like dyspepsia) (6,7). FD/IBS overlap utilizing Rome III criteria has previously been demonstrated in a number of studies performed across a variety of populations (8,9). While the Rome III prevalence for overlap was similar to pre-Rome III, overlap in Rome III was more associated with a specific FD subtype, namely PDS (10). Aziz and colleagues further added to the existing literature by assessing overlap of Rome IV defined FD with other FGIDs and associations with aspects of psychosocial functioning and broader physical symptoms. They found that adults with FD demonstrated a significantly increased prevalence of IBS (32% *vs.* 3%) and heartburn (12% *vs.* <1%), respectively, as compared to those who did not fulfill FD criteria (1). The overall prevalence is similar to what was reported utilizing Rome III. This again contrasts with initial pediatric data where there was a 3-fold increase in the diagnosis of overlap when applying Rome IV criteria to a pediatric population as compared to applying the Rome III criteria to the same population (5).

Recognition of overlap is important as these patients experience greater symptom burden and increased healthcare utilization (9). Previous studies support the existence of FD overlap with gastroesophageal reflux and overactive bladder syndrome in both adults and children (11-13). In addition, overlap has been associated with increased anxiety, depression, and somatization, as well as decreased health-related quality of life (HRQOL) (10,14,15). An association between FD and somatization (i.e., broad physical complaints), specifically, has been reported prior to the transition to Rome III (16). This association also has been reported utilizing Rome III criteria in adults, but like FD/IBS overlap, has been more specifically associated with PDS (17,18). Aziz and colleagues have confirmed the association of somatization with Rome IV defined FD, including the specific association with PDS (1). They reported increased somatization, decreased HRQOL, increased likelihood of having seen a doctor, and increased medication use as an indicator of heavy disease burden (1). Overlapping PDS/EPS was associated with increased somatization and decreased HRQOL as compared to PDS or EPS alone (1). PDS alone was associated with increased somatization, while somatization in EPS was similar to controls (1). The sum of this literature indicates that FD is often associated with other functional gastrointestinal conditions regardless of how the definition of FD has evolved over time; however, this association has become better defined with the recognition that overlap is more prevalent in those adults with FD fulfilling PDS criteria. The impact of Rome IV subtype on overlap prevalence in youth is not as well defined at present, although overlap between conditions is higher overall and may influence detection of subtype associations.

While not a new finding, the confirmation by Aziz and colleagues of an association between somatization and FD, particularly PDS, is worthy of discussion (1). While somatization may be psychological in nature, it is also possible that there may be other pathophysiologic mechanisms that not only lead to dyspeptic symptoms but also a variety of other systemic symptoms. Transition to Rome III FD subtypes led to work demonstrating differential pathophysiologic associations for PDS and EPS. One area of particular focus has been non-diagnostic mucosal inflammation. A systematic review and meta-analysis of microscopic inflammation in FD found 37 studies reporting mucosal cell counts and/or cytokine levels (19). These studies demonstrated increased mast cells and eosinophils (but not intraepithelial lymphocytes or neutrophils) in the antrum and duodenum (19). While this review did not report a difference in duodenal eosinophils by FD subtype, individual studies have reported an association between duodenal eosinophils and PDS (20,21). A pediatric study also found an increase in antral mast cells in patients with PDS while epigastric pain was associated with decreased antral mast cell density (22). This same pediatric study also found a positive correlation between mast cell density and somatization scores (22). An association between somatization and mast cells seems plausible given that gastrointestinal and other somatic symptoms may both result from mast cell mediator release. Many questions that appear on somatization scales refer to symptoms and events (such as headache, shortness of breath, dizziness, and frequent doctor visits) that could be seen in association with mast cell activation.

Recognition of distinct subtypes of FD as defined by Rome III have resulted in inquiries, such as those above, which have begun to clarify our understanding of the relationships between putative pathophysiologic mechanisms. In adults, given the similarity between Rome III and Rome IV FD criteria, it is likely that relationships demonstrated utilizing Rome III criteria would also hold true for Rome IV. Some initial confirmation of this has been provided by Aziz and colleagues. However, a similar statement cannot be made for pediatric patients, as Rome IV has dramatically altered FD criteria. Further, emerging findings do not always parallel those of adults, making extrapolation from adults to youth more challenging.

While previous relationships found for FD need to be re-confirmed under new criteria for both adults and youth, it may be equally true that previous studies finding no relationship between FD and a specific factor need to be re-evaluated to determine if the negative findings continue to hold true. As an example of this, Aziz and colleagues found a negative association between the use of antidepressants (types not defined) and FD, particularly PDS (1). In short, adults who were taking an antidepressant were found to be less likely to have a diagnosis of FD. While cause-and-effect certainly cannot be determined from the study design, this finding raises the possibility that antidepressants may have a beneficial effect on FD, and particularly on PDS. This stands in contrast to a previous systematic review and meta-analysis which concluded that tricyclic antidepressants (TCAs), but not selective serotonin reuptake inhibitors (SSRIs), are effective in FD (23). This systematic review and meta-analysis ultimately assessed 13 previous studies, only 3 of which utilized Rome III criteria and none of these 3 evaluated treatment with an SSRI.

The cause for the possible discrepancy between the systematic review and the Aziz study is not clear. It is possible that TCAs accounted for a significant portion of the subjects in the Aziz study. It is also possible that the findings in the Aziz study represent the real-world experience of FD treatment with antidepressants that involves a more robust response as opposed to what occurs in a controlled treatment trial. It is equally possible that SSRIs, for example, are effective if given to subjects with Rome III or Rome IV defined FD as compared to pre-Rome III. Of note, Aziz and colleagues hypothesize that antidepressants may down-regulate the brain-gut axis and mediate mechano-sensory function. Thus, it is certainly also plausible that the antidepressants may have prevented the conditions for which they were prescribed (e.g., depression or anxiety) from initiating or contributing to altered physiology which would have eventually led to the development of FD. For patients diagnosed with both a mood or anxiety disorder and an FGID, approximately two-thirds have onset of the mood or anxiety disorder before the FGID while one-third have onset of the FGID first (24). For non-healthcare seekers, approximately one-half have onset of the mood or anxiety disorder first and the other half have onset of the FGID first (24). These data would suggest that mood or anxiety disorder may predispose to, or be the result of, an FGID, though this may be epiphenomenon. In a population study, there was nearly an 8-fold increase in FD over 10 years in those with major anxiety (but not depression) (18). Even more interesting in light of evolving criteria, this relationship was limited to the PDS subtype. The findings of Aziz and colleagues suggest that further evaluation is warranted as to how antidepressants alter gastrointestinal physiology related to inflammatory cell activation and mechano-sensory functioning, if at all, in order to tease apart the directionality of the association found. Importantly, it also points out the need to conduct SSRI trials in patients with Rome IV defined FD and, further, to re-examine previous null findings pre-Rome III to ensure that changes in the criteria do not uncover a previously suppressed effect.

The biggest limitation of the study by Aziz and colleagues, as acknowledged by the authors, is that it is not known whether the subjects had previous endoscopy and certainly it could not have been performed in a standardized fashion (1). Thus, the study may have included a mixed group of subjects with uninvestigated dyspepsia (likely the largest group), FD patients with negative endoscopies (but possibly with non-diagnostic mucosal inflammation), and subjects with clear organic disease. This is likely a minor limitation and one that probably needs to be accepted in order to perform large epidemiologic studies of this nature. With regard to somatization, this distinction may not be important as mean somatization scores and numbers of somatic symptoms have been reported to be similar in FD and dyspepsia associated with organic disease in adults (25). However, this does limit our ability to use such epidemiologic studies to better understand putative pathophysiologic mechanisms, particularly as they relate to FD subtypes.

It could be argued that the work of the members of the various Rome committees has been the single most important factor in moving the research agenda forward, and that has furthered our understanding of the mechanisms

responsible for—or contributing to—FGIDs at a much faster rate than prior. The Rome criteria provide the framework for integrating new findings into a more cohesive model. The intentional iterative process of re-evaluating and adapting the criteria to incorporate new research findings has been key in having the criteria continue to be relevant to researchers (and hopefully clinicians). This may be particularly true in the case of FD criteria in adults where evolution to Rome III criteria, which have largely been carried through to Rome IV, ignited a new wave of research yielding important insights that have the potential to translate into improvements in clinical care. That being said, the evolution of the criteria does come with some risk, as outlined here, and should not be undertaken lightly. Significant changes may, to some degree, invalidate previous research findings or at least make them more challenging to reconcile with current definitions and findings. It may be difficult for the clinician, in particular, to keep abreast of current terminology and sort out implications for their own practice.

Finally, Rome IV pediatric criteria were largely adapted from adult criteria with some limited initial pediatric data. It cannot be assumed that the value of the FD criteria change will be as significant as it was in adults, or result in a similar finding. Initial data suggests that, indeed, the Rome IV criteria may be behaving in unexpected ways relative to our accumulating experience with adults. We will need to continue to examine the criteria from a developmental context, ensuring that we are adapting the criteria in the right way for youth with FGIDs, including the language used at different ages to describe similar sensations or symptoms, and that we understand how conditions, associations, and mechanisms may remain constant or vary across the developmental lifespan.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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