Understanding and managing patients with overlapping disorders of gut-brain interaction

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Abstract

Disorders of Gut-Brain interaction (DGBI) are frequently encountered in clinical practice, and recommendations for diagnosis and management are well established. In a large subset of patients, more than one DGBI diagnosis is present, and in this overlap group symptom severity and impact is higher and the management approach is not well established. This review aims to guide clinicians to understand, recognize and manage overlapping DGBI by identifying causes and pitfalls of overlap conditions, and presenting potential practical approaches to diagnosis, treatment and follow-up. A number of clinical factors may contribute to finding overlapping DGBI, including the anatomical basis of the Rome classification, the potential confusion of symptom descriptors, and patients biases towards higher symptom intensity ratings. Overlapping DGBI may also be caused by mechanistic factors such as pathophysiological mechanisms involving multiple gastrointestinal segments, and the impact of disorders in one segment on sensorimotor function in remote gastrointestinal parts, through neural or hormonal signaling. In terms of management, detailed history taking, which can be facilitated using pictograms, as well as careful assessment of relative timing and cohesion of different symptoms and recognition of associated psychosocial dysfunction are key initial steps. Unnecessary technical investigations and complex combination treatment schedules should be avoided. Based on identification of the dominant symptom pattern and putative underlying pathophysiological mechanisms a single treatment modality is preferably initiated, taking into account the efficacy spectrum of different therapies. Follow-up of the patient's condition allows to adjust the therapeutic approach as needed, while avoiding unnecessary additional technical investigations.

Introduction

In up to 50% of patients seen in gastroenterology clinical practice, routine diagnostic investigations fail to identify an abnormality that readily explains the symptoms (1). In these patients, who are referred to as having functional gastrointestinal disorders or disorders of gut-brain interaction (DGBI), it is hypothesized that alterations of gastrointestinal sensorimotor function underlie symptom generation (2). The Rome process, updated most recently in the 2016 Rome IV consensus, classifies these patients in different diagnostic categories based on anatomical regions (esophageal, gastroduodenal, biliopancreatic, bowel and anorectal disorders) and symptom groupings (2). The aspiration and underlying assumption is to identify homogeneous patient groups in terms of symptom presentation and underlying pathophysiology, which require specific management and respond more predictably to particular therapeutic approaches.

However, the occurrence of overlap between different categories of DGBI hampers the concept of separate symptom-based diagnostic entities with a particular management and therapeutic approach (3). The fact that large overlap between entities exists has been one of the major points of criticism of the Rome approach (4,5). Managing patients with overlapping DGBI also constitutes a major challenge for clinicians, as currently available diagnostic and management algorithms target single disease entities (6). To some extent, the Rome process has aimed at decreasing overlap through the definitions of entities. For instance, the Rome III and IV functional (FC) constipation diagnostic criteria require that criteria for irritable bowel syndrome (IBS) are not fulfilled (7). When the Rome III requirement that patients meeting IBS criteria cannot be given a diagnosis of FC is suspended, most patients fulfill criteria for both (8).

Our aim was to provide guidance on the clinical management of patients with overlapping DGBI. Relevant literature was assessed through a Pubmed search using “Rome criteria, functional gastrointestinal disorders, overlapping disorders, irritable bowel syndrome or functional dyspepsia or chronic constipation or heartburn” in English language, since 1990. Given the lack of diagnostic and interventional studies published on overlapping disorders, the yield of a systematic review for the practicing clinician would be low. The manuscript is a narrative review of the literature which

reflects extensive experience in dealing with complex patients in a referral center for DGBI, where overlap is the norm rather than the exception.

Prevalence and relevance of overlapping conditions

The literature has provided extensive evidence for the occurrence of overlapping DGBI, both at the epidemiological and at the clinical care level (3, 9-12). The Rome Global Epidemiology Study showed that of the 40% of the general population meeting Rome IV DGBI criteria, more than 30% fulfill criteria for DGBI in 2 or more anatomical regions (3). Symptom severity scores, psychosocial co-morbidity and healthcare utilization increase with the number of overlapping conditions while quality of life decreases (3). In the advanced care clinical setting, patients presenting with overlapping disorders are the biggest group and symptom severity and impact are highest in those with overlapping conditions (11,12). Hence, in clinical practice, patients with overlapping conditions represent a common challenge.

Mechanisms underlying the occurrence of overlapping conditions

A number of mechanisms, clinical as well as pathophysiological, may contribute to the high prevalence of overlapping DGBI in the general population and in the clinical setting (Figure 1).

1. The anatomical basis of the Rome diagnostic criteria

The Rome diagnostic category scheme is based on the presumed anatomical site of origin of the symptoms to classify patients with DGBI into esophageal, gastroduodenal, biliopancreatic, bowel and anorectal disorder categories (2). A factor analysis of the symptom groupings in a population-based sample of 5931 respondents from 3 countries who filled out the Rome diagnostic questionnaire provided objective support for the Rome symptom groupings (13). On the other hand, a study in 1805 DGBI patients from 11 Asian countries who filled out a more extensive questionnaire identified 3 symptom clusters that involved more than one anatomical region, which

are consequently not considered in the Rome classification scheme (14). In the Rome classification approach, any entity involving more than one anatomical region would be categorized as at least two different Rome diagnostic entities. It is conceivable that cultural and linguistic factors contribute to the different cluster findings in Asia versus other continents such as Europe and North America (the West), although a role for the questionnaire design used cannot be excluded (13-16). Whether the same clusters can also be identified in a Western population is the topic of an ongoing international study using a comprehensive integrated questionnaire (17).

2. Symptom descriptors and intensity ratings

Diagnostic categorization of DGBI depends on accurate assessment of the presenting symptom pattern and severity, as revealed by the patient during history taking (2). Indeed, as currently no suitable biomarkers are available, the symptom pattern is the main determinant of individual DGBI diagnosis (18) This requires sufficient time and skill from the clinician and also ability of the patient to understand and express individual symptoms and their distinctions (19). Additionally, diagnostic categorization of DGBI as defined by the Rome consensus is not only driven by the presence of specific symptoms, but also their level of intensity and frequency, which need to exceed specific diagnostic threshold values (2,6,7). DGBI patients, for instance those with IBS, have a lowered objective response threshold for using negative affective terms to label bodily experiences and for using higher bothersome or intensity ratings (20,21). Such bias towards higher intensity ratings increases the likelihood of reaching diagnostic thresholds for DGBI, and hence of overlapping conditions. Several studies on DGBI have confirmed the relevance of psychosocial co-morbidities, especially anxiety and somatization, as determinants of the presence and impact of DGBI, including their overlap (3,22-24). Somatization - used here in the descriptive sense of “widespread somatic symptoms” in line with the Rome IV consensus and with the use of the word in DGBI literature - is potentially the most important mechanism generating a higher intensity rating bias (22-24). A similar mechanism may underlie the reported instability of DGBI diagnoses over time, where prospectively followed patients may change questionnaire-based diagnoses over time (25). It remains to be established whether a

true shift in symptom pattern occurs, or whether limited differences in symptom intensity and frequency rating result in different diagnostic categorisation.

3. The role of common pathophysiological mechanisms

While the pathophysiological basis of DGBI remains incompletely understood, some of the plausible candidate mechanisms may involve several anatomical sites and hence be relevant to a number of Rome DGBI diagnostic entities. Visceral hypersensitivity, often driven by central sensitization of signals from visceral afferents in the gut-brain axis, is a key factor determining symptom severity both in upper and lower gastrointestinal DGBI, and if present is likely to contribute to the presence of overlapping conditions (26).

Hypocontractility of the gastrointestinal tract is another pathophysiological finding which often involves several anatomical regions (27). Alterations in immune cell composition – and function have been shown in IBS and functional dyspepsia (FD) patients at both the mucosal and systemic level, as recently reviewed (28). Most recently, atypical allergic reactions to food have been reported both in IBS and in FD, in the duodenum and the rectum possibly contributing to overlap of these DGBI (29-31).

4. (Alterations in one segment may affect sensorimotor function in other segments of the gastrointestinal tract)

Besides the often wider presence of hypocontractility in the gastrointestinal tract, disordered motility in one part of the gastrointestinal tract may impact on the function of other parts, and this is presumably mediated through gut peptide or prevertebral neural reflex pathways (32). Delayed gastric emptying, for instance, is commonly observed in patients with slow transit constipation, but inflating a balloon in the rectum is able to significantly delay gastric emptying in healthy controls (33). Possibly through a similar mechanism, slow transit constipation is also associated with impaired gastric accommodation, a key pathophysiological mechanism in FD (34). Impaired gastric accommodation has also been identified as a key trigger for transient lower esophageal sphincter relaxations, the main mechanism underlying gastroesophageal reflux events (35). Fermentation and the presence of short chain fatty acids in the colon

also decreases postprandial pressure in the lower esophageal sphincter and is associated with enhanced transient lower esophageal sphincter relaxation occurrence (36).

Clinical approach and management of overlapping conditions

This section aims at providing guidance to clinicans managing patients with overlapping DGBI, and provides some potential solutions to the issues outlined above. The stepwise approach is summarized in Figure 2.

1. Detailed history taking to evaluate symptoms suggestive of (overlapping) DGBI and consideration of underlying pathophysiological mechanisms

In view of the relevance of symptom criteria for DGBI diagnoses, a systematic assessment of the symptom pattern is mandatory to accurately identify the presence of (overlapping) DGBI (3). The quality of the history taking and interaction with the patient is determined by the physician's and patient's communication skills (19). Moreover, there my be a discrepancy in anatomical understanding and description of a perceived symptom between the patient and clinician (37). Hence, even a dedicated history taking by an experienced clinician may not allow all patients to fully express the individual and multidimensional nature of their symptoms (37). In these cases, pictograms accompanying verbal descriptors are able to significantly improve symptom descriptors by patients and may help clarify overlap, as well as identify the most bothersome symptom (37,38). An integrated "waiting room questionnaire" with symptom descriptors and pictograms for the main DGBI showed promise as a tool to facilitate accurately diagnosing DGBI (39).

The presence of DGBI symptoms from different anatomical locations already implies that overlapping conditions are present (2). Overlapping DGBI can also be present within the same anatomical region: postprandial distress syndrome with nausea and vomiting for instance comprises two distinct gastroduodenal disorders (40,41).

In case of overlapping conditions, it is important to determine the temporal relationship between symptoms belonging to different DGBI or anatomical regions. The history

taking should establish whether these symptoms usually occur, worsen and improve together, have a fixed timing towards each other, or whether they evolve separately.In addition, the relationship of symptoms belonging to different DGBI or anatomical regions to physiological events such as food intake, belching or passing stools or gas, is an important clinical indicator. For instance, when epigastric pain and diarrhea are present in the same patient, it is relevant to question whether they do occur simultaneously or not, with food-induced reactions as a common mechanism in mind (29-31). Similarly, with the associations of colonic stasis with delayed emptying and impaired accommodation outlined above (33,34), it is relevant in a patient expressing constipation as well as postprandial fullness or early satiation, to evaluate whether the latter symptoms also improve after a bowel movement or worsen during constipation episodes.

2. Evaluation of the presence of psychosocial co-morbidities that enhance symptom intensity reporting

As outlined above, psychosocial factors such as anxiety, depression and especially somatization may lead to amplified symptom reporting, thereby increasing the likelihood of overlapping DGBI diagnoses (20-24). Psychosocial co-morbidities are a key part of the Multi-Dimensional Clinical Profile, which summarizes factors besides the categorical DGBI diagnosis that are relevant to consider in clinical care of DGBI patients (43). The presence of these amplifying and confounding factors can be evaluated through history taking or aided by validated questionnaires such as the Patient Health Questionnaires and the Hospital Anxiety and Depression questionnaire (22,41). More in-depth and practical guidance on using these questionnaires in clinical practice are provided elsewhere (42).

3. Selection of limited and targeted additional technical investigations

While overlapping DGBI are highly prevalent in clinical practice, diagnostic guidelines have focused on patients with single DGBI diagnoses. There is a need for systematically collected diagnoscticand outcome studies in DGBI overlap patients. Besides the symptom assessment, as outlined in the previous sections, the presence

of risk or alarm factors should also be evaluated. The presence of these symptoms or findings, such as weight loss, blood in the stools, the family history (of inflammatory bowel disease, coeliac disease or abdominal cancer), or age above the threshold for upper or lower gastrointestinal screening endoscopy should determine the extent of the technical investigations as indicated by international consensus (7,40). The presence of multiple symptoms should not lower the thresholds for additional technical investigations.

In patients with multiple symptoms, for instance in case of overlapping DGBI diagnosis, diagnostic uncertainty and likelihood of incomplete response to therapy is larger. However, the yield of additional technical examinations such as repeat endoscopy, radiological imaging or more sophisticated function testing remains low (7,44-48). Clinicians should thus positively diagnose the respective (overlap of) DGBI if the criteria are fulfilled and limited diagnostic workup has ruled out organic disease as recommended by current guidelines pertaining to the relevant DGBI (49,50). Of note, in clinical practice patients may also be diagnosed with DGBI before symptom duration reaches the diagnostic threshold (51).

4. Determination of the therapeutic target

The presence of overlapping DGBI does not implicate combination therapy from the onset. Based on the symptom pattern assessment and identification of potential underling pathophysiological features, the primary DGBI entity or symptom to target needs to be determined (3,9-12). The therapeutic target will often be driven by the predominant symptom, as indicated by the patient (37,52). Based on presumed underlying pathophysiology, another target may be chosen, for instance targeting colonic transit in case of overlapping postprandial distress syndrome with chronic constipation, in patients whose symptoms evolve in parallel (34). However, there is a lack of studies that investigates whether this type of clinical markers is able to predict therapeutic outcome.

The available literature shows that associated symptoms, which are not necessarily a part of the cardinal symptom pattern may also improve with therapy, even when not directly targeted by the mode of action of the chosen pharmacotherapeutic agent (53-55). Furthermore, for a number of therapeutic approaches, efficacy on symptoms

outside their primary indication has been demonstrated, either in treatment trials, or can be expected based on their pharmacological effects on gastrointestinal (patho-) physiology (53-73). Knowledge of the spectrum of symptom improvement with these approaches, summarized in Table 1, can help to choose the optimal first-line therapy choice. For instance, as shown in Table 1, the 5-HT_3 receptor antagonist ondansetron may improve nausea as well as diarrhea and urgency, and the 5-HT1A agonist buspirone may improve dysphagia, PDS as well as rectal urgency (53,60-62,70). Patients should be made aware of the triggered symptom pattern and that improvement of overlapping symptoms might not occur simultaneously but sequentially in order to appropriately manage expectations. While the preceding statements and Table 1 favor a single treatment choice, there is a clear need to compare the efficacy of single treatment initiation based on the predominant symptom to the use of combination therapies as initial approach.

Table 1 does not address the use of brain-gut behavioral therapies, which have a potential to offer improvement throughout the entire spectrum of DGBI (74). Psychological therapies such as cognitive behavioural therapies can be considered early on in patients that recognize the relationship of psychological factors and fluctuation of symptoms, especially if they are motivated to take on an active role in self-management (74). Brain-gut behavioral therapies are especially valuable to address hypervigilance, gastrointestinal fear conditioning and visceral anxiety which aggravate symptom severity and impact, especially in patients with overlapping DGBI (3,74). However, specific research is needed to establish whether the overlapping DGBI population has a superior response to brain-directed therapies. Neuromodulators should be considered depending on the predominant symptom profile and additional psychosocial factors as presented in table 1 and explained in detail elsewhere (70). Major psychological co-morbidity should be recognized and treated separately if clinically relevant and severe enough (70). They are especially appropriate in case of overlapping painful conditions where neuromodulators can restore defective anti-nociceptive processes leading to visceral hypersensitivity and allodynia (70). In patients with a high somatization score, a long-term goal of gradual symptom improvement, rather than elimination, is probably most realistic and should be discussed (9,23,24,74-77).

5. Follow-up

The long-term prognosis of patients with overlapping compared to those with single DGBI still needs to be studied. After starting the first-line therapy, the timing of follow-up will depend on the response profile of the treatment, and may vary from 4 to 12 weeks (53-73). Currently available patient reported outcome measures mainly focus single diagnostic entities, and may need to be combined or specifically developed for this group. Adjustment of therapy will depend on the magnitude of the initial response. In case of insufficient improvement, therapy can be switched to another choice. In case of incomplete improvement, combination therapy can be considered depending on the nature of the residual non-responding symptom(s). Adding technical investigations and referral of the patient to other specialists in case of insufficient treatment response should be carefully considered, especially in patients with widespread somatic symptoms (gastrointestinal and extra-intestinal) (76,77).

Conclusion

In epidemiological studies as well as in clinical practice, DGBI commonly overlap in the same subject. The presence of overlapping DGBI is associated with higher symptom severity and impact. Currently available guidelines only address the management of patients with a single DGBI, and algorithms are lacking for the overlap group, in spite of the high clinical burden and need. Multiple factors contribute to the frequent occurrence of overlapping disorders, including both clinical characteristics and evaluations, as well as common pathophysiological pathways.

While overlapping DGBI are highly prevalent in clinical practice, research and management guidelines have focused on patients with single DGBI diagnoses. There is a need for systematically collected phenotyping and outcome studies in DGBI overlap patients. Patient reported outcome measures may need to be combined or specifically developed for this group. The efficacy of single treatment initiation based on the predominant symptom needs to be compared to the use of combination therapies as initial approach. Peripherally acting pharmacotherapeutic or dietary approaches need to be compared to neuromodulator therapies and to brain-gut behavioral therapies, to establish whether the overlapping DGBI population has a superior response to brain-directed therapies and whether clinical markers are able to

predict therapeutic outcome. Finally, the long-term prognosis of single versus overlapping DGBI needs to be compared.

In terms of current management recommendations, detailed history taking, which can be aided by pictogram containing symptom questionnaires, as well as careful assessment of relative timing and cohesion of different symptoms is key to understanding the patients' DGBI diagnoses and detailed symptom pattern. The presence of psychosocial dysfunction, which aggravate symptom reporting, should be considered, and only targeted additional technical investigations should be used. A single treatment modality is preferably initiated, based on identification of the dominant symptom pattern and taking into account putative underlying pathophysiological mechanism and the efficacy spectrum of different therapies. Follow-up visits allow to adjust or change the therapeutic approach, while avoiding unnecessary repeat or additional technical investigations for the broad symptom spectrum in overlapping DGBI patients.

Figure legends

Figure 1. Factors contributing to overlapping of Disorders of Gut-Brain Interaction.

Figure 2. Stepwise clinical approach in the management of patients with overlapping Disorders of Gut-Brain Interaction

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