

**Developing a Novel Approach to Subgrouping People with Irritable  
Bowel Syndrome: Moving Beyond Stool Pattern Alone**

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### CHAPTER 1: Introduction.

- Barberio B, Houghton LA, Yiannakou Y, Savarino EV, **Black CJ**, Ford AC. Symptom Stability in Rome IV vs. Rome III Irritable Bowel Syndrome. *Am J Gastroenterol*. 2021;116(2):362-371. The highlighted joint last author collected all data, and co-authored the manuscript.
- **Black CJ** and Ford AC. Global Burden of Irritable Bowel Syndrome: Trends, Predictions and Risk Factors. *Nat Rev Gastroenterol Hepatol*. 2020;17(8):473-486. The first author wrote the manuscript after which it was critically reviewed by the remaining author.
- Oka P, Parr H, Barberio B, **Black CJ**, Savarino EV, Ford AC. Global Prevalence of Irritable Bowel Syndrome According to Rome III or IV Criteria: A Systematic Review and Meta-Analysis. *Lancet Gastroenterol Hepatol*. 2020;5(10):908-917. The highlighted author was jointly involved in conceiving and drafting the study, and critically reviewed and commented on drafts of the final manuscript.
- **Black CJ** and Ford AC. Editorial: Subgroups in Irritable Bowel Syndrome – More Than Just Diarrhoea and Constipation? *Aliment Pharmacol Ther*.

2017;46(7):697. The first author wrote the manuscript following which it was critically reviewed by the remaining author.

- **Black CJ**, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional Gastrointestinal Disorders: Advances in Understanding and Management. *Lancet*. 2020;396(10263):1664-1674. The first author wrote the introduction, the section on epidemiology, and the section on natural history, and commented on drafts of the final manuscript.
- **Black CJ**, Yiannakou Y, Houghton LA, Shuweihdi F, West R, Guthrie EA, Ford AC. Anxiety-Related Factors Associated with Symptom Severity in Irritable Bowel Syndrome. *Neurogastroenterol Motil*. 2020;32(8);e13872. doi: 10.1111/nmo.13872. The first author was jointly involved in conceiving and drafting the study, collected all the data, and was jointly involved in drafting the manuscript, following which it was critically reviewed by all authors.
- **Black CJ** and Ford AC. How Effective are Antibiotics for the Treatment of Irritable Bowel Syndrome? *Expert Opin Pharmacother*. 2020;21(18):2195-2197. The first author wrote the manuscript following which it was critically reviewed by the remaining author.
- **Black CJ** and Ford AC. Rational Investigations in Irritable Bowel Syndrome. *Frontline Gastroenterol*. 2019;11(2):140-147. The first author wrote the manuscript following which it was critically reviewed by the remaining author.
- **Black CJ** and Ford AC. Chronic Idiopathic Constipation in Adults: Epidemiology, Pathophysiology, Diagnosis and Clinical Management. *Med J Aust*. 2018;209(2):86-91. The first author wrote the manuscript following which it was critically reviewed by the remaining author.
- **Black CJ** and Ford AC. Best Management of Irritable Bowel Syndrome. *Frontline Gastroenterol*. 2020. doi: 10.1136/flgastro-2019-101298. The first

author wrote the manuscript following which it was critically reviewed by the remaining author.

CHAPTER 3: Assessing the Relative Efficacy of Secretagogues in Patients with Irritable Bowel Syndrome with Constipation.

- **Black CJ**, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of Secretagogues in Patients with Irritable Bowel Syndrome with Constipation: Systematic Review and Network Meta-analysis. *Gastroenterology*. 2018;155(6):1753-1763. The first author conducted the literature search, collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.
- **Black CJ**, Burr NE, Ford AC. #Gut Blog – Choosing Treatments in IBS: How Network Meta-Analysis Can Guide Our Practice. 2020. Available from: <http://blogs.bmj.com/gut/2020/04/23/gut-blog-choosing-treatments-in-ibs-how-network-meta-analysis-can-guide-our-practice>. The first author wrote the manuscript following which it was critically reviewed by the remaining authors.

CHAPTER 4: Assessing the Relative Efficacy of Pharmacological Therapies in Patients with Irritable Bowel Syndrome with Diarrhoea or Mixed Stool Pattern.

- **Black CJ**, Burr NE, Camilleri M, Earnest DL, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of Pharmacological Therapies in Patients with Irritable Bowel Syndrome with Diarrhoea and Mixed Stool Pattern: Systematic Review and Network Meta-analysis. *Gut*. 2020;69(1):74-82. The first author conducted the literature search, collected the data, undertook all analyses, and

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CHAPTER 5: Describing the Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome and Exploring Differences Based on the Rome IV Versus Rome III Criteria.

- **Black CJ**, Yiannakou Y, Houghton LA, Ford AC. Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome Based on the Rome IV Versus Rome III Criteria. *Clin Gastroenterol Hepatol*. 2020;18(2):392-398. The first author collected the data and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 6: Using Latent Class Analysis to Identify Distinct and Reproducible Subgroups of People with Irritable Bowel Syndrome Based on Gastrointestinal Symptoms and Psychological Profiles.

- **Black CJ**, Yiannakou Y, Guthrie EA, West R, Houghton LA, Ford AC. A Novel Method to Classify and Subgroup Patients with IBS Based on Gastrointestinal Symptoms and Psychological Profiles. *Am J Gastroenterol*. 2021;116(2):372-381. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 7: Examining the Natural History and Prognostic Value of a Novel Classification System for Irritable Bowel Syndrome.

- **Black CJ**, Yiannakou Y, Guthrie EA, West R, Houghton LA, Ford AC. Longitudinal Follow-up of a Novel Classification System for Irritable Bowel Syndrome: Natural History and Prognostic Value. *Aliment Pharmacol Ther.* 2021;53(10):1126-1137. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

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My own contributions, fully and explicitly indicated in the thesis, have been:

- Design of all study protocols
- Conducting literature searches and data extraction for network meta-analyses
- Data collection and database construction
- Statistical analysis of data
- Drafting of all manuscripts; first author of all published articles relating to results chapters
- Design and drafting of thesis

The other members of the group and their contributions have been as follows:

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- Assistance in analysing data (NEB, ACF, LAH, RW)
- Critical review of drafted manuscripts for publication (NEB, MC, DLE, ACF, EAG, LAH, PM, EMMQ, RW, YY)

## **Abstract**

**Introduction:** Conventionally, irritable bowel syndrome (IBS) is subgrouped using predominant stool pattern, yet it is a complex disorder, with multiple biopsychosocial contributors. This thesis aimed to explore an alternative approach to subgrouping by incorporating factors beyond stool pattern alone.

**Methods:** Two network meta-analyses, examining the relative efficacy of secretagogues for IBS-C, and of pharmacological therapies for IBS-D or IBS-M, respectively, were conducted to evaluate the merits of subgrouping people with IBS using stool pattern alone. A large cohort of people who self-identified as having IBS was recruited, and the clinical and psychological differences between individuals based on the Rome IV versus Rome III criteria were examined. In the same cohort, latent class analysis was used to derive new IBS subgroups by combining data on gastrointestinal symptoms and psychological health. Longitudinal follow-up was undertaken to assess the natural history and prognostic value of these new subgroups.

**Results:** The efficacy of treatments for both IBS-C and IBS-D or IBS-M was modest overall, with little difference between individual drugs. In total, 1375 individuals who self-identified as having IBS were recruited. Individuals with Rome IV-defined IBS had significantly more severe symptoms and poorer psychological health, compared with those who only met the Rome III criteria for IBS. In both Rome IV and Rome III-defined IBS, people could be divided into seven distinct subgroups defined by a pattern of gastrointestinal symptoms (diarrhoea-related, constipation-related, or mixed) and further differentiated by the presence of abdominal pain not relieved by defaecation, and by the extent of psychological comorbidity. Follow-up showed that people in clusters with high psychological burden at baseline had significantly more severe symptoms at follow-up, which had a greater impact on daily activities, received a significantly higher



mean number of subsequent treatments, and were significantly more likely to consult a doctor than people in clusters with low psychological burden.

**Conclusions:** Directing treatment according to predominant stool pattern alone results in modest outcomes at best. Additional factors, such as psychological health, may influence treatment response, and people with IBS can be divided into unique subgroups characterised by differences in gastrointestinal symptoms, extra-intestinal symptoms, and mood. Subgroups with higher psychological burden were predictive of a more severe disease course. Personalising treatment according to these novel subgroups, including earlier use of psychological therapies, may improve outcomes in IBS.

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## Glossary of Terms

5-HT	5-hydroxytryptamine
ANOVA	analysis of variance
BIC(LL)	Bayesian information criterion of the log-likelihood
b.i.d.	twice-daily
BM	bowel movement
BMI	body mass index
BSFS	Bristol stool form scale
CBT	cognitive behavioural therapy
CI	confidence interval
CIC	chronic idiopathic constipation
CNS	central nervous system
CPSS	Cohen perceived stress scale
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CSBM	complete spontaneous bowel movement
ESR	erythrocyte sedimentation rate
FBC	full blood count
FDA	Food and Drug Administration
FODMAP	fermentable oligo, di-, and mono-saccharides, and polyols
GFD	gluten-free diet

GI	gastrointestinal
GP	general practitioner
GWAS	genome-wide association study
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhoea
IBS-M	irritable bowel syndrome with mixed stool pattern
IBS-SSS	irritable bowel syndrome severity scoring system
IBS-U	irritable bowel syndrome unclassified
Ig	immunoglobulin
IL	interleukin
LCA	latent class analysis
LR	likelihood ratio
MDCP	multi-dimensional clinical profile
MeSH	medical subject heading
NICE	National Institute for Health and Care Excellence
o.d.	once-daily
OR	odds ratio
PEG	polyethylene glycol
PHQ-15	patient health questionnaire 15



PI-IBS	post-infection irritable bowel syndrome
PRISMA	preferred reporting items for systematic reviews and meta-analyses
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SERT	serotonin reuptake transporter
SNRI	serotonin norepinephrine reuptake inhibitor
SOB	shortness of breath
SSRI	serotonin reuptake inhibitor
TATT	tired all the time
TCA	tricyclic antidepressant
t.i.d.	three-times daily
TNF- $\alpha$	tissue necrosis factor alpha
UK	United Kingdom
USA	United States of America
VSI	visceral sensitivity index

**CHAPTER 1**  
**Introduction**

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder. It is a common condition, affecting 5-10% of people worldwide at any given time. The impact of IBS on the individual, in terms of their quality of life, and on healthcare services and society as a whole, in terms of economic costs, is substantial. A diagnosis of IBS is made using the Rome criteria. These are symptom-based criteria that define IBS according to a specific pattern of gastrointestinal symptoms reported by the patient; namely, the presence of abdominal pain related to defaecation, associated with a change in stool pattern. The predominant stool pattern reported is used to subgroup patients in order to guide treatment. The pathophysiology of IBS is complex and incompletely understood. Psychological comorbidity, psychological stressors, such as a history of trauma and abuse, and previous enteric infection have all been recognised as risk factors for developing IBS. Moreover, additional factors, such as genetics, dietary changes, alterations in the gut microbiome, and physiological mechanisms, such as visceral hypersensitivity, have been identified as playing a potential role in the pathogenesis of the condition. In recognition of the fact that IBS is a disorder with multiple biopsychosocial influences, recent revisions to diagnostic criteria have reclassified IBS as a disorder of gut-brain interaction. Treatment of IBS should start by providing the patient with a clear explanation about the condition using a sensitive and empathic approach to communication. Drug treatment is focussed on addressing a patient's most troublesome gastrointestinal symptoms; antispasmodic drugs, laxatives, and antidiarrhoeals can all be used first-line, in addition to simple dietary and lifestyle changes, such as increases in fibre intake. If patients fail to respond to these, central neuromodulators, such as tricyclic antidepressants (TCAs), can be tried, and more recently a number of second-line drugs targeting abnormal stool pattern have been developed. Psychological therapies are also beneficial, but identifying who is most likely to benefit from these in everyday clinical practice is difficult, partly because

routine assessment of psychological comorbidity is not currently considered in the diagnosis or subgrouping of the condition. Consequently, other approaches to subgrouping patients, which incorporate factors beyond stool pattern, may better represent the complex, multifaceted nature of IBS, and facilitate a more personalised approach to treatment, with the potential to improve outcomes.

This chapter will provide an overview of how the definition of IBS has evolved over time, including the concurrent development of symptom-based diagnostic criteria. The current practice of subgrouping people with IBS according to their predominant stool pattern will be examined in detail, and the grounds for exploring new approaches to subgrouping patients that look beyond gastrointestinal symptoms will be appraised in order to understand the rationale for conducting the body of work presented in this thesis. The epidemiology, natural history, and impact of IBS will be reported with a view to highlighting the importance of IBS to healthcare infrastructure and to society, as well as to individual patients with the condition. Risk factors for the development of IBS, and the pathophysiology of the disorder, will be summarised for the purpose of exploring which factors, in addition to gastrointestinal symptoms, could be incorporated into novel subgrouping models. Finally, the management of IBS will be evaluated in order to inform discussion of how new approaches to subgrouping people with IBS might be used to personalise treatment.

## **1.1 Defining Irritable Bowel Syndrome**

The definition of IBS that is widely used in clinical and research practice today was first proposed by the Rome Foundation 30 years ago; however, the earliest descriptions of the disorder can be traced back to the observations of physicians made two centuries ago. Although our understanding of the epidemiology, pathophysiology, and treatment of this common gastrointestinal disorder has advanced considerably since that time, knowledge that has informed several revisions to the Rome Foundation

definition of IBS, it is striking that throughout its history, IBS has always been defined according to a specific pattern of gastrointestinal symptoms reported by the patient.

### **1.1.1 Historical Context**

In his paper *On Certain Painful Affections of the Intestinal Canal*, published in 1820, the physician Dr Richard Powell gave a description of a disorder characterised by the presence of abdominal pain and the passage of mucus *per rectum*.<sup>1</sup> At that time, the cause of such symptoms was generally attributed to intestinal inflammation, but Powell noted that “the most remarkable circumstance in the history of [these] cases was the production of an effect usually ascribed to inflammatory action without its previous existence”.<sup>2</sup> This observation appears to be the first recognition of a clinical situation in which a patient may report physical gastrointestinal symptoms in the absence of clear organic pathology. It is similar to Sir William Osler’s later description that the mucus was “closely adherent to the mucosa of the colon, but capable of separation without any lesion on the surface”.<sup>3</sup>

In a subsequent paper from 1859, published in *The Lancet*, Dr Andrew Clark of the London Hospital, described his experience of the “mucous disease of the colon”.<sup>4</sup> He characterised this as a single disorder with three stages, although it is more likely from his descriptions that these stages, in fact, represented separate gastrointestinal diseases, including inflammatory bowel disease. The first stage, however, was a benign disorder, from which the patient “generally recovered”, akin to Powell’s earlier observations. Clark recommended treatment by removal of the mucus using laxatives or enemas, followed by a range of treatments to prevent recurrence. Some of these suggestions, such as the “application of cutaneous friction”, were almost certainly of little value. However, Clark also reported success with various therapeutic strategies that are still in use today, including dietary modification, with the exclusion of

vegetables and fruits, avoidance of caffeine and alcohol, daily exercise, and the regulation of the bowel with “astringents and tonics”.

A more detailed case series describing this disorder, instead referred to as “membranous enteritis”, was provided by the American physician J. M. Da Costa, in his paper of 1871.<sup>5</sup> The cardinal features were, again, the presence of abdominal pain and the passage of mucus, but Da Costa elaborated further, describing a chronic disorder, with distinct exacerbations, that may, in more severe cases, be continuous. Moreover, he also noted that a change in bowel habit was a hallmark of the condition: “Between attacks the bowels are irregular, sometimes constipated, at others loose; and tenesmus is often complained of”.

These 19<sup>th</sup> century observations were summarised by Sir William Osler as a disease called “mucous colitis” in his esteemed work of 1892, *The Principles and Practice of Medicine*.<sup>3</sup> Osler noted that the condition had a strong female predominance, with 80% of recorded cases affecting women. At the time, it was felt that the condition had a primarily psychological basis, with hysteria, hypochondriasis, and melancholia being frequently reported amongst sufferers, and “mental emotions and worry of any sort” being often cited as the trigger for an attack. A study of 60 cases of the disorder, published in *The Lancet* in 1905, also observed that it was frequently associated with many forms of neurosis, and therefore suggested that the nervous system might be implicated in its causation.<sup>6</sup> In addition, it was noted that the disorder was commoner in younger adults, and in those of higher socioeconomic class. Later accounts of “mucous colitis” by Bockus, Bank, and Wilkinson in 1928,<sup>7</sup> although different to Osler’s definition in terms of precise clinical characteristics, with individuals being primarily “constipated, dyspeptic, and exhausted”,<sup>8</sup> are nevertheless similar in their general description of symptoms occurring in the absence of organic colonic pathology. Indeed, they describe the rectal mucosa as having a “glistening,

glairy, shining, or lustrous” appearance at sigmoidoscopy,<sup>7</sup> descriptions recognisable as those of macroscopically normal colonic mucosa.

By the 1920s, the concept of the spastic colon had emerged, characterised by abdominal discomfort or pain, in the absence of organic disease, the colon often palpable and tender. Dr John Ryle described 50 such cases in 1928, some of whom also reported the passage of mucus *per rectum*, including 11 individuals who were diagnosed as having mucous colitis.<sup>9</sup> Smoking, anxiety, menses, and defaecation were all identified as exacerbating the spastic colon, and Ryle also noted that a prior history of dysenteric infection was a predisposing factor in some individuals. It was Ryle’s opinion that spastic colon and mucous colitis were, in fact, the same condition, a view corroborated by another study published in the same year, which suggested that they resulted from dysfunction of the autonomic nervous system, possibly related to a specific personality disorder.<sup>8</sup> This was explored in detail by White, Cobb, and Jones in 1939, in a case series of 60 patients with mucous colitis, in which they suggested that there was a close relationship between psychological factors and the onset of symptoms, mediated via the autonomic nervous system and cholinergic effects on intestinal smooth muscle.<sup>10</sup>

The 1920s also saw usage of the term “irritable colon” to describe a situation in which normal colonic motility was interrupted due to “a disturbance in the tonus and irritability of the musculoneural tissue”.<sup>11</sup> Using investigation with barium enema to observe patterns of colonic motility, Jordan and Kiefer identified irritable colon as the cause of symptoms in around one-third of patients seen in gastroenterology clinics, many of whom reported altered stool consistency. It was not until 1944, however, that the specific term “irritable bowel syndrome” was first coined,<sup>12</sup> and began to replace previous nomenclature.

### 1.1.2 Early Attempts to Classify Irritable Bowel Syndrome

In 1962, Chaudhary and Truelove made an initial attempt to systematically classify patients with IBS, which they defined as pain of colonic origin, and disordered bowel habit, with either diarrhoea or constipation.<sup>13</sup> The passage of mucus *per rectum* might sometimes occur, but this symptom no longer featured as prominently as it had in earlier descriptions of the disorder. They conducted a retrospective analysis of 130 patients who had received a clinical diagnosis of IBS following normal investigation with routine bloods, sigmoidoscopy, and barium enema to exclude organic disease. Around two-thirds were female, and many reported long-standing symptoms, sometimes in excess of 10 years' duration, at the time of their diagnosis.

Following a detailed analysis of the clinical features of this cohort, two main subgroups of the disorder were identified: those with spastic colon, and those with painless diarrhoea. All of the patients in the spastic colon group had abdominal pain, considered to be of colonic origin, and a variable bowel habit; sometimes stools were normal, and sometimes patients reported either episodes of diarrhoea or constipation, or else alternated between the two symptoms. The spastic colon group was the larger of the two, comprising around 80% of individuals. The second smaller group, those with painless diarrhoea, reported no abdominal pain, and diarrhoea was the sole clinical manifestation. Although classified here as a subtype of IBS, painless diarrhoea in the absence of organic disease would now be classified as a separate disorder, namely functional diarrhoea.<sup>14</sup> Alternatively, these patients may have been suffering from bile acid diarrhoea, now known to be a common cause of such symptoms among patients with suspected IBS,<sup>15,16</sup> but remaining hitherto unrecognised at that time, having only been first described in 1967.<sup>17</sup> All patients underwent a psychological evaluation, and it was observed that the presence of psychological factors was especially important for



both triggering and perpetuating gastrointestinal symptoms. A small subset of patients reported symptom onset following a gastrointestinal infection.

### 1.1.3 The Manning Criteria

Among all of the descriptions of IBS discussed thus far, there is a common theme emerging: that the disorder can be identified based on certain patterns of gastrointestinal symptoms, occurring in the absence of organic pathology. There is, however, no clear consensus as yet regarding which specific pattern of symptoms should be preferred, there being marked variability between clinical definitions. This highlights the importance of the landmark paper by Manning *et al.*, published in the *British Medical Journal* in 1978, which was the first to propose a clear set of symptom-based criteria for diagnosing IBS, later termed the Manning criteria.<sup>18</sup> Crucially, these criteria were examined to evaluate their ability to discriminate IBS from organic disease. Symptom-based diagnostic criteria, although extensively revised over the intervening years, remain the cornerstone of IBS diagnosis today, illustrating the vital importance of this work to the field.

109 patients, referred to the outpatient clinic with abdominal pain, diarrhoea, or constipation, were asked to complete a questionnaire enquiring about the occurrence, over the preceding 12 months, of 15 symptoms thought to be characteristic of IBS. When these patients were followed-up, 65 ultimately received a final diagnosis, of whom 32 were diagnosed with IBS (49.2%), the remainder having organic pathology. The incidence of each of the 15 questionnaire symptoms was compared between the two patient groups, identifying four symptoms that were significantly more common among patients with IBS: looser stools at onset of pain, more frequent bowel movements at onset of pain, pain eased after bowel movement, and visible abdominal distension. Over 90% of patients with IBS endorsed two or more of these symptoms, compared with only 30% of those with organic disease. Passage of mucus *per rectum* and tenesmus, the

sensation of incomplete evacuation, were more common among patients with IBS, but the difference was not statistically significant. Nevertheless, when these two symptoms were used in combination with the other four, the ability to discriminate between IBS and organic disease was increased, all six symptoms being present in six patients with IBS (19%), but only one patient (3%) with organic disease. The authors suggested that the use of these criteria might enable clinicians to be more confident in making a diagnosis of IBS, thereby reducing the use of unnecessary investigations.

#### **1.1.4 The Kruis Score**

In 1984, Kruis *et al.* proposed a scoring system for diagnosing IBS and discriminating it from organic disease.<sup>19</sup> They collected data from 479 consecutive outpatient referrals, identifying 399 patients who complained of abdominal pain, flatulence, or altered bowel habit. These patients underwent extensive diagnostic testing, including laboratory testing of blood and stool, endoscopic investigation, and radiological examination, to determine whether they had IBS or were suffering from an organic condition. Following this process, 56 patients were excluded for technical reasons, leaving 209 with organic disease, 108 with IBS, and 26 with an overlap between the two.

Patients answered a short questionnaire about their symptoms, and the patient's physician completed a checklist regarding the presence of eight features suggestive of organic disease, including blood abnormalities, such as anaemia or raised erythrocyte sedimentation rate (ESR), abnormal findings on clinical examination, and concerning features in the clinical history, such as blood in the stools. Logistic regression analysis was conducted using these data to derive a weighted score for distinguishing IBS from organic disease, with typical IBS symptoms reported by the patient attracting positive values, and clinical signs suggestive of organic pathology assigned negative values. It

was determined that the optimum threshold was a score of  $\geq 44$ , diagnosing IBS with a sensitivity of 64% and a specificity of 99%.

Following its original publication, the Kruis scoring system has been evaluated in three other studies.<sup>20-22</sup> When results from all four studies were combined, encompassing a total of 1,171 patients, the pooled sensitivity and specificity were 77% (95% confidence interval (CI), 68% - 85%) and 89% (95% CI, 76% - 97%), respectively.<sup>23</sup> Despite its reasonable performance for diagnosing IBS accurately, the Kruis scoring system, or similar statistical models, have never been widely adopted, due, in part, to technological limitations<sup>24</sup> and will, therefore, not be discussed further. However, it is worth noting that, more recently, attention has returned to statistical modelling approaches for diagnosing and subgrouping IBS,<sup>25-27</sup> and the ready availability of computing capabilities, including smartphones, would make such an approach easier to utilise nowadays than when it was first proposed.<sup>24</sup>

### **1.1.5 The Rome Criteria**

Subsequently, the focus returned to the development of symptom-based diagnostic criteria for IBS, with factor analysis studies demonstrating that the lower gastrointestinal symptoms thought to constitute IBS clustered together,<sup>28</sup> the aim being to augment the performance of the existing Manning criteria.<sup>29</sup> This led to the publication of the Rome criteria in 1990.<sup>30</sup> These criteria are the work of the Rome Foundation, a committee of gastroenterologists and allied academics in the field of gastrointestinal health who, based on a consensus of expert opinion, and with reference to current available evidence, have sought to categorise not only IBS, but all functional gastrointestinal disorders. The Rome criteria continue to be the accepted gold standard for diagnosing IBS and, as new research has emerged over the years, the Rome Foundation have revised the criteria three times, most recently in 2016.<sup>14</sup> Use of these criteria aims to promote making a positive diagnosis of IBS, with recourse to limited

clinical investigations, and to facilitate the recruitment of homogeneous populations of patients to research studies investigating epidemiology, underlying pathophysiological mechanisms, and trials of treatments.

The original version of the criteria, Rome I, defined IBS according to more restrictive criteria than those used previously.<sup>30</sup> They mandated the presence of abdominal pain or discomfort, either relieved by defaecation, or else associated with a change in the frequency or consistency of stools. In contrast to the Manning criteria, which emphasised the presence of looser stools only,<sup>18</sup> it was recognised that a constipated bowel habit, with hard or less frequent stools, was equally relevant. The passage of mucus was no longer a primary diagnostic criterion, considered instead to be a supporting feature of the diagnosis that might be present in some cases, and the same applied to the presence of abdominal bloating or distension. Finally, symptoms needed to have been present, either continuously or intermittently, for at least 3 months, the first time a minimum duration of symptoms had been specified. Similarly, the frequency of some symptoms was also detailed, the irregular pattern of defaecation needing to be present at least 25% of the time, although formal subgrouping of IBS according to stool pattern would not be introduced until Rome II. In addition, the need to avoid unnecessary investigation was stipulated, but limited testing, mainly to exclude inflammatory pathology, was advised. This comprised blood tests, namely a full blood count (FBC) and an ESR, and a sigmoidoscopy.

Rome II, the first revision of the criteria, were published in 1999.<sup>31</sup> The key diagnostic features, though benefitting from some additional clarification, remained essentially unchanged, and although symptoms needed to have been present for at least 3 of the previous 12 months, it was suggested that these need not have been consecutive. Examination of the large bowel, whether endoscopic or radiological, was still recommended, but should be guided by factors such as the age of the patient and

the nature of their symptoms. The Rome III criteria, published in 2006, retained the same cardinal symptoms, abdominal pain or discomfort associated with a change in stool frequency or form, but they also defined the minimum required frequency of abdominal pain or discomfort for the first time, this being at least 3 days per month over the last 3 months.<sup>32</sup> Overall, to diagnose IBS, the full criteria needed to be fulfilled for the last 3 months, with symptom onset at least 6 months previously.

The most recent iteration of the diagnostic criteria for IBS, Rome IV, were published in 2016, and made some important changes compared with their predecessor.<sup>14</sup> Firstly, “discomfort” was removed from the definition, as this was felt to be a vague term that was not understandable in some languages.<sup>33</sup> Second, the minimum required frequency of abdominal pain was increased from at least 3 days per month, to at least 1 day per week. This change reflected the findings of a normative survey showing that adopting a higher threshold for the frequency of abdominal pain required to meet criteria would lead to fewer healthy people in the general population being misclassified as having IBS, potentially making the Rome IV criteria more specific for IBS compared with Rome III.<sup>33</sup> Third, it was no longer necessary for abdominal pain to be relieved by defaecation. Instead, it should be “related to defaecation”, acknowledging that some patients with IBS report that their pain worsens following a bowel movement.<sup>14</sup> Limited clinical investigation to exclude certain organic diseases that can mimic IBS, such as coeliac disease or inflammatory bowel disease, continued to be recommended.

The specific details of each version of the Rome criteria are summarised in Table 1.1, together with the Manning criteria.

**Table 1.1. Symptom-based Diagnostic Criteria for IBS.**

<b>Criteria</b>	<b>Symptom-based Definition</b>	<b>Minimum Symptom Duration</b>
<b>Manning</b> <sup>18</sup>	<ol style="list-style-type: none"> <li>1. Looser stools at onset of pain</li> <li>2. More frequent bowel movements at the onset of pain</li> <li>3. Pain eased after bowel movement (often)</li> <li>4. Visible abdominal distension</li> <li>5. Mucus <i>per rectum</i></li> <li>6. Feeling of incomplete bowel emptying</li> </ol> <p>The more of these symptoms that are present, the more likely it is that a patient's abdominal pain, altered bowel habit, or both, are due to IBS</p>	None specified
<b>Rome I</b> <sup>30</sup>	<ol style="list-style-type: none"> <li>1. Abdominal pain or discomfort, relieved by defaecation, or associated with a change in frequency or consistency of stool; <i>and</i></li> <li>2. An irregular pattern of defaecation at least 25% of the time (three or more of): <ol style="list-style-type: none"> <li>a. altered stool frequency</li> <li>b. altered stool form</li> <li>c. altered stool passage (straining/urgency/tenesmus)</li> <li>d. passage of mucus</li> <li>e. bloating or feeling of abdominal distension</li> </ol> </li> </ol>	≥3 months
<b>Rome II</b> <sup>31</sup>	<p>Abdominal discomfort or pain that has two of three features:</p> <ol style="list-style-type: none"> <li>a. Relieved with defaecation; <i>and/or</i></li> <li>b. Onset associated with a change in frequency of stool; <i>and/or</i></li> <li>c. Onset associated with a change in form of stool</li> </ol>	≥12 weeks (which need not be consecutive) in the past 12 months

<p><b>Rome III</b> 32</p>	<p>Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:</p> <ul style="list-style-type: none"> <li>a. Improvement with defaecation</li> <li>b. Onset associated with a change in frequency of stool</li> <li>c. Onset associated with a change in form of stool</li> </ul>	<p>Symptom onset <math>\geq 6</math> months prior to diagnosis</p>
<p><b>Rome IV</b> <sup>14</sup></p>	<p>Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:</p> <ul style="list-style-type: none"> <li>a. Related to defaecation</li> <li>b. Associated with a change in frequency of stool</li> <li>c. Associated with a change in form of stool</li> </ul>	<p>Symptom onset <math>\geq 6</math> months prior to diagnosis</p>

### 1.1.6 Validation of the Rome Criteria for Diagnosing IBS

The accuracy of the Rome criteria for diagnosing IBS has been examined in a number of validation studies.<sup>23, 33-37</sup> Accuracy of a diagnostic test is usually described in terms of the sensitivity, the probability of the test being positive if the disease is present, and specificity, the probability of the test being negative if the disease is absent. However, the positive and negative likelihood ratios (LR), which are derived from the sensitivity and specificity, provide a more useful measure of the diagnostic performance of a test for use in clinical practice. These summarise how many times more or less likely patients with the disease are to have a particular test result than patients without the disease. LRs above 10 or below 0.1 are generally regarded as useful for ruling in or ruling out a disease, respectively.<sup>38</sup>

A systematic review and meta-analysis from 2008 identified a single eligible study reporting the diagnostic accuracy of the Rome I criteria among 602 patients referred to a gastroenterology clinic.<sup>23</sup> All patients had symptoms suggestive of IBS and underwent investigation to exclude organic disease. The sensitivity and specificity of the Rome I criteria for diagnosing IBS were 71% and 85%, respectively, with a positive LR of 4.8. At that time, there were no validation studies evaluating the Rome II or Rome III criteria; however, a subsequent Canadian study, published in 2013, assessed the diagnostic performance of all versions of the Rome criteria published at that time, in 1,848 consecutive adult patients with gastrointestinal symptoms who underwent colonoscopy and testing of coeliac serology to exclude organic disease.<sup>34</sup> The sensitivity and specificity of the Rome II criteria were 90.2% and 71.7% respectively, with a positive LR of 3.19 and a negative LR of 0.14. Similarly, the Rome III criteria had a positive LR of 3.35 and a negative LR of 0.39, whilst sensitivity and specificity were 68.8% and 79.5%, respectively. The modest performance of these criteria was confirmed by the findings of an updated systematic review from 2015,<sup>35</sup> and a



subsequent validation study, which showed very similar performance of the Rome III criteria with a positive and negative LR for diagnosing IBS of 3.87 and 0.37, respectively.<sup>36</sup>

It is important to note that, overall, the accuracy of the Rome III criteria for diagnosing IBS was very similar to the performance of previous iterations. Hence, with the publication of Rome IV, the aim was to make the criteria more specific for diagnosing IBS, as already described, and validation studies suggest that this aim has been achieved. One such study, performed by the Rome Foundation, that included more than 800 patients with a functional gastrointestinal disorder, estimated the sensitivity of the Rome IV criteria for diagnosing IBS to be 63%.<sup>33</sup> Specificity was reported to be 97%, based on findings from a separate cohort of almost 6000 people from the general population.<sup>33</sup> These results give a positive LR of the Rome IV criteria in diagnosing IBS of 21; in other words, patients meeting these criteria are 21 times more likely to have IBS than to not have IBS. This calculation was, however, based on findings from two separate cohorts, rather than a single validation study. A subsequent independent validation study in over 500 patients, which also compared the Rome IV criteria with the Rome III criteria, reported more modest performance; the sensitivity and specificity were 82.4% and 82.9% respectively, with a positive LR of 4.82 and a negative LR of 0.21.<sup>37</sup> Nevertheless, the Rome IV criteria performed better than the Rome III criteria, the latter having positive and negative LRs for diagnosing IBS of 2.45 and 0.22 respectively, with a sensitivity of 85.8% and a specificity of 65.0%.<sup>37</sup> Overall, if applied to a patient population with a pre-test probability of IBS of 50%, such as might be the case in people with lower gastrointestinal symptoms referred to secondary care, the Rome IV criteria would identify IBS with a post-test probability of >80%.<sup>37</sup>

### **1.1.7 Clinical Consequences of Moving to the Rome IV Diagnostic Criteria for IBS and the Stability of an IBS Diagnosis**

The changes made to the Rome IV criteria for IBS were intended to increase their specificity over prior iterations, which, as discussed, had shown only modest success in diagnosing IBS among unselected patients with lower gastrointestinal symptoms.<sup>34,39</sup> Although recent validation studies suggest this aim has been achieved,<sup>37</sup> because Rome IV is more restrictive, the prevalence of IBS among individuals in population-based surveys is likely to fall when using the Rome IV criteria. Studies that have examined the implications of the changes made between the Rome III and Rome IV criteria for diagnosing IBS, however, have suggested that there is limited difference. Aziz *et al.* reported that 85% of 542 patients from a tertiary referral population in Sweden with Rome III-defined IBS met the Rome IV criteria, but noted that symptoms were more severe among those with Rome IV IBS, and quality of life was impaired to a greater extent.<sup>40</sup> A second study, conducted in secondary and tertiary care in the Netherlands, reported almost identical findings; more than 85% of people meeting the Rome III criteria for IBS still met the Rome IV criteria, albeit symptoms were more severe, and quality of life worse, in people with Rome IV-defined IBS.<sup>41</sup>

It is important, however, to recognise that both of these studies have some key limitations. Crucially, neither study applied the Rome III and Rome IV criteria for IBS simultaneously, but instead approximated Rome IV by using a surrogate measure from their existing questionnaire data. In the first study, this comprised the reporting of abdominal pain on  $\geq 2$  days in the last 10 days,<sup>40</sup> whereas the reporting of abdominal pain once per week in a symptom diary was used in the second study.<sup>41</sup> Any methodology that approximates the Rome IV criteria retrospectively, rather than applying the full criteria contemporaneously, requires caution when interpreting the results because the true impact of using the Rome IV criteria relative to the Rome III

criteria is likely to have been misrepresented, the effect being at risk of either over- or underestimation.

Another important consideration is what happens to individuals who met Rome III criteria for IBS, but who no longer meet criteria for IBS when Rome IV is applied instead, in terms of being reclassified to another functional bowel disorder. Only one study has examined this, with approximately one-third of patients meeting criteria for functional constipation, functional diarrhoea, or functional abdominal bloating or distension.<sup>41</sup> This issue is clinically important because disorders like functional diarrhoea and functional bloating are less well understood than IBS, with far fewer evidence-based treatments available.

In contrast to the other two studies, a third tertiary care study, which applied both iterations of the criteria simultaneously, demonstrated less diagnostic agreement between Rome III and Rome IV, with only 45.6% of those with Rome III-defined IBS meeting the Rome IV criteria.<sup>42</sup> Symptom severity was once again higher among those with Rome IV IBS, but there were few other differences. However, this study included only 175 patients with Rome-defined IBS from a highly specialised tertiary care setting meaning that the findings may not be generalisable to patients with IBS consulting in other clinical settings, such as primary care.

Overall, further studies, recruiting larger populations of patients with IBS across a range of clinical settings, and which apply the Rome III and Rome IV criteria for IBS simultaneously, are needed in order to adequately explore the effect of the changes made between the two iterations on the characteristics of people with IBS. As well as being relevant to clinical practice, this issue has implications for the conduct of research studies and drug trials in IBS, where the Rome criteria are commonly used to define study inclusion. Indeed, it seems likely that trials recruiting patients according to Rome

IV criteria are evaluating treatments in patients with more severe symptoms compared with previous trials that used Rome III, and this needs to be considered when interpreting study results and comparing treatments.

## **1.2 Subgrouping Patients with IBS**

Once a diagnosis of IBS has been made based on the cardinal features, current diagnostic criteria advocate subgrouping people with IBS based on their stool pattern, and this is intended to help guide treatment. However, because IBS is a disorder with multiple biological, psychological, and social influences, the Rome Foundation have also recommended evaluating a broader range of factors, not limited to gastrointestinal symptoms, in the assessment of anyone with IBS. Currently, this approach is intended for use on an individual patient basis only; however, the inclusion of factors beyond stool pattern in the formal subgrouping of IBS might create a framework that more accurately represents this complex disorder.

### **1.2.1 IBS Subgroups Based on Stool Form**

For the first time, the Rome II criteria recommended that patients with IBS should be classified into different subgroups based on their stool pattern – those with predominant diarrhoea and those with predominant constipation – to help direct treatment, and for entry into clinical trials targeting a specific stool pattern.<sup>31</sup> This classification system was refined and expanded for Rome III, the different subgroups now being defined according to the percentage of all bowel movements with abnormal stool form.<sup>32</sup> Patients experiencing hard or lumpy stools for  $\geq 25\%$  of all bowel movements and loose or watery stools for  $< 25\%$  of all bowel movements were classified as having IBS with constipation (IBS-C), whereas reciprocally, if  $\geq 25\%$  of all bowel movements were loose or watery and  $< 25\%$  were hard or lumpy, patients were classified as having IBS with diarrhoea (IBS-D). If both stool forms occurred for  $\geq 25\%$

of all bowel movements, patients were classified as having IBS with mixed stool form (IBS-M), whereas if there was insufficient abnormality of stool consistency to meet any of these three stool subgroups, patients were determined to have IBS unclassified (IBS-U).

The Rome IV criteria used a broadly similar system of subgrouping, but with two important changes.<sup>14</sup> Firstly, subgrouping calculations were now based only on days with at least one abnormal bowel movement, rather than including all bowel movements, reflecting the fact that many patients with IBS have periods when their bowel movements are normal. Second, abnormal bowel habit was defined with specific reference to the Bristol stool form scale (BSFS),<sup>43</sup> whereby constipation refers to BSFS types 1 and 2 and diarrhoea refers to types 6 and 7 (Table 1.2). The different approaches to subgrouping patients with IBS are shown in Table 1.3.

Use of this classification system is important because the current management of IBS is symptom-based, with treatment choice largely dictated by the patient's predominant stool pattern. Indeed, most drugs used to treat IBS are designed to address either constipation or diarrhoea, and hence, if they were used in an incorrect subgroup, this might lead to a worsening of bowel symptoms. It is, therefore, important to understand, when assessing the clinical utility of the current approach to subgrouping patients with IBS, whether these stool subgroups remain stable over time.

**Table 1.2 The Bristol Stool Form Scale.** <sup>43</sup>

<b>Type</b>	<b>Description</b>
<b>1</b>	Separate hard lumps like nuts (difficult to pass)
<b>2</b>	Sausage shaped but lumpy
<b>3</b>	Like a sausage but with cracks on its surface
<b>4</b>	Like a sausage or snake, smooth and soft
<b>5</b>	Soft blobs with clear-cut edges (passed easily)
<b>6</b>	Fluffy pieces with ragged edges, a mushy stool
<b>7</b>	Watery, no solid pieces, entirely liquid

**Table 1.3 Subgrouping Patients with IBS According to Different Iterations of the Rome Criteria.**

Criteria	Method of Subgrouping
<p><b>Rome II</b> <sup>31</sup></p>	<ol style="list-style-type: none"> <li>1. Fewer than three bowel movements a week</li> <li>2. More than three bowel movements a week</li> <li>3. Hard or lumpy stools</li> <li>4. Loose (mushy) or watery stools</li> <li>5. Straining during a bowel movement</li> <li>6. Urgency</li> </ol> <p><i>Diarrhoea-predominant:</i> One or more of 2, 4, or 6 and none of 1, 3, or 5</p> <p><i>Constipation-predominant:</i> One or more of 1, 3, or 5 and none of 2, 4, or 6</p>
<p><b>Rome III</b> <sup>32</sup></p>	<ul style="list-style-type: none"> <li>• IBS-C: hard or lumpy stools <math>\geq 25\%</math> and loose (mushy) or watery stools <math>&lt; 25\%</math> of bowel movements</li> <li>• IBS-D: loose (mushy) or watery stools <math>\geq 25\%</math> and hard or lumpy stools <math>&lt; 25\%</math> of bowel movements</li> <li>• IBS-M: hard or lumpy stools <math>\geq 25\%</math> and loose (mushy) or watery stools <math>\geq 25\%</math> of bowel movements</li> <li>• IBS-U: insufficient abnormality of stool to meet criteria for IBS-C, IBS-D, or IBS-M</li> </ul>
<p><b>Rome IV</b> <sup>14</sup></p>	<ul style="list-style-type: none"> <li>• IBS-C: Bristol stool form types 1 or 2 <math>\geq 25\%</math> and Bristol stool form types 6 or 7 <math>&lt; 25\%</math> of bowel movements <sup>a</sup></li> <li>• IBS-D: Bristol stool form types 6 or 7 <math>\geq 25\%</math> and Bristol stool form types 1 or 2 <math>&lt; 25\%</math> of bowel movements <sup>a</sup></li> <li>• IBS-M: Bristol stool form types 1 or 2 <math>\geq 25\%</math> and Bristol stool form types 6 or 7 <math>\geq 25\%</math> of bowel movements <sup>a</sup></li> <li>• IBS-U: insufficient abnormality of stool to meet criteria for IBS-C, IBS-D, or IBS-M (i.e. Bristol stool form types 1 or 2 <math>&lt; 25\%</math> and Bristol stool form types 6 or 7 <math>&lt; 25\%</math> of bowel movements <sup>a</sup>)</li> </ul> <p>a. Based only on days with abnormal bowel movements</p>

### 1.2.2 Stability of Subgroups Based on Stool Form

Overall, studies suggest that IBS subgroups defined according to predominant stool pattern lack stability.<sup>44-48</sup> One study assessed 317 female patients with Rome II IBS using questionnaires and stool diaries at 3-monthly intervals over 1 year.<sup>44</sup> At baseline, 36% had IBS-D, 31% IBS-M, and 34% IBS-C, and there were no differences between groups, aside from stool frequency. Throughout the 1-year follow-up period, although the proportion of individuals in each subgroup remained consistent, more than 75% of people transitioned to another subgroup at least once. IBS-M was the least stable subgroup, and changes between IBS-D and IBS-C were uncommon. Two other studies among patients with IBS showed broadly similar findings, with most changes in subgroup being either from or to IBS-M, and transition from diarrhoea to constipation or *vice versa* being rare.<sup>45, 46</sup>

In another study of 185 people with Rome III IBS, there was considerable variability in stool consistency over a 3-month period – 78% experienced both loose/watery and hard/lumpy stools.<sup>47</sup> There was an average of three fluctuations between these two stool forms per month; however, an individual's overall stool pattern was stable from month to month. A subsequent study showed that loose/watery stools and hard/lumpy stools generally occurred as discrete, well-defined episodes.<sup>48</sup>

Overall, the explanation for this fluctuation between different IBS subgroups remains uncertain. A number of factors are likely to be involved, including the natural variability of the condition, the impact of treatment, and the role of differing pathophysiologies between patients, but the relative importance of these is unknown. Furthermore, the degree of fluctuation may vary according to the diagnostic criteria used to define IBS. In a recent study, comparing IBS symptoms at baseline and 1-year follow-up, there was a change in IBS stool subgroup in up to one-in-three people, and this was higher when IBS was defined according to the Rome IV criteria compared with



Rome III.<sup>49</sup> Moreover, fluctuation between IBS stool subgroups did not depend solely on whether a new treatment was initiated, or whether the choice of treatment was deemed appropriate based on IBS stool subgroup at baseline.

### **1.2.3 Multi-Dimensional Clinical Profile (MDCP)**

Importantly, although relied upon for classifying patients with IBS, stool pattern is only one element of this complex, multi-faceted disorder. As will be discussed, IBS is a disorder of gut-brain interaction, and mood and psychological health play an important role in the development and persistence of symptoms.<sup>50-54</sup> Moreover, mood disorders are much more common in people with IBS than among healthy individuals,<sup>55</sup> and the reporting of extra-intestinal symptoms, also referred to as somatisation, is common. In addition, as will be highlighted, there are multiple risk factors for IBS and the pathophysiology is complex, including genetic factors, alterations in the microbiome, and changes in visceral sensitivity. Conceivably, therefore, alternative approaches, integrating factors other than stool pattern, may offer a more nuanced means of classifying people with IBS.

An alternative algorithm could involve use of gastrointestinal symptoms, including stool pattern, in combination with psychological profiles, such as anxiety, depression, and extra-intestinal symptoms, as well as key pathophysiologies, for example visceral hypersensitivity, which may be an important contributor to symptom severity, independent of psychological factors such as somatisation, anxiety, or depression.<sup>56</sup> Indeed, there are those patients with IBS whose symptoms are predominantly gastrointestinal, and who have only minimal psychological distress and, conversely, those patients for whom IBS symptoms are part of a broader picture that includes anxiety, depression, and somatisation-type behaviours.

In acknowledgment of the fact that IBS is a disorder of gut-brain interaction, with biopsychosocial influences, the Rome Foundation developed the multi-dimensional clinical profile (MDCP). This is a framework that, in addition to the cardinal clinical symptoms needed to make a diagnosis of IBS, includes assessment of additional clinical features, psychological factors, and impact of the illness, in order to build a unique clinical profile for each patient (Table 1.4).<sup>57</sup> The MDCP is intended to guide a clinician in their treatment of an individual patient by focusing attention on a holistic approach, aiming to address sometimes overlooked dimensions of the illness experience, thereby optimising management. However, the MDCP has yet to be adopted into routine clinical practice, and is not incorporated into current diagnostic criteria, but rather stands alone as an optional adjunct to be applied on a case-by-case basis.

**Table 1.4 Rome Foundation Multi-Dimensional Clinical Profile for IBS.** <sup>57</sup>

Component	Explanation
<b>A. Categorical Diagnosis</b>	The standard diagnosis of IBS according to the Rome criteria
<b>B. Clinical Modifiers</b>	<p>Additional symptoms or subtypes, historical information, physical signs, or investigation results that would potentially affect treatment planning.</p> <p>For example:</p> <ul style="list-style-type: none"> <li>• Post-infection IBS</li> <li>• Stool pattern – IBS-D, -C, -M, or -U</li> <li>• Urgency</li> <li>• Faecal incontinence</li> <li>• Bloating</li> <li>• Overlap with inflammatory bowel disease</li> </ul>
<b>C. Impact on Daily Activities</b>	<p>“Overall, how much do your symptoms currently interfere with life (work, school, social activities, self-care, concentration, and performance)”</p> <ul style="list-style-type: none"> <li>• None</li> <li>• Mild</li> <li>• Moderate</li> <li>• Severe</li> </ul>
<b>D. Psychosocial Modifiers</b>	<p>Psychological and psychosocial modifiers and comorbidities that influence the patient’s experience of illness and behaviours that will affect treatment decisions, judged to be relevant by the treating clinician.</p> <p>For example:</p> <ul style="list-style-type: none"> <li>• Existing psychiatric or psychological diagnosis, or quantitative measure e.g. anxiety state using hospital anxiety and depression scale</li> <li>• Patient reported e.g. traumatic life event, such as history of trauma or abuse, major work disruption, significant bereavement</li> </ul>
<b>E. Physiological Modifiers of Function and Biomarkers*</b>	<p>Physiological or biochemical parameters that may have clinical relevance</p> <p>For example:</p> <ul style="list-style-type: none"> <li>• Colonic motility and transit: manometry, radio-opaque marker x-ray, scintigraphy, magnetic resonance imaging</li> <li>• Colonic visceral sensitivity: rectal barostat</li> <li>• Evidence of inflammation: faecal calprotectin, colonic biopsies and histology</li> <li>• Other: microbiome analysis and profiling</li> </ul>

\*Note: No biomarker currently exists for diagnosing IBS. Clinical testing on per patient basis.

### 1.2.4 Novel Approaches to Subgrouping Patients with IBS

If the approach advocated by the MDCP is to be translated into a formal classification system for IBS, being able to demonstrate that statistical models incorporating factors other than gastrointestinal symptoms can be used to derive new and distinct patient subgroups, and that those additional factors are of relevance to clinical management, would provide useful supporting evidence.<sup>58</sup> Previous studies examining whether the performance of the Rome criteria for diagnosing IBS can be augmented by the addition of other factors are inconsistent. One study found that, by incorporating clinical information regarding nocturnal stools, extra-intestinal symptom reporting, and mood disorders, as well as haemoglobin and C-reactive protein (CRP) measurements, the positive LR and specificity of the Rome III criteria for IBS were both increased.<sup>36</sup> However, another study found no significant improvement in the performance of the Rome III or Rome IV criteria for diagnosing IBS when abnormal levels of anxiety or depression, or high levels of extra-intestinal symptom reporting, were included.<sup>37</sup>

Both of these studies examined the utility of making changes to the symptom-based criteria for diagnosing IBS. Adopting a similar approach, but instead modifying how individuals with IBS are subgrouped once a diagnosis has been made according to Rome criteria, might be more valuable. Four previous studies have examined this issue by using a combination of gastrointestinal symptoms and psychological profiles,<sup>26, 27, 59</sup> and in one study, physiological parameters were also included.<sup>60</sup> The first of these was conducted in 172 patients with IBS in a tertiary care setting in Sweden,<sup>26</sup> and the second study, from the same group of investigators, included people meeting criteria for IBS in an internet-based survey of healthy adults in the general population in the United States of America (USA), Canada, and the United Kingdom (UK).<sup>27</sup> In both of these studies distinct subgroups of patients appeared to exist, and generally comprised those

whose symptoms were predominantly intestinal, and who had only minimal psychological distress, and those for whom IBS symptoms were part of a broader picture, which included anxiety, depression, or extra-intestinal symptoms.

These subgroups were not, however, reproducible across different patient cohorts or different iterations of the Rome criteria, with variation seen in both the number and specific characteristics of the subgroups between studies. Moreover, as one study was conducted in a small number of patient in tertiary care, this may limit the generalisability of the findings,<sup>26</sup> and although participants in the population-based study met the Rome criteria for IBS, this does not necessarily mean that they had the condition.<sup>27</sup> A third study included 107 patients diagnosed with IBS using the now outdated Rome I criteria and conducted a K means cluster analysis using intestinal symptoms, psychological health, and rectal distension thresholds.<sup>60</sup> Three distinct groups of patients were observed, two of which had low rectal distension thresholds and were distinguished by low or high psychological co-morbidity. The third group had high rectal distension thresholds and low disease impact overall. A final study, involving 332 adults in the community, who met the Rome criteria and had received a medical diagnosis of IBS, demonstrated clusters distinguished by low or high severity of intestinal and extra-intestinal symptoms, which were further differentiated by the extent of impairment in IBS-related quality of life.<sup>59</sup> However, the study combined patients meeting either the Rome II or Rome III criteria together, and did not, therefore, examine whether there were any differences in the subgroups dependent on how IBS was defined.

In addition, all of these studies failed to validate the models they proposed. This means that, although each model may be a good fit for classifying the patient cohort in which it was derived, it may perform less well in other cohorts of people with IBS. Nonetheless, although the three models were unique, having each been constructed

using different variables, and with IBS defined according to different iterations of the Rome criteria, the general principle that patients can be separated into groups using their psychological profile as well as their gastrointestinal symptoms is a consistent finding in these studies.

Further studies are required that explore novel approaches to subgrouping in larger cohorts of people with IBS, and that make comparisons between different iterations of the Rome criteria. Moreover, subgrouping models require validation, and longitudinal follow-up of novel subgrouping models should be undertaken in order to understand their natural history and prognostic value. In turn, this will help to determine whether using these subgroups to personalise treatment may be a useful approach to adopt in clinical practice.

### **1.3 The Epidemiology, Natural History, and Impact of IBS**

It has already been discussed that symptom-based diagnostic criteria, such as the Rome criteria, aim to make a positive diagnosis of IBS without recourse to extensive investigation, and that the subsequent subgrouping of people according to their predominant stool pattern is intended to help direct treatment. Novel approaches to subgrouping people with IBS may lead to more personalised treatment of the condition, and this could improve outcomes and reduce costs. In order to place this in context and understand why it might be valuable, it is vital to appreciate that IBS is a common and costly condition, which has substantial implications for the individual patient, and for society as a whole.

#### **1.3.1 Epidemiology**

##### **1.3.1.1 Global Prevalence of IBS**

In 2012, a systematic review and meta-analysis involving 260,960 individuals across 81 countries worldwide calculated a pooled global prevalence of IBS of 11%.<sup>61</sup>

The prevalence varied widely, however, dependent on both the criteria used to define IBS and also according to country, ranging from 1.1% in one Iranian study and another conducted in the USA, to 45% in Pakistan. The specific reasons for this variation were unclear. Although there might be genuine differences in the population prevalence of IBS between countries, possibly mediated by ethnicity or the differential effect of risk factors such as diet or genetics, any differences might equally be the result of methodological variation between studies. For example, prevalence was higher when participants were allowed to self-administer the study questionnaire, compared with when it was administered face-to-face or over the telephone by an interviewer.<sup>61</sup> Indeed, heterogeneity between studies was substantial in many of the analyses, confirming that differences in either the methodology, the clinical characteristics of participants, or a combination of these factors was probably relevant to understanding the variability in reported prevalence between studies. In addition, the potential diversity of IBS symptoms between countries and the complexities of applying diagnostic criteria to non-Western populations might also be relevant. A Rome Foundation working group re-examined the literature in 2017.<sup>62</sup> Again, the reported prevalence of IBS varied widely, from 1.1% in France and Iran to 35.5% in Mexico, and the extent of methodological variance between studies was substantial with measures of heterogeneity approaching 100%. This finding led the authors to conclude that calculating a pooled global prevalence was unlikely to be meaningful.

Overall, the findings of these two studies serve to illustrate the problems inherent in characterising the prevalence of IBS around the world. Furthermore, in some countries, including the majority of African nations, the prevalence of IBS was unknown as there were no available data, and there was also a lack of data from many Eastern European, Middle Eastern, and Central American countries.<sup>61, 62</sup> A subsequent study published in 2019 used an online population-based survey to estimate the

prevalence of functional gastrointestinal disorders in the USA, Canada, and the UK using both the Rome III and Rome IV criteria.<sup>63</sup> The prevalence of IBS using the Rome IV criteria was very similar between the three countries, ranging between 4.4% and 4.8%. Rome IV-defined IBS was only around half as prevalent as Rome III-defined IBS, mainly because of the increased minimum frequency of abdominal pain required by the Rome IV criteria.

Due to the uncertainty surrounding pooled estimates of global prevalence, and the variation in prevalence between countries in separate studies, a Rome Foundation global survey sought to quantify the prevalence of several disorders of gut–brain interaction, including IBS, among 73,000 adults in 33 countries around the world using the Rome III and IV diagnostic criteria.<sup>64</sup> The worldwide prevalence of IBS was 4.1% using the Rome IV criteria, compared with 10.1% when the Rome III criteria were used. Most recently, the systematic review and meta-analysis from 2012 has been updated, and includes the results of this global survey.<sup>65</sup> This meta-analysis reported a pooled prevalence of IBS according to the Rome III criteria of 9.2%, based on the results of 53 studies, with almost 400,000 participants, from 38 countries. Once again, the pooled prevalence of IBS defined using the Rome IV criteria was lower at 3.8%, based on findings from six studies, conducted in 34 countries, and comprising approximately 82,000 individuals.

The marked fall in the prevalence of IBS that results from the changes made between the Rome III and Rome IV criteria is noteworthy, and reflects the more restrictive nature of Rome IV. As discussed, this has important clinical implications because, although, and as intended, the criteria are now more specific for diagnosing IBS,<sup>37</sup> many patients' symptoms will no longer be considered consistent with IBS. Instead, they will be diagnosed as having another functional bowel disorder, such as functional diarrhoea or unspecified functional bowel disorder, that are much less well



understood than IBS, and for which there is a lack of evidence-based treatments.

Moreover, there will be an impact on treatment trials, and the interpretation of results, because the patient populations recruited using the Rome IV criteria will differ from those recruited using Rome III criteria, and may have more severe symptoms and higher degrees of psychological comorbidity.

### **1.3.1.2 Prevalence According to Sex and Age**

In an analysis of 56 studies worldwide, the prevalence of IBS was modestly, but significantly, higher in women than men (odds ratio (OR) 1.67; 95% CI: 1.53–1.82).<sup>66</sup> A recently updated meta-analysis reported similar findings based on 30 studies using the Rome III criteria (OR 1.46; 95% CI: 1.33-1.59), but found no studies reporting IBS prevalence according to sex using the Rome IV criteria.<sup>65</sup> When data were examined according to country, however, there were no differences between the prevalence of IBS in women compared with men in studies conducted in South Asian, South American, or African countries.<sup>61</sup> Indeed, in contrast to findings in Western cohorts, epidemiological studies in India have consistently found no difference in prevalence between the sexes.<sup>67</sup> With respect to age, the prevalence of IBS decreased modestly with increasing age, although this trend did not reach statistical significance.<sup>61</sup> However, the odds of IBS were significantly lower in those aged  $\geq 50$  years compared with those  $< 50$  years (OR 0.75; 95% CI: 0.62–0.92), although heterogeneity was substantial.

### **1.3.1.3 Prevalence According to Ethnicity**

Although variations exist in the prevalence of IBS according to geography, data relating to the role of ethnicity are very limited. One US study found that IBS occurs less frequently in African-Americans compared with white individuals,<sup>68</sup> which was also the finding of a systematic review on this topic.<sup>69</sup> This review also identified three community surveys from Singapore and Malaysia that showed no difference in prevalence between individuals of Chinese, Malay, or Indian ethnicity.<sup>70-72</sup>

### 1.3.2 Natural History

Overall, the incidence of IBS in Western populations is estimated to be 1-2% per year.<sup>73</sup> Consequently, many people will suffer with IBS symptoms over the course of their lives. Moreover, IBS is a chronic condition; a survey of nearly 4,000 individuals in the general population demonstrated that, of those with IBS at baseline, around two-thirds of patients reported persistent symptoms at 10-year follow-up.<sup>73</sup> In the same study, around 15% of those who did not have IBS originally developed the condition over the same time period. The development of symptoms in those who were previously asymptomatic may reflect, in part, the role of the bi-directional gut-brain axis. As discussed, in one study higher levels of anxiety and depression at baseline were significant predictors of the development of IBS after 1 year of follow-up.<sup>52</sup> Similarly, some patients who have IBS at baseline, no longer meet criteria for IBS at follow-up.<sup>74</sup> However, although symptoms fluctuate, the prevalence of IBS remains fairly stable, because the number of people whose symptoms disappear are matched by the number who develop new-onset symptoms.<sup>39</sup> Moreover, when patients no longer meet criteria for IBS, this is often because, rather than having resolved, their gastrointestinal symptoms have instead changed, such that there can be transition between different functional gastrointestinal disorders.<sup>75,76</sup> Indeed, a Swedish study found that there was considerable symptom fluctuation between those reporting IBS, dyspepsia, or minor symptoms not meeting criteria for a functional gastrointestinal disorder over a 7-year period.<sup>77</sup> Symptom overlap is also frequently observed, such that IBS may co-exist with other functional gastrointestinal disorders,<sup>78</sup> or with other medically unexplained conditions, such as chronic fatigue syndrome,<sup>79</sup> or fibromyalgia.<sup>80</sup> Finally, it is alarming to note that around one-third of patients with functional gastrointestinal disorders will undergo unnecessary abdominal surgery for their symptoms, including cholecystectomy and hysterectomy.<sup>81</sup> A multivariate analysis examining rates of

surgery in patients with IBS, and adjusting for multiple confounders, showed that having IBS was independently associated with rates of cholecystectomy three-fold higher, appendicectomy and hysterectomy two-fold higher, and back surgery 50% higher, compared with people without IBS.<sup>82</sup>

### 1.3.3 The Impact of IBS

#### 1.3.3.1 Quality of Life

It has long been recognised that IBS has a substantial effect on quality of life,<sup>83</sup><sup>84</sup> which might be greatest in those with IBS-D,<sup>85</sup> for whom the fear of incontinence in a social situation can be especially debilitating.<sup>86</sup> Indeed, patients with IBS-D report more avoidance of places without bathrooms and reluctance to leave home, whereas individuals with IBS-C are more likely to report avoiding sex, difficulty concentrating, and feeling self-conscious.<sup>87</sup> The effects of IBS symptoms on work, including loss of earnings, socialising, and the ability to travel also have a negative effect on quality of life.<sup>88</sup> Overall, patients with IBS report feeling a loss of freedom and spontaneity, highlight the unpredictability of their symptoms, and can feel stigmatised by family, friends, and physicians, who might struggle to understand the effects on their life.<sup>89</sup> Indeed, patients with severe symptoms appear more willing to accept substantial degrees of risk for resolution of their symptoms. For example, a questionnaire-based study showed they would accept a median 1% risk of sudden death from a hypothetical medication in return for a 99% chance of a cure.<sup>90</sup> In another questionnaire study, people with IBS were found to be willing to give up 25% of their remaining life expectancy, an average of 15 years, to be symptom-free.<sup>91</sup>

Consulting with a gastroenterologist regarding IBS symptoms has, unfortunately, been associated with only a small, non-statistically significant improvement in quality of life, which was not maintained over time in one study.<sup>92</sup> This finding might reflect the fact that many patients with IBS report dissatisfaction with clinical management overall, and feel that a patient-centred approach is lacking. Indeed, it has been suggested that long term quality of life might be affected more by psychological well-being than by improvement in gastrointestinal symptom severity.<sup>93</sup>

<sup>94</sup> This understanding highlights the importance of adopting a holistic attitude to care, which can be sometimes overlooked in favour of a largely symptom-driven approach.

### **1.3.3.2 Healthcare Costs**

Overall, direct care costs of IBS — those costs that are entirely attributable to resource use for healthcare delivery, including investigation and treatment of the condition — are substantial. Estimates range from £45.6–200 million per annum in the UK, <sup>95</sup> \$2 billion per annum in China, <sup>96</sup> and €3–4 billion per annum in Germany. <sup>97</sup> An appraisal in 2013, based on an analysis of 35 studies, suggested direct cost estimates in the USA vary considerably, with figures of between \$1,562 and \$7,547 per patient per year. <sup>98</sup> Estimates encompassing six European countries, although more conservative, were nevertheless considerable at between €1,183–3,358 per capita, <sup>99</sup> and similar values were seen in an evaluation of European patients with IBS-C, <sup>100</sup> for whom the biggest cost drivers were hospitalisation and visits to the emergency department. However, comparing costs between countries is difficult due to variations in methods used to calculate them, and the year in which the analyses were conducted. Indeed, many of the available cost analyses require updating in order to reflect current tariffs, and no study has sought to map the global health economic landscape of IBS.

### **1.3.3.3 Issues for Society**

Patients with IBS often find it difficult to work due to their symptoms. Accordingly, they might take time off, referred to as absenteeism, or instead report that, although at work, they struggle to perform at their best, so-called presenteeism. Studies relating to absenteeism in IBS are conflicting. It has been suggested that although people with IBS are more likely to take time off work, the total amount of time is no different to people without IBS. <sup>101</sup> However, one survey of 40,000 individuals across a number of European countries demonstrated that those with IBS took almost twice as many days off per year compared with those without IBS. <sup>102</sup> Overall, studies in Europe

and Canada suggest that anywhere between 5–50% of people with IBS require some time off work due to symptoms.<sup>86,95</sup> A questionnaire study in 2018 of 525 patients with IBS reported that 24% of employed patients reported absenteeism.<sup>103</sup> Presenteeism is more difficult to quantify due its subjective nature, but was reported by 86% of patients with IBS in the same questionnaire study, for whom higher degrees of work impairment were linked to severity of symptoms and gastrointestinal-specific symptom anxiety.<sup>103</sup> Estimates of presenteeism are somewhat lower in other studies, ranging between 2–32%.<sup>95</sup>

Indirect costs of absenteeism and presenteeism, in terms of loss of work productivity, are considerable and similar to those for other chronic conditions, such as asthma or migraine.<sup>104</sup> In an analysis of data from 13 European countries, an estimated mean per-capita indirect cost for IBS was €2,314 per year,<sup>99</sup> higher than in China (~€670).<sup>96</sup> Although an updated analysis is needed, a study in 2003 found that absenteeism cost employers in the USA an average of \$901 each year per employee with IBS, compared with \$528 per employee without IBS.<sup>105</sup> Additional costs to society might be incurred if patients who are unable to work due to their IBS symptoms claim sickness or disability benefits. In a longitudinal population-based study in Denmark, the expected number of weeks on sickness benefits was 61% higher among those with IBS symptoms, which remained statistically significant following adjustment for age, sex, time in education, comorbidity, and mental vulnerability.<sup>106</sup> There was also a trend towards an increased number of weeks on disability benefits among those with IBS symptoms, compared with people without IBS symptoms, but this difference was not statistically significant following adjusted analysis.<sup>106</sup>

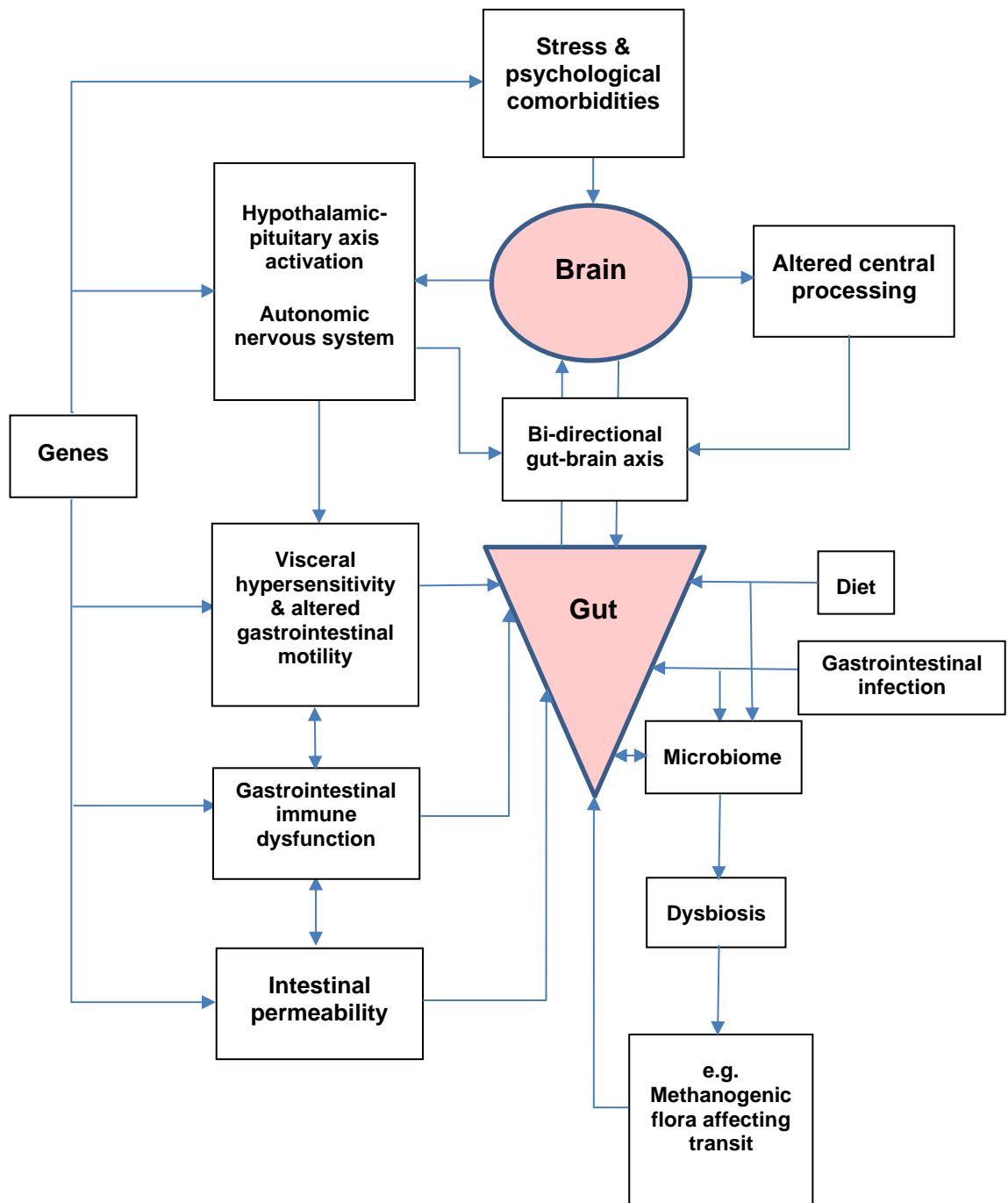
Finally, the effect on families of those with IBS is relatively unknown. In one study, the partners of 152 patients with IBS were under significantly more strain, and bore a greater perceived burden, compared with the partners of 39 healthy controls, and

this effect increased in correlation with the severity of a patient's IBS.<sup>107</sup> It is conceivable that these effects have implications for the health and economic contribution of partners, which are absent from previous assessments of the cost of IBS to society, but this situation requires further research.

#### **1.4 Pathophysiology of, and Risk Factors for, IBS**

The pathophysiology of IBS is complex and incompletely understood (Figure 1-1). As discussed, IBS is defined according to a pattern of symptoms, but it is likely that the underlying pathophysiology varies between patients, such that the same, or similar, symptoms may have a variety of different causes. Indeed, differences in underlying pathophysiology or risk factors for IBS might be hitherto underappreciated factors in the differentiation of IBS subgroups. These are alluded to by the MDCP, but conventional subgrouping uses only stool pattern, and attempts to generate new subgrouping models have, thus far, augmented this approach using only psychological factors. Conceivably, however, any quantifiable risk factor could be incorporated into a subgrouping model, contingent on methodological feasibility, and so a more detailed appraisal of IBS pathophysiology and risk factors is merited.

**Figure 1-1. Proposed Pathophysiological Mechanisms in IBS.**





### 1.4.1 The Gut-Brain Axis and Psychological Comorbidity

Psychological comorbidity, including stress, anxiety, or depression is frequently associated with IBS and might exacerbate symptoms. Indeed, this is highlighted within the MDCP framework. One meta-analysis demonstrated that the prevalence of both anxiety disorders and depressive disorders among patients with IBS was 23%, with anxiety and depressive symptoms being even more common, with a prevalence of 39% and 29%, respectively.<sup>55</sup> Psychological comorbidity contributes to the aetiology of IBS as part of an integrated biopsychosocial model. It is important to consider that psychological symptoms might have developed as a consequence of the severity and effect of IBS on an individual, or might instead have been present prior to the onset of gastrointestinal symptoms.<sup>108</sup>

Within this construct, the gut-brain axis, the interaction between the central nervous system (CNS) and the enteric nervous system, is important in the pathophysiology of IBS and functions in a bi-directional manner.<sup>51</sup> The CNS can alter gut physiology, such as motility or visceral sensitivity, which in turn mediates IBS symptomatology, such as transit and stool pattern, or the experience of pain. Similarly, changes in the gut can feed back to the brain, resulting in effects on psychological well-being and health. The microbiome might also be important in this mechanism.<sup>109</sup> Indeed, higher levels of anxiety and depression at baseline in people without IBS were significant predictors for the development of IBS after 1 year of follow-up.<sup>52</sup> When these findings were examined over the longer term, with follow-up at 12 years, the same association was seen for anxiety, but not for depression.<sup>51</sup> Both these studies also found that, among patients with IBS with no psychological comorbidity at baseline, there was a significant increase in the reporting of anxiety and depression at follow-up.<sup>51, 52</sup>

In addition to the presence of mood disorders, people with IBS often complain of extra-intestinal symptoms, such as fatigue, insomnia, headache, palpitations, dizziness,

or breathlessness, and this is particularly the case among those with IBS-M.<sup>110</sup> The association between IBS and extra-intestinal symptom reporting, often referred to as somatisation, could relate to CNS sensitisation, a neurophysiological mechanism that would explain the occurrence of both painful and non-painful symptoms.<sup>111</sup> Studies suggest that individuals with high levels of somatisation have more severe IBS symptoms,<sup>112,113</sup> which might, in part, be due to an association between increased somatisation and visceral hypersensitivity,<sup>114</sup> and these individuals are more likely to consult with a doctor regarding their IBS.<sup>113</sup> In addition, the relationship between general anxiety, which, as already discussed, is common in IBS, and IBS symptom severity might be mediated by somatisation,<sup>112</sup> or instead by gastrointestinal symptom-specific anxiety.<sup>115,116</sup> Fear and worry related to gastrointestinal symptoms in IBS has been postulated as a key driver of symptom severity and quality of life impairment,<sup>117,118</sup> although findings of a recent study cast doubt on whether gastrointestinal symptom-specific anxiety plays such a central role.<sup>119</sup> Nevertheless, the study concluded that awareness of both gastrointestinal and extra-intestinal symptoms is strongly associated with reporting of more severe symptoms in IBS overall.<sup>119</sup>

#### **1.4.2 Psychological Stressors**

It is widely acknowledged that a history of abuse, whether psychological, physical, or sexual, and other forms of psychological trauma, are strongly associated with IBS,<sup>120</sup> and that this may especially be the case among patients with symptoms that are refractory to medical management.<sup>121</sup> In a study of 206 consecutive female patients who were referred to secondary care with gastrointestinal symptoms, 44% reported a history of sexual or physical abuse, of whom one-third had never disclosed this information before.<sup>122</sup> A history of physical and sexual abuse was more likely among people with functional gastrointestinal disorders than those with organic disease (OR 11.4; 95% CI: 2.22-58.5, and OR 2.08; 95% CI: 1.03-4.21, respectively), and those

reporting abuse had significantly more extra-intestinal symptoms ( $p < 0.001$ ). Among patients referred to the gastroenterology outpatient department, those with a history of abuse were significantly more likely to report IBS-type symptoms compared with those with no history abuse (OR 1.7; 95% CI: 1.2-2.5).<sup>123</sup> The prevalence of sexual abuse among people with IBS was 31.6% in one study of 196 outpatients, significantly higher than the prevalence among patients with organic disease (14%,  $p = 0.0005$ ), and healthy controls (7.6%,  $p < 0.0001$ ).<sup>124</sup> Similarly, the prevalence of general trauma, physical punishment, and emotional abuse, in early life, before the age of 18, are all significantly higher among IBS patients than healthy individuals,<sup>125</sup> and associated with increased symptom severity.<sup>126</sup> Nevertheless, the association between IBS and abuse, whether occurring in childhood or adult life, might be explained in part by controlling for other psychosocial factors, for example having a diagnosis of depression, in logistic regression analyses.<sup>127, 128</sup>

### **1.4.3 Genetic Susceptibility**

Many patients with IBS report having relatives who share their diagnosis, or who report similar symptoms, and indeed studies have observed familial aggregation of IBS, suggesting an underlying genetic component.<sup>129, 130</sup> Nonetheless, such findings are confounded by the fact that, within families, individuals will often have shared childhood experiences or environmental exposures in common, which might equally explain clustering of IBS symptomatology. Moreover, findings from twin studies are conflicting. Some studies demonstrate increased concordance of an IBS diagnosis in monozygotic twins compared with dizygotic twins,<sup>131, 132</sup> and others show no notable difference.<sup>133</sup> In one study having a mother with IBS was equally as important as having a monozygotic twin with IBS.<sup>131</sup> Consequently, any genetic influence in IBS is likely to be polygenic, whereby common variants in a large number of genes and their interaction with environmental factors have a role in determining the clinical

manifestations of IBS. As a result, efforts have focused on trying to identify possible genetic markers in IBS and how these might correlate with certain patient subgroups.

Owing to the role that serotonin (5-hydroxytryptamine (5-HT)) has in the gut-brain axis, as both a brain neurotransmitter related to mood and as an enteric neurotransmitter important in mediating gastrointestinal motility and physiology, the genetics of serotonergic pathways are amongst the most widely studied, specifically genetic variations in the serotonin reuptake transporter (SERT).<sup>134</sup> It has been suggested that a genetic polymorphism in the promotor region of the *SLC6A4* gene encoding SERT might be associated with IBS. In a meta-analysis of 27 studies with 7,039 participants, the risk of IBS was significantly associated with the SERT insertion or deletion polymorphism in both Asian (dominant model:  $P=0.001$ ; recessive model:  $P=0.0003$ ; allele model:  $P=0.001$ ) and white individuals (dominant model:  $P=0.04$ ; additive model:  $P<0.0001$ ), but only for those with IBS-C when patients were stratified by stool pattern (recessive model:  $P=0.04$ ).<sup>135</sup> Other studies have identified rare pathogenic variants in genes encoding sucrase–isomaltase<sup>136</sup> or *SCN5A*,<sup>137</sup> a voltage gated sodium channel, suggesting that IBS symptoms in a small proportion of patients might relate to disaccharide intolerance or ion channelopathies. Indeed, a genome-wide association study (GWAS) meta-analysis of five European cohorts supports the hypothesis of ion-channel involvement in IBS pathophysiology.<sup>138</sup>

Another GWAS study comparing UK biobank data from 9,576 people with IBS and 336,449 healthy controls looked for significant genome-wide findings and investigated associations further in a multicentre population of tertiary care patients from Europe and the USA and a small Swedish population cohort.<sup>139</sup> This study identified variants at a locus on chromosome 9 that were associated with risk of IBS in women only, and additionally associated with constipation, which might support a rationale for investigating the role of sex hormones in the pathophysiology of IBS. In

addition, familial dysautonomia has been linked to mutations of a gene residing at this locus.<sup>140</sup> This is a rare condition affecting the autonomic and sensory nervous systems, which leads to a variety of symptoms including labile blood pressure, altered pain sensation, speech difficulties, episodic vomiting and abnormal gastrointestinal motility. Consequently, this finding might support the role of autonomic dysfunction in IBS pathophysiology; however, these associations are tentative and require further examination.

Studies in Japanese individuals have identified associations between IBS symptoms and single nucleotide polymorphisms in genes encoding the corticotropin-releasing hormone (CRH) receptor 1 and 2.<sup>141, 142</sup> CRH is key to the body's stress response and studies have shown that administration of exogenous CRH can induce an increase in colonic motility, and that motility can be reduced using CRH-receptor antagonists. These findings, together with the fact that altered gastrointestinal motility is a component of IBS pathophysiology, have led some to conclude that the CRH pathway plays a part in IBS.<sup>141, 142</sup>

Although our understanding of the role that genetics might play in the aetiology of IBS is expanding, many unanswered questions remain, particularly whether these gene mutation associations actually contribute to pathophysiological mechanisms. Consequently, current knowledge does not support a role for genetic testing in clinical practice, because how these findings should be interpreted and acted upon is unclear at the present time.

#### **1.4.4 Dietary Factors**

Patients with IBS frequently report that symptoms are associated with eating certain foods.<sup>143, 144</sup> Consequently, many patients will exclude these from their diet with the aim of improving symptoms.<sup>145</sup> However, should they report a positive response,

this is more likely to reflect the fact that, to some degree at least, symptoms of IBS are expected to be meal-related, as per diagnostic criteria, rather than reflecting a true food allergy, mediated via an immune response.

Patients may seek to identify perceived food intolerances using bloods tests, although there is currently insufficient evidence to support this approach. In one randomised controlled trial (RCT), 150 patients were randomised to either a 12-week diet excluding foods to which they showed cross-reactivity on immunoglobulin (Ig) G antibody testing, or to a sham diet, where they excluded the same number of foods to which they had tested positive, but not the specific foods to which they reacted.<sup>146</sup> A greater proportion of patients following the true exclusion diet reported symptom improvement, but this was not statistically significant. In another study, leucocyte activation testing of peripheral blood samples was conducted to identify possible food intolerance, and patients were randomised to a true versus sham elimination diet.<sup>147</sup> Participants following a true elimination diet had a significantly greater improvement in symptom scores, compared with those allocated to a sham diet. However, there was no significant difference in the proportion of patients reporting adequate relief of IBS symptoms, nor in quality of life measures. More recently, one study suggested that people with IBS may have atypical food allergies, which are not mediated via classical IgE pathways, although this requires corroboration.<sup>148</sup> Although individual dietary components might be a factor in the pathogenesis of IBS, the interaction of diet with the gut microbiome and the composition of microorganisms living in the gut might also be important.<sup>149</sup>

#### **1.4.5 The Gut Microbiome**

Interest has been growing into the role that the gut microbiome, with a particular focus on bacteria, might play in health and gastrointestinal disease. It has previously been shown that the faecal microbiota of people with IBS differs significantly from that

of healthy individuals,<sup>150</sup> and might influence colonic transit, contributing to altered bowel habits.<sup>151</sup> The existence of a microbiome ‘signature’ specific to IBS has been proposed, with reduced microbial diversity and the presence of methanogenic or Clostridiales species associated with more severe symptoms.<sup>152</sup> Indeed, Clostridiales species might adversely affect gastrointestinal physiological activity via their possible role in serotonin synthesis, although this speculative link requires further investigation.<sup>153</sup> However, in contrast to these findings, a recent study found no such microbial signature when comparing the faecal microbiome of people with IBS with healthy individuals.<sup>154</sup> Inflammatory pathways, changes in intestinal permeability, and the gut metabolome, which includes products of bacterial metabolism of intestinal contents, have also been suggested to play a part in a microbiome-related construct of gastrointestinal disease.<sup>155</sup> In addition, dietary changes, such as long-term restriction of fermentable oligo-, di-, and mono-saccharides, and polyols (FODMAP), can lead to alterations in the microbiome.<sup>156</sup> Overall, understanding of this field is in its infancy and examining the faecal microbiome remains a tool for researchers, not clinicians. Current knowledge is not sufficiently well-developed to enable reliable interpretation of an individual’s faecal microbiome, understand how this might relate to the pathophysiology of IBS, and use this information to target treatment appropriately.<sup>157</sup>

#### **1.4.6 Post-Infection IBS**

Infective gastroenteritis is frequently identified as a risk factor for developing IBS, referred to as post-infection IBS (PI-IBS),<sup>158</sup> with such patients generally experiencing looser and more frequent stools rather than constipation.<sup>159</sup> Early studies determined that a quarter of individuals with infective gastroenteritis reported persistence of altered bowel habits 6 months after their infective episode, with one in 14 people developing IBS.<sup>160</sup> A range of bacterial pathogens have been implicated in PI-IBS, including *Campylobacter jejuni*, *Escherichia coli*, and *Salmonella enterica* serovar

Typhimurium,<sup>161</sup> as well as *Clostridioides difficile*<sup>162</sup> and *Vibrio cholerae*.<sup>163</sup>

Symptoms can persist for many years following the initial infection,<sup>164</sup> sometimes for more than a decade in some studies,<sup>165</sup> and the development of IBS in this context appears to be independent of other risk factors, such as age and sex.<sup>166</sup> Associations have also been demonstrated between viral infections such as norovirus,<sup>167, 168</sup> and protozoal infections such as *Giardia lamblia*.<sup>169, 170</sup> However, there are far fewer available studies than for bacterial pathogens,<sup>171</sup> and symptoms following viral infection might be relatively transient with a similar prevalence of IBS among exposed and non-exposed individuals by 6 months.<sup>158, 168</sup>

A systematic review and meta-analysis of 45 cohort studies involving 21,421 individuals with infective enteritis who were followed for between 3 months and 10 years to identify the development of IBS, reported a pooled prevalence of IBS at 12 months following infection of 10%, rising to 15% beyond 12 months.<sup>172</sup> The risk of IBS in those with enteritis was four-fold higher than in individuals without, and this risk was significantly associated with female sex (OR 2.2; 95% CI: 1.6–3.1), psychological comorbidity, such as anxiety (OR 2.0; 95% CI: 1.3–2.9) or somatisation (OR 4.1; 95% CI: 2.7–6.0), and antibiotic use (OR 1.7; 95% CI: 1.2–2.4). Individuals with protozoal enteritis were found to be at highest risk of IBS, with around 40% developing the condition compared with 13% of those with a bacterial aetiology.<sup>172</sup> Although an increased risk was seen across different geographic regions, the majority of studies were in European and North American populations. One study of PI-IBS from Bangladesh in 345 patients with acute gastroenteritis demonstrated that, although patients with a history of acute gastroenteritis had a significantly higher prevalence of IBS than age-matched and sex-matched healthy controls, approximately one in 10 of those fulfilling criteria for PI-IBS actually had post-infection malabsorption or sprue following investigation.<sup>173</sup> A study in East Indian patients hospitalised with acute gastroenteritis



found that a quarter developed IBS within 6 months of the infection, and this finding was associated with younger age and increased duration of the gastroenteritis.<sup>174</sup>

Another prospective cohort study of individuals with shigellosis, following an outbreak in a Korean hospital, observed a significantly increased risk of developing IBS up to 3 years after the infection (OR 3.93; 95% CI: 1.20–12.86), but by 10 years the prevalence of IBS was similar between the *Shigella* cohort and healthy controls (23.3% versus 19.7%;  $P=0.703$ ).<sup>175</sup> Overall, the prognosis for PI-IBS and non-PI-IBS appears to be the same, with symptoms persisting beyond 12 months in ~75% of cases and few differences in clinical features between the stool subgroups.<sup>159</sup>

#### **1.4.7 Low-Grade Gut Mucosal Inflammation and Immune Activation**

The role of low-grade mucosal inflammation in the pathogenesis of IBS was first proposed in the early 1960s. In an analysis of surgically resected colon specimens from patients with IBS, Hiatt and Katz observed increased numbers of mast cells in the *muscularis externa* of the bowel wall, a finding similar to the increase seen in colonic resection specimens from people with ulcerative colitis.<sup>176</sup> It has been suggested that, rather than being separate conditions, IBS and inflammatory bowel disease may be part of spectrum, albeit the precise nature of the inflammatory process differs between the two diseases.<sup>177</sup> Among those with IBS, it is the increase in mucosal mast cell density throughout the gastrointestinal tract, but particularly in the colon, that has been the most consistent histological finding.<sup>178</sup> Indeed, a previous systematic review identified 16 studies examining the presence of low-grade inflammation in full-thickness intestinal or endoscopic mucosal biopsies obtained from patients with IBS and healthy controls.<sup>179</sup> The numbers of mast cells, and to a lesser extent T lymphocytes and B lymphocytes, were all increased among people with IBS, but no study showed a significant difference in numbers of neutrophils or eosinophils between the two groups. Although duodenal eosinophilia has been proposed as an important pathophysiological mechanism in

functional dyspepsia, on the whole, evidence does not support a comparable role of eosinophils in IBS.<sup>180</sup> Of note, however, a recent study has discovered evidence of atypical food allergies in some patients with IBS, mediated via eosinophil activation, and further investigation of these findings is required.<sup>148</sup>

The increase in mucosal mast cells in IBS may be due to exogenous triggers. For example, enteric infection can result in immune sensitisation to microbial antigens, leading to mast cell activation and degranulation.<sup>181</sup> Food antigens and chronic stress could have similar sensitising effects.<sup>182</sup> The release of histamine and tryptase alters visceral sensitivity and adversely affects normal gastrointestinal motor function,<sup>181</sup> resulting in persistent gastrointestinal symptoms even after an enteric infection has resolved. This mechanism offers a potential explanation for why some people develop PI-IBS, although this has not been proven. A subsequent systematic review from 2019 again noted increased colonic mast cells among people with IBS, but also suggested that alterations in lymphocyte populations, particularly gut-homing T lymphocytes, might indicate that loss of mucosal homeostasis is an important driver of symptoms in IBS.<sup>183</sup> This increase in T lymphocytes and the accompanying cytokine response, in addition to the potential role of mast cells, is evidence that increased immune activation might be relevant to the pathophysiology of IBS. A detailed systematic review of immune markers in people with IBS demonstrated a consistent reduction in interleukin (IL)-10 in the peripheral circulation and increased levels of IL-6, IL-8, and tissue necrosis factor alpha (TNF- $\alpha$ ).<sup>184</sup> IL-10 was similarly reduced in intestinal mucosal samples across a number of studies. IL-10 is an anti-inflammatory cytokine,<sup>185</sup> which is responsible for regulating TNF- $\alpha$ -converting enzyme.<sup>186</sup> Consequently, a reduction in IL-10 leads to elevated levels of TNF- $\alpha$ , a cytokine involved in systemic inflammation and responsible for the regulation of immune cells.<sup>187</sup> In inflammatory bowel disease, TNF- $\alpha$  is thought to be an important driver of mucosal inflammation, and is a target for biologic drugs,

such as infliximab, which have proven efficacy for treating the disease.<sup>188</sup> These findings hint at a role for cytokine-driven inflammation in IBS; however, there are some inconsistencies in the available evidence. Although increased levels of circulating TNF- $\alpha$  were found in people with IBS compared with healthy controls in one meta-analysis, there was no difference in circulating levels of IL-10.<sup>189</sup>

Overall, identifying the presence of low-grade mucosal inflammation and immune activation would probably require patients to undergo routine colonoscopy and biopsies, and this approach would not be cost-effective. In addition, it would be unpleasant for the patient, and the emphasis is on making a diagnosis of IBS without recourse to invasive investigations.<sup>190</sup> Moreover, there is currently no evidence that identifying mucosal inflammation in IBS can change patient management or alter clinical outcomes. Similarly, serological analysis of cytokines in IBS, although offering a less invasive approach, has no evidence of benefit, and has not been validated for use in everyday clinical practice.

#### **1.4.8 Intestinal Permeability**

The physical integrity of the mucosal barrier in the gut is maintained by tight junctions, also called intracellular adhesion complexes, which are proteins, composed of intra-membrane proteins, occludins, and claudins.<sup>191</sup> Tight junctions encircle the epithelial cells of the luminal epithelium and attach them to one another.<sup>191</sup> In simple terms, they are important for regulating paracellular permeability to ions, water, and molecules, and prevent microbes and unwanted antigens from crossing into the systemic circulation.<sup>191</sup> This physical barrier is further enhanced via the production of mucus by goblet cells, and by a biochemical barrier comprising digestive secretions, antimicrobial peptides, and other mucosal cell products, such as cytokines, as well as by an immunological barrier, organised within the lymphoid follicles, comprising B cells, T cells, dendritic cells, and neutrophils.<sup>192</sup> The normal intestinal barrier can be challenged

by a variety of factors, such as dietary constituents, enteric infections and associated toxins, and the presence of chronic inflammation. This can result in an increase in intestinal permeability, which, in turn, leads to an increase in antigen presentation to the mucosal immune system.<sup>193</sup>

Increased intestinal permeability may have a role in the pathogenesis of IBS, most likely via an integrated pathway in which it both contributes to, and is partly driven by, low-grade mucosal inflammation.<sup>194</sup> Moreover, by invoking an immune response, increased permeability may adversely affect afferent nerves, leading to visceral hypersensitivity and pain.<sup>194</sup> Although the details of these mechanisms require further investigation, several studies have been able to demonstrate the presence of increased intestinal permeability in some people with IBS, albeit there are inconsistencies in the findings. One of the earliest studies demonstrated a significant increase in gut permeability among patients with PI-IBS following *Campylobacter* enteritis,<sup>195</sup> and a subsequent study noted subtle increases in intestinal permeability among those with IBS irrespective of whether they had a history of prior enteric infection.<sup>196</sup> In a third study, small intestinal permeability was significantly increased among people with IBS-D compared with healthy controls,<sup>197</sup> and those without a history of gastroenteritis had more severe defects. Finally, a study assessing paracellular permeability in colonic biopsies found it was significantly higher in patients with IBS, regardless of stool subgroup, compared with healthy controls.<sup>198</sup>

Other studies have examined possible causes of increased permeability in IBS. One study used confocal endoscopic microscopy to image the terminal ileum during diagnostic colonoscopy in order to quantify the epithelial gap density of people with IBS compared with healthy controls.<sup>199</sup> IBS patients had significantly more epithelial gaps in the mucosa of their small intestine, suggesting that abnormal epithelial cell extrusion may be the cause of altered intestinal permeability. Exposure to certain food

antigens can also increase epithelial gaps.<sup>200</sup> Cell extrusion is a mechanism of homeostatic regulation normally intended to remove cells in response to stressors, such as cellular overcrowding in tissues.<sup>201</sup> However, a number of enteric pathogens, such as *Salmonella*, can hijack this process and use it to invade host gut epithelium,<sup>202</sup> which may be particularly relevant to the pathogenesis of PI-IBS. In addition, colonic biopsies from people with IBS exhibit increased translocation of commensal and pathogenic bacteria compared with controls, and this may be driven by mast cells.<sup>203</sup> Another study examined the expression of tight junction proteins in colonic mucosal biopsies.<sup>204</sup> Expression of tight junction proteins was significantly lower in people with IBS compared with healthy controls; however, subgroup analysis according to stool pattern showed this finding was restricted to those with IBS-D, and there was no difference between patients with either IBS-C or IBS-M and healthy individuals. Overall, although increased intestinal permeability is present in some individuals with IBS, its precise role in the pathophysiology of the disorder requires clarification, and whether it might offer new targets for treatment is uncertain.

#### **1.4.9 Gastrointestinal Transit and Motility**

Changes in gastrointestinal transit and motility have long been postulated as contributing to symptoms in IBS. Various techniques for measuring colonic transit are available, including colonic scintigraphy and wireless motility capsule, although most are unavailable outside of specialist centres.<sup>205</sup> The standard means of assessing colonic transit is the radio-opaque marker test, which is relatively simple, and widely available. A capsule containing 20 radio-opaque markers is swallowed by the patient, and a plain abdominal radiograph is taken 5 days later.<sup>206</sup> Retention of five or more markers is indicative of slow transit, but care must be taken not to over-interpret the result, as it has been shown that the number of retained markers does not correlate with symptom severity or quality of life among people with constipation.<sup>207</sup> Moreover, stool

consistency, defined using the BSFS, has been demonstrated to correlate well with transit time,<sup>43</sup> so using investigations to measure this routinely in clinical practice is probably unnecessary.

Studies have sought to better understand the relationship between transit time and symptoms in IBS. One study in 21 female patients with IBS, which assessed changes in colonic transit, stool frequency, and stool consistency between baseline and 12-week follow-up, confirmed the correlation between transit time and altered bowel habit.<sup>208</sup> In another study of 359 patients with IBS, colonic transit time was abnormal in 72 participants (20%), of whom around three-quarters had accelerated transit and one-quarter had delayed transit.<sup>209</sup> A significant association was seen between these abnormalities in colonic transit time and abnormal stool pattern, subgrouped as per the Rome III criteria for IBS, but they were of very limited relevance to other GI symptoms in IBS, including abdominal pain and bloating. Conversely, a study of patients with IBS-C found that they experienced more abdominal bloating, and had prolonged colonic and oro-caecal transit times, compared with healthy controls.<sup>210</sup> Moreover, IBS-C patients with delayed gastrointestinal transit had a greater degree of abdominal distension compared with IBS-C patients with normal transit.<sup>210</sup> However, a recent study, which examined a wide range of neurophysiological parameters and their association with gastrointestinal symptoms in IBS, found no significant correlation between colonic transit time and bloating, although this study included patients with IBS-M and IBS-D in the analysis, as well as those with IBS-C.<sup>211</sup>

In addition to abnormal transit, other changes in gastrointestinal motility may also be relevant to IBS pathophysiology. A recent study of neurophysiological parameters in IBS used a transnasal catheter to assess small bowel motility, finding no significant correlation with gastrointestinal symptoms.<sup>211</sup> However, previous studies have observed a number of abnormalities in small bowel motor activity among patients

with IBS, although none appears to be specific to the condition.<sup>212</sup> These include increased frequency and duration of discrete cluster contractions,<sup>213</sup> increased retrograde jejunal contractions,<sup>214</sup> and an exaggerated motor response to meal ingestion.<sup>215</sup> Exaggerated colonic motility in response to eating has also been observed in people with IBS,<sup>216</sup> and those with IBS-D tend to have increased colonic motility in terms of numbers of high amplitude propagating contractions, whilst the opposite is true of IBS-C.<sup>217</sup> Finally, some patients with IBS have delayed gastric emptying, especially those with IBS-C,<sup>218</sup> or where there is symptom overlap with functional dyspepsia.<sup>219</sup> Nevertheless, overall, the extent to which any of these physiological changes are responsible for causing symptoms in IBS remains uncertain.

5-HT might play an important role, and has long been recognised to affect intestinal motility in humans.<sup>220</sup> It may contribute to symptoms in IBS via its effects on gut transit and intestinal fluid secretion.<sup>221</sup> Studies have shown elevated postprandial plasma 5-HT levels in patients with IBS-D,<sup>222</sup> and reduced postprandial levels in patients with IBS-C.<sup>223,224</sup> These findings may reflect reduced 5-HT reuptake in IBS-D and impaired release in IBS-C,<sup>225</sup> and studies have also suggested 5-HT metabolism is relevant, with higher turnover of mucosal 5-HT in patients with IBS-D.<sup>226</sup> In patients with constipation, the frequency of defaecation has been shown to be inversely related to plasma 5-HT levels.<sup>224</sup> The role of 5-HT in IBS is further supported by the findings of drug trials which demonstrate that antagonists of the 5-HT<sub>3</sub> receptor are effective treatments for IBS-D.<sup>227,228</sup> Similarly, agonists of the 5-HT<sub>4</sub> receptor are effective for treating constipation.<sup>205</sup>

#### **1.4.10 Visceral Sensitivity**

Abnormal visceral sensitivity has been demonstrated in patients with IBS.<sup>229,230</sup> Visceral perception is quantified by pain and discomfort thresholds, or sensory ratings in response to rectal or colonic distension, usually administered by a barostat, which is a

computerised distension device.<sup>231</sup> Visceral hypersensitivity, or reduced pain thresholds to rectal distension, has been demonstrated in up to 60% of patient with IBS,<sup>232</sup> but to a greater extent in those with IBS-D than IBS-C, with an approximate prevalence of 60% and 40%, respectively.

Studies examining the relationship between visceral sensitivity and gastrointestinal symptoms are unclear and inconsistent. Although some studies have shown an association between visceral hypersensitivity and IBS symptom severity, and the severity of abdominal pain and bloating,<sup>56, 233-235</sup> others have not.<sup>224, 236</sup> This has led to the suggestion that visceral hypersensitivity may simply reflect cognitive and emotional factors, an increased tendency to report symptoms, or both,<sup>237</sup> but again not all studies support this.<sup>224</sup> Indeed, a recent study reported a gradual increase in gastrointestinal symptom severity with increasing visceral sensitivity, which was consistent across several large patient cohorts from Sweden, Belgium, and the USA, even after adjustment for the tendency to report symptoms or psychological comorbidity.<sup>56</sup>

The association between abnormal visceral sensitivity and bowel habit is even less clear, likely in part because stool consistency and stool form, and to a much lesser extent frequency, are generally considered to be related to gastrointestinal transit time, as discussed.<sup>43</sup> However, one study reported a weak, but significant, inverse correlation between rectal pain thresholds and the severity of diarrhoea in patients with IBS,<sup>235</sup> and another study in a small number of patients with IBS-C reported a tendency for stool frequency, but not stool form, to correlate inversely with rectal sensory threshold.<sup>224</sup> Patients with IBS-C who have lost their natural call to stool (non-urge) are also more likely to be rectally hyposensitive than IBS-C patients who experience a constant sensation of incomplete evacuation.<sup>238</sup> All these studies suggest that, in terms of bowel habit, rectal sensation may be equally as important as transit time, by altering patient perception of rectal faecal contents and the frequency of defaecation in individuals with



functional bowel disorders. The potential importance of intact rectal sensation for normal bowel function is also supported by the observation that patients with functional evacuation disorders or pelvic floor dyssynergia often exhibit rectal hyposensitivity.<sup>239</sup> Overall, although visceral sensitivity is likely to be an important pathophysiological mechanism in IBS, both with respect to abdominal pain and altered stool pattern, it is not routinely measured as part of the clinical assessment of a patient, but, instead, remains a focus for research in IBS.

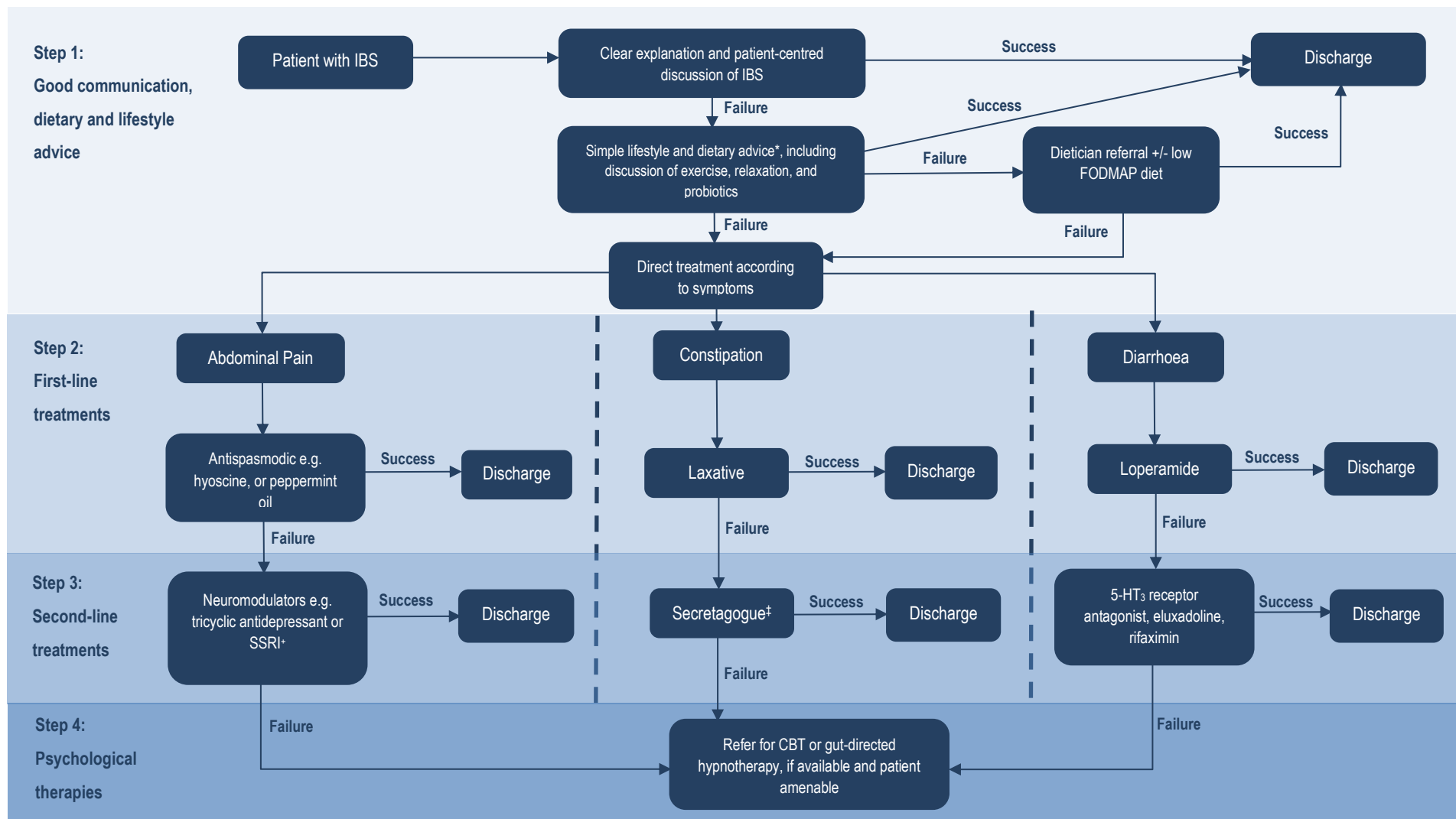
### **1.5 The Treatment of IBS**

In general, treatment is targeted at addressing a patient's most troublesome symptoms, be that abdominal pain, diarrhoea, constipation, or bloating. Although, as discussed already, several factors have been implicated in the pathogenesis of IBS, including the gut-brain axis, alterations in the microbiome, genetic factors, and visceral hypersensitivity, there is currently no role for using these to guide therapy in routine clinical practice. Moreover, it is likely that, even among patients with the same symptoms, the underlying pathophysiology responsible for them will vary. Consequently, although treatments may be designed to address theoretical pathophysiological abnormalities, there is no way to assess response through objective measurement of these and, instead, the clinician must rely on patient-reported symptom response to determine treatment success.

Subgrouping patients with IBS is designed to help facilitate targeted treatment, and one of the principle benefits of developing new methods of subgrouping patients that go beyond gastrointestinal symptoms in isolation, would be the opportunity to help personalise the management of patients. In particular, although the current practice of using stool pattern to subgroup people with IBS might help to identify those who may benefit from antidiarrhoeal medications or laxatives, it does not, for example, assist in prioritising who is most likely to need, or benefit from, psychological therapies. A

greater emphasis on personalised treatment could, therefore, help to reduce the costs to the individual, to healthcare, and society which, as discussed, are considerable. It is therefore important to review what treatments are currently available for IBS, and the current management of IBS is summarised in Figure 1-2.

**Figure 1-2. Suggested Algorithm for the Management of IBS.**



\*As per NICE IBS dietary advice sheet, plus consider ispaghula husk.

+Tricyclic antidepressants should be first choice, starting at a dose of 10mg at night, and titrating slowly (e.g. by 10mg per week) according to response and tolerability. Continue for at least 6 months if patient reports symptomatic response.

‡Review efficacy after 3 months of treatment, and discontinue if no response.

### 1.5.1 The Importance of Good Communication

Before embarking on the prescription of any treatment, it is vital to recognise the role that good communication plays in management. An online survey of people with IBS revealed that many had a negative view of their relationship with healthcare professionals, with concerns about not being heard and a lack of empathy.<sup>240</sup> Indeed, patients report a sense of frustration and isolation, stating that consultation with medical experts rarely clarified their understanding of IBS or improved their management.<sup>241</sup> This might in part reflect unrealistic expectations of patients, many of whom demonstrate a willingness to try any treatment in their desperation for a cure, only to be left disappointed when symptoms are not relieved completely.<sup>242</sup> However, it also reflects a mismatch between patients' ideal expectations of a consultation, and the reality of their experiences. In one survey of over 1000 patients, more than 90% wanted their doctor to give comprehensive information about IBS and provide sources for additional information, to listen well and answer questions, and to provide information about medication.<sup>243</sup> Unfortunately, in recalling their prior experiences of healthcare, only 40% felt that their doctor provided information, 64% felt they had been listened to, and 47% felt supported.

Equally, many patients have significant misconceptions regarding the nature of IBS and the prognosis. In one questionnaire study of over 250 patients with IBS, less than one-third knew abdominal pain was a key symptom, 40% thought colonoscopy could diagnose IBS, 30% believed IBS increased the risk of developing inflammatory bowel disease, and one in seven believed that IBS could lead to cancer.<sup>244</sup> There are also issues with doctors' perceptions of IBS; the majority of general practitioners (GPs) in one study believed it was primarily a psychological disorder,<sup>245</sup> or in another survey a response to stress.<sup>246</sup> Moreover, a qualitative study revealed that many doctors hold two contrasting views of IBS, the first being a publicly expressed "medical" definition,

and the second being a private view, incorporating their own experiences of managing patients and absorbed prejudices.<sup>247</sup>

It is therefore clear that there is a mismatch between views of doctors and patients regarding IBS, which may limit the usefulness of the patient-clinician interaction. A recent systematic review identified five practices that help foster a more positive, meaningful, and engaged consultation.<sup>248</sup> First, doctors should prepare with intention, taking a moment to focus before greeting a patient. Second, they should listen intently and completely. Third, they should explore what the patient cares about, and agree on what matters most, setting priorities in partnership. Fourth, they should seek to connect with the patient's story, considering life experiences that influence their health, as well as acknowledging positive action and success. Finally, doctors should explore the patient's emotions, taking note of any emotional cues.

Adopting this holistic approach has the potential to improve outcomes for patients with IBS,<sup>249</sup> ensuring that their ideas and concerns are elicited. It is also vital to provide a clear explanation about the nature of IBS as a functional gastrointestinal disorder and what this means, including why investigations have been normal, and that this is expected. Patient expectations should also be managed appropriately with discussion focusing on the prognosis of IBS, explaining that around two-thirds of patients experience chronic symptoms,<sup>73</sup> with treatment targeted at improving symptoms, rather than complete symptom relief. Finally, doctors should outline treatment options, including the role of second-line treatment if initial management strategies prove unsuccessful.

## **1.5.2 General Dietary and Lifestyle Advice**

A discussion of simple dietary and lifestyle advice should be part of the care of all patients with IBS. The concept of self-help is important in empowering patients to take control of managing their condition.

### **1.5.2.1 Diet**

Empirical dietary management represents an important first-line treatment strategy. The National Institute for Health and Care Excellence (NICE) endorse a food fact sheet produced by the British Dietetic Association, providing patients with clear and concise dietary advice.<sup>250</sup> This gives general recommendations, emphasising the importance of eating regular meals, limiting alcohol and caffeine intake, maintaining adequate hydration, and reducing processed food consumption. There is also advice relating to specific symptoms. For example, patients with flatulence and bloating are recommended to limit intake of gas-producing food like beans and pulses, and are informed of the potentially beneficial effects of eating linseeds. However, the latter is based primarily on anecdotal observations. A 4-week RCT in 40 patients failed to show a benefit for either whole or ground linseeds over normal diet in terms of improvement in IBS symptom severity, or individual symptoms, including bloating.<sup>251</sup> Patients with diarrhoea are cautioned to avoid sugar-free sweets, mints, gum, and soft drinks that contain sorbitol, mannitol, or xylitol. Advice is also given regarding dietary fibre, which is discussed in greater detail below, with an increased intake recommended for those with constipation, but a reduction in patients with diarrhoea.

### **1.5.2.2 Fibre**

The role of dietary fibre in treating IBS was first examined over 40 years ago. Bran is an example of insoluble fibre, which undergoes little physical change as it passes through the gut, bulking stools and increasing stool water content, with the potential to accelerate gastrointestinal transit times.<sup>252</sup> However, fibre may also be

soluble in water, such as ispaghula, forming a gel that interacts with gut bacteria, resulting in production of metabolites, including short-chain fatty acids and secondary bile acids.<sup>253</sup> These metabolites may, in turn, stimulate gastrointestinal transit, possibly through effects on enteric nerves and smooth muscle, or play a role in immune-mediated anti-inflammatory pathways.<sup>254</sup>

A systematic review and meta-analysis published in 2014 examined effect of dietary fibre supplementation on IBS symptoms.<sup>255</sup> Overall, there was a significant benefit of fibre on global symptoms (relative risk (RR) of symptoms persisting = 0.86; 95% CI 0.80-0.94) in 14 RCTs, containing 906 patients. However, subgroup analysis demonstrated that benefit was confined to RCTs of ispaghula (RR = 0.83; 95% CI 0.73-0.94), with no evidence for bran (RR = 0.90; 95% CI 0.79-1.03). Fibre can exacerbate pain, bloating, and flatulence, and, although the meta-analysis found there were insufficient data to enable analysis of adverse events according to fibre type, these side-effects are generally considered to be a greater issue for insoluble fibres.<sup>256</sup>

Due to its ability to improve stool viscosity and frequency, fibre is perhaps deployed most logically for treating IBS-C, although the evidence for this is inconclusive, and there remains a need for larger and more rigorously conducted trials. Overall, soluble fibre is simple to use, inexpensive, and safe; however, patients should be reminded to increase their intake slowly to avoid exacerbating symptoms. Bran should not be recommended.

### **1.5.2.3 Probiotics**

As discussed, some investigators have demonstrated that the faecal microbiome of patients with IBS differs significantly from that of healthy volunteers,<sup>150</sup> and this might, in part, be responsible for causing symptoms, either directly, or via effects on gastrointestinal transit.<sup>152, 257</sup> This has led to interest in whether probiotics, which are



live or attenuated microorganisms that may have beneficial effects in humans, can be used to alter the microbiome, and thereby improve symptoms.

The results of a systematic review and meta-analysis of 53 RCTs of probiotics, involving 5545 patients, showed that combination probiotics, evaluated in 21 RCTs, had a significant effect (RR = 0.79; 95% CI 0.68-0.91).<sup>258</sup> A total of 33 RCTs reported effect of probiotics on either global IBS symptoms and abdominal pain. Once again, combination probiotics showed a significant benefit over placebo in this analysis; however, for single-organism probiotics containing either *Lactobacillus* or *Bifidobacterium* alone, no benefit was observed. With respect to effect on bloating, combination probiotics showed a non-significant trend towards a reduction in bloating scores, but there was no evidence of benefit with *Lactobacillus*, *Bifidobacterium*, or *Saccharomyces*.

On balance, these results suggest some probiotics may be beneficial in IBS; however, which combination, strain, or species should be preferred in any individual patient remains unclear. The longer-term efficacy of probiotics is unknown, and the mechanism by which they may work, and their effect on the microbiome, requires clarification. The quality of evidence is also low as the majority of trials are small, and many are at an unclear risk of bias. Moreover, there is substantial heterogeneity between studies of probiotics with respect to bacterial strains and species, and caution is therefore needed when interpreting the results of these meta-analyses. Overall, it is reasonable to advise patients wishing to try probiotics to take a combination product for up to 12 weeks, but to discontinue treatment if they fail to experience symptomatic improvement.

#### **1.5.2.4 Exercise**

It is widely accepted that physical exercise plays an important role in maintaining good physical and mental health,<sup>259-261</sup> and that benefit is derived from even small increases in physical activity.<sup>261</sup> With respect to gastrointestinal symptoms, exercise can accelerate gastrointestinal transit,<sup>262</sup> improve intestinal gas clearance in patients with bloating,<sup>263</sup> and might increase gut microbial diversity, with the potential to positively impact symptoms via the gut-brain axis.<sup>264</sup> It is therefore reasonable to assume that exercise will benefit patients with IBS.

One RCT, comparing 12 weeks of an exercise intervention with usual care, invited 305 patients with IBS to participate, of whom only 56 (18%) agreed.<sup>265</sup> The exercise group reported significant improvements in constipation, compared with patients assigned to usual care, but there were no significant improvements in other IBS symptoms, or quality of life. In a second trial, 102 patients with IBS were randomised to a physical exercise programme or usual care for 12 weeks, 75 of whom completed the trial.<sup>266</sup> There was a significant difference in improvement in IBS symptom severity scores with exercise. These positive effects persisted in 39 patients followed up for a median of 5.2 years.<sup>267</sup>

A systematic review from 2018 summarised findings from 14 RCTs of exercise therapy in IBS, involving a total of 683 patients,<sup>268</sup> and included the two aforementioned RCTs.<sup>265, 266</sup> Other interventions studied were diverse, including aerobic exercise, yoga, Tai Ji, and mountaineering. The authors concluded that exercise appeared to be an effective treatment, but highlighted that studies were at high risk of bias. Moreover, heterogeneity of study design prevented formal meta-analysis. Nevertheless, patients with IBS should be encouraged to increase physical activity, where feasible, as there is the potential for symptom improvement.

#### **1.5.2.5 Leisure Time and Relaxation**

NICE guidelines for the treatment of IBS advise encouraging patients to make the most of their leisure time, and to create opportunities for relaxation.<sup>269</sup> The impact of this advice on symptoms and quality of life is uncertain; however, it has been demonstrated that everyday stress and IBS symptoms are related,<sup>270</sup> and patients with IBS report greater stress than controls.<sup>271</sup> Although the relationship between stress and gastrointestinal symptoms may be reciprocal, rather than causal, there remains a clear logic for promoting relaxation among patients with IBS, which may benefit some individuals. The role of formal psychological therapy is discussed in more detail below.

### **1.5.3 Specialised Dietary Advice**

If first-line dietary advice is ineffective, patients should be referred for assessment by a specialist dietitian. It is important to recognise that, although exclusion diets are commonplace in IBS management, the mechanisms by which they might work remain unclear. Dietetic assessment is key to ensuring that any diet is followed correctly, and that nutritional requirements are not compromised.

#### **1.5.3.1 Low FODMAP Diet**

One of the most widely utilised diets in IBS is a low FODMAP diet.<sup>272</sup> A systematic review and meta-analysis published in 2018 identified seven RCTs comparing a low FODMAP diet with various dietary controls, including habitual diet or a high FODMAP diet, involving 397 participants.<sup>273</sup> Meta-analysis demonstrated a benefit in patients adopting a low FODMAP diet, compared with control (RR = 0.69; 95% CI 0.54-0.88). However, quality of evidence was very low. No trials were at low risk of bias, due primarily to the difficulties of blinding in dietary intervention studies, sample sizes were small, and heterogeneity was significant, driven by the variation in the control interventions used in trials. This means the efficacy of a low FODMAP diet may have been overestimated. Furthermore, trials only examined the initial exclusion

phase of the diet, and did not evaluate effects of the managed re-introduction of FODMAP-containing foods according to tolerance, which is recommended longer-term. Overall, the exclusion of foods high in FODMAPs may reduce IBS symptoms, and can be recommended to patients, although there is a need for higher quality evidence to guide management.

### **1.5.3.2 Gluten-Free Diet**

As already discussed, all patients with IBS symptoms should be tested for coeliac disease; however, patients testing negative may still report that they experience symptoms related to eating food containing gluten. This situation is described as non-coeliac gluten sensitivity, the pathogenesis of which is poorly understood, and for which there is no specific diagnostic test.<sup>274</sup> Management therefore relies upon a period of gluten exclusion, and assessment of symptomatic response.

A systematic review and meta-analysis from 2018 identified two RCTs of a gluten-free diet (GFD) in IBS, involving 111 patients.<sup>273</sup> In each trial, participants had already noted a symptomatic response to gluten exclusion, and were randomised to either continue a GFD, or consume a diet contaminated with gluten. Individually, both trials reported statistically significant results in favour of a GFD, showing that a greater proportion of those randomised to receive a gluten-contaminated diet reported IBS symptom flares.<sup>275,276</sup> However, when study results were pooled, there was no significant difference (RR 0.42; 95% CI 0.11-1.55).<sup>273</sup> It is important to recognise that the gluten-challenge design of the trial might increase the likelihood of some patients reporting symptoms, due to their anticipation of the potential for negative consequences.

Overall, if a patient with IBS has already adopted a GFD and experienced an improvement in their symptoms, it might be reasonable for them to continue this

approach, following dietetic assessment. However, current evidence does not support the routine recommendation of a GFD for IBS treatment and further trials are needed.

## 1.5.4 First-Line Drug Treatments

If dietary and lifestyle advice are inadequate for improving symptoms, then a number of first-line drug treatments, targeting individual symptoms, are available.

### 1.5.4.1 Antispasmodics and Peppermint Oil

Conventional analgesic drugs, such as paracetamol, non-steroidal anti-inflammatory drugs, and opiates are unlikely to relieve pain in IBS, and some have the potential to exacerbate gastrointestinal symptoms. Instead, antispasmodic drugs, including peppermint oil, should be used to ameliorate pain and bloating, based on the theory that dysmotility and gut spasm might be the underlying cause of these symptoms, and that antispasmodics relax gut smooth muscle.

A meta-analysis from 2008 identified 22 studies comparing 12 different antispasmodics with placebo in 1778 patients.<sup>277</sup> Fewer patients assigned to antispasmodics had persistent symptoms after treatment compared with those taking placebo (RR = 0.68; 95% CI 0.57-0.81), although heterogeneity between studies was significant. The analysis included a wide range of drugs, including some, such as otilonium, cimetropium, and pinaverium that are unavailable in many countries. However, hyoscine is widely available, and pooled results from three RCTs in over 400 patients showed that it was an efficacious treatment (RR = 0.63; 95% CI 0.51-0.78). Conversely, neither mebeverine nor alverine were more efficacious than placebo, although, in both cases, data came from a single small trial. Overall, total adverse events were significantly more common with antispasmodics, particularly dry mouth, blurred vision, and dizziness. Another meta-analysis conducted as part of the American College of Gastroenterology guidelines in 2018,<sup>278</sup> and pooling data from seven RCTs, demonstrated a statistically significant result in favour of peppermint oil compared with placebo (RR = 0.54; 95% CI 0.39-0.76). However, there was significant heterogeneity

between study results, and the overall quality of evidence was low. Total adverse events were no more common with peppermint oil compared with placebo.

Overall, currently available evidence, although modest, supports the role of antispasmodics, particularly hyoscine, and peppermint oil in treating IBS, and NICE recommends that physicians should consider prescribing them.<sup>269</sup> The two can be used in combination, if desired. However, these drugs may appear less effective from the perspective of secondary care physicians since many patients referred with IBS are likely to have failed to respond to these treatments in primary care.

#### **1.5.4.2 Antidiarrhoeals**

As discussed, patients with IBS-D can be particularly debilitated by loose stools, with urgency and incontinence,<sup>279</sup> restricting and disrupting daily life.<sup>86</sup> Consequently, many patients use loperamide to control their diarrhoeal symptoms. Although widely used, evidence for its efficacy is lacking. There have been only two small trials in IBS, both conducted over 30 years ago, and involving only 42 patients with either IBS-D,<sup>280</sup> or IBS-M.<sup>281</sup> A pooled analysis of data from these trials demonstrated no statistically significant effect of loperamide, compared with placebo on global IBS symptoms,<sup>278</sup> although in the RCTs themselves there were improvements in stool frequency and consistency. Despite the fact that patients frequently report inadequate symptom relief with the drug,<sup>282</sup> and due in part to a lack of efficacious alternatives, it is likely some patients will continue to use loperamide. Indeed, NICE guidance advocates loperamide as the first-choice drug for diarrhoea in IBS,<sup>269</sup> but physicians should be aware that patients may be dissatisfied with this strategy.

#### **1.5.4.3 Laxatives**

NICE guidelines recommend laxatives should be considered for treating IBS-C, with patients advised on how to adjust the dose according to clinical response.<sup>269</sup>

Lactulose should be avoided as it may cause bloating, but otherwise, which laxatives should be preferred is unclear. Both osmotic and stimulant laxatives are efficacious in chronic constipation.<sup>283</sup> However, there is little evidence in IBS-C, beyond the findings of two trials of polyethylene glycol (PEG), an osmotic laxative. In the first of these studies, 42 patients with IBS-C were randomised to either PEG or placebo for 30 days.<sup>284</sup> There was relief of symptoms and an increase in bowel movements in both the treatment and the placebo arms of the trial; however, there was no significant difference between the two. Conversely, in another study, which recruited 139 patients with IBS-C, there was a significant increase in spontaneous bowel movements with PEG, compared with placebo, after 4 weeks.<sup>285</sup> There was also a trend towards improvements in bloating with PEG, but no evidence of benefit in terms of effect on abdominal pain. Unfortunately, the long-term efficacy of laxatives in IBS, which is important given the chronicity of symptoms, remains unclear. Overall, these limited data suggest that PEG might be efficacious in terms of improving bowel frequency in IBS-C, at least in the short-term, but the impact on global symptoms appears minimal. Nevertheless, use of laxatives, which are widely available and relatively inexpensive, is a reasonable first-line approach, with escalation to second-line drugs reserved for patients who report an unsatisfactory clinical response.

### **1.5.5 Second-Line Drug Treatments**

Patients may report inadequate relief of symptoms with first-line treatments, and for patients who are referred to see a gastroenterologist, it is perhaps more likely that this will be the case. In this situation, second-line treatment with central neuromodulators, such as TCAs or selective serotonin reuptake inhibitors (SSRIs), can be utilised. Again, this approach is endorsed by NICE guidelines.<sup>269</sup> Their use is underpinned by the central role of the gut-brain axis in IBS pathophysiology, which has



already been discussed. Central neuromodulators might act on pathways between gut and brain to improve IBS symptoms.

A systematic review and meta-analysis from 2019 identified 18 RCTS comparing TCAs or SSRIs with placebo in IBS, recruiting a total of 1127 patients, with a significant benefit in favour of central neuromodulators (RR = 0.66; 95% CI 0.57-0.76).<sup>286</sup> However, there was significant heterogeneity between studies, although only among trials of SSRIs. A subgroup analysis showed an overall benefit in favour of TCAs for abdominal pain, compared with placebo (RR = 0.59; 95% CI 0.42-0.83). The effect of these drugs on bowel habit is unclear. Most studies did not recruit participants on the basis of stool pattern, nor did they evaluate specific stool consistency endpoints. Given that constipation is a frequently reported side effect of TCAs, these drugs may have a positive impact in IBS-D, but only one trial examined this.<sup>287</sup> Equally, using TCAs to treat abdominal pain in patients with IBS-C may exacerbate constipation. In terms of safety, eight RCTS provided data for total adverse events, with a significantly higher incidence with central neuromodulators (RR of any adverse event = 1.56; 95% CI 1.23-1.98).

Overall, the available data supports the use of central neuromodulators for treating IBS, when first-line treatments are ineffective. TCAs should be preferred, and the dose increased depending on symptomatic response, although dose titration beyond 50mg may lead to higher rates of adverse events. If symptoms do not improve, SSRIs are a reasonable alternative. Although there is no evidence from RCTs to support the use of serotonin norepinephrine reuptake inhibitors (SNRIs), they are beneficial in other chronic painful disorders,<sup>288</sup> and there are reports of efficacy in some patients with IBS, particularly those with psychological comorbidity.<sup>289</sup> Therefore, SNRIs can be considered for the treatment of abdominal pain in some patients with IBS for whom other central neuromodulators have proven ineffective.

## **1.5.6 Second-Line Drug Treatments Targeting Abnormalities of Stool**

### **Pattern**

As already discussed, antidiarrhoeals and laxatives can be used in the treatment of abnormal stool pattern; however, where these prove ineffective, second-line drugs targeting abnormalities in stool pattern are available.

#### **1.5.6.1 Drugs for Constipation**

A number of novel secretagogues have been developed over the last 10 years, although not all are widely available. These share a common general mechanism of action, although the precise pharmacological effects differ between drugs. Broadly, they activate ion channels in epithelial cells of the gut mucosa, increasing electrolyte and fluid content of the intestinal lumen, thereby softening stools and increasing gastrointestinal transit.

One of the first of these drugs to be developed and licensed was lubiprostone, a prostaglandin E<sub>1</sub> derivative. It activates chloride type-2 channels on the apical surface of intestinal enterocytes. The efficacy of lubiprostone 8mcg twice daily in IBS-C was evaluated in two placebo-controlled trials, in a total of 1,171 patients.<sup>290</sup> In both trials, a significantly greater proportion of patients randomised to lubiprostone reported moderate or significant relief of IBS symptoms; however, nausea was a common adverse event, affecting 8% of participants.

Linaclotide and plecanatide stimulate the guanylate cyclase-C receptor. In two RCTs conducted in North America, linaclotide 290mcg once daily was superior to placebo for IBS-C, at 12 weeks in one trial, and 26 weeks in the second.<sup>291, 292</sup> The primary endpoint used was a composite of improvement in both abdominal pain and stool frequency, as recommended by the Food and Drug Administration (FDA) for IBS treatment trials. Plecanatide, at doses of 3mg or 6mg once daily, was superior to placebo in two RCTs, recruiting 2,189 patients with IBS-C,<sup>293</sup> and using the same endpoint,

although there was no difference in efficacy between the two doses. Perhaps unsurprisingly, the main adverse event reported for both drugs was diarrhoea.

Finally, tenapanor, which inhibits the gastrointestinal sodium-hydrogen exchanger-3, is licensed for the treatment of IBS-C in the USA. A phase III placebo-controlled trial of 12 weeks of tenapanor 50mg twice daily, in 629 patients, assessed response using the FDA composite endpoint.<sup>294</sup> The drug was significantly more efficacious than placebo. The main adverse event was diarrhoea; 6.5% of those taking tenapanor discontinued the drug as a result, compared with 0.7% of those taking placebo.

Overall, these findings support the use of secretagogues in IBS-C. They may be best placed for patients who report inadequate relief following optimal or maximum tolerated doses of laxatives from different classes.<sup>269</sup>

#### **1.5.6.2 Drugs for Diarrhoea**

A number of second-line drugs with a diverse range of mechanisms of action are available for treating IBS-D. One of these is the minimally absorbed antibiotic rifaximin. The rationale for its use is the observation that patients with IBS can exhibit changes in their faecal microbiota,<sup>152</sup> and because some studies have shown an overlap between small intestinal bacterial overgrowth and IBS, although evidence for this is largely of low quality.<sup>295</sup> In two RCTs, each recruiting almost 600 patients, rifaximin 500mg three times daily for 14 days was superior to placebo.<sup>296</sup> Efficacy was defined as adequate relief of IBS symptoms for 2 of the first 4 weeks after completion of treatment. However, the difference in response rates between treatment and placebo arms was modest, at around 8%. The main adverse event was headache, affecting 6% of patients. Due to the modest effect, and concerns over potential for adverse events with repeated courses of rifaximin, FDA approval was not forthcoming. A “re-treatment”

trial was therefore conducted. In this study, 2579 patients with IBS-D received a 2-week course of open-label rifaximin. The 636 patients who responded and then relapsed were re-randomised to up to two further 2-week courses of rifaximin, 10 weeks apart, or placebo.<sup>297</sup> After the first course, 33% of those taking rifaximin responded compared with 25% of those taking placebo, with similar response rates following the second course. In each case, these differences reached statistical significance, but again the therapeutic gain was modest.

Drugs that activate  $\mu$ -opioid receptors in the intestine, such as loperamide, retard gut motility and can treat diarrhoea, whereas those acting on  $\delta$ -opioid receptors can improve pain. Eluxadoline, a mixed  $\mu$ - and  $\delta$ -opioid receptor drug, has been evaluated in two RCTs in IBS-D, recruiting over 2400 patients.<sup>298</sup> The primary endpoint was a composite of improvement in abdominal pain and stool consistency at 12 weeks. Both trials demonstrated that eluxadoline at doses of 75mg twice daily and 100mg twice daily were significantly more efficacious than placebo; however, differences in response rates were modest. In a subsequent study, 346 adults with IBS-D who reported inadequate symptom relief with loperamide were randomised to receive eluxadoline 100mg twice daily or placebo for 12 weeks.<sup>299</sup> Once again, a significantly greater proportion of patients taking eluxadoline achieved the composite endpoint, compared with those taking placebo. A particular concern with eluxadoline is the risk of pancreatitis, especially in patients with prior cholecystectomy.

5-HT<sub>3</sub> receptor antagonists, such as alosetron and ramosetron, retard gut motility. A previous meta-analysis of eight RCTs of alosetron for the treatment of IBS-D, involving 4987 patients, demonstrated a benefit of alosetron (RR = 0.79; 95% CI 0.69-0.90) when compared with placebo.<sup>300</sup> Although licensed for use in women with IBS-D in the USA, the drug was withdrawn due to subsequent safety concerns relating to ischaemic colitis and severe constipation. It has been reintroduced for the treatment

of severe IBS-D in women in the USA, and observational data from around 2000 patients suggest it is safe and efficacious in this patient group,<sup>301</sup> but it is not available elsewhere. There are no such safety concerns with ramosetron, and data from five Japanese RCTs demonstrate consistently that it is significantly more efficacious than placebo for treating IBS-D.<sup>302</sup> Ramosetron is only available in Japan and some other Asian countries. However, data from a small crossover trial of ondansetron,<sup>228</sup> and a recent trial of bimodal release ondansetron,<sup>303</sup> suggest this 5-HT<sub>3</sub> receptor antagonist may also be beneficial in IBS-D.

Unfortunately, the availability of second-line drug options for IBS-D is limited. Rifaximin is licensed in North America for IBS, but is not universally available, and eluxadoline has been withdrawn in many countries. It would appear that 5-HT<sub>3</sub> receptor antagonists are efficacious and, where alosetron or ramosetron are unavailable, ondansetron may be a reasonable alternative. Other options include bile acid sequestrants, such as colesevelam, given the overlap between IBS and bile acid diarrhoea, although there are no RCTs of these agents in IBS-D.<sup>304</sup>

### **1.5.7 Psychological Therapies**

The efficacy of a number of psychological therapies in IBS has been investigated. Among the most widely utilised is cognitive behavioural therapy (CBT). Early trials of CBT suggested it was efficacious in IBS,<sup>305,306</sup> although individual trial results are conflicting, with some RCTs finding no benefit compared with standard IBS care.<sup>307</sup> One problem with any trial of psychological therapy is the inability to blind participants to treatment, meaning studies are rarely at low risk of bias. Furthermore, sample sizes are often small, reflecting the intensive nature of psychological interventions, which often require a skilled practitioner working face-to-face with a motivated patient over several weeks. These practical constraints may limit availability in clinical practice. More recently, larger studies have examined the role of minimal-

contact CBT,<sup>308</sup> which participants can self-administer at home, or CBT delivered via the telephone or internet.<sup>309</sup> These approaches require therapist input, but at a reduced frequency, meaning they can be made more widely available. Results of such trials suggest these approaches are efficacious at improving IBS symptoms.<sup>308, 309</sup> The beneficial effects of CBT delivered over the telephone or via the internet persisted up to 24 months after completion of treatment in one study.<sup>310</sup>

Gut-directed hypnotherapy has also been used in IBS, and, again, small studies indicate it is likely to be efficacious,<sup>311, 312</sup> although it has been suggested that delivery outside specialist centres is less beneficial.<sup>313</sup> Similar to CBT, treatment with hypnotherapy requires a skilled practitioner, but it has been delivered remotely in one uncontrolled study.<sup>314</sup> Group hypnotherapy may also improve patient access to treatment. In a multicentre RCT comparing individual and group hypnotherapy with educational support as a control, hypnotherapy was significantly more efficacious than education for adequate relief of symptoms at 3 months and, in a per-protocol analysis, group hypnotherapy was non-inferior to individual hypnotherapy.<sup>315</sup>

Overall, several psychological therapies are efficacious in IBS, although it remains difficult to know which should be preferred, and patient access may be limited. CBT-based treatment and gut-directed hypnotherapy have the largest evidence base, and CBT has demonstrated longer-term efficacy. NICE recommends psychological therapies for patients who remain symptomatic following medical treatment, but only after 12 months has elapsed.<sup>269</sup> There is an argument for earlier deployment of such therapies, especially among patients with evidence of psychological comorbidity at baseline as, given our understanding of the role of the gut-brain axis, this could alter the clinical course of IBS, preventing symptoms from becoming refractory and improving outcomes. This should be a focus for future treatment trials.

### **1.5.8 Personalised Treatment in IBS**

This summary of the current treatment paradigm for IBS has highlighted that a broad range of options are available. Most are intended to address a single gastrointestinal symptom, such as abdominal pain, and, indeed, current guidelines for the management of IBS recommend targeting treatment towards the patient's predominant symptom(s). In addition, subgrouping people with IBS according to their stool pattern can help direct treatment with respect to diarrhoea and constipation. Nevertheless, there are a number of problems with this situation.

Firstly, most patients experience a cluster of different gastrointestinal symptoms simultaneously and may have an alternating bowel habit. Therefore, understanding how best to deploy combinations of different treatments is important, but difficult. Second, most gastrointestinal symptoms have a range of different treatments options available. Although this choice is helpful, knowing which drug should be preferred is challenging. As has been shown, conventional meta-analysis is a useful tool for understanding the efficacy of individual treatments by pooling all available trial data together. It does not, however, facilitate comparison of different drugs, and there are few head-to-head drug trials in IBS, with most drugs having been compared with placebo only. Fortunately, network meta-analysis is a statistical technique that can help to resolve this uncertainty, enabling estimation of the relative efficacy of treatments. This can assist physicians and patients to make better informed treatment choices. Finally, IBS is a complex condition, a disorder of gut-brain interaction, with a complicated underlying pathophysiology that is likely to differ between patients, even in the presence of identical gastrointestinal symptoms. Extra-intestinal symptoms and psychological comorbidity are important, but the current management paradigm does not emphasise these, and psychological therapies are often the last step in current treatment algorithms.

Consequently, more integrated approaches to management that seek to direct treatment according to a mixture of factors, rather than focussing on a single gastrointestinal symptom in isolation, may offer a means of personalising the care of people with IBS, which might improve outcomes. To some extent, this could be achieved on a case-by-case basis by the individual physician, particularly one with an interest in the management of IBS, who strives to apply the recommendations of the MDCP in their daily clinical practice. However, new approaches to the subgrouping of all patients with IBS might provide a more widely applicable framework, and one that could be easily utilised, even by those gastroenterologists without a subspecialist interest in functional gastrointestinal disorders. Not only might this promote a more personalised attitude to treatment overall, but it could also help to ensure that the approach was standardised between patients, with the aim of providing high-quality and high-value care to all those suffering from IBS.



**CHAPTER 2**  
**Aims and Objectives**

The overarching aims of this thesis are to investigate new approaches to subgrouping people with IBS which look beyond gastrointestinal symptoms in isolation, and incorporate additional factors, such as measures of psychological health, and to assess the stability of these new subgroups in order to understand whether they could be used to personalise treatment or predict clinical outcomes. This will be achieved by firstly examining the current practice of subgrouping people with IBS according to predominant stool pattern, and using this to direct treatment, through investigation of the relative efficacy of drugs developed specifically to target either IBS-C, or IBS-D and IBS-M. Second, a cohort of individuals with IBS will be characterised at baseline, examining whether demographic and clinical differences exist between people dependent on whether the Rome IV or Rome III criteria are used to define IBS. Finally, mathematical modelling will be used to derive new subgroups in the cohort, including making a comparison between the Rome III and Rome IV criteria, and longitudinal follow-up will be undertaken. The following pieces of work have been conducted:

## **2.1 Assessing the Relative Efficacy of Secretagogues in Patients with Irritable Bowel Syndrome with Constipation**

As discussed, the Rome criteria advocate subgrouping patients with IBS according to their predominant stool form, be that constipation, diarrhoea, or a mixture of both stool types. The aim of this classification is to help direct treatment. First-line treatment for IBS-C includes dietary changes, such as increasing fibre intake, and use of laxatives; however, a number of second-line drugs, called secretagogues, have also been developed. These drugs, including linaclotide, plecanatide, lubiprostone, and tenapanor, treat constipation by increasing electrolyte and fluid flux into the intestinal lumen, and increasing gut motility. Each secretagogue has been evaluated individually in rigorous RCTs which demonstrate that they are effective for the treatment of IBS-C in

comparison to placebo; however, their relative efficacy remains uncertain because no head-to-head trials have been conducted.

Consequently, the aim of this study, described in Chapter 3, was to conduct a network meta-analysis to appraise the relative efficacy and safety of secretagogues for the treatment of IBS-C. Network meta-analysis is a statistical technique that facilitates indirect treatment comparisons between active therapies in different trials, where these therapies share a common comparator, such as a placebo. It also enables the ranking of treatments to inform clinical decision making.

Although it makes clinical sense to identify and treat individual symptoms, such as constipation, with a suitable drug, it is plausible that treatment response is mediated, at least in part, by additional factors, such as fundamental pathophysiological abnormalities or psychological health, that are not routinely assessed. Similarly, the underlying cause of a particular symptom might also vary between patients. Consequently, by considering treatment outcomes across a number of drugs designed specifically to target stool form abnormalities, this network meta-analysis also allows some assessment of the extent to which subgrouping patients with IBS using stool pattern alone, as per Rome criteria for IBS-C, is useful for determining choice of treatment, and whether all drugs have similar efficacy.

## **2.2 Assessing the Relative Efficacy of Pharmacological Therapies in Patients with Irritable Bowel Syndrome with Diarrhoea or Mixed Stool Pattern**

The treatment of people with IBS-D or IBS-M is broadly similar to the approach taken with respect to people with IBS-C; should individuals report an inadequate response to first-line therapies, such as anti-diarrhoeal medications, a range of second-line drugs are available. These drugs, which include alosetron, ramosetron, eluxadoline, and rifaximin, have contrasting mechanisms of action. Alosetron and ramosetron may retard gut motility and alter rectal compliance via serotonergic pathways, eluxadoline is

a peripherally-acting mixed opioid receptor agonist and antagonist that reduces visceral sensitivity and slows gut transit, and rifaximin is a minimally absorbed antibiotic that may exert its therapeutic effects via changes to the gut microbiome. Again, each of these drugs has been shown to be effective for the treatment of IBS-D and IBS-M in placebo-controlled trials, but their relative efficacy is unknown because, similar to secretagogues in IBS-C, head-to-head trials are lacking.

Thus, the aim of Chapter 4, was to conduct a network meta-analysis of second-line pharmacological therapies for IBS-D and IBS-M to evaluate their relative efficacy and safety, and to facilitate ranking of treatments. This study, therefore, complements the work conducted in Chapter 3 analysing treatment trials in IBS-C. It also offers a further opportunity to appraise the merits of directing treatment according to predominant stool pattern in isolation, in this case IBS-D or IBS-M, using drugs specifically intended for this purpose, among patients who were subgrouped in this way using the Rome criteria.

## **2.3 Describing the Epidemiological, Clinical, and Psychological**

### **Characteristics of Individuals with Self-reported Irritable Bowel Syndrome and Exploring Differences Based on the Rome IV Versus Rome III Criteria**

As discussed, IBS is diagnosed according to symptom-based criteria, called the Rome criteria. These criteria define the cardinal symptoms of IBS as abdominal pain, related to defaecation, associated with a change in the frequency and/or form of stools. The most recent iteration, Rome IV, was published in 2016 and made several key changes to their predecessor, Rome III, in an attempt to make the criteria more specific for diagnosing IBS. Changes included removing the term “discomfort” from the definition, whilst also increasing the minimum frequency of abdominal pain required to meet criteria from at least three times per month to at least once per week. Together, these changes serve to make the Rome IV criteria more restrictive. This has potentially

important implications for clinical practice and recruitment to research studies, as many previous drug trials, such as several of those detailed in Chapters 2 and 3, recruited patients using the Rome III criteria, which may select patients with less severe symptoms, compared with trials applying the stricter Rome IV criteria. Although previous studies suggest that most people meeting Rome III criteria for IBS still meet Rome IV criteria, these studies had important methodological flaws including, most notably, use of a retrospective surrogate set of criteria to approximate Rome IV, rather than applying the full Rome III and Rome IV criteria simultaneously.

Consequently, the aim of the study reported in Chapter 5 was to recruit a large cohort of people with IBS, and examine whether demographic and clinical differences exist between participants dependent on whether the Rome IV or Rome III criteria are used to define IBS, by applying both sets of criteria simultaneously. The study also examined what happened to individuals who met Rome III criteria for IBS, but no longer met criteria according to Rome IV, in terms of their reclassification to one of the other four functional bowel disorders. Having comprehensively evaluated the baseline characteristics of this cohort, these data were subsequently used to fulfil the aim of exploring novel approaches to subgrouping patients with IBS as outlined below.

#### **2.4 Using Latent Class Analysis to Identify Distinct and Reproducible Subgroups of People with Irritable Bowel Syndrome Based on Gastrointestinal Symptoms and Psychological Profiles**

In addition to the pattern of gastrointestinal symptoms that define IBS, it is recognised that other factors, such as psychological health and the reporting of extra-intestinal symptoms, called somatisation, are also relevant to IBS symptomatology. Consequently, the current practice of subgrouping people with IBS according to their predominant stool pattern does not accurately reflect the complex, multifactorial nature of this disorder. In turn, this means that, although this classification system might help

clinicians to select treatments for diarrhoea or constipation, as described in Chapters 3 and 4, it does not help to identify individuals who may benefit from other treatments, such as psychological therapies, or combinations of different approaches. Although the Rome IV criteria have placed greater emphasis on elements of the illness experience other than gastrointestinal symptoms, such as considering the impact of IBS on daily life, or the role of psychological stressors, this approach is only designed to be used on a case-by-case basis. If, instead, patients with IBS could be classified, not only by clinical symptoms, but also by psychological profiles, this may lead to more a tailored approach to treatment, with the potential to improve outcomes and reduce costs. The few studies that have examined this issue have suggested that such an approach is feasible. Nevertheless, these studies have limitations, including a failure to validate the subgrouping models they derived, and one study used a small cohort of patients recruited in a subspecialty setting. There are, therefore, issues regarding the generalisability of these findings, including inconsistencies in the number, and characteristics, of subgroups between studies, as well as within studies, dependent on which iteration of the Rome criteria was used to define IBS.

Consequently, having explored the broader contrasts between Rome III and Rome IV-defined IBS in Chapter 5, in terms of both gastrointestinal symptoms and psychological health, the aim of this study, detailed in Chapter 6, was to derive new subgroups of people with IBS by using a combination of these factors. Moreover, the study aimed to investigate whether these were reproducible, irrespective of diagnostic criteria used to define IBS, and examined whether there are differences between the subgroups with respect to demographic characteristics. The subgroups were derived using latent class analysis, a method of cluster-based mathematical modelling, and the study also aimed to validate the statistical model, thereby assessing whether it could legitimately be applied to other cohorts of people with IBS. This is an important

requirement of any new classification system if it is to be incorporated into clinical practice.

## **2.5 Examining the Natural History and Prognostic Value of a Novel Classification System for Irritable Bowel Syndrome**

Previous longitudinal studies have demonstrated that the stool subgroups used to classify people with IBS are unstable over time. Patients often move between subgroups, and this fluctuation is not entirely explained by the treatment that patients receive. An alternative approach to subgrouping people with IBS, such as is described in Chapter 6, may prove better suited to promoting a more personalised approach to treatment, since it includes assessment of psychological health in addition to gastrointestinal symptoms. However, in order to appraise the feasibility of this concept, a longitudinal follow-up study is required, and this was the aim of the work described in Chapter 7. By applying the baseline model to follow-up data collected after 12-months in the same cohort of people, it was possible to assess the stability of these novel subgroups over time. In addition, the reasons for any changes in subgroup membership could be examined, including the role of treatment, and the prognostic value of the subgroups, in terms of predicting disease course or health resource use, could also be investigated.

**CHAPTER 3**

**Assessing the Relative Efficacy of Secretagogues in Patients with  
Irritable Bowel Syndrome With Constipation**



### 3.1 Introduction

It has already been discussed that patients with IBS are subgrouped according to the predominant stool pattern they experience, into those who report diarrhoea  $\geq 25\%$  of the time (IBS-D), constipation  $\geq 25\%$  of the time (IBS-C), or experience mixed stool pattern IBS and report both diarrhoea and constipation  $\geq 25\%$  of the time (IBS-M).<sup>14</sup> This classification system according to predominant stool pattern is important, because it is used to guide treatment and, increasingly, novel pharmacological therapies are directed towards either IBS-C or IBS-D. Traditionally, first-line treatment for IBS-C has included soluble fibre, such as ispaghula.<sup>278</sup> A previous systematic review and meta-analysis identified seven RCTs of ispaghula,<sup>255</sup> and although this was superior to placebo in terms of global symptom improvement, only one of these trials was at low risk of bias,<sup>316</sup> and none restricted their recruitment to patients with IBS-C. Laxatives, such as PEG, are often used for the treatment of IBS-C,<sup>269</sup> but there have been only two RCTs conducted,<sup>284,285</sup> and although both trials reported a significant improvement in number of stools, there was no effect on abdominal pain scores.

In the last 10 years, several novel secretagogues have been developed for the treatment of IBS-C. Lubiprostone is a prostaglandin E<sub>1</sub> derivative, which activates the intestinal chloride channel type-2 on the apical surface of small intestinal enterocytes. Activation leads to chloride and water efflux into the luminal cavity. Linaclotide and plecanatide are peptides that stimulate the guanylate cyclase-C receptor, leading to electrolyte and fluid transport into the intestinal lumen. Tenapanor is a small-molecule inhibitor of the gastrointestinal sodium-hydrogen exchanger-3, which results in increased intraluminal sodium and water excretion. Although there is evidence from high-quality RCTs that all of these therapies are effective for the treatment of IBS-C, their relative efficacy is unknown. This is because there have been no head-to-head trials of these drugs. It is unlikely that any such trials will ever be performed, as they

would be expensive to conduct, because they would need huge numbers of patients in order to demonstrate superiority of one drug over another.

Network meta-analysis can circumvent this problem to some extent, allowing indirect treatment comparisons between active therapies in placebo-controlled trials, and enabling the ranking of treatments in order to inform clinical decisions.<sup>317</sup>

Unfortunately, individual RCTs do not always use an identical design, recruit homogeneous groups of patients, or assess efficacy using the same endpoints. However, in the case of IBS-C, the FDA have made recommendations for the design of treatment trials, and endorsed standardised endpoints that should be used to judge the efficacy of novel therapies. It has, therefore, been possible to conduct a network meta-analysis of RCTs of very similar design, using identical treatment duration and, in many instances, identical efficacy endpoints, in order to examine the relative efficacy and safety of secretagogues tested in IBS-C.

Another important consideration is that, even though it is logical to treat constipation with an appropriate drug as part of the management of people with IBS-C, it is plausible that treatment response is mediated, at least in part, by additional factors that do not form part of a routine clinical assessment. It has already been highlighted that these factors, such as fundamental pathophysiological abnormalities or psychological health, are potentially important with respect to IBS symptomatology. Moreover, the cause of constipation, and the relative role of these different contributory factors, might also vary between patients. Consequently, by considering treatment outcomes across a number of drugs designed specifically to target stool pattern abnormalities, this network meta-analysis also allows some assessment of the extent to which subgrouping patients with IBS using stool pattern alone, as per Rome criteria for IBS-C, is useful for determining choice of treatment, and whether all drugs have similar efficacy.

## **3.2 Methods**

### **3.2.1 Search Strategy and Study Selection**

A search of the medical literature was conducted using MEDLINE (1947 to June 2018), EMBASE, EMBASE Classic (1947 to June 2018), and the Cochrane central register of controlled trials. In addition, clinicaltrials.gov was searched for unpublished trials, or supplementary data for potentially eligible studies. RCTs examining the effect of secretagogues (lubiprostone, linaclotide, plecanatide, and tenapanor) in adult patients (>16 years) with IBS-C were eligible for inclusion (Table 3-1). The first period of cross-over RCTs were also eligible for inclusion

**Table 3-1. Eligibility Criteria.**

Randomised controlled trials.
Adults (participants aged >16 years).
Diagnosis of IBS with constipation based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared lubiprostone, linaclotide, plecanatide, or tenapanor with each other, or with placebo.
Minimum treatment duration of 12 weeks.
Follow-up duration of 12 weeks.
Dichotomous assessment of response to therapy in terms of effect on global IBS symptoms following therapy†.

\*Manning, Krusik score, Rome I, II, III, or IV.

†Preferably patient-reported, and according to the FDA-recommended endpoint for IBS with constipation, but if this was not available then as assessed by a physician or questionnaire data.

A diagnosis of IBS-C was based on either a clinician's opinion, or meeting specific diagnostic criteria, for example the Rome criteria. Studies recruiting patients with chronic idiopathic constipation (CIC), or mixed populations of patients with IBS-C or CIC, where data were not reported separately for IBS-C, were ineligible. Only RCTs that examined the efficacy of currently licensed doses of lubiprostone, linaclotide, and plecanatide or, in the case of tenapanor, the dose taken forward to phase III trials, and which compared them with each other, or with placebo, were considered eligible. A minimum treatment duration of 12 weeks was required, in line with FDA recommendations for the design of treatment trials for the functional gastrointestinal disorders. All endpoints were extracted at 12 weeks, even for RCTs that provided efficacy data at other time points. This was done in order to provide as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, as the placebo effect tends to wane with time.<sup>318</sup> Studies had to report a dichotomous assessment of response to therapy. First and senior authors of studies were contacted to provide additional information on trials, where required.

The literature search was conducted independently by two investigators. Studies on IBS were identified with the terms: *irritable bowel syndrome* and *functional disease(s), colon* (both as medical subject headings (MeSH) and free text terms), and *IBS, spastic colon, irritable colon, or functional adj5 bowel* (as free text terms). These were then combined using the set operator AND with studies identified with the following terms: *lubiprostone* (both as a MeSH and free text term), and *Amitiza, linaclotide, Constella, Linzess, plecanatide, Trulance, and tenapanor* (as free text terms).

There were no language restrictions, and abstracts identified by the initial search were evaluated independently by two investigators for eligibility. All potentially

relevant papers were obtained and evaluated in detail. Foreign language papers were translated, where required. Articles were assessed independently by two investigators, using pre-designed eligibility forms, according to the pre-defined eligibility criteria. Disagreements between investigators were resolved by discussion.

### **3.2.2 Outcome Assessment**

The efficacy of all drugs, compared with each other or with placebo, in IBS-C was assessed in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. Secondary outcomes included adverse events occurring as a result of therapy (overall numbers, as well as individual adverse events, including diarrhoea, headache, abdominal pain, abdominal distension, or nausea).

### **3.2.3 Data Extraction**

All data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). Some of the included eligible RCTs used different primary endpoints. However, the majority of trials of linaclotide, plecanatide, and tenapanor adhered to the FDA-recommended endpoint for patients with IBS-C, and reported treatment efficacy according to the proportion of patients experiencing a  $\geq 30\%$  improvement in abdominal pain accompanied by an increase of  $\geq 1$  complete spontaneous bowel movement (CSBM) per week from baseline for  $\geq 50\%$  of weeks. The RCTs of lubiprostone also applied these criteria retrospectively to a subset of patients in the two phase III studies.

In addition, due to the multitude of endpoints reported within the individual trials, it was also possible to assess the efficacy of therapies according to other dichotomous endpoints to define response to treatment, including: a) the primary endpoint used in each individual RCT; b) a  $\geq 30\%$  improvement in abdominal pain for

≥50% of weeks (abdominal pain responder); c) an increase of ≥1 CSBMs per week from baseline for ≥50% of weeks (CSBM responder); and d) a ≥30% improvement in bloating for ≥50% of weeks (bloating responder).

For all included studies the following data were also extracted for each trial, where available: country of origin, number of centres, criteria used to define IBS-C, proportion of female patients, and dose and duration of therapy. Data were extracted as intention-to-treat analyses, with drop-outs assumed to be treatment failures (i.e. no response to therapy), wherever trial reporting allowed. If this was not clear from the original article, an analysis was performed on all patients with reported evaluable data.

### **3.2.4 Quality Assessment and Risk of Bias**

Two investigators performed this independently at the study level. Disagreements were resolved by discussion. The Cochrane handbook was used to assess risk of bias,<sup>319</sup> by recording the method used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

### **3.2.5 Data Synthesis and Statistical Analysis**

A network meta-analysis was performed using the frequentist model, with the statistical package “netmeta” (version 0.9-0, <https://cran.r-project.org/web/packages/netmeta/index.html>)<sup>320</sup> in R (version 3.4.2),<sup>321</sup> and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for network meta-analyses,<sup>322</sup> in order to explore indirect treatment comparisons of the efficacy and safety of each medication. Network meta-analysis results usually give a more precise estimate, compared with results from

standard, pairwise analyses,<sup>323, 324</sup> and can also rank treatments to inform clinical decisions.<sup>317</sup>

The symmetry and geometry of the evidence was examined by producing a network plot with node and connection size corresponding to the number of study subjects and number of studies respectively. A comparison adjusted funnel plot was produced to explore publication bias or other small study effects, for all available comparisons versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects.<sup>325</sup> A pooled RR with 95% CIs was calculated to summarise the effect of each comparison tested, using a random effects model as a conservative estimate. There were no direct comparisons between the active treatment groups, so it was not possible to perform consistency modelling to check the correlation between direct and indirect evidence.<sup>326</sup>

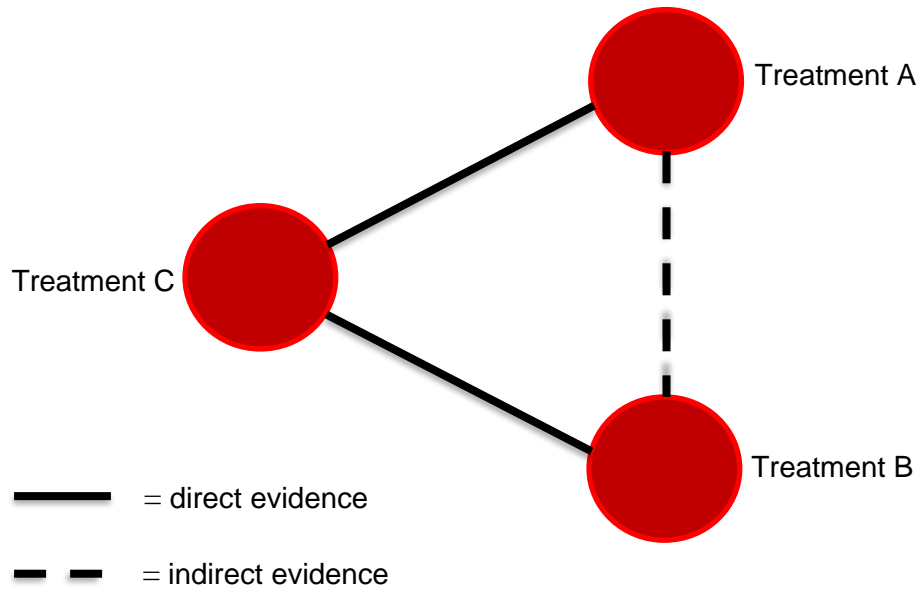
Global statistical heterogeneity across all comparisons was assessed using the  $I^2$  measure from the “netmeta” statistical package. The  $I^2$  measure ranges between 0% and 100%, and is typically considered low, moderate, and high for values of 25% to 49%, 50% to 74%, and  $\geq 75\%$  respectively.<sup>327</sup> The treatments were ranked according to their P-score. The P-score is a value between 0 and 1, with a higher score indicating a greater probability of the treatment being ranked as best.<sup>328</sup> However, the magnitude of the P-score should be considered, as well as the treatment rank. The mean value of the P-score is always 0.5, so if treatments cluster around this value they are likely to be of similar efficacy. In the main analysis, data for the FDA-recommended endpoint to define treatment response in IBS-C was pooled, for all included RCTs that reported these data.



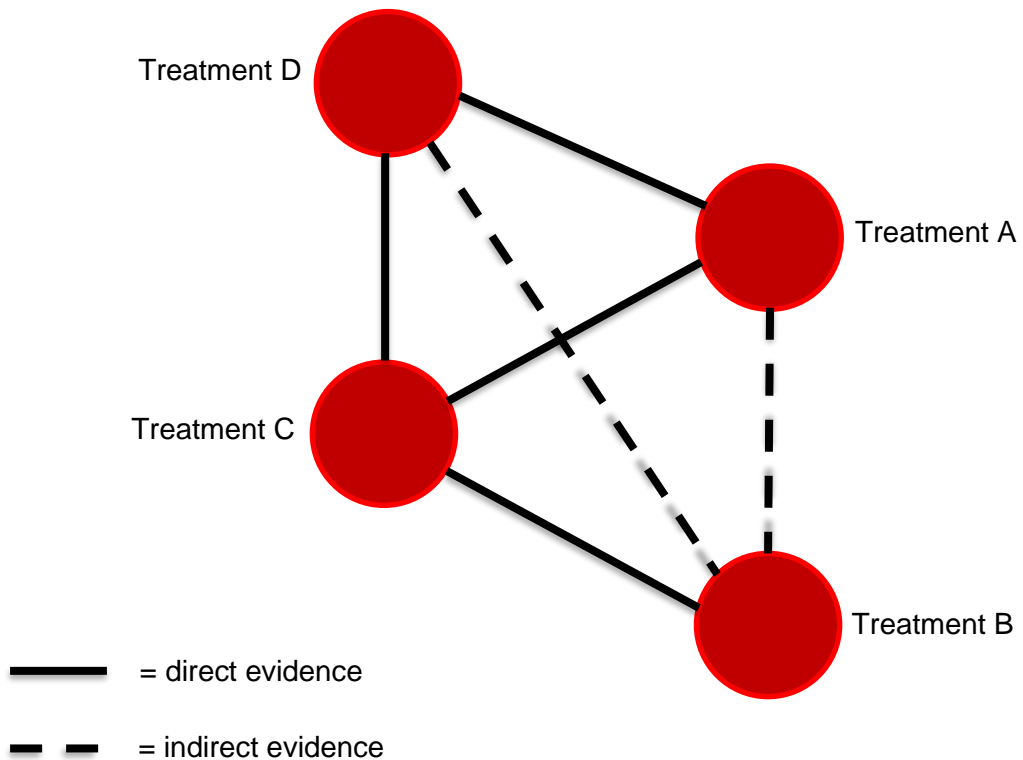
In addition, analyses were performed to assess the overall safety of each medication, including overall numbers of adverse events, as well as occurrence of diarrhoea, headache, abdominal pain, abdominal distension, or nausea.

### **3.2.6 Principles of Network Meta-Analysis**

In simple terms, where two treatments, A and B, share a common comparator, for example a placebo, C, but have not themselves been directly compared in a trial, network meta-analysis enables the treatment effect between A and B to be estimated indirectly (Figure 3-1). This is because the magnitude and direction of the effect between treatment A and B and the shared comparator, placebo C, are all known from existing trial data. These data are referred to as direct evidence. If treatment D is now included, which has been compared with both treatment A and placebo C (Figure 3-2), the connections of the network become more complex and, by considering all the direct and indirect treatment estimates together, the relative efficacy of all included treatments can be estimated. Furthermore, as discussed, statistics can be used to rank treatments based on the probability of which one is likely to be the most effective across the network.

**Figure 3-1. Direct and Indirect Treatment Estimates.**

Treatment A and treatment B have both been compared with treatment C directly in trials. This data can be used to calculate the treatment estimate between treatments A and B indirectly.

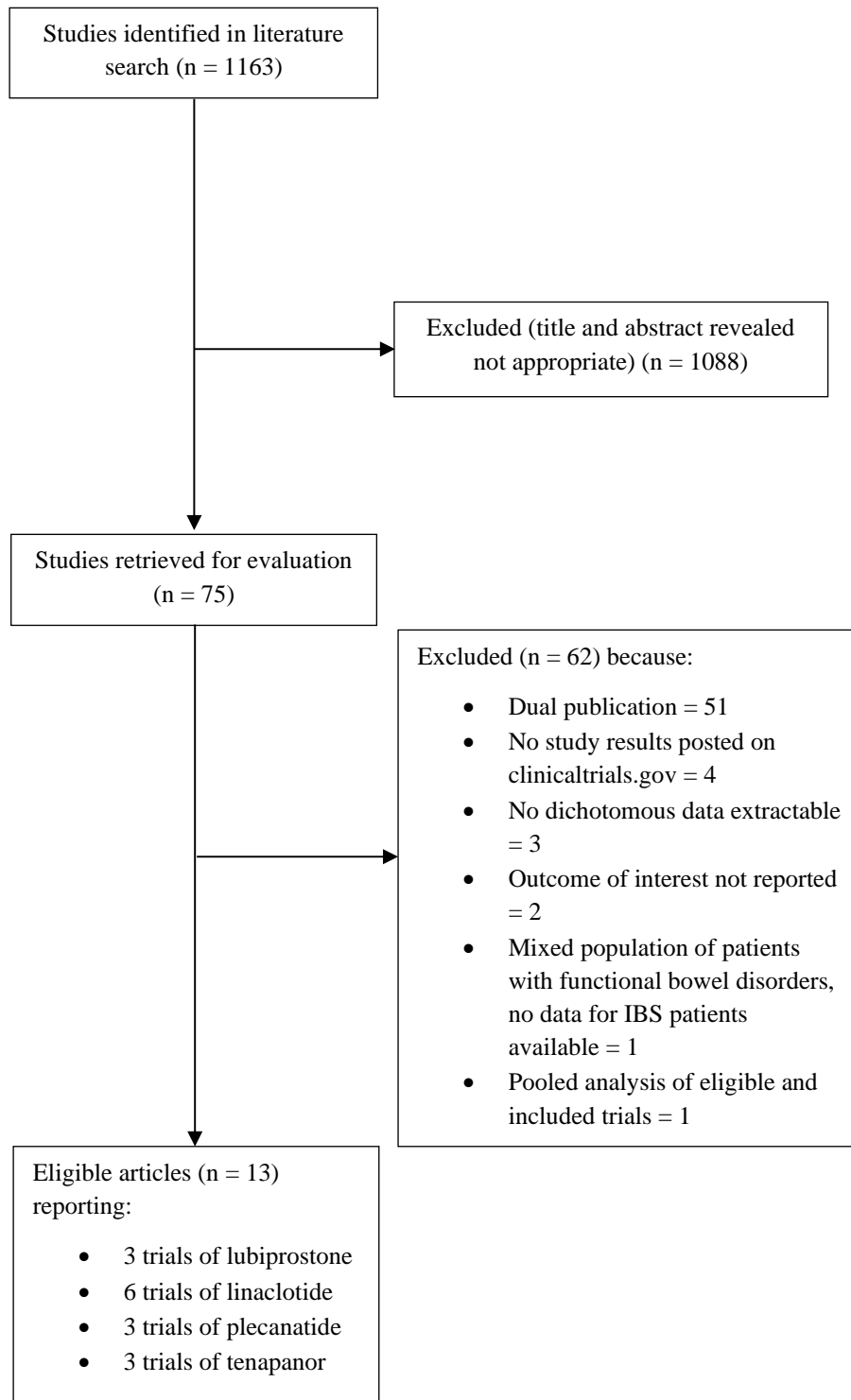
**Figure 3-2. Building a Network.**

Treatment D has now been added to the network. Treatment A and treatment D have been compared directly, but an indirect estimate is also available between them via their comparisons with treatment C. Overall, this diagram illustrates how treatments in the network can be compared with one another, either directly, indirectly, or using both approaches, if data is available.

### 3.3 Results

The search strategy generated 1163 citations, 75 of which appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 3-3). Of these, 62 were excluded for various reasons, leaving a total of 13 eligible articles, reporting on 15 trials that contained a total of 8462 patients. There were three RCTs, reported in two articles,<sup>290, 329</sup> of lubiprostone in IBS-C, six trials of linaclotide (four of which used linaclotide 290mcg once-daily (o.d.), the licensed dose in the USA,<sup>291, 292, 330, 331</sup> and two a dose of 250mcg or 500mcg o.d., the licensed doses in Japan),<sup>332, 333</sup> three RCTs of plecanatide, reported in two articles,<sup>293, 334</sup> and three RCTs of tenapanor.<sup>335-337</sup> A further article was also included because it provided supplementary data, reporting efficacy according to FDA-recommended endpoints for lubiprostone in the two phase III RCTs.<sup>338</sup> However, it should be pointed out that this article did not report data for all patients included in these two trials. This was because some of the recruited patients would not have met the updated FDA-recommended CSBM and abdominal pain thresholds for inclusion in an IBS-C treatment trial, and they were, therefore, excluded from the analysis.

**Figure 3-3. Flow Diagram of Assessment of Studies Identified in the Systematic Review.**



Agreement between investigators for trial eligibility for the 75 articles retrieved was excellent (Kappa statistic = 0.96). Detailed characteristics of individual RCTs are provided in Table 3-2. Risk of bias for all included trials is reported in Table 3-3. Twelve trials were at low risk of bias.<sup>291, 292, 329-333 290, 293, 335</sup> No trials making head-to-head comparisons of one drug versus another were identified, meaning that direct evidence was only available in comparison with placebo. Active medications could, therefore, only be compared with each other using an indirect evidence meta-analysis.

**Table 3-2. Characteristics of Randomised Controlled Trials of Secretagogues Versus Placebo in IBS-C.**

<b>Study</b>	<b>Country and Number of Centres</b>	<b>Diagnostic Criteria Used for IBS</b>	<b>Primary Endpoint Used to Define Symptom Improvement Following Therapy</b>	<b>Number of Patients (% female)</b>	<b>Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy</b>
<b>Johanson 2008</b> <sup>329</sup>	USA, 19 sites	Rome II criteria	Treatment effectiveness rated as at least ‘moderately effective’ for all 4 weeks of the month, or ‘quite a bit effective’ for 2 or more of the 4 weeks of the month	100 (90.0)	52 patients received lubiprostone 8mcg b.i.d.* for 12 weeks
<b>Drossman 2009a</b> <sup>290</sup> <b>and Chang 2016a</b> <sup>338</sup>	USA, multiple sites	Rome II criteria	Moderate or significant relief of IBS symptoms for all 4 weeks of the month, or significant relief for 2 or more of the 4 weeks of the month for 2 out of 3 months	590 (90.0)	396 patients received lubiprostone 8mcg b.i.d. for 12 weeks
<b>Drossman 2009b</b> <sup>290</sup> <b>and Chang 2016b</b> <sup>338</sup>	USA, multiple sites	Rome II criteria	Moderate or significant relief of IBS symptoms for all 4 weeks of the month, or significant relief for 2 or more of the 4 weeks of the month for 2 out of 3 months	581 (90.0)	387 patients received lubiprostone 8mcg b.i.d. for 12 weeks
<b>Johnston 2010</b> <sup>330</sup>	USA and Canada, 92 sites	Rome II criteria	≥3 CSBMs† per week and an increase of 1 CSBM per week from baseline for ≥9 of 12 weeks	170 (92.4)	85 patients received linaclotide 290mcg o.d.± for 12 weeks

<b>Chey 2012</b> <sup>292</sup>	USA, 102 sites	Rome II criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	805 (89.6)	402 patients received linaclotide 290mcg o.d. for 26 weeks
<b>Rao 2012</b> <sup>291</sup>	USA and Canada, 118 sites	Rome II criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	803 (90.5)	406 patients received linaclotide 290mcg o.d. for 12 weeks
<b>Fukudo 2018</b> <sup>332</sup>	Japan, 66 sites	Rome III criteria	Global assessment of relief of IBS symptoms	331 (90.5)	112 and 107 patients received linaclotide 250mcg or 500mcg o.d. respectively for 12 weeks
<b>Yang 2018</b> <sup>331</sup>	China, USA, Canada, Australia, and New Zealand	Rome III criteria	Considerable or complete relief of IBS symptoms for 6 of 12 weeks	839 (82.0)	406 patients received linaclotide 290mcg o.d. for 12 weeks
<b>NCT02316899 (unpublished)</b> <sup>333</sup>	Japan, 61 sites	Rome III criteria	Global assessment of relief of IBS symptoms	500 (87.8)	249 patients received linaclotide 500mcg o.d. for 12 weeks
<b>Miner 2014</b> <sup>334</sup>	USA, 99 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	171 (unclear)	86 patients received plecanatide 3mg o.d. for 12 weeks



<b>Brenner 2018a</b> <sup>293</sup>	North America, 130 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	1054 (76.4)	351 and 349 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks
<b>Brenner 2018b</b> <sup>293</sup>	North America, 140 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	1135 (71.8)	377 and 379 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks
<b>Chey 2017</b> <sup>335</sup>	USA, 79 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	178 (86.8)	89 patients received tenapanor 50mg b.i.d. for 12 weeks
<b>NCT02621892 (unpublished)</b> <sup>336</sup>	USA, 111 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	610 (81.4)	309 patients received tenapanor 50mg b.i.d. for 12 weeks
<b>NCT02686138 (unpublished)</b> <sup>337</sup>	USA, 117 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	593 (unclear)	293 patients received tenapanor 50mg b.i.d. for 26 weeks

\* b.i.d.; twice-daily

±o.d.; once-daily

**Table 3-3. Risk of Bias of Randomised Controlled Trials of Secretagogues Versus Placebo in IBS-C.**

<b>Study, drugs, and doses</b>	<b>Method of Generation of Randomisation Schedule Stated?</b>	<b>Method of Concealment of Treatment Allocation Stated?</b>	<b>Blinding?</b>	<b>No Evidence of Incomplete Outcomes Data?</b>	<b>No Evidence of Selective Reporting of Outcomes?</b>	<b>Low Risk of Bias?</b>
<b>Johanson 2008 <sup>329</sup>, lubiprostone 8mcg b.i.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Drossman 2009a <sup>290</sup> and Chang 2016a <sup>338</sup>, lubiprostone 8mcg b.i.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Drossman 2009b <sup>290</sup> and Chang 2016b <sup>338</sup>, lubiprostone 8mcg b.i.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Johnston 2010 <sup>330</sup>, linaclotide 290mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Chey 2012 <sup>292</sup>, linaclotide 290mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes

<b>Rao 2012 <sup>291</sup>, linaclotide 290mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Fukudo 2018 <sup>332</sup>, linaclotide 250mcg or 500mcg</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Yang 2018 <sup>331</sup>, linaclotide 290mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>NCT02316899 (unpublished) <sup>333</sup>, linaclotide 500mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Miner 2014 <sup>334</sup>, plecanatide 3mg o.d.</b>	No	No	Double	Yes	Yes	No
<b>Brenner 2018a <sup>293</sup>, plecanatide 3mg or 6mg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Brenner 2018b <sup>293</sup>, plecanatide 3mg or 6mg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Chey 2017 <sup>335</sup>, tenapanor 50mcg b.i.d.</b>	Yes	Yes	Double	Yes	Yes	Yes

<b>NCT02621892 (unpublished)</b> <sup>336</sup> , tenapanor 50mcg b.i.d.	No	No	Double	Yes	Yes	No
<b>NCT02686138 (unpublished)</b> <sup>337</sup> , tenapanor 50mcg b.i.d.	No	No	Double	Yes	Yes	No

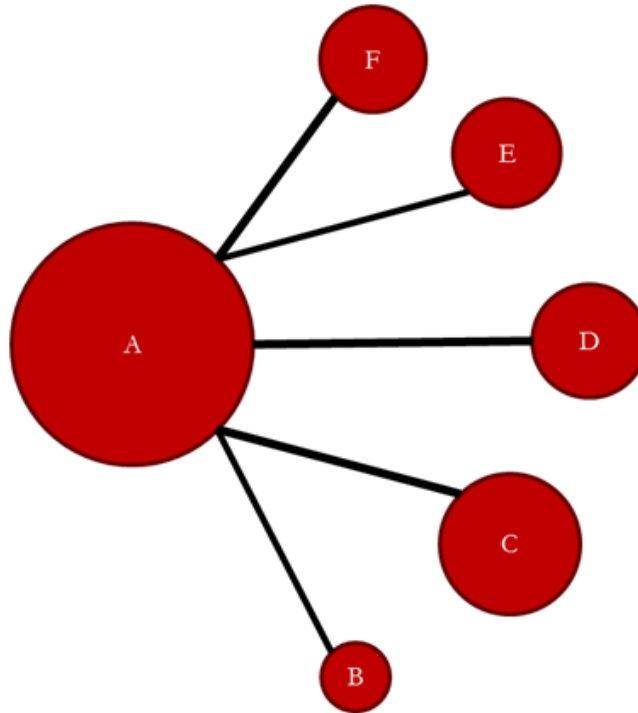
Boxes shaded green denote that the risk of bias item was reported, while those shaded red denote it was not reported

### 3.3.1 Efficacy

#### 3.3.1.1 Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response

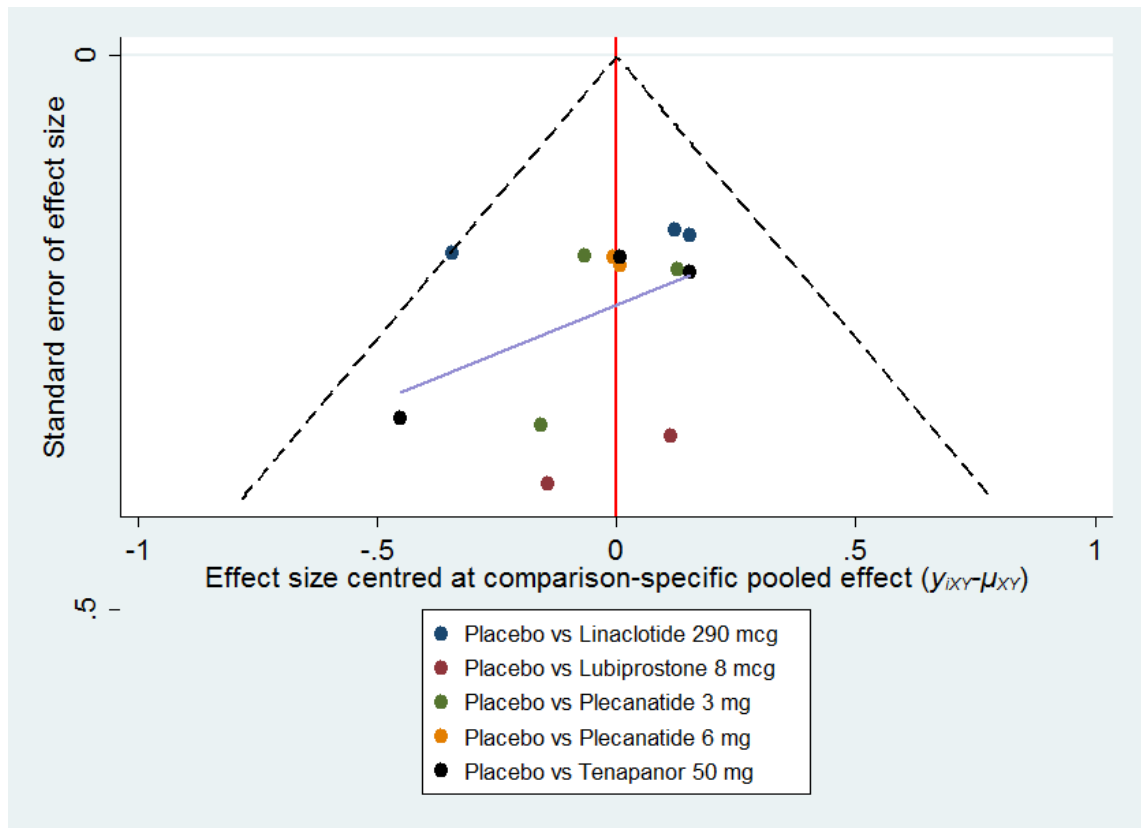
Eleven RCTs, reported in nine separate articles,<sup>291-293, 331, 334-338</sup> provided dichotomous data for failure to achieve the FDA-recommended endpoint to define relief of global symptoms in IBS-C. One of these was a *post hoc* analysis of the two phase III RCTs of lubiprostone, which reported efficacy according to FDA-recommended endpoints.<sup>338</sup> These trials included a total of 6641 patients, 3747 of whom were randomised to active treatment, and 2894 to placebo. The network plot is provided in Figure 3-4. When data were pooled there was borderline moderate global statistical heterogeneity ( $I^2 = 29.4\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 3-5). All treatments were significantly more effective than placebo, but linaclotide 290mcg o.d. was ranked as the most effective (P-score 0.91), in three RCTs (RR 0.81; 95% CI 0.76 to 0.86) (Figure 3-6). This means that the probability of linaclotide being the most effective when all treatments, including placebo, were compared with each other was 91%. Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages (Table 3-4).

**Figure 3-4. Network Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



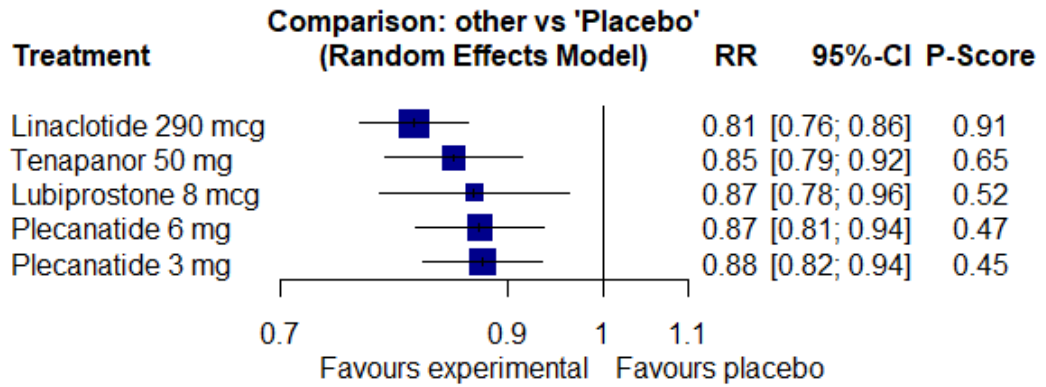
Drug	Abbreviation	Number of Trials	Number of Patients
Placebo	A	11	2,894
Lubiprostone 8mcg b.i.d.	B	2	289
Linaclotide 290mcg o.d.	C	3	1,225
Plecanatide 3mg o.d.	D	3	814
Plecanatide 6mg o.d.	E	2	728
Tenapanor 50mg b.i.d.	F	3	691

**Figure 3-5. Funnel Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 3-6. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.



**Table 3-4. League Table of Results for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**

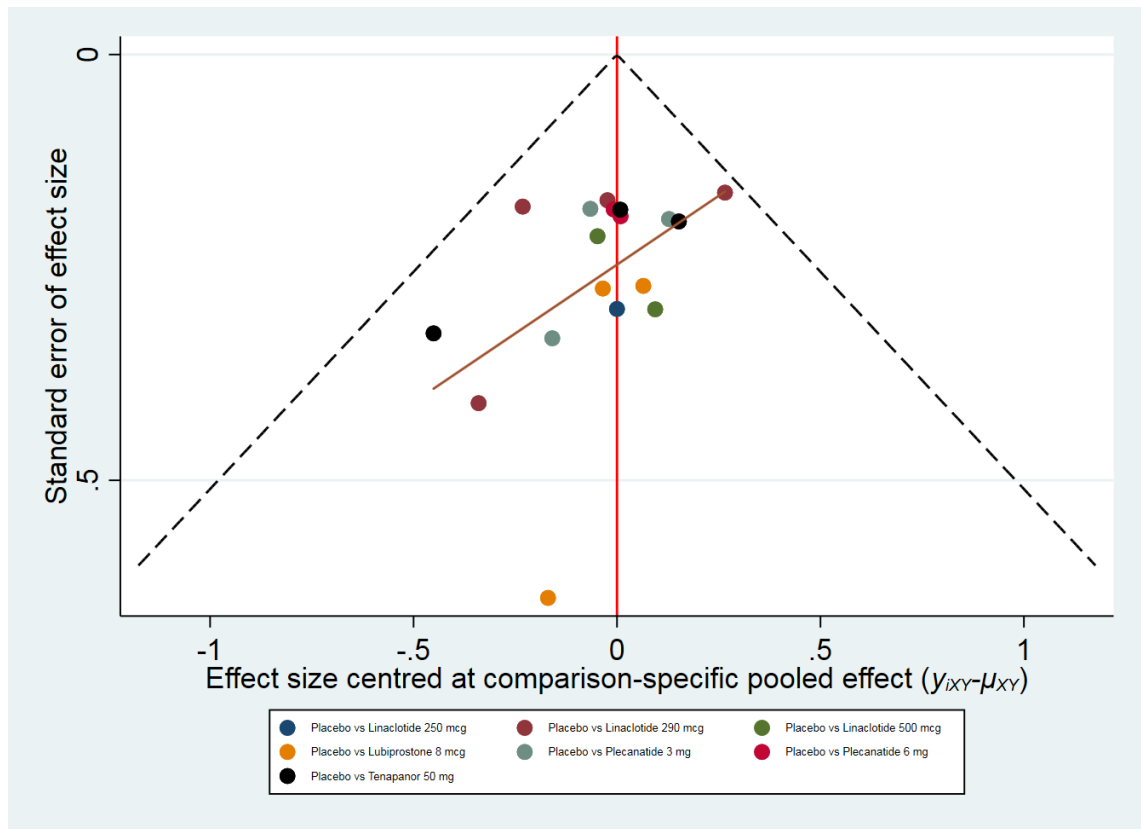
<b>Linaclotide 290mcg o.d.</b>					
0.96 (0.87; 1.06)	<b>Tenapanor 50mg b.i.d.</b>				
0.94 (0.83; 1.06)	0.98 (0.86; 1.11)	<b>Lubiprostone 8mcg b.i.d.</b>			
0.93 (0.85; 1.02)	0.97 (0.88; 1.08)	0.99 (0.88; 1.13)	<b>Plecanatide 6mg o.d.</b>		
0.93 (0.85; 1.01)	0.97 (0.88; 1.07)	0.99 (0.88; 1.12)	1.00 (0.91; 1.10)	<b>Plecanatide 3mg o.d.</b>	
0.81 (0.76; 0.86)	0.85 (0.79; 0.92)	0.87 (0.78; 0.96)	0.87 (0.81; 0.94)	0.88 (0.82; 0.94)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

### **3.3.1.2 Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial**

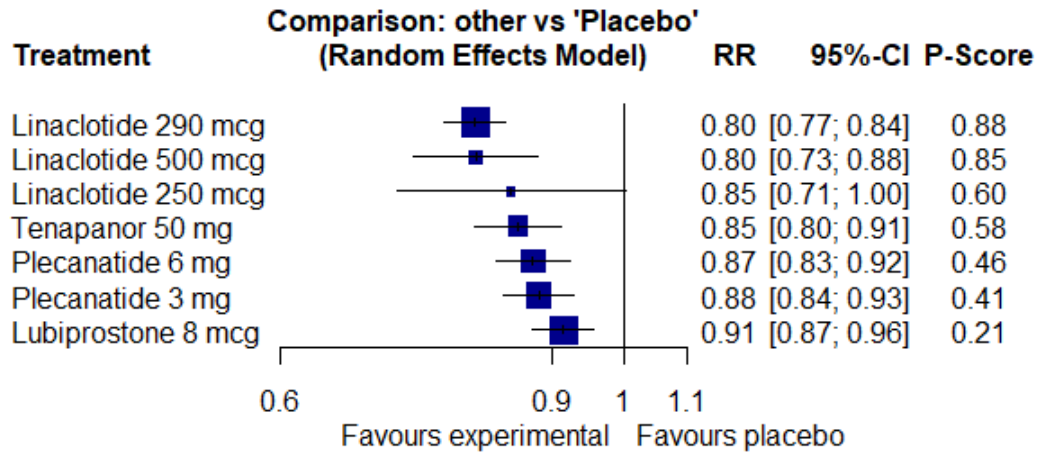
When dichotomous data were pooled for failure to achieve relief of global symptoms of IBS-C, according to the primary endpoint used in each of the 15 eligible trials,<sup>290-293, 329-337</sup> there were 4846 patients randomised to active treatment and 3616 to placebo. There was no global statistical heterogeneity ( $I^2 = 1.8\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed some asymmetry around the zero line (Figure 3-7). All treatments were significantly more effective than placebo, with the exception of linaclotide 250mcg o.d., although the latter analysis was based on only 112 patients receiving this dose in one RCT, the summary RR was similar to the other drugs, and the CIs were wide. Overall, again linaclotide 290mcg o.d. was ranked as the most effective (P-score 0.88), in four RCTs (RR 0.80; 95% CI 0.77 to 0.84) (Figure 3-8). On indirect comparison of active treatments, significant differences were seen with linaclotide 290mcg o.d. compared with plecanatide 3mg o.d., plecanatide 6mg o.d., and lubiprostone 8mcg twice-daily (b.i.d.), and between linaclotide 500mcg o.d. and lubiprostone 8mcg b.i.d. (Table 3-5).

**Figure 3-7. Funnel Plot for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 3-8. Forest Plot of the Indirect Evidence for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 3-5. League Table of Results for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.**

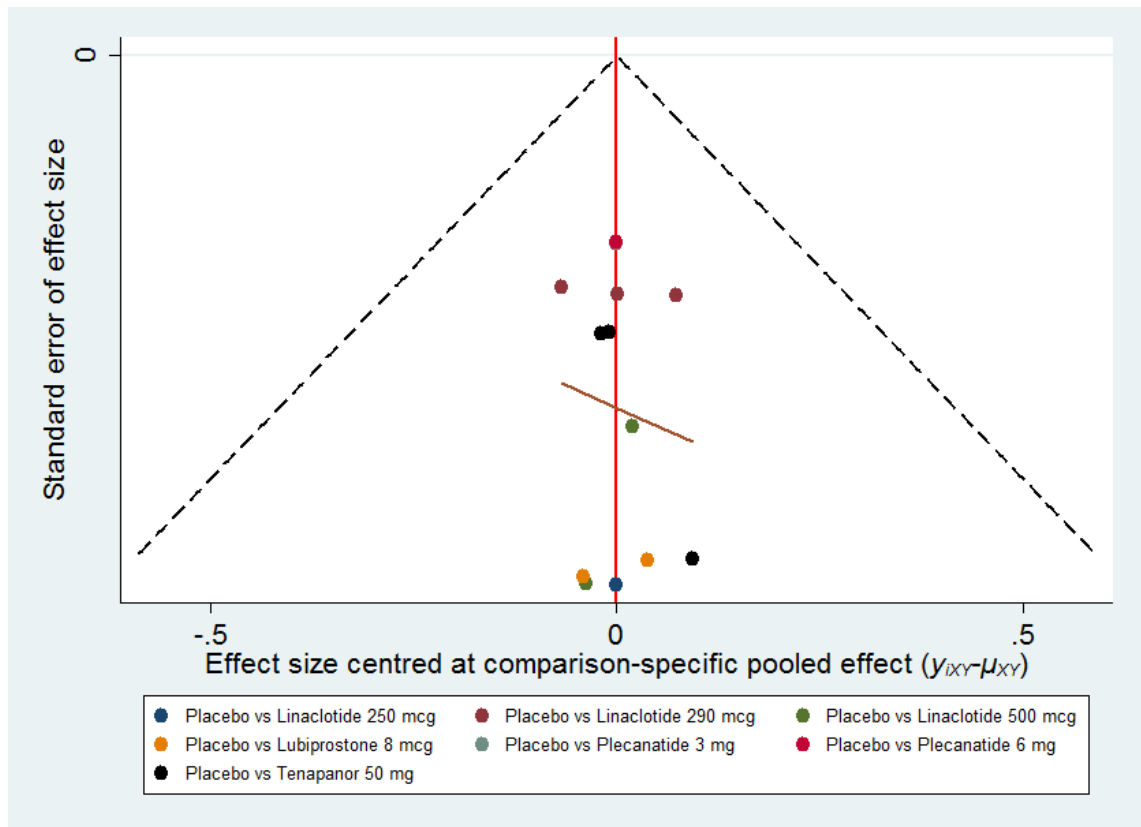
<b>Linacotide 290mcg o.d.</b>							
1.00 (0.90; 1.11)	<b>Linacotide 500mcg o.d.</b>						
0.95 (0.80; 1.13)	0.95 (0.78; 1.15)	<b>Linacotide 250mcg o.d.</b>					
0.94 (0.87; 1.02)	0.94 (0.84; 1.05)	0.99 (0.83; 1.19)	<b>Tenapanor 50mg b.i.d.</b>				
0.92 (0.86; 0.99)	0.92 (0.83; 1.02)	0.97 (0.81; 1.16)	0.98 (0.90; 1.06)	<b>Plecanatide 6mg o.d.</b>			
0.91 (0.85; 0.97)	0.91 (0.82; 1.01)	0.96 (0.80; 1.15)	0.97 (0.89; 1.05)	0.99 (0.92; 1.07)	<b>Plecanatide 3mg o.d.</b>		
0.88 (0.82; 0.94)	0.88 (0.79; 0.97)	0.93 (0.78; 1.10)	0.93 (0.86; 1.01)	0.96 (0.89; 1.03)	0.96 (0.90; 1.03)	<b>Lubiprostone 8mcg b.i.d.</b>	
0.80 (0.77; 0.84)	0.80 (0.73; 0.88)	0.85 (0.71; 1.00)	0.85 (0.80; 0.91)	0.87 (0.83; 0.92)	0.88 (0.84; 0.93)	0.91 (0.87; 0.96)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

### 3.3.1.3 Failure to Achieve an Abdominal Pain Response

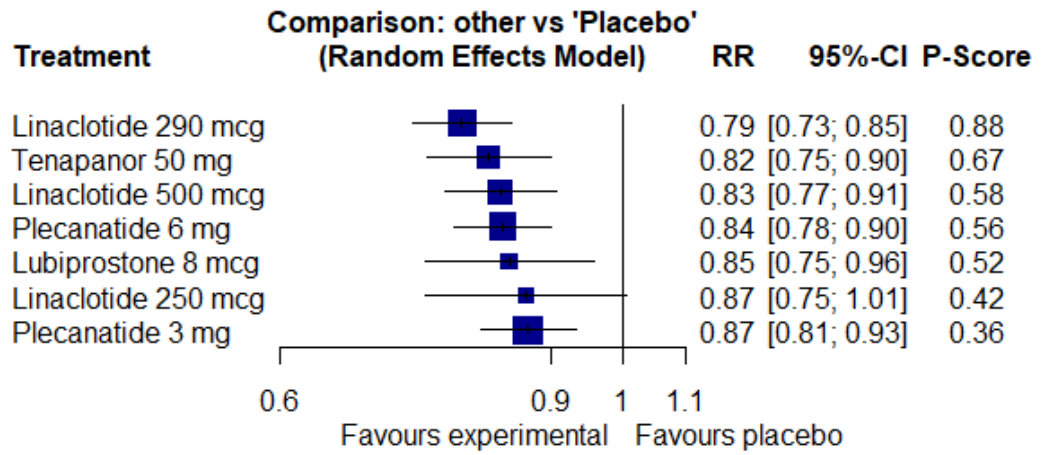
There were 12 trials recruiting 7302 patients, reported in 10 separate articles,<sup>291-293, 331-333, 335-338</sup> that reported dichotomous data for failure to achieve an abdominal pain response. Again, one of these papers reported a *post hoc* analysis of the two phase III RCTs of lubiprostone.<sup>338</sup> There were 4129 patients assigned to active therapy, and 3173 allocated to placebo. When data were pooled there was no global statistical heterogeneity ( $I^2 = 0\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 3-9). All treatments were significantly more effective than placebo, with the exception of linaclotide 250mcg o.d. Again, linaclotide 290mcg o.d. was ranked as the most effective treatment (P-score 0.88), in three RCTs (RR 0.79; 95% CI 0.73 to 0.85) (Figure 3-10). Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Table 3-6).

**Figure 3-9. Funnel Plot for Failure to Achieve an Abdominal Pain Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 3-10. Forest Plot of the Indirect Evidence for Failure to Achieve an Abdominal Pain Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.



**Table 3-6. League Table of Results for Failure to Achieve an Abdominal Pain Response.**

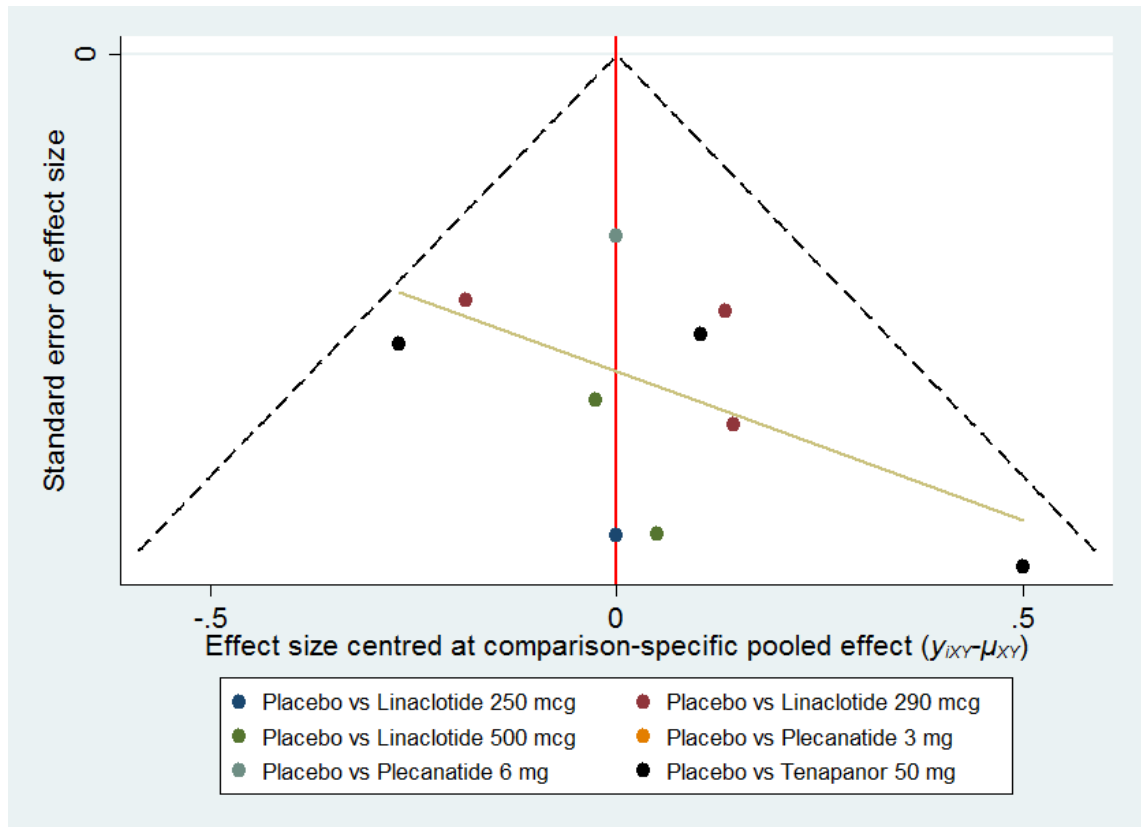
<b>Linacotide 290mcg o.d.</b>							
0.96 (0.85; 1.08)	<b>Tenapanor 50mg b.i.d.</b>						
0.94 (0.85; 1.06)	0.98 (0.87; 1.11)	<b>Linacotide 500mcg o.d.</b>					
0.94 (0.85; 1.04)	0.98 (0.87; 1.10)	1.00 (0.89; 1.11)	<b>Plecanatide 6mg o.d.</b>				
0.93 (0.81; 1.08)	0.97 (0.83; 1.13)	0.99 (0.85; 1.15)	0.99 (0.86; 1.14)	<b>Lubiprostone 8mcg b.i.d.</b>			
0.91 (0.77; 1.07)	0.95 (0.79; 1.13)	0.96 (0.81; 1.14)	0.97 (0.82; 1.14)	0.98 (0.80; 1.18)	<b>Linacotide 250mcg o.d.</b>		
0.91 (0.82; 1.00)	0.94 (0.84; 1.06)	0.96 (0.86; 1.07)	0.96 (0.87; 1.07)	0.97 (0.84; 1.12)	1.00 (0.85; 1.18)	<b>Plecanatide 3mg o.d.</b>	
0.79 (0.73; 0.85)	0.82 (0.75; 0.90)	0.83 (0.77; 0.91)	0.84 (0.78; 0.90)	0.85 (0.75; 0.96)	0.87 (0.75; 1.01)	0.87 (0.81; 0.93)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

### 3.3.1.4 Failure to Achieve a CSBM Response

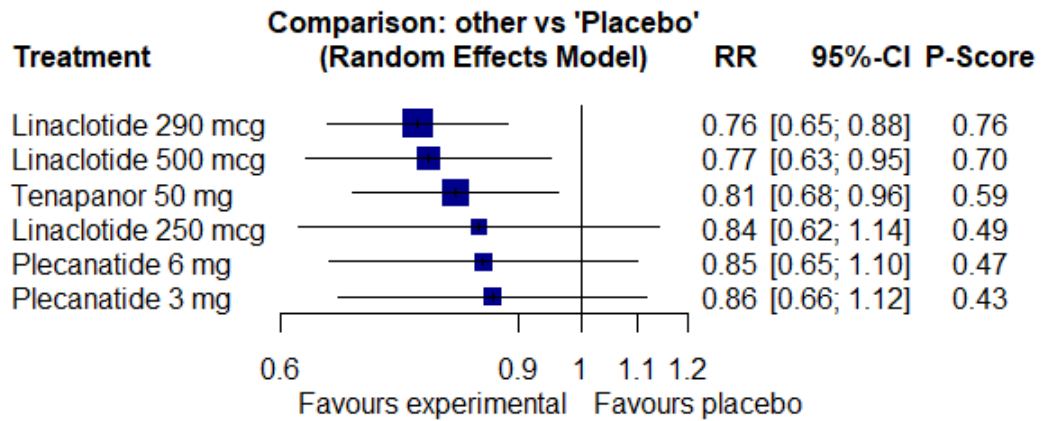
Failure to achieve a CSBM response was reported by 10 RCTs, which included 6850 patients, and were published as nine separate articles.<sup>291-293, 331-333, 335-337</sup> In total, 3840 patients were randomised to active therapy, and 3010 to placebo, and there was a high level of global statistical heterogeneity when data were pooled ( $I^2 = 82.0\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 3-11). Only linaclotide 290mcg o.d., linaclotide 500mcg o.d., and tenapanor 50mg b.i.d. were significantly more effective than placebo, with linaclotide 290mcg o.d. ranked first (P-score 0.76), in three RCTs (RR 0.76; 95% CI 0.65 to 0.88) (Figure 3-12). Again, indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Table 3-7).

**Figure 3-11. Funnel Plot for Failure to Achieve a CSBM Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 3-12. Forest Plot of the Indirect Evidence for Failure to Achieve a CSBM Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 3-7. League Table of Results for Failure to Achieve a CSBM Response.**

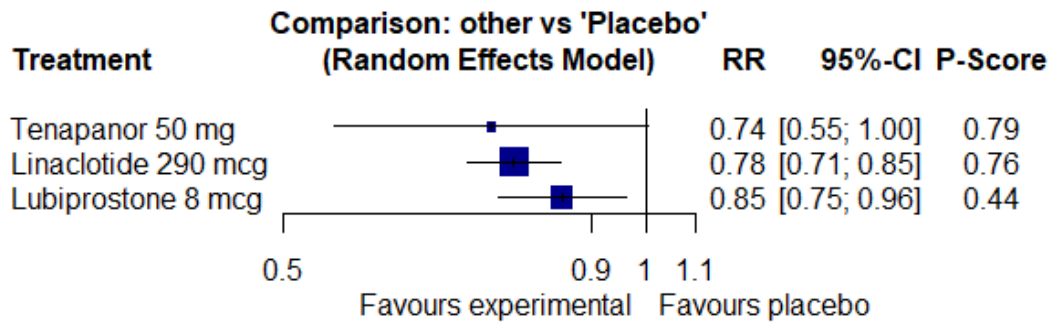
<b>Linacotide 290mcg o.d.</b>						
0.98 (0.76; 1.27)	<b>Linacotide 500mcg o.d.</b>					
0.94 (0.74; 1.18)	0.96 (0.73; 1.25)	<b>Tenapanor 50mg b.i.d.</b>				
0.90 (0.64; 1.27)	0.92 (0.63; 1.33)	0.96 (0.68; 1.37)	<b>Linacotide 250mcg o.d.</b>			
0.90 (0.66; 1.21)	0.91 (0.65; 1.27)	0.95 (0.70; 1.31)	0.99 (0.66; 1.49)	<b>Plecanatide 6mg o.d.</b>		
0.88 (0.65; 1.19)	0.90 (0.64; 1.25)	0.94 (0.69; 1.28)	0.98 (0.65; 1.46)	0.98 (0.68; 1.42)	<b>Plecanatide 3mg o.d.</b>	
0.76 (0.65; 0.88)	0.77 (0.63; 0.95)	0.81 (0.68; 0.96)	0.84 (0.62; 1.14)	0.85 (0.65; 1.10)	0.86 (0.66; 1.12)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

### 3.3.1.5 Failure to Achieve a Bloating Response

Only five RCTs reported dichotomous data for failure to achieve a bloating response, and these were reported in four separate articles,<sup>291, 292, 335, 338</sup> and included 2257 patients. Again, one of these papers reported a *post hoc* analysis of both of the two phase III RCTs of lubiprostone.<sup>338</sup> There were 1200 patients assigned to active therapy, and 1057 to placebo. When data were pooled there was low global statistical heterogeneity ( $I^2 = 25.5\%$ ). There were too few studies to assess for publication bias, or other small study effects. Tenapanor 50mg b.i.d., linaclotide 290mcg o.d., and lubiprostone 8mcg b.i.d. were all more effective than placebo, with tenapanor ranked as the most effective treatment (P-score 0.79), in one RCT (RR 0.74; 95% CI 0.55 to 1.00) (Figure 3-13). However, the 95% CIs were wide and touched 1, and the P-score and RR were very similar to that for linaclotide 290mcg o.d. in two trials (P-score 0.76, RR = 0.78; 95% CI 0.71 to 0.85). Given this was a secondary endpoint, with few trials reporting data, it is likely the network was underpowered to detect any differences. Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Table 3-8).

**Figure 3-13. Forest Plot of the Indirect Evidence for Failure to Achieve a Bloating Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 3-8. League Table of Results for Failure to Achieve a Bloating Response.**

<b>Tenapanor 50mg b.i.d.</b>			
0.96 (0.70; 1.31)	<b>Linaclotide 290mcg o.d.</b>		
0.87 (0.63; 1.21)	0.91 (0.78; 1.06)	<b>Lubiprostone 8mcg b.i.d.</b>	
0.74 (0.55; 1.00)	0.78 (0.71; 0.85)	0.85 (0.75; 0.96)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

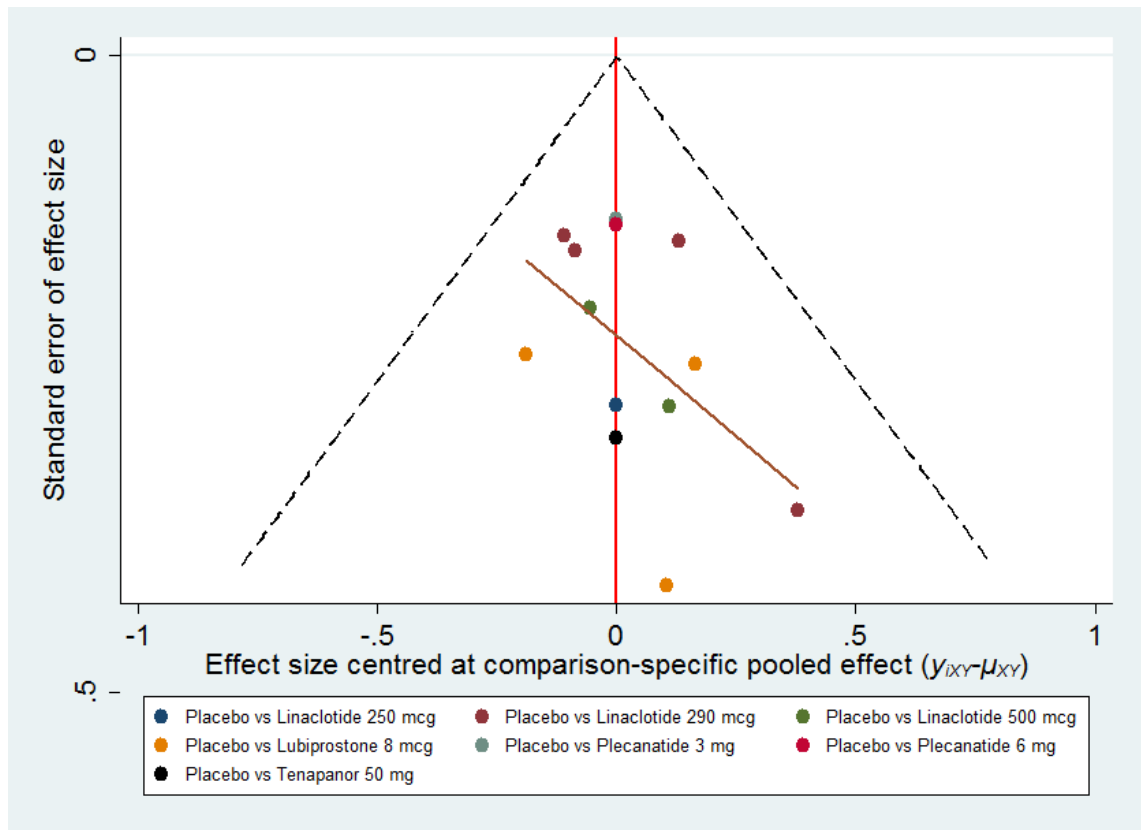


### 3.3.2 Safety

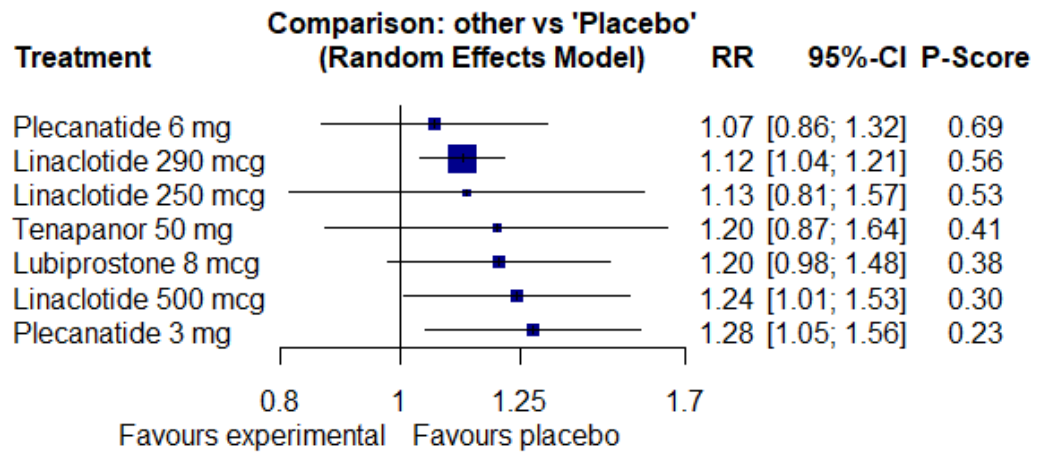
#### 3.3.2.1 Overall Adverse Events

Twelve trials, recruiting 7088 patients and reported in 10 articles, provided overall adverse events.<sup>290-293, 329-333, 335</sup> There was no global statistical heterogeneity ( $I^2 = 0\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 3-14). When comparing pooled overall adverse events, linaclotide 290mcg o.d. (four RCTs, RR = 1.12; 95% CI 1.04 to 1.21), linaclotide 500mcg o.d. (two RCTs, RR = 1.24; 95% CI 1.01 to 1.53), and plecanatide 3mg o.d. (two RCTs, RR = 1.28; 95% CI 1.05 to 1.56) were associated with a significant increase in overall adverse events, compared with placebo (Figure 3-15). When ranked using a P-score, plecanatide 6mg o.d. was the best, and plecanatide 3mg o.d. the worst, in terms of overall adverse events (P-scores 0.69 and 0.23 respectively). As rates of individual adverse events were not reported separately in the plecanatide trials, other than the number of patients experiencing diarrhoea, which were almost identical with both doses of plecanatide, reasons for the higher rate of overall adverse events with the 3mg o.d. dose are uncertain. There may have been greater heterogeneity between trials of plecanatide 3mg o.d.; however, importantly, on indirect comparison there were no significant differences between plecanatide 3mg o.d. and plecanatide 6mg o.d., or any of the other active treatments or dosages, in terms of overall adverse events (Table 3-9).

**Figure 3-14. Funnel Plot for Overall Adverse Events.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 3-15. Forest Plot of the Indirect Evidence for Overall Adverse Events.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 3-9. League Table of Results for Overall Adverse Events.**

<b>Placebo</b>							
1.07 (0.86; 1.32)	<b>Plecanatide 6mg o.d.</b>						
1.12 (1.04; 1.21)	1.05 (0.84; 1.32)	<b>Linaclotide 290mcg o.d.</b>					
1.13 (0.81; 1.57)	1.06 (0.72; 1.57)	1.01 (0.72; 1.41)	<b>Linaclotide 250mcg o.d.</b>				
1.20 (0.87; 1.64)	1.12 (0.77; 1.64)	1.07 (0.77; 1.48)	1.06 (0.67; 1.67)	<b>Tenapanor 50mg b.i.d.</b>			
1.20 (0.98; 1.48)	1.13 (0.84; 1.51)	1.07 (0.86; 1.33)	1.06 (0.72; 1.57)	1.00 (0.69; 1.46)	<b>Lubiprostone 8mcg b.i.d.</b>		
1.24 (1.01; 1.53)	1.17 (0.87; 1.57)	1.11 (0.89; 1.38)	1.10 (0.74; 1.62)	1.04 (0.71; 1.52)	1.03 (0.77; 1.39)	<b>Linaclotide 500mcg o.d.</b>	
1.28 (1.05; 1.56)	1.20 (0.90; 1.61)	1.14 (0.92; 1.41)	1.13 (0.77; 1.66)	1.07 (0.74; 1.56)	1.07 (0.80; 1.42)	1.03 (0.77; 1.38)	<b>Plecanatide 3mg o.d.</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

### 3.3.2.2 Adverse Events Leading to Dropout

Adverse events leading to dropout were provided by 12 trials, reported in 10 papers.<sup>290-293, 329-333, 335</sup> Linaclotide 290mcg o.d. (four RCTs, RR = 2.72; 95% CI 1.62 to 4.57), plecanatide 6mg o.d. (two RCTs, RR = 5.37; 95% CI 1.42 to 20.4), and plecanatide 3mg o.d. (two RCTs, RR = 6.04; 95% CI 1.61 to 22.7) were all associated with significantly higher trial dropout rates due to adverse events, compared with placebo. When ranked using a P-score, lubiprostone 8mcg b.i.d. was the least likely to cause adverse events leading to dropout, and plecanatide 3mg o.d. the most likely (P-scores 0.81 and 0.11 respectively). On indirect comparison of active treatments, significant differences were seen with lubiprostone 8mcg b.i.d. compared with linaclotide 290mcg o.d., plecanatide 6mg o.d., and plecanatide 3mg o.d., as well as between linaclotide 250mcg o.d. and plecanatide 3mg o.d.

### 3.3.2.3 Individual Adverse Events

In terms of individual adverse events, rates of diarrhoea were provided by 14 of the eligible trials, reported in 12 articles.<sup>290-293, 329-333, 335-337</sup> All drugs, with the exception of lubiprostone 8mcg b.i.d., were associated with an increased risk of diarrhoea and, when ranked using a P-score, lubiprostone 8mcg b.i.d. was the least likely to cause diarrhoea, and linaclotide 500mcg o.d. the most likely (P-scores 0.87 and 0.20 respectively). Indirect comparison of active treatments revealed that both placebo and lubiprostone 8mcg b.i.d. were significantly less likely to cause diarrhoea than all other individual drugs, and dosages, but there were no other differences between the remaining individual drugs and dosages. There were no significant differences between any of the active therapies and placebo, in terms of incidence of abdominal pain, abdominal distension, or headache. Six RCTs, reported in five articles,<sup>290, 329, 330, 335, 336</sup> provided information concerning nausea. Only lubiprostone 8mcg b.i.d. was associated

with a significantly increased incidence of nausea, and this was the worst ranked treatment in this analysis (P-score 0.18).

### 3.4 Discussion

This systematic review and network meta-analysis has demonstrated that all secretagogues tested in IBS-C were more effective than placebo for global symptoms. Although all drugs performed similarly, linaclotide 290mcg o.d. was ranked first in terms of efficacy for global symptoms. This was irrespective of the outcome measure used, whether it be the FDA-recommended endpoint to define relief of global symptoms in IBS-C, or the primary endpoint used to define global symptom improvement in each trial. For the latter endpoint the probability of linaclotide being superior to another competing treatment, or placebo, was 88% but this does not exceed 90% to 95%, which may be desirable according to the literature.<sup>328</sup> However, for the former endpoint the probability was 91%. Linaclotide 290mcg o.d. was also ranked first in terms of the effect on both abdominal pain response and CSBM response. Tenapanor 50mg b.i.d. was ranked first in terms of effect on bloating response, although confidence intervals were wide and the P-score was very similar to that for linaclotide 290mcg o.d. In the analysis that used the primary endpoint to define global symptom improvement in each trial, linaclotide 290mcg o.d. was superior to plecanatide 3mg and 6mg o.d., as well as lubiprostone 8mcg b.i.d. In terms of safety, plecanatide 6mg o.d. was the drug least likely to cause adverse events, and lubiprostone 8mcg b.i.d. was significantly less likely than all other individual drugs and dosages to cause diarrhoea, but was more likely to cause nausea.

A contemporaneous and exhaustive literature search was performed, which included searching the “grey” literature and clinicaltrials.gov, allowing analysis of data from 15 RCTs of pharmacological therapies for IBS-C, recruiting 8462 patients. The literature search, eligibility assessment, and data extraction were all undertaken

independently by two reviewers. An intention-to-treat analysis was used, wherever trial reporting allowed, and pooled data with a random effects model, to provide a more conservative estimate of the efficacy and safety of individual drugs. Finally, one Japanese article was translated,<sup>333</sup> attempts were made to contact authors of individual studies, and [clinicaltrials.gov](http://clinicaltrials.gov) was accessed in order to obtain extra information, where required.

Limitations include the fact that none of the trials were head-to-head studies of one drug versus another, which means that these analyses were based on indirect comparisons, and are not protected by randomisation. This could lead to confounding due to underlying differences between individual RCTs.<sup>339</sup> However, as the design of the included trials was very similar, and the endpoints used and duration of follow-up identical, this issue should have been minimised. In addition, three of the RCTs were at unclear risk of bias,<sup>334, 336, 337</sup> and original authors did not respond to all queries concerning individual studies. This may mean the efficacy of some pharmacological therapies in IBS-C has been overestimated.<sup>340</sup> Data was extracted from all RCTs based on a comparatively short treatment duration of 12 weeks, and therefore the relative efficacy and safety of these drugs in the longer term are unknown. This is a potentially important clinical point, as patients often complain that they become tolerant to the effects of non-prescription laxatives over time, but this would not be uncovered by a trial lasting only 12 weeks. The vast majority of trials were conducted in North America, meaning that involved individuals may not be generalisable to patients with IBS-C in other countries. There were moderate levels of global statistical heterogeneity in the analysis using the FDA-recommended endpoint to define treatment response, and high levels of heterogeneity in the analysis for CSBM response. The comparison adjusted funnel plot for the analysis based on the primary endpoint to define global symptom improvement in each trial showed some asymmetry, suggestive of publication

bias or other small study effects, although three of the trials that were identified had not been published as either full papers or conference abstracts,<sup>333, 336, 337</sup> and were only identified during a search of clinicaltrials.gov. Finally, there were limited safety data for tenapanor.

All of the secretagogues examined in this network meta-analysis have proved their efficacy in placebo-controlled trials in IBS-C. However, when considering the results of this study, it is important to point out some of the limitations of the original trials themselves. Firstly, as has already been alluded to, complete safety data for the two phase III RCTs of tenapanor were not available at the time this network meta-analysis was conducted.<sup>336, 337</sup> Secondly, all three trials of lubiprostone, and the earlier trials of linaclotide, used the less stringent Rome II criteria for IBS. Thirdly, definitions of each of the adverse events were not standardised between individual trials, as these were not the primary endpoints of interest. This has led to some debate about the relative safety of some of the drugs, in terms of their likelihood of causing diarrhoea. A recent meta-analysis reported that, based on meta-regression, there were no differences in the rates of diarrhoea between linaclotide and plecanatide in treatment trials in IBS-C and CIC,<sup>341</sup> an observation supported by the findings of this network meta-analysis. However, it is important to point out that there were subtle differences in the way that diarrhoea was recorded in these RCTs,<sup>342</sup> which mean that the data may not be comparable, even in a network meta-analysis. Fourthly, for the FDA-recommended endpoint to define treatment response in IBS-C, as well as abdominal pain and bloating response, the analyses for lubiprostone were based on a *post hoc* analysis of the two phase III trials. As a result, data from almost two-thirds of the recruited patients were unavailable, as they would not have met the updated FDA-recommended CSBM and abdominal pain thresholds for inclusion in an IBS-C treatment trial. This may have led to an overestimation of the efficacy of lubiprostone in these analyses, although



excluding these RCTs from the analyses would not have led to any change in the relative efficacy of the other three drugs. Finally, given that by the time the trials of plecanatide and tenapanor were conducted both linaclotide and lubiprostone were FDA-approved for the treatment of IBS-C, it may be that patients in these more recent RCTs had already failed treatment with one, or both, of these drugs. This would imply that a more treatment-resistant group of patients were being studied in the trials of plecanatide and tenapanor but, as the RCTs did not report the proportion of patients who had previously received treatment with either linaclotide or lubiprostone, this is speculation. Although this may partly explain why linaclotide 290mcg o.d. was ranked first in almost all efficacy analyses in the network meta-analysis, lubiprostone was FDA-approved for the treatment of IBS-C in 2008, whereas linaclotide was approved in 2012, so participants in the linaclotide trials may have failed therapy with lubiprostone prior to study entry.

The cost of all of these drugs relative to other treatments for IBS-C is also a consideration, but there have been no RCTs conducted against a less expensive, but potentially effective, comparator such as ispaghula or PEG. A recent cost-effectiveness analysis for the use of linaclotide in Scotland reported an incremental cost-effectiveness ratio of £7370 per quality-adjusted life year (QALY), versus an antidepressant, in patients with IBS-C who had already failed an antispasmodic and/or a laxative.<sup>343</sup> The authors reported that the likelihood that linaclotide was cost-effective at a willingness to pay of £20,000 per QALY was 73%. The choice of amitriptyline as the comparator in this analysis seems odd, given that although tricyclic antidepressants have the most evidence for their efficacy in IBS,<sup>286</sup> one of their side effects is constipation. Cost-effectiveness data for the other three drugs studied in this meta-analysis are lacking.

Performing a network meta-analysis of secretagogues for IBS-C could be criticised due to the absence of trials making direct comparisons. As a result, all of the

conclusions in this study were derived from data based on indirect treatment comparisons. However, it is unlikely that pharmaceutical companies would ever conduct head-to-head RCTs of these agents, and even if such a study were to be conducted, it is likely that it would be designed as a non-inferiority trial.<sup>344</sup> A network meta-analysis circumvents this problem, allowing a credible ranking system of the likely efficacy and tolerability of all of the secretagogues tested in IBS-C to be developed, even in the absence of trials making direct comparisons. The results of this study are therefore still likely to be important for both patients and policy makers, in order to help inform treatment decisions for patients with IBS-C.

Nevertheless, it is interesting to note that the performance of all of the drugs examined in this network meta-analysis was modest overall. This is despite all of these drugs having very precise modes of action, aimed specifically at targeting symptoms in IBS-C, which suggests that factors other than gastrointestinal symptoms may have a role in mediating treatment response. All studies were rigorous in recruiting homogeneous populations of patients with IBS-C using the Rome criteria, and they conducted a detailed assessment of baseline characteristics, in terms of gastrointestinal symptoms and demographic data. However, as discussed, IBS is a complex disorder of gut-brain interaction, and psychological comorbidity and altered CNS processing have been shown to be key drivers of symptom development in some patients.<sup>51, 52</sup> Similarly, poor psychological health, in terms of anxiety and somatisation, and the reporting of extra-intestinal symptoms, has been associated with increased symptom severity in IBS.<sup>112-114, 117</sup> Consequently, an individual's psychological health may play a role in governing how well they will respond to a peripherally acting drug, such as a secretagogue. Other pathophysiological mechanisms, such as altered visceral sensitivity or changes in the gut microbiome, may also be relevant. Unfortunately, no trial in the network conducted any form of psychological evaluation at baseline, thereby precluding

an assessment of whether, and to what extent, symptom-response is influenced by factors such as mood or extra-intestinal symptom reporting. Understanding this has implications for how treatment is directed in IBS, and, if shown to be important, could encourage a more integrated clinical assessment of people with IBS, such as recommended by the Rome Foundation MDCP,<sup>57</sup> and facilitate a more personalised approach to management overall.

In summary, although all drugs performed similarly and were superior to placebo in most analyses, this network meta-analysis ranked linaclotide 290mcg o.d. first in terms of efficacy profile overall, and across several different endpoints. No difference was observed between individual treatments when the FDA-recommended endpoint was used to define relief of global symptoms in IBS-C, although linaclotide 290mcg o.d. was still ranked first. However, when treatments were ranked according to the primary endpoint used to define treatment response in each trial, linaclotide 290mcg o.d. appeared superior to plecanatide 3mg and 6mg o.d., as well as lubiprostone 8mcg b.i.d. In terms of safety, plecanatide 6mg o.d. was the drug least likely to cause adverse events, and lubiprostone 8mcg b.i.d. was significantly less likely than any of the other drugs to cause diarrhoea. In the absence of head-to-head trials, this information should help clinicians to make decisions as to which drug to use, based on efficacy, safety, and most troublesome symptom, when first-line therapies for IBS-C fail. However, the modest performance of these drugs, despite their precise modes of action, raises questions about whether factors other than gastrointestinal symptoms at baseline, such as psychological health, might be important in determining treatment response in any individual patient. Understanding the relative efficacy of drugs and the merits of directing therapy according to predominant stool pattern are issues that are not only relevant to IBS-C, but are equally applicable to treatments for IBS-D and IBS-M. This will be the focus of the study reported in the next chapter.

**CHAPTER 4**

**Assessing the Relative Efficacy of Pharmacological Therapies in  
Patients with Irritable Bowel Syndrome with Diarrhoea or Mixed Stool  
Pattern**

## 4.1 Introduction

As discussed, IBS has a substantial impact on quality of life for patients with active symptoms,<sup>83</sup> which is more pronounced for patients with IBS-D or IBS-M,<sup>85</sup> who account for over 50% of people with IBS.<sup>61</sup> These patients often report a fear of incontinence due to loose stools and urgency,<sup>279</sup> and can therefore find working and socialising extremely challenging.<sup>86</sup> Although up to one-third of these patients use loperamide,<sup>282</sup> a  $\mu$ -opioid agonist, as an antidiarrhoeal agent, there is little evidence for its efficacy in IBS,<sup>278</sup> and many patients report inadequate relief of symptoms, other than diarrhoea, with the drug.<sup>282</sup> In addition, although other well-established treatments for IBS, such as antispasmodics or tricyclic antidepressants, may improve abdominal pain,<sup>277, 286</sup> many are not licensed for treatment of IBS.

Consequently, over the last 20 years, a number of other pharmacological therapies have been licensed for the treatment of IBS-D and IBS-M. Although they have different mechanisms of action, in clinical practice all these drugs tend to be utilised when first-line treatments have failed. Alosetron and ramosetron are both antagonists of the 5-HT<sub>3</sub> receptor, an action that may serve to slow gastrointestinal transit, alter rectal compliance,<sup>345, 346</sup> and reduce visceral sensitivity.<sup>347</sup> Rifaximin is a minimally absorbed broad-spectrum antibiotic that has been tested in IBS-D and IBS-M, on the basis that alterations in gastrointestinal microbiota may, in part, be responsible for symptoms.<sup>348</sup> Finally, eluxadoline is a peripherally acting mixed  $\mu$ - and  $\kappa$ -opioid receptor agonist, and  $\delta$ -opioid receptor antagonist, with minimal oral bioavailability, which reduces visceral hypersensitivity and slows gastrointestinal transit.<sup>349</sup>

High-quality placebo-controlled RCTs have confirmed that all of these licensed drugs are effective treatments for IBS-D and/or IBS-M,<sup>278, 298, 300, 350-352</sup> but, as is the case for secretagogues for the treatment of IBS-C, there have been no head-to-head trials conducted to evaluate relative efficacy. As it is unlikely that any such trials will be

performed, the aim of this study was to conduct a network meta-analysis to allow comparisons to be made between all of these drugs, as well as to enable ranking of treatments, in order to inform clinical decisions.

The validity of such network meta-analyses can be undermined if there are differences in the design and endpoints used in individual RCTs. However, in this case, the efficacy of all these drugs has been assessed according to endpoints recommended currently for pharmacological therapies in IBS by the FDA. In addition, as many trials reported the efficacy of each of these drugs, in terms of their effect on individual symptoms, such as abdominal pain or stool consistency, relative efficacy for each drug according to each of these endpoints can also be assessed. This study, therefore, complements the work conducted in Chapter 3 analysing treatment trials of secretagogues in IBS-C. It also offers a further opportunity to appraise the merits of directing treatment according to predominant stool form in isolation, in this case IBS-D or IBS-M, using drugs specifically intended for this purpose, among patients who were subgrouped in this way using the Rome criteria.

## **4.2 Methods**

### **4.2.1 Search Strategy and Study Selection**

MEDLINE (1947 to November 2018), EMBASE, EMBASE Classic (1947 to November 2018), and the Cochrane central register of controlled trials were searched to identify potential studies. In addition, clinicaltrials.gov was searched for unpublished trials, or supplementary data for potentially eligible studies. In order to identify studies published only in abstract form, conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2018 were hand-searched. Finally, a recursive search was performed, using the bibliographies of all obtained articles.

Eligible RCTs examined the effect of licensed pharmacological therapies (alosetron, eluxadoline, ramosetron, or rifaximin) in adult patients (>18 years) with IBS-D or IBS-M (Table 4-1). The first period of cross-over RCTs were eligible for inclusion if they provided efficacy data prior to cross-over. The definitions of IBS of interest included either a clinician's opinion, or meeting specific diagnostic criteria, for example the Rome criteria. Only RCTs that examined the efficacy of standard doses of the drugs of interest, and which compared them with each other, or with placebo, were considered eligible.

**Table 4-1. Eligibility Criteria.**

Randomised controlled trials
Adults (participants aged >18 years)
Diagnosis of IBS-D or IBS-M based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared alosetron, eluxadoline, ramosetron, or rifaximin with each other, or with placebo.
Minimum follow-up duration of 12 weeks.
Dichotomous assessment of response to therapy at 12 weeks†.

\*Manning, Krusik score, Rome I, II, III, or IV.

†Preferably patient-reported, and according to the FDA-recommended endpoint for treatment trials in IBS, but if this was not available then as assessed by a physician or questionnaire data.



A minimum follow-up duration of 12 weeks was required, in line with FDA recommendations for the design of treatment trials for functional gastrointestinal disorders. All endpoints were extracted at 12 weeks, even for RCTs providing efficacy data at other time points. This was done to ensure as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, as the placebo effect tends to wane with time.<sup>318</sup> Studies had to report a dichotomous assessment of response to therapy. First and senior authors of studies were contacted to provide additional information on individual trials, where required.

Two investigators conducted the literature search, independently from each other. Studies on IBS were identified with the terms: *irritable bowel syndrome* and *functional disease(s)*, *colon* (both as MeSH and free text terms), and *IBS*, *spastic colon*, *irritable colon*, or *functional adj5 bowel* (as free text terms). These were then combined using the set operator AND with studies identified with the following terms: *alosetron*, *Lotronex*, *eluxadoline*, *Viberzi*, *Truberzi*, *ramosetron*, *Irribow*, *rifaximin*, and *Xifaxan* (all as free text terms).

There were no language restrictions. Two investigators evaluated all abstracts identified by the search for eligibility, again independently from each other. All potentially relevant papers were obtained and evaluated in more detail, using pre-designed forms, in order to assess eligibility independently, according to the pre-defined criteria. Foreign language papers were translated, where required. Disagreements between investigators were resolved by discussion.

### **4.2.2 Outcome Assessment**

The efficacy of all drugs, compared with each other or with placebo, in IBS-D and IBS-M was assessed in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. Secondary outcomes included adverse events occurring as a result of therapy (overall numbers of adverse events, as well as adverse events leading to study withdrawal, and individual adverse events, including constipation, headache, abdominal pain, or nausea).

### **4.2.3 Data Extraction**

Two investigators extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). The included eligible RCTs often used different primary endpoints. However, some of the trials adhered to FDA-recommended endpoints, and either reported treatment efficacy according to a composite of improvement in both abdominal pain and stool consistency, or it was possible to obtain these data from the original investigators. Three of the RCTs of alosetron also applied these criteria retrospectively to a subset of patients in the phase III studies. In addition, because individual trials reported efficacy according to several other secondary endpoints, it was possible to assess the efficacy of therapies according to other dichotomous endpoints to define response to treatment. These included: a) relief of global IBS symptoms (global IBS symptom responder); b) relief of abdominal pain (abdominal pain responder); and c) improvement in stool consistency (stool consistency responder).

For all included studies, the following data were also extracted for each trial, where available: country of origin, number of centres, criteria used to define IBS, stool subgroup of IBS, proportion of female patients, and dose and duration of therapy. Data were extracted as intention-to-treat analyses, with dropouts assumed to be treatment

failures (i.e. no response to therapy), using the total number of patients randomised to each treatment arm as the denominator, wherever trial reporting allowed. If this was not clear from the original article, an analysis was performed on all patients with reported evaluable data.

#### **4.2.4 Quality Assessment and Risk of Bias**

This was performed at the study level, by two investigators independently, using the Cochrane risk of bias tool.<sup>319</sup> Disagreements were resolved by discussion. The method used to generate the randomisation schedule and conceal treatment allocation was recorded, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

#### **4.2.5 Data Synthesis and Statistical Analysis**

A network meta-analysis was performed using the frequentist model, with the statistical package “netmeta” (version 0.9-0, <https://cran.r-project.org/web/packages/netmeta/index.html>)<sup>320</sup> in R (version 3.4.2).<sup>321</sup> This was reported according to the PRISMA extension statement for network meta-analyses,<sup>322</sup> in order to explore indirect treatment comparisons of the efficacy and safety of each medication. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses,<sup>323,324</sup> and can also rank treatments to inform clinical decisions.<sup>317</sup> This methodology is described in detail in Chapter 3, but the salient points are reiterated briefly below.

The symmetry and geometry of the evidence was examined by producing a network plot, and comparison adjusted funnel plots were used to explore publication bias or other small study effects, for all available comparisons versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). A pooled RR with 95% CIs

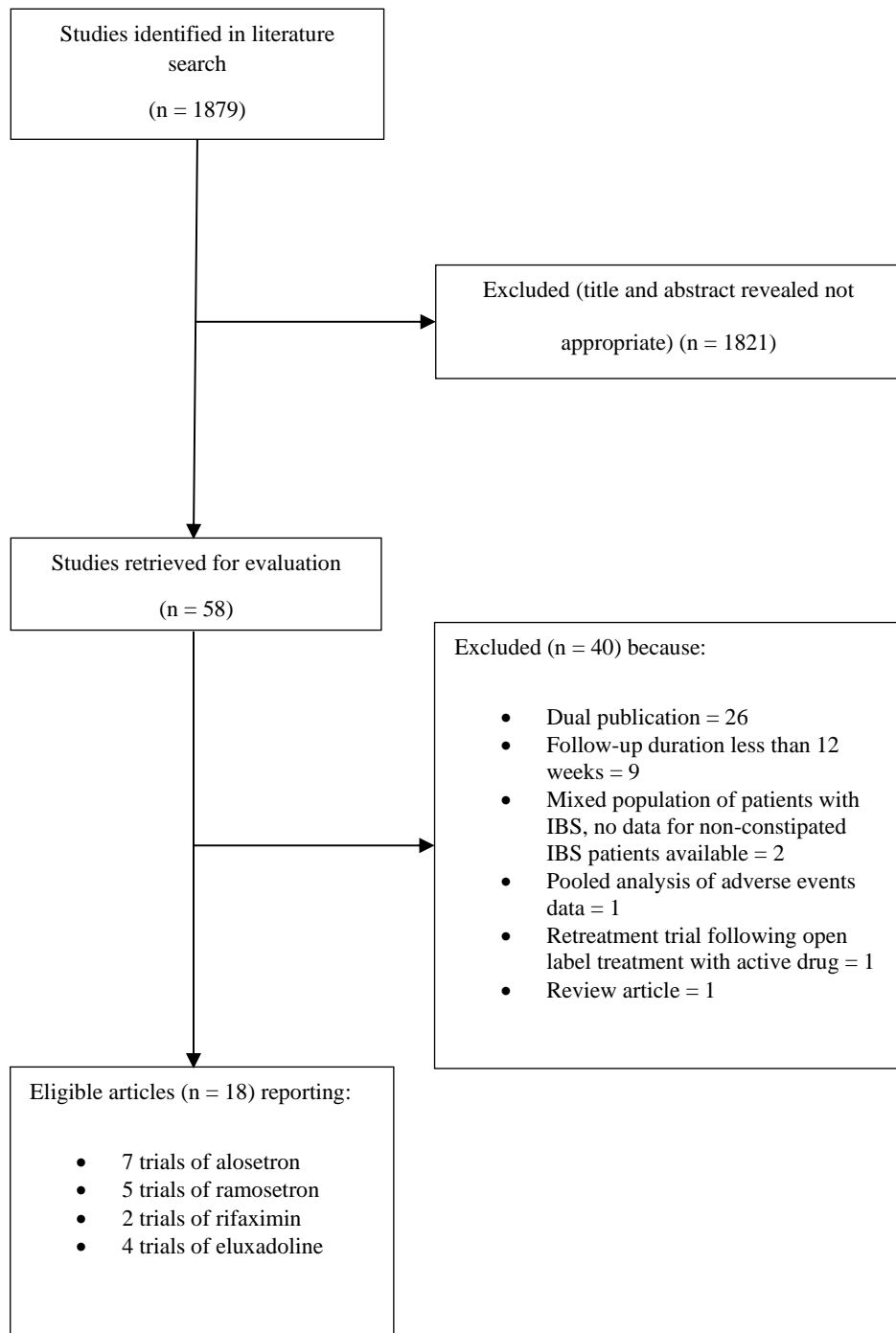
was calculated to summarise the effect of each comparison tested, using a random effects model as a conservative estimate. The RR of failure to achieve each of the endpoints of interest was calculated, where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of the drug over placebo. As there were no direct comparisons between the active treatment groups, it was not possible to perform consistency modelling to check the correlation between direct and indirect evidence.<sup>326</sup> Global statistical heterogeneity across all comparisons was assessed using the  $I^2$  measure from the “netmeta” statistical package. Treatments were ranked according to their P-score. The primary analysis pooled data for the FDA-recommended composite endpoint to define treatment response, for all included RCTs that reported these data. Analyses were also performed to assess the safety of each medication, including overall numbers of adverse events, and number of adverse events leading to study withdrawal, as well as individual adverse events.

### 4.3 Results

The search strategy generated 1849 citations, 58 of which appeared to be relevant and were retrieved for further assessment (Figure 4-1). Of these, 40 were excluded for various reasons, leaving 18 eligible articles reporting on 18 separate trials, which contained a total of 9844 patients.<sup>227, 298, 299, 350-364</sup> There were seven RCTs of alosetron (1951 patients alosetron, 1583 placebo),<sup>227, 351, 353-357</sup> five trials of ramosetron (1015 patients ramosetron, 913 placebo),<sup>352, 358-361</sup> two RCTs of rifaximin (625 patients rifaximin, 635 placebo), reported in one article,<sup>350</sup> and four RCTs of eluxadoline (1967 patients eluxadoline, 1155 placebo), reported in three articles.<sup>298, 299, 362</sup> A further two articles were also included because together they provided supplementary data,<sup>363, 364</sup> reporting efficacy according to FDA-recommended endpoints for alosetron in three phase III RCTs.<sup>227, 351, 357</sup> These two articles restricted their analyses to female patients who met criteria for severe IBS-D. In addition, the rifaximin trials did not report raw

data for many of the analyses of interest in the original article,<sup>350</sup> but these data were obtained from the pharmaceutical company.

**Figure 4-1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.**



Agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.80). Detailed characteristics of individual RCTs are provided in Table 4-2. Risk of bias for all included trials is reported in Table 4-3. Ten trials, reported in eight articles, were at low risk of bias.<sup>298, 350-352, 357, 360-362</sup> No trials made head-to-head comparisons of one drug versus another, meaning that direct evidence was only available in comparison with placebo. As a result, active medications could only be compared with each other using an indirect evidence meta-analysis.

**Table 4-2 Characteristics of Randomised Controlled Trials of Pharmacological Therapies Versus Placebo in IBS-D or IBS-M.**

Study	Country and Number of Centres	Diagnostic Criteria Used for IBS and Stool Subgroups of IBS Recruited	Primary Endpoint Used to Define Symptom Improvement Following Therapy by the Original Investigators	Number of Patients (% female)	Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy
<b>Camilleri 1999</b> 353	Multinational, 68 sites	Rome I criteria, 100% IBS-D or IBS-M	Adequate relief of pain and discomfort for $\geq 6$ of the 12 weeks of therapy	152 (44.1)	72 patients received alosetron 1mg b.i.d.* for 12 weeks
<b>Camilleri 2000</b> 351	USA, 119 sites	Rome I criteria, 70.8% IBS-D, 27.8% IBS-M	Adequate relief of IBS pain and discomfort for $\geq 2$ weeks per month for each of 3 months	647 (100)	324 patients received alosetron 1mg b.i.d. for 12 weeks
<b>Camilleri 2001</b> 227	USA, 104 sites	Rome I criteria, 71.2% IBS-D, 27.0% IBS-M	Adequate relief of IBS pain and discomfort for $\geq 2$ weeks per month for each of 3 months	626 (100)	309 patients received alosetron 1mg b.i.d. for 12 weeks
<b>Lembo 2001</b> 356	USA, 180 sites	Rome II criteria, 97.8% IBS-D, 2.2% IBS-M	Substantial or moderate improvement in global IBS symptoms over the last 4 weeks of therapy	801 (100)	532 patients received alosetron 1mg b.i.d. for 12 weeks
<b>Chey 2004</b> <sup>354</sup>	Multinational, 138 sites	Rome I criteria, 100% IBS-D†	Weekly adequate relief of IBS pain and discomfort at week 48 of treatment $\pm$	569 (100)	279 patients received alosetron 1mg b.i.d. for 48 weeks



<b>Chang 2005</b> <sup>355</sup>	USA and Canada, 186 sites	Rome I criteria, 100% IBS-D	Adequate relief of IBS pain and discomfort for weeks 5 to 12 of treatment	386 (0)	127 patients received alosetron 0.5mg b.i.d. and 131 received alosetron 1mg b.i.d. for 12 weeks
<b>Krause 2007</b> <sup>357</sup>	USA, number of sites not reported	Rome II criteria, 100% IBS-D	Moderate or substantial improvement in global IBS symptoms over the last 4 weeks of therapy	353 (100)	177 patients received alosetron 1mg b.i.d. for 12 weeks
<b>Matsueda 2008a</b> <sup>359</sup>	Japan, number of sites not reported	Rome II criteria, 100% IBS-D	Complete or considerable relief of global IBS symptoms for $\geq 2$ of the last 4 weeks of therapy	212 (27.3)	103 patients received ramosetron 5mcg o.d.§ for 12 weeks
<b>Matsueda 2008b</b> <sup>358</sup>	Japan, number of sites not reported	Rome II criteria, 100% IBS-D	Complete or considerable relief of global IBS symptoms for $\geq 2$ of the last 4 weeks of therapy	539 (17.9)	270 patients received ramosetron 5mcg o.d. for 12 weeks
<b>Fukudo 2014</b> <sup>360</sup>	Japan, 52 sites	Rome III criteria, 100% IBS-D	A weekly mean BSFS¶ score of $\geq 3$ to $\leq 5$ and a decrease of $\geq 1$ point in mean BSFS score from baseline for $\geq 2$ of the first 4 weeks of therapy $\pm$	296 (0)	147 patients received ramosetron 5mcg o.d. for 12 weeks
<b>Fukudo 2016</b> <sup>352</sup>	Japan, 70 sites	Rome III criteria, 100% IBS-D	Complete or considerable relief of global IBS symptoms for $\geq 2$ of the last 4 weeks of therapy	576 (100)	292 patients received ramosetron 2.5mcg o.d. for 12 weeks

<b>Fukudo 2017</b> 361	Japan, 61 sites	Rome III criteria, 100% IBS-D	Complete or considerable relief of global IBS symptoms for $\geq 2$ of the last 4 weeks of therapy	305 (100)	104 and 99 patients received ramosetron 2.5mcg or 5mcg o.d. respectively for 12 weeks
<b>Pimentel 2011a</b> (Target 1) <sup>350</sup>	USA and Canada, 179 sites	Rome II criteria, 100% IBS-D or IBS-M	Adequate relief of global IBS symptoms for $\geq 2$ of the first 4 weeks after therapy $\pm$	623 (73.4)	309 patients received rifaximin 550mg t.i.d.‡ for 2 weeks
<b>Pimentel 2011b</b> (Target 2) <sup>350</sup>	USA and Canada, 179 sites	Rome II criteria, 100% IBS-D or IBS-M	Adequate relief of global IBS symptoms for $\geq 2$ of the first 4 weeks after therapy $\pm$	637 (71.2)	316 patients received rifaximin 550mg t.i.d. for 2 weeks
<b>Dove 2013</b> <sup>362</sup>	USA, 263 sites	Rome III criteria, 100% IBS-D	$\geq 30\%$ reduction in worst abdominal pain score and at least 2 points, and a daily BSFS score of 3 or 4 on $\geq 66\%$ of daily diary entries at week 4 $\pm$	348 (69.3)	176 patients received eluxadoline 100mg b.i.d. for 12 weeks
<b>Lembo 2016a</b> (IBS-3001) <sup>298</sup>	USA, Canada and UK, 295 sites	Rome III criteria, 100% IBS-D	$\geq 30\%$ reduction in worst abdominal pain score on $\geq 50\%$ of days and, on the same days, a daily BSFS score of $< 5$ at week 12	1282 (65.4)	429 and 426 patients received eluxadoline 75mg or 100mg b.i.d. respectively for 26 weeks

<b>Lembo 2016b</b> <b>(IBS-3002)</b> <sup>298</sup>	USA, Canada and UK,  261 sites	Rome III criteria, 100% IBS-  D	≥30% reduction in worst abdominal pain score on  ≥50% of days and, on the same days, a daily  BSFS score of <5 at week 12	1146 (67.0)	381 and 383 patients received  eluxadoline 75mg or 100mg b.i.d.  respectively for 26 weeks
<b>Brenner 2018</b> <b>(RELIEF)</b> <sup>299</sup>	USA and Canada,  number of sites not  reported	Rome III criteria, 100% IBS-  D	≥40% reduction in worst abdominal pain score on  ≥50% of days and a daily BSFS score of <5 at  week 12	346 (69.9)	172 patients received eluxadoline  100mg b.i.d. for 12 weeks

\* b.i.d.; twice-daily

†Also recruited patients with IBS-M, but data were only extractable for those with IBS-D at 12 weeks

±Efficacy data were extracted at 12 weeks for the purpose of this analysis

§o.d.; once-daily

¶BSFS; Bristol stool form scale

‡t.i.d.; three times daily

**Table 4-3. Risk of Bias of Randomised Controlled Trials of Pharmacological Therapies Versus Placebo in IBS-D or IBS-M.**

Study, drug, and dose	Stated Method of Generation of Randomisation Schedule	Stated Method of Concealment of Treatment Allocation	Blinding	No Evidence of Incomplete Outcomes Data	No Evidence of Selective Reporting of Outcomes	Low Risk of Bias
Camilleri 1999 <sup>353</sup> , alosetron 1mg b.i.d.	No	No	Double	No	Yes	No
Camilleri 2000 <sup>351</sup> , alosetron 1mg b.i.d.	Yes	Yes	Double	Yes	Yes	Yes
Camilleri 2001 <sup>227</sup> , alosetron 1mg b.i.d.	Yes	No	Double	Yes	Yes	No
Lembo 2001 <sup>356</sup> , alosetron 1mg b.i.d.	No	No	Double	No	Yes	No
Chey 2004 <sup>354</sup> , alosetron 1mg b.i.d.	No	No	Double	Yes	Yes	No

<b>Chang 2005 <sup>355</sup>, alosetron 0.5mg or 1mg b.i.d.</b>	Yes	No	Double	Yes	Yes	No
<b>Krause 2007 <sup>357</sup>, alosetron 1mg b.i.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Matsueda 2008a <sup>359</sup>, ramosetron 5mcg o.d.</b>	No	Yes	Double	Yes	Yes	No
<b>Matsueda 2008b NCT00189696 <sup>358</sup>, ramosetron 5mcg o.d.</b>	No	No	Double	Yes	Yes	No
<b>Fukudo 2014 NCT01225237 <sup>360</sup>, ramosetron 5mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Fukudo 2016 NCT01870895 <sup>352</sup>, ramosetron 2.5mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes
<b>Fukudo 2017 NCT01274000 <sup>361</sup>, ramosetron 2.5mcg or 5mcg o.d.</b>	Yes	Yes	Double	Yes	Yes	Yes

<b>Pimentel 2011a</b>  (Target 1) NCT00731679 <sup>350</sup> , rifaximin 550mg t.i.d.	Yes	Yes	Double	Yes	Yes	Yes
<b>Pimentel 2011b</b>  (Target 2) NCT00724126 <sup>350</sup> , rifaximin 550mg t.i.d.	Yes	Yes	Double	Yes	Yes	Yes
<b>Dove 2013</b> NCT01130272 <sup>362</sup> , eluxadoline 100mg b.i.d.	Yes	Yes	Double	Yes	Yes	Yes
<b>Lembo 2016a</b>  (IBS-3001) NCT01553591 <sup>298</sup> , eluxadoline 75mg or 100mg b.i.d.	Yes	Yes	Double	Yes	Yes	Yes
<b>Lembo 2016b</b>  (IBS-3002) NCT01553747 <sup>298</sup> , eluxadoline 75mg or 100mg b.i.d.	Yes	Yes	Double	Yes	Yes	Yes

<b>Brenner 2018 (RELIEF)</b> <b>NCT02959983 <sup>299</sup>, eluxadoline</b> <b>100mg b.i.d.</b>	No	No	Double	Yes	Yes	No
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Boxes shaded green denote that the risk of bias item was reported, while those shaded red denote it was not reported.

### 4.3.1 Efficacy

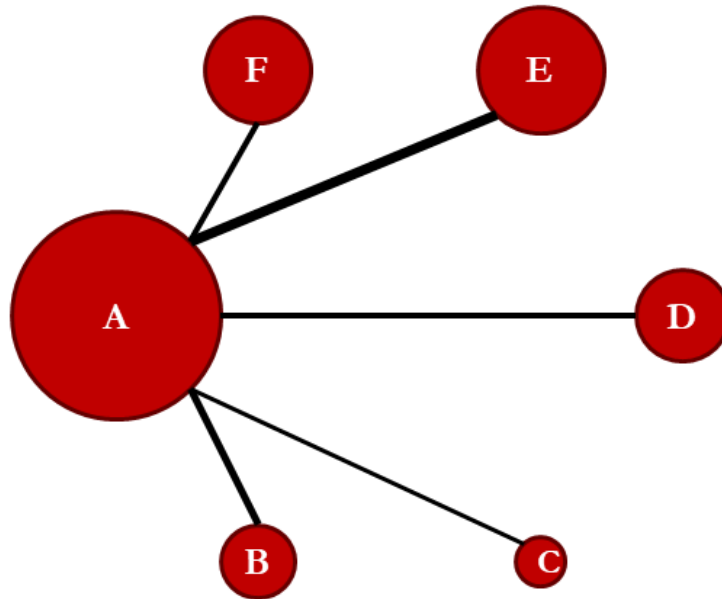
#### 4.3.1.1 Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response

Ten RCTs, reported in seven separate articles, provided dichotomous data for failure to achieve the FDA-recommended composite endpoint, based on an improvement in abdominal pain and stool consistency.<sup>298, 299, 350, 352, 362-364</sup> Two of the articles, between them, provided sufficient information to enable a *post hoc* analysis of three of the phase III RCTs of alosetron, which reported efficacy according to FDA-recommended endpoints only in women with severe IBS-D.<sup>363, 364</sup>

These 10 trials included a total of 5517 patients, 3156 of whom were randomised to active treatment, and 2361 to placebo. The network plot is provided in Figure 4-2. When data were pooled there was no global statistical heterogeneity ( $I^2 = 2.3\%$ ), and no evidence of publication bias, or other small study effects (Figure 4-3). All treatments were significantly more effective than placebo, but alosetron 1mg b.i.d. was ranked as the most effective (P-score 0.97), in three RCTs (RR 0.69; 95% CI 0.60 to 0.80) (Figure 4-4). This means that the probability of alosetron being the most effective when all treatments, including placebo, were compared with each other was 97%. After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d., compared with all other treatments except ramosetron 2.5mcg o.d. (Table 4-4).

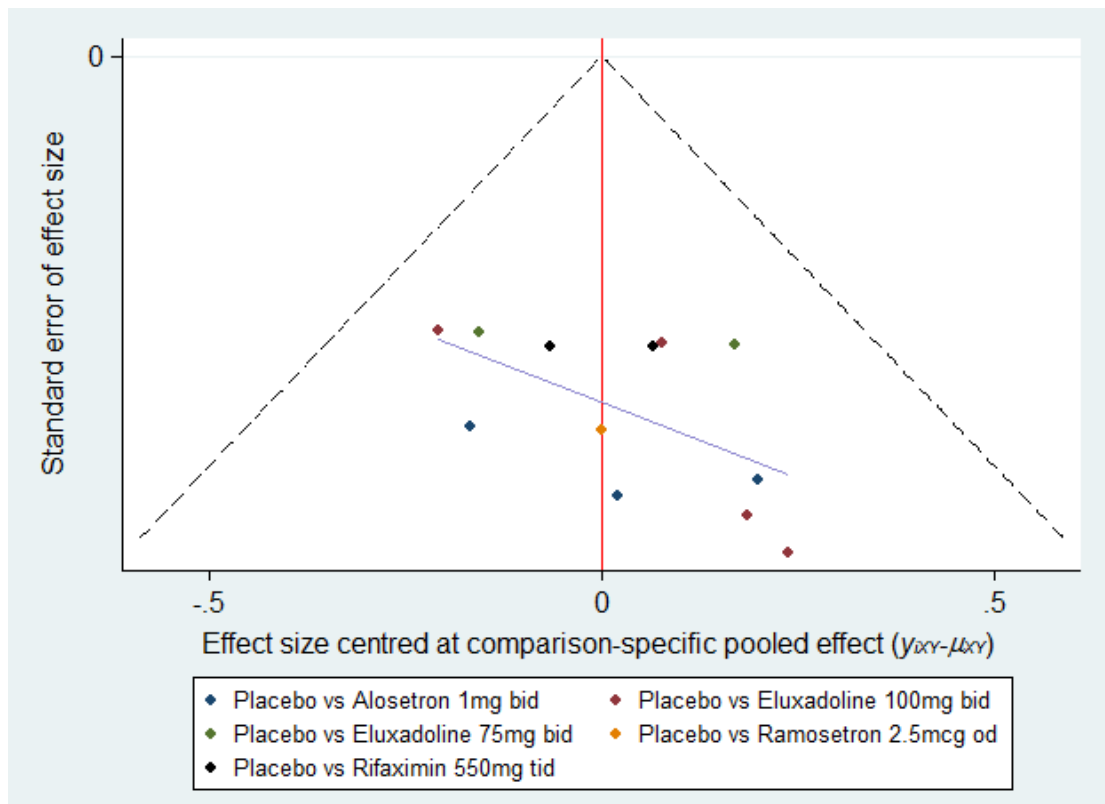


**Figure 4-2. Network Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



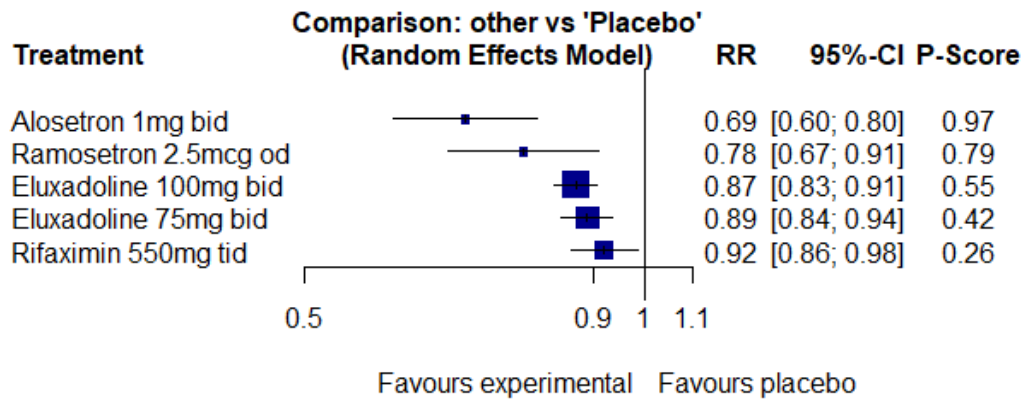
Drug	Abbreviation	Number of Trials	Number of Patients
Placebo	A	10	2,361
Alosetron 1mg b.i.d.	B	3	391
Ramosetron 2.5mcg o.d.	C	1	173
Rifaximin 550mg t.i.d.	D	2	625
Eluxadoline 100mg b.i.d.	E	4	1,157
Eluxadoline 75mg b.i.d.	F	2	810

**Figure 4-3. Funnel Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 4-4. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 4-4. League Table for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.**

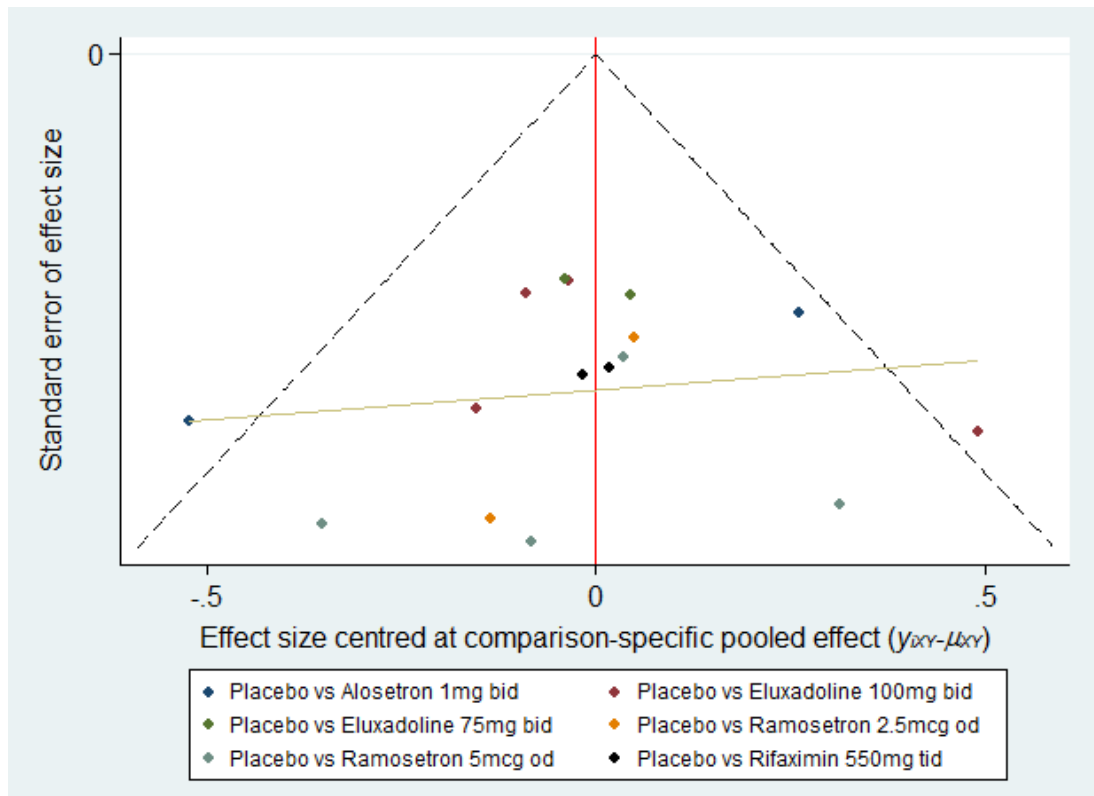
<b>Alosetron 1mg b.i.d.</b>					
0.89 (0.72; 1.10)	<b>Ramosetron 2.5mcg o.d.</b>				
0.80 (0.69; 0.93)	0.90 (0.77; 1.05)	<b>Eluxadoline 100mg b.i.d.</b>			
0.78 (0.67; 0.91)	0.88 (0.75; 1.03)	0.98 (0.91; 1.05)	<b>Eluxadoline 75mg b.i.d.</b>		
0.75 (0.64; 0.89)	0.85 (0.72; 1.00)	0.94 (0.87; 1.02)	0.97 (0.89; 1.05)	<b>Rifaximin 550mg b.i.d.</b>	
0.69 (0.60; 0.80)	0.78 (0.67; 0.91)	0.87 (0.83; 0.91)	0.89 (0.84; 0.94)	0.92 (0.86; 0.98)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

#### 4.3.1.2 Failure to Achieve a Global IBS Symptom Response

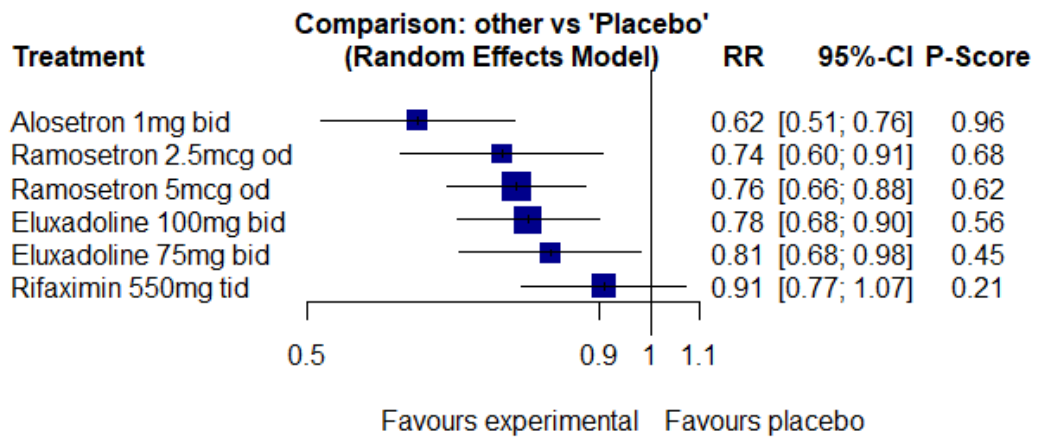
When dichotomous data were pooled for failure to achieve relief of global symptoms of IBS, there were 13 RCTs, reported in 11 articles, recruiting 7464 patients.<sup>298, 299, 350, 352, 356-362</sup> Of these, 4316 were randomised to active treatment and 3148 to placebo. When data were pooled there was moderate global statistical heterogeneity ( $I^2 = 67.4\%$ ), which was driven by the trials of alosetron 1mg b.i.d. The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 4-5). All treatments were significantly more effective than placebo, with the exception of rifaximin 550mg three-times daily (t.i.d.), but alosetron 1mg b.i.d. was ranked as the most effective (P-score 0.96), in two RCTs (RR 0.62; 95% CI 0.51 to 0.76) (Figure 4-6). After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d. compared with rifaximin 550mg t.i.d. (Table 4-5).

**Figure 4-5. Funnel Plot for Failure to Achieve a Global IBS Symptom Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 4-6. Forest Plot of the Indirect Evidence for Failure to Achieve a Global IBS Symptom Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 4-5. League Table for Failure to Achieve a Global IBS Symptom Response.**

<b>Alosetron 1mg b.i.d.</b>						
0.84 (0.63; 1.12)	<b>Ramosetron 2.5mcg o.d.</b>					
0.82 (0.65; 1.04)	0.97 (0.76; 1.24)	<b>Ramosetron 5mcg o.d.</b>				
0.80 (0.63; 1.02)	0.95 (0.74; 1.22)	0.98 (0.80; 1.19)	<b>Eluxadoline 100mg b.i.d.</b>			
0.77 (0.59; 1.00)	0.91 (0.69; 1.19)	0.93 (0.74; 1.18)	0.96 (0.76; 1.21)	<b>Eluxadoline 75mg b.i.d.</b>		
0.69 (0.53; 0.89)	0.81 (0.63; 1.06)	0.84 (0.68; 1.04)	0.86 (0.69; 1.07)	0.90 (0.70; 1.15)	<b>Rifaximin 550mg t.i.d.</b>	
0.62 (0.51; 0.76)	0.74 (0.60; 0.91)	0.76 (0.66; 0.88)	0.78 (0.68; 0.90)	0.81 (0.68; 0.98)	0.91 (0.77; 1.07)	<b>Placebo</b>

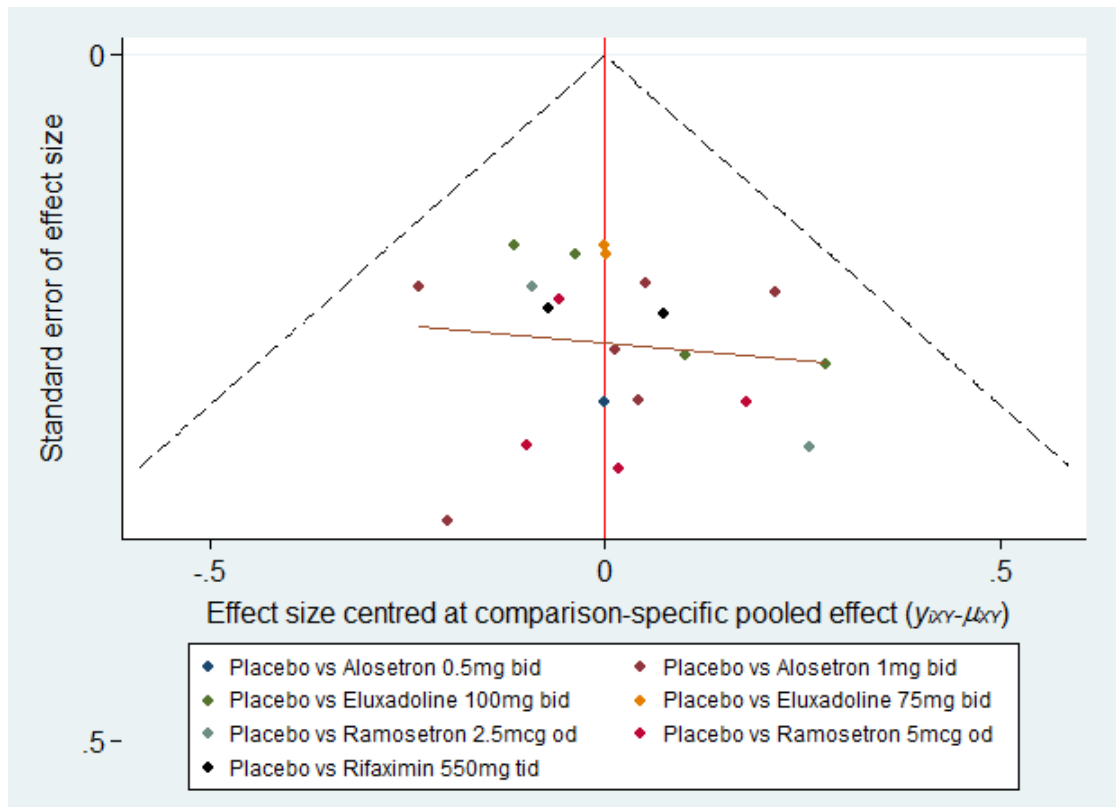
Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.



#### 4.3.1.3 Failure to Achieve an Abdominal Pain Response

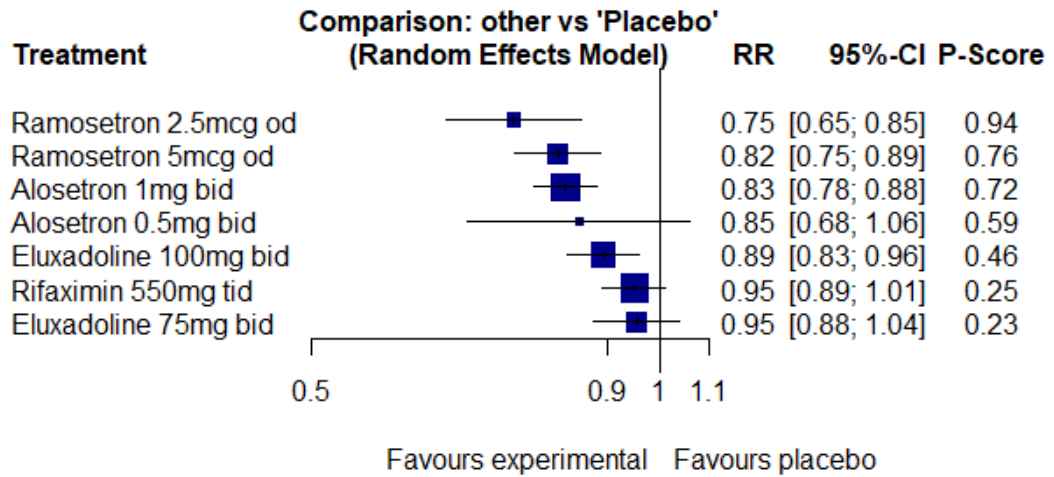
There were 17 trials recruiting 9043 patients, reported in 15 separate articles,<sup>227, 298, 299, 350-355, 357-362</sup> that reported dichotomous data for failure to achieve an abdominal pain response. There were 5026 patients assigned to active therapy, and 4017 allocated to placebo. When data were pooled there was no global statistical heterogeneity ( $I^2 = 0\%$ ), and no evidence of publication bias, or other small study effects (Figure 4-7). Ramosetron 2.5mcg o.d., ramosetron 5mcg o.d., alosetron 1mg b.i.d., and eluxadoline 100mg b.i.d. were all significantly more effective than placebo. Overall, ramosetron 2.5mcg o.d. was ranked as the most effective treatment (P-score 0.94), in two RCTs (RR 0.75; 95% CI 0.65 to 0.85) (Figure 4-8). On indirect comparison of active treatments, significant differences were seen with ramosetron 2.5mcg o.d. compared with eluxadoline 75mg b.i.d., eluxadoline 100mg b.i.d., and rifaximin 550mg t.i.d., as well as for ramosetron 5mcg o.d. compared with eluxadoline 75mg b.i.d. and rifaximin 550mg t.i.d. Significant differences were also seen for alosetron 1mg b.i.d. compared with eluxadoline 75mg b.i.d. and rifaximin 550mg t.i.d. (Table 4-6).

**Figure 4-7. Funnel Plot for Failure to Achieve an Abdominal Pain Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 4-8. Forest Plot of the Indirect Evidence for Failure to Achieve an Abdominal Pain Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 4-6. League Table for Failure to Achieve an Abdominal Pain Response.**

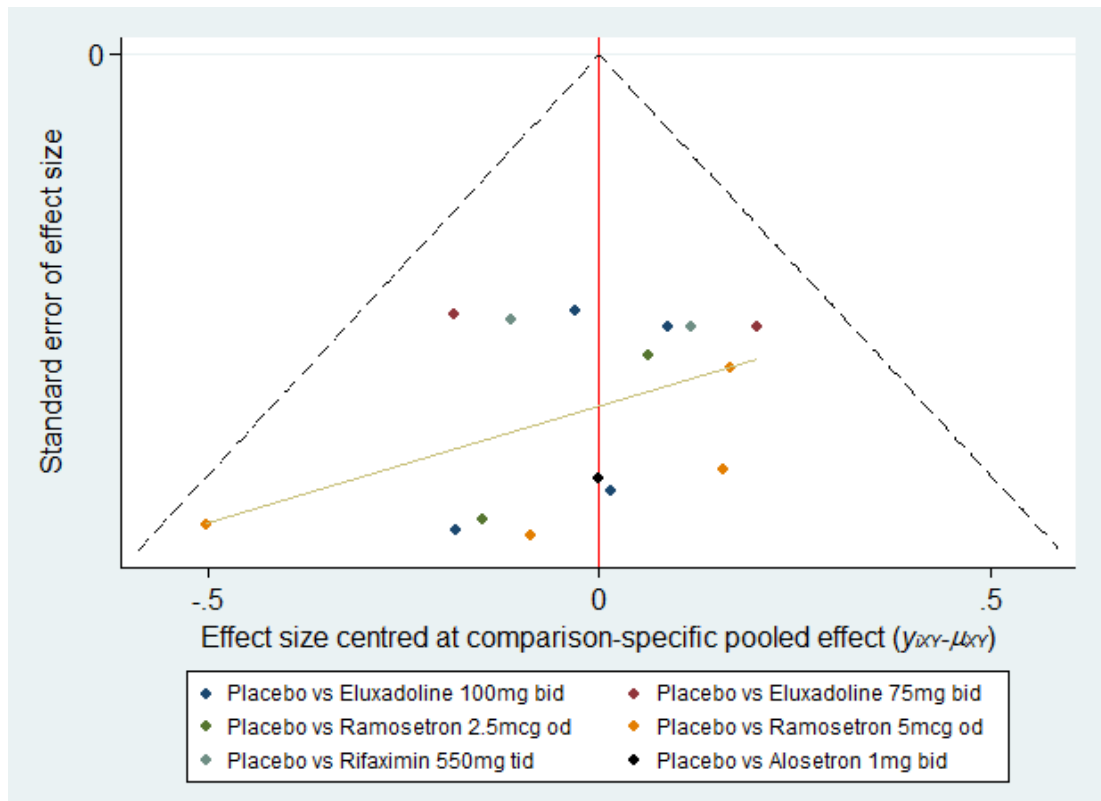
<b>Ramosetron 2.5mcg o.d.</b>							
0.91 (0.78; 1.07)	<b>Ramosetron 5mcg o.d.</b>						
0.90 (0.78; 1.04)	0.99 (0.89; 1.10)	<b>Alosetron 1mg b.i.d.</b>					
0.88 (0.68; 1.13)	0.96 (0.76; 1.21)	0.97 (0.77; 1.22)	<b>Alosetron 0.5mg b.i.d.</b>				
0.84 (0.72; 0.97)	0.91 (0.82; 1.02)	0.93 (0.84; 1.02)	0.95 (0.76; 1.20)	<b>Eluxadoline 100mg b.i.d.</b>			
0.79 (0.68; 0.91)	0.86 (0.77; 0.96)	0.87 (0.80; 0.95)	0.90 (0.71; 1.13)	0.94 (0.86; 1.03)	<b>Rifaximin 550mg t.i.d.</b>		
0.78 (0.67; 0.92)	0.86 (0.76; 0.97)	0.87 (0.78; 0.96)	0.89 (0.70; 1.13)	0.94 (0.84; 1.05)	1.00 (0.90; 1.11)	<b>Eluxadoline 75mg b.i.d.</b>	
0.75 (0.65; 0.85)	0.82 (0.75; 0.89)	0.83 (0.78; 0.88)	0.85 (0.68; 1.06)	0.89 (0.83; 0.96)	0.95 (0.89; 1.01)	0.95 (0.88; 1.04)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

#### 4.3.1.4 Failure to Achieve a Stool Consistency Response

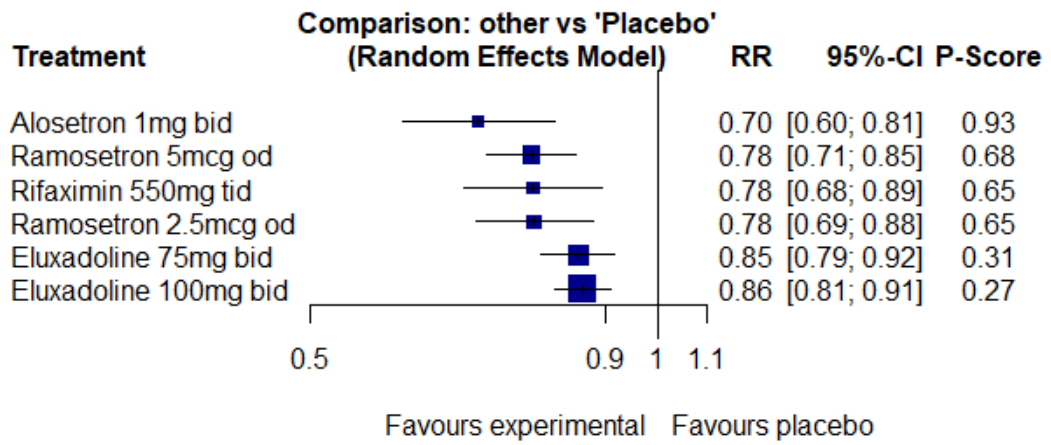
Twelve RCTs reported dichotomous data for failure to achieve a stool consistency response, and these were reported in 10 separate articles, and included 6663 patients.<sup>298, 299, 350, 352, 357-362</sup> There were 3784 patients assigned to active therapy, and 2879 to placebo. When data were pooled, there was no global statistical heterogeneity ( $I^2 = 18.4\%$ ). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Figure 4-9). All treatments were significantly more effective than placebo, but alosetron 1mg b.i.d. ranked as the most effective treatment (P-score 0.93), although in only one RCT (RR 0.70; 95% CI 0.60 to 0.81) (Figure 4-10). After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d., compared with eluxadoline 75mg b.i.d. and eluxadoline 100mg b.i.d. (Table 4-7).

**Figure 4-9. Funnel Plot for Failure to Achieve a Stool Consistency Response.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 4-10. Forest Plot of the Indirect Evidence for Failure to Achieve a Stool Consistency Response.**



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 4-7. League Table for Failure to Achieve a Stool Consistency Response.**

<b>Alosetron 1mg b.i.d.</b>						
0.90 (0.76; 1.07)	<b>Ramosetron 5mcg o.d.</b>					
0.90 (0.73; 1.10)	1.00 (0.85; 1.18)	<b>Rifaximin 550mg t.i.d.</b>				
0.90 (0.74; 1.08)	0.99 (0.86; 1.15)	1.00 (0.83; 1.20)	<b>Ramosetron 2.5mcg o.d.</b>			
0.82 (0.69; 0.97)	0.91 (0.81; 1.02)	0.91 (0.78; 1.07)	0.92 (0.80; 1.05)	<b>Eluxadoline 75mg b.i.d.</b>		
0.81 (0.69; 0.96)	0.90 (0.81; 1.00)	0.91 (0.78; 1.05)	0.91 (0.80; 1.03)	0.99 (0.90; 1.09)	<b>Eluxadoline 100mg b.i.d.</b>	
0.70 (0.60; 0.81)	0.78 (0.71; 0.85)	0.78 (0.68; 0.89)	0.78 (0.69; 0.88)	0.85 (0.79; 0.92)	0.86 (0.81; 0.91)	<b>Placebo</b>

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

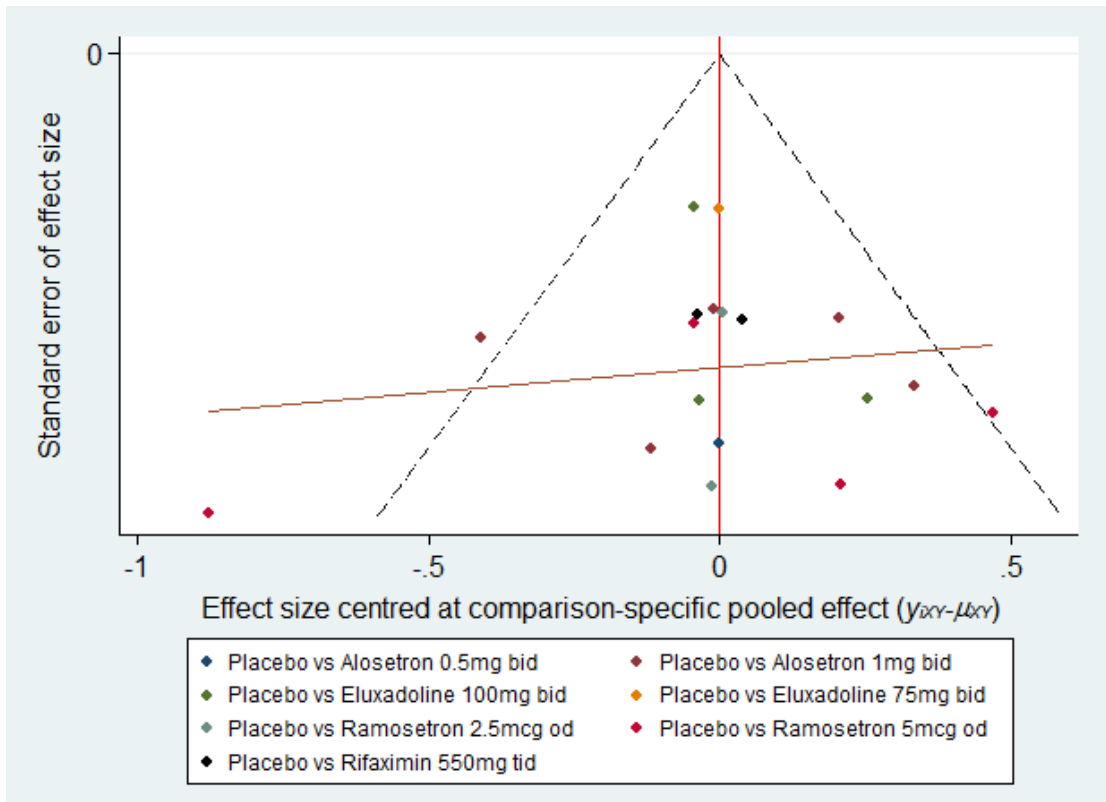


## 4.3.2 Safety

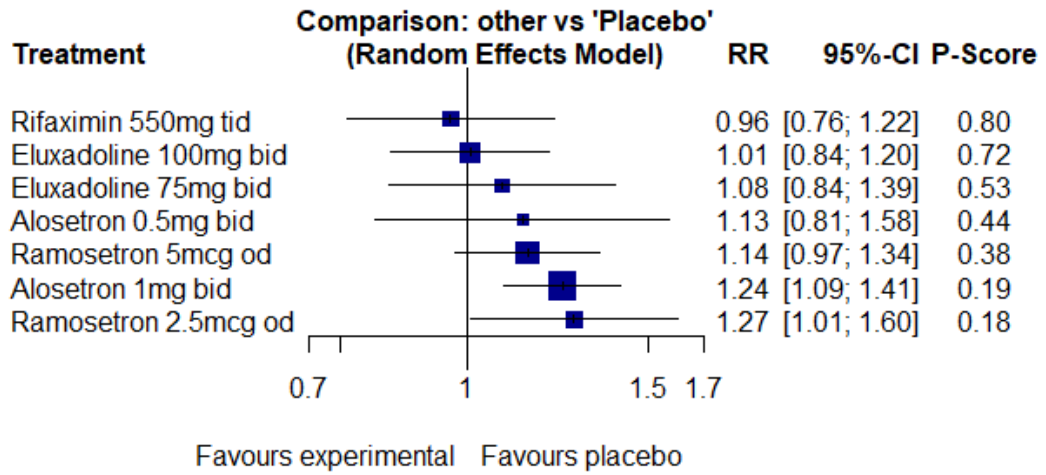
### 4.3.2.1 Overall Adverse Events

Sixteen trials, recruiting 9134 patients and reported in 14 articles,<sup>227, 298, 299, 350-352, 355-362</sup> provided data for overall adverse events. There was moderate global statistical heterogeneity ( $I^2 = 64.2\%$ ), but no evidence of publication bias, or other small study effects (Figure 4-11). Heterogeneity was driven by the trials of alosetron 1mg b.i.d. and ramosetron 5mcg o.d. When comparing pooled overall adverse events, alosetron 1mg b.i.d. (five RCTs, RR = 1.24; 95% CI 1.09 to 1.41), and ramosetron 2.5mcg o.d. (two RCTs, RR = 1.27; 95% CI 1.01 to 1.60) were associated with a significant increase in overall adverse events, compared with placebo (Figure 4-12). When ranked using a P-score, rifaximin 550mg t.i.d. was the best, and ramosetron 2.5mcg o.d. the worst, in terms of overall adverse events (P-scores 0.80 and 0.18 respectively). Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages.

**Figure 4-11. Funnel Plot for Overall Adverse Events.**



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

**Figure 4-12. Forest Plot of the Indirect Evidence for Overall Adverse Events.**

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

### 4.3.2.2 Adverse Events Leading to Dropout

Adverse events leading to dropout were provided by 15 trials, reported in 13 papers.<sup>227, 298, 299, 350, 352, 353, 356-362</sup> Eluxadolone 75mg b.i.d. (two RCTs, RR = 1.88; 95% CI 1.25 to 2.81), eluxadolone 100mg b.i.d. (four RCTs, RR = 1.88; 95% CI 1.31 to 2.70), and alosetron 1mg b.i.d. (four RCTs, RR = 1.97; 95% CI 1.48 to 2.63) were all associated with significantly higher trial dropout rates due to adverse events, compared with placebo. When ranked using a P-score, ramosetron 2.5mcg o.d. was the best, and alosetron 1mg b.i.d. the worst, in terms of adverse events leading to dropout (P-scores 0.92 and 0.16 respectively). On indirect comparison of active treatments, significant differences were seen with ramosetron 2.5mcg o.d. compared with eluxadolone 100mg b.i.d., eluxadolone 75mg b.i.d., and alosetron 1mg b.i.d.

### 4.3.2.3 Individual Adverse Events

In terms of individual adverse events, rates of constipation were provided by 16 of the eligible trials, reported in 15 articles.<sup>227, 298, 299, 350-353, 355-362</sup> All drugs, with the exception of rifaximin 550mg t.i.d., were associated with an increased risk of constipation and, when ranked using a P-score, rifaximin 550mg t.i.d. was the best, and alosetron 0.5mg b.i.d. the worst (P-scores 0.99 and 0.06 respectively). Indirect comparison of active treatments revealed that both placebo and rifaximin 550mg t.i.d. were significantly less likely to cause constipation than all other individual drugs, and dosages, but there were no other differences. There were no significant differences between any of the active therapies and placebo, in terms of incidence of either nausea or headache. Nine RCTs, reported in seven articles, provided information concerning abdominal pain.<sup>298, 350, 355-358, 362</sup> Eluxadolone 100mg b.i.d. and alosetron 1mg b.i.d. were more likely than placebo to cause abdominal pain, with rifaximin 550mg t.i.d. the best, and alosetron 1mg b.i.d. the worst (P scores 0.89 and 0.18 respectively). Indirect comparison of active treatments revealed that both placebo and rifaximin 550mg t.i.d.

were significantly less likely to cause abdominal pain than either eluxadoline 100mg b.i.d. or alosetron 1mg b.i.d.

#### **4.4 Discussion**

It is widely accepted that the licensed pharmacological therapies studied in this systematic review and network meta-analysis are more effective than placebo for the treatment of IBS-D and IBS-M. Using the FDA-recommended composite endpoint, although all drugs were more effective than placebo, alosetron 1mg b.i.d. ranked first, according to the available evidence. The probability of alosetron being superior to another competing treatment, according to this endpoint, was 97%, which exceeds the 90% to 95% threshold that the available literature suggests is desirable.<sup>328</sup> Alosetron 1mg b.i.d. continued to be ranked first when efficacy was assessed in terms of improvement in global IBS symptoms and stool consistency. Ramosetron 2.5mcg and 5mcg o.d. were ranked first and second when effect on abdominal pain was studied. Rifaximin 550mg t.i.d. was no better than placebo for global IBS symptoms, and rifaximin 550mg t.i.d., alosetron 0.5mg b.i.d., and eluxadoline 75mg b.i.d. were no more effective than placebo for abdominal pain. Alosetron 1mg b.i.d. and ramosetron 2.5mcg o.d. were both associated with a significant increase in overall adverse events, compared with placebo. Constipation was significantly more likely with all drugs, except rifaximin 550mg t.i.d., which ranked first for safety overall. The latter observation may be consistent with the observation that rifaximin may actually accelerate colonic transit,<sup>365</sup> and improve symptoms of IBS-C.<sup>366</sup> Finally, more patients reported abdominal pain as an adverse event with eluxadoline and alosetron than with placebo, although whether this is due to the fluctuating natural history of IBS, an associated feature of drug-induced constipation, or a specific adverse event associated with both drugs is unclear.

A contemporaneous and exhaustive literature search was undertaken. This was conducted independently by two reviewers, and included searching conference proceedings, the “grey” literature, and clinicaltrials.gov. Assessment of eligibility and data extraction was also performed independently, and in duplicate. Subsequently the authors of two trials of rifaximin,<sup>350</sup> and one trial of eluxadoline,<sup>299</sup> were contacted in order to obtain the necessary data for the study analyses, as these were not available in the original papers. This inclusive approach enabled analysis of data from 18 RCTs of pharmacological therapies for IBS-D and IBS-M, recruiting almost 10,000 patients, with data extracted at 12 weeks for all endpoints. An intention-to-treat analysis was used and data were pooled using a random effects model to minimise the risk that the efficacy of the drugs studied would be overestimated. Finally, adverse events were extracted and pooled, where reported, in order to provide summary safety data.

No head-to-head studies of one drug versus another were identified, meaning that all analyses were based on indirect comparisons, which are not protected by randomisation. This could lead to confounding due to underlying differences between individual RCTs,<sup>339</sup> although the use of very similar endpoints to define efficacy after 12 weeks of treatment in all trials should minimise this. However, this means that the relative efficacy and safety of these drugs in the longer term are unknown. In addition, eight of the 18 trials were at unclear risk of bias,<sup>227, 299, 353-356, 358, 359</sup> which may mean the efficacy of some of the drugs has been overestimated.<sup>340</sup> It is likely that these deficiencies represent omissions of reporting, rather than true design flaws, given the oversight of national regulatory agencies for many of the included trials. There were moderate levels of global statistical heterogeneity in the analysis using an improvement in global IBS symptoms to define treatment response, and for total adverse events, but no heterogeneity in any of the other analyses. Of note, heterogeneity was absent in the analysis of the FDA-recommended composite endpoint to define treatment response.

This reflects that this is a standardised assessment of global symptom improvement in IBS compared with the other definitions of global symptom improvement which often differed between trials. In addition, it is important to point out that, as in most trials of pharmacological therapies in IBS, adverse events were not reported according to standardised endpoints, unlike efficacy data, which may mean making comparisons between individual treatments is less valid. Finally, there may have been subtle differences in symptom severity among the populations studied in each of these trials, which mean the results are not directly comparable. However, this should have been minimised, as 16 of the trials used similar combinations of a minimum abdominal pain threshold and a minimum stool consistency threshold, during a run-in period, to confirm eligibility prior to study entry. Among the remaining two RCTs, one did not report these data, as it was in abstract form,<sup>299</sup> and one used a minimum urgency threshold.<sup>356</sup>

Ranking of these pharmacological therapies provides useful information to aid clinical decision making, but it is important to acknowledge that not all of these drugs are available in all countries or, indeed, to all patients with IBS-D or IBS-M. Alosetron was withdrawn in the US because of adverse events, including ischemic colitis and severe constipation. It was re-introduced, via a risk evaluation and mitigation strategy, for women with severe IBS-D. In the first 9 years after re-introduction, 29 cases of probable ischemic colitis were reported; an incidence of 1 case per 1000 patient-years.<sup>367</sup> This is similar to the background rate of ischemic colitis in female patients with IBS, which ranges from 0.40 cases/1000 patient-years to 1.79 cases/1000 patient-years.<sup>368</sup> Whether alosetron is effective in men with IBS-D is unclear, as only one RCT recruited solely men,<sup>355</sup> and participants in the remaining trials were either predominantly, or exclusively, women. However, cilansetron, another 5-HT<sub>3</sub> receptor antagonist, appeared to be effective in both men and women with IBS-D.<sup>300</sup> Although ramosetron can be prescribed for men with IBS-D, as well as women, it is only licensed in Japan and some

other South, and South-East, Asian countries, at a dose of 2.5mcg o.d. in women and 5mcg o.d. in men. However, three of the trials conducted using 5mcg o.d. recruited women.<sup>358, 359, 361</sup> If this dose was either not as effective or less well-tolerated in women, one would have expected this to have diluted efficacy, or led to more adverse events, yet 5mcg o.d. was ranked second for its effect on both abdominal pain and stool consistency, and was by no means the lowest ranked drug in terms of safety.

Although both alosetron and ramosetron appeared to perform the best in this network meta-analysis, many patients with IBS will be unable to access these drugs. Two recent RCTs of ondansetron, another 5-HT<sub>3</sub> receptor antagonist, which is widely available and has a robust safety profile, suggest that this drug is also of benefit in IBS.<sup>228, 303</sup> Neither of these trials were eligible for inclusion in this network, as the drug is not licensed for IBS; one trial was a cross-over RCT with a treatment duration of 10 weeks,<sup>228</sup> and the other was a parallel arm trial of only 8 weeks duration.<sup>303</sup> A 12-week trial has been undertaken in the UK,<sup>369</sup> however, it is yet to report its findings. Another issue is that all of the RCTs of ramosetron were conducted in Japan, and the majority of the trials of alosetron, eluxadoline, and rifaximin in North American populations, so the findings may not be generalisable to individuals with IBS-D or IBS-M in other countries.

Because these studies span the last 20 years of clinical practice, during which time the Rome criteria for IBS have undergone multiple revisions,<sup>14, 30-32</sup> there are variations between individual trial populations, in terms of how the diagnosis of IBS was determined. The majority of the alosetron trials and the earlier ramosetron RCTs used the Rome I or II criteria,<sup>30, 31</sup> which are arguably less restrictive than the Rome III criteria,<sup>32</sup> used in later trials of ramosetron, and all studies of rifaximin and eluxadoline. However, agreement between these criteria for the diagnosis of IBS is good,<sup>34</sup> and such differences are mitigated against, to some extent, by being able to compare all drugs



using the standardised FDA-recommended endpoint for trials in IBS-D. It is important to highlight that, because these endpoints had not been agreed at the time some of the earlier drug trials were conducted, the data for alosetron are based entirely on a *post hoc* analysis of three trials.<sup>363, 364</sup> Around 50% of patients in these trials were absent from the analysis, because they failed to meet the updated FDA-recommended symptom thresholds for inclusion in an IBS treatment trial. This may mean that the efficacy of alosetron has been overestimated for this endpoint, although as only patients with severe IBS-D were included in this analysis, this seems unlikely. In addition, the strength of the P-score for alosetron, together with the absence of global statistical heterogeneity, suggests that the treatment ranking reported in this network meta-analysis is likely to be accurate.

All of the drugs considered in this network meta-analysis are likely to be prescribed as second-line therapy, after failure of antidiarrhoeal and antispasmodic drugs. It would therefore be important to understand how they perform relative to these first-line therapies, particularly as loperamide is available over the counter in many countries, and has evidence of short-term efficacy for reducing diarrhoea.<sup>278</sup> Unfortunately, there are few trials examining this issue. One RCT demonstrated that 12 weeks of alosetron 1mg b.i.d. was superior to mebeverine 135mg t.i.d., in terms of adequate relief of abdominal pain, in a mixed population of patients with IBS of all stool subgroups,<sup>370</sup> but a trial of 4 weeks of ramosetron 5mcg o.d. versus mebeverine 135mg t.i.d. demonstrated no significant differences.<sup>371</sup>

There have also been no head-to-head trials of these drugs against other second-line therapies, such as tricyclic antidepressants. Additionally, there are no RCTs of tricyclic antidepressants, or other pharmacological therapies used off-license for IBS, that have been conducted solely in patients with IBS-D or IBS-M over 12 weeks reporting identical endpoints to the ones used in these trials,<sup>278</sup> and which could

therefore have been included in this network meta-analysis. Pregabalin has been shown to improve abdominal pain in IBS,<sup>372,373</sup> and a recent trial found significant improvements in diarrhoea and bloating scores compared with placebo,<sup>374</sup> suggesting that this drug might be beneficial for treating IBS-D. However, the trial recruited a mixed IBS population that included people with IBS-C and so was ineligible for inclusion in this network meta-analysis. Another RCT has compared 24 weeks of alosetron 1mg b.i.d. with traditional pharmacotherapy, which in some patients consisted of tricyclic antidepressants, in almost 2000 female patients with severe IBS-D.<sup>301</sup> In this trial, treatment with alosetron 1mg b.i.d. resulted in significantly greater relief of global IBS symptoms. There were also significant reductions in number of visits to see a physician for IBS, use of over the counter medications, and days of lost work productivity. However, this beneficial effect was accompanied by non-serious constipation, occurring in one-third of patients, compared with constipation in <1% of those allocated to traditional pharmacotherapy. Initiating alosetron at a dose of 0.5mg b.i.d., and increasing the dose subsequently if there is inadequate clinical improvement, as is currently recommended, may minimise this. Finally, the two large, phase III trials of eluxadoline have reported efficacy of the drug in a subset of patients who had previously failed loperamide,<sup>298</sup> with similar efficacy demonstrated in this *post hoc* analysis.<sup>282</sup> The most recent RCT of eluxadoline that was identified had recruited only patients with IBS-D who reported, subjectively, that they had previously failed loperamide, again with similar results.<sup>299</sup>

Given the lack of head-to-head trials, performing a network meta-analysis could be criticised, because all of the conclusions are derived from data based on indirect treatment comparisons. However, as discussed previously, it is unlikely that pharmaceutical companies will ever conduct such studies, or even undertake a trial of one of these drugs against an antidiarrhoeal or tricyclic antidepressant. Network meta-

analyses circumvent this problem to some extent, allowing credible ranking systems of the likely efficacy and safety of different treatments to be developed, even in the absence of trials making direct comparisons. The results of this study are therefore still likely to be important for both patients and policy makers, in order to help inform treatment decisions for IBS-D and IBS-M.

Although all drugs were superior to placebo, according to the FDA-recommended composite endpoint for trials in IBS, alosetron 1mg b.i.d. ranked first in terms of efficacy in this network meta-analysis. It was also the top ranked treatment when either global relief of symptoms or improvement in stool consistency were used to define treatment response, but ramosetron 2.5mcg o.d. was ranked first in terms of improving abdominal pain. With regard to safety, rifaximin 550mg t.i.d. was least likely to cause adverse events, and was the only drug that did not significantly increase the risk of constipation. However, it demonstrated relatively poor efficacy across many of the treatment endpoints that were studied. Eluxadoline 100mg b.i.d., meanwhile, was significantly better than placebo across all endpoints, but its overall performance was modest. This information will hopefully assist clinicians in choosing a second-line treatment for IBS-D, and to a lesser extent IBS-M, based on the patient's most troublesome symptom, prioritising both efficacy and safety. Alosetron and ramosetron remain unavailable in many countries, including the UK. Given the chronic and frequently debilitating nature of IBS, this lack of availability may need to be reconsidered, in order to widen access to potentially effective second-line treatments for those patients with IBS-D or IBS-M when conventional first-line therapies fail.

Overall, the results reported here and in the preceding chapter provide valuable insights into the relative efficacy of second-line drugs targeting abnormal stool pattern in IBS, and could help physicians and patients to make better informed treatment choices. These drugs exemplify the principle that patients with IBS should be

categorised according to their predominant stool pattern, be that IBS-C, IBS-D, or IBS-M, and that these subgroups should be used to guide treatment. However, despite having been developed with this aim in mind, it is notable that, overall, only 20% to 30% of patients might expect to experience symptom-improvement with these drugs,<sup>290, 291, 293, 335, 349, 350</sup> and there is little to choose between many individual drugs, in terms of efficacy.

The reasons underlying this relatively modest performance are unclear; however, one hypothesis is that, due to the complex nature of IBS, even though all trial participants across both network meta-analyses met the Rome criteria for either IBS-C, or IBS-D or IBS-M, based on their gastrointestinal symptoms, they were differentiated by other factors that were not evaluated. Indeed, just as no study of secretagogues for IBS-C included any evaluation of psychological health, the same applies to all the trials included in this network meta-analysis of treatments for IBS-D and IBS-M. However, as already outlined, psychological health may be an important determinant of IBS symptom severity and impact on quality of life, and together with other pathophysiological factors, may be responsible for shaping an individual's clinical response to certain treatments. For example, with respect to alosetron, which acts via serotonergic pathways, it has been shown that genetic polymorphisms in the promoter for synthesis of SERT influence response to the drug.<sup>375</sup> Similarly, there are differences in mucosal serotonin metabolism in people with IBS-D, and those with the lowest concentrations in rectal biopsies have been shown to be the most responsive to treatment with ondansetron, another 5-HT<sub>3</sub>-receptor antagonist.<sup>226</sup> Studies have also highlighted the role that certain CNS pathways may play in determining clinical response to drugs. In one placebo-controlled trial of alosetron, there was an association between subjective symptom improvement and reduced activity in the amygdala,<sup>376</sup> which is a component of the limbic system that is more active during visceral

stimulation in people with non-constipated IBS compared with healthy controls.<sup>377</sup>

Patients who exhibited less activity in the orbitofrontal cortex bilaterally, and in the left medial temporal gyrus, in response to rectal distension using a barostat at baseline also appear to respond better to treatment with alosetron, and these alterations in CNS activity seem to correlate with lower levels of psychological distress.<sup>378</sup> Consequently, novel approaches to subgrouping people with IBS that include factors other than stool pattern might reveal who is more likely to respond to a peripherally acting drug in isolation, and who is liable to need additional treatments, such as centrally acting neuromodulators or psychological therapies. This will be the focus of the work presented in Chapters 6 and 7, using mathematical modelling to derive new IBS subgroups in a large cohort of people who identify as having IBS. However, prior to conducting this analysis, it is first necessary to examine the epidemiological, clinical, and psychological characteristics of the study cohort, and this is the aim of the study reported in Chapter 5.

**CHAPTER 5**

**Describing the Epidemiological, Clinical, and Psychological  
Characteristics of Individuals with Self-reported Irritable Bowel  
Syndrome and Exploring Differences Based on the Rome IV Versus  
Rome III Criteria**

## 5.1 Introduction

This chapter describes the recruitment of a large cohort of people who self-identify as having IBS. Their data will be used to examine new approaches to subgrouping individuals with IBS, as detailed in Chapter 6. However, this data also provides a valuable opportunity to examine whether demographic and clinical differences exist between people with IBS dependent on whether the Rome IV or Rome III criteria are used to define IBS, because both sets of criteria were applied simultaneously. As will be discussed, understanding this is important in its own right, being relevant to both treatment and research in IBS. However, it also has implications for subgrouping people with IBS, as it may be that mathematical modelling derives subgroups that differ both in number and characteristics, dependent on how IBS is defined in the model.

The role of symptom-based diagnostic criteria for making a diagnosis of IBS has already been described in detail. The aim of these criteria is to reduce unnecessary and exhaustive investigation before a diagnosis of IBS is reached, as well as to facilitate the recruitment of homogeneous groups of patients into research studies that examine either underlying pathophysiological mechanisms in IBS, or the efficacy of therapies, such as the trials included in the network meta-analyses reported in Chapters 3 and 4. The current gold standard for diagnosing IBS are the Rome IV criteria. These were described in 2016,<sup>14</sup> and were modified from the previous Rome III criteria.<sup>32</sup> As discussed already, there were three main changes made in moving from the Rome III criteria to Rome IV, which are summarised again here. Firstly, abdominal discomfort was removed from the definition of IBS, as this was felt to be an ambiguous term, with no equivalent in some languages. It was hypothesised that, regardless of whether the term abdominal pain or abdominal discomfort was used, the same individuals would meet criteria for IBS.<sup>33</sup> Second, the threshold for the frequency of abdominal pain

required to meet criteria for IBS was increased from 3 days per month, to one day per week, based on a normative survey of the frequency of the occurrence of abdominal pain in the general population.<sup>33</sup> Finally, there was an appreciation that abdominal pain in IBS is related to, rather than just relieved by, defaecation.

The aim of these changes was to increase the specificity of the Rome IV criteria, over prior iterations, which have performed only modestly in diagnosing IBS in previous studies conducted among unselected patients with lower gastrointestinal symptoms.<sup>23,34</sup> A recent validation study suggests that this aim has been achieved;<sup>37</sup> however, due to their more restrictive nature, the prevalence of symptoms compatible with IBS among individuals in population-based surveys is likely to fall when using the Rome IV criteria. Other investigators have suggested that among patients with IBS in secondary or tertiary care, implementation of these criteria, in preference to Rome III, has few implications, other than an increase in the severity of symptoms among those with Rome IV IBS. Most patients with Rome III-defined IBS still meet the Rome IV criteria for IBS,<sup>40,41</sup> and there are little in the way of demographic differences between individuals when the different criteria are used.<sup>42</sup>

Unfortunately, most of these studies did not actually apply the Rome III and Rome IV criteria simultaneously in their study design, but rather used a retrospective surrogate set of criteria approximating Rome IV. In addition, as the spectrum of patients in secondary and tertiary care is likely to be relatively narrow, there may be other consequences for individuals with IBS in the community when moving from Rome III to Rome IV, which were not uncovered by the design of these studies. This study therefore applied the Rome III and Rome IV criteria simultaneously to people who were not recruited from a referral population.



There were several hypotheses. First, despite believing they have IBS, many of these individuals would not meet Rome IV criteria for IBS. Second, the degree of agreement between Rome III and Rome IV would be only modest. Third, many of those with Rome III-defined IBS, but who did not meet the Rome IV criteria for IBS, would instead be classified as suffering from one of the other functional bowel disorders, and that this may have implications in terms of available treatment options. Fourth, there may be substantial implications for clinical trials of novel therapies for IBS, in terms of symptom severity, mood, and psychological health among individuals now defined as having IBS according to the Rome IV criteria.

## **5.2 Methods**

### **5.2.1 Participants and Setting**

The study was conducted among individuals who self-identified as having IBS, and who were registered with three organisations in the UK. The first was the IBS network, the registered charity for people living with the condition. The second was TalkHealth, an online social health community providing information about various medical conditions. The third was ContactMe-IBS, a dedicated register allowing individuals with IBS not receiving specialist care currently to participate in research. There were no exclusion criteria, other than an inability to understand written English. All individuals registered with these organisations were contacted via a postal and electronic mailshot, between December 2017 and December 2018. This correspondence directed them to a website, where they were able to access further information about the study. Those who wanted to participate could complete a questionnaire online, with their responses stored in an online database. The University of Leeds School of Medicine research ethics committee approved the study in November 2017 (reference MREC17-018).

## **5.2.2 Data Collection and Synthesis**

### **5.2.2.1 Demographic Data**

Basic demographic data, including age, gender, ethnicity, marital status, educational level, lifestyle (tobacco and alcohol use), height (in metres), and weight (in kilograms), which were used to calculate body mass index (BMI), were collected using the questionnaire. Respondents were also asked to state whether their IBS symptoms commenced after an acute enteric infection, and whether they had seen a GP or a gastroenterologist with their symptoms.

### **5.2.2.2 Definitions of Functional Bowel Disorders**

Lower gastrointestinal symptom data were captured using the Rome III and Rome IV questionnaires.<sup>379, 380</sup> The presence or absence of either Rome III or Rome IV-defined IBS among all individuals was assigned according to the scoring algorithms proposed for use with the Rome III and Rome IV questionnaires,<sup>14, 32</sup> which are detailed in Table 1.1. The study then examined whether using the Rome IV criteria to define IBS led to individuals who would previously have met the Rome III criteria for IBS being reclassified as suffering from another functional bowel disorder, including functional constipation, functional diarrhoea, functional abdominal bloating or distension, and unspecified functional bowel disorder. The proportion of participants with other lower gastrointestinal symptoms, such as urgency and faecal incontinence, was also assessed.

### **5.2.2.3 Assessment of Symptom Severity and Impact on Activities of Daily Living**

The severity of IBS symptoms was assessed using the IBS severity scoring system (IBS-SSS).<sup>381</sup> This is a seven-item self-administered questionnaire measuring presence, severity, and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit, and degree to which IBS symptoms

are affecting, or interfering with, the person's life in general. The maximum score is 500 points: <75 points indicates remission of symptoms; 75-174 points mild symptoms; 175-299 points moderate symptoms; and 300-500 points severe symptoms. It was also possible to assess the degree to which IBS symptoms were impacting on activities of daily living using some of the items in the Rome IV questionnaire.

#### **5.2.2.4 Assessment of Mood and Somatoform-type Behaviour**

Anxiety and depression data were collected using the hospital anxiety and depression scale (HADS).<sup>382</sup> The total HADS score ranges from a minimum of 0 to a maximum of 21 for either anxiety or depression. Severity for each was categorised into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10), or abnormal ( $\geq 11$ ).<sup>382</sup> Somatisation data were collected using the patient health questionnaire-15 (PHQ-15),<sup>383</sup> which is derived from the validated full PHQ.<sup>384</sup> The total PHQ-15 score ranges from a minimum of 0 to a maximum of 30. Somatisation severity was categorised, as previously recommended,<sup>383</sup> using the total PHQ-15 score, into high (total PHQ-15  $\geq 15$ ), medium (10-14), low (5-9) or minimal ( $\leq 4$ ) levels.

#### **5.2.2.5 Assessment of Perceived Stress**

The 10-item version of the Cohen perceived stress scale (CPSS) was used to assess perceived stress. This is derived from the original 14-item instrument,<sup>385</sup> has been used widely, and is considered to be psychometrically reliable and comparable with its predecessor.<sup>386</sup> It measures the degree to which the individual feels he or she has experienced stress in the previous month. It has been used widely in research on stress and immune function. High CPSS scores appear to be associated with poor quality of life and poor coping in other gastrointestinal diseases, including inflammatory bowel disease.<sup>387</sup> As there are no validated cut offs to define low, medium, or high levels of perceived stress, these data were divided into tertiles of equal size.

### 5.2.2.6 Assessment of Gastrointestinal Symptom-specific Anxiety

Gastrointestinal Symptom-specific Anxiety was assessed using the visceral sensitivity index (VSI),<sup>115</sup> which is a 15-item instrument measuring gastrointestinal symptom-specific anxiety. Replies to each of the questions are provided on a six-point scale from “strongly disagree” (scored as 0) to “strongly agree” (scored as 5). Again, as there are no validated cut offs to define low, medium, or high levels of visceral sensitivity, these data were divided into tertiles of equal size.

### 5.2.3 Statistical Analysis

The proportions of individuals who self-identified as having IBS and who met either the Rome III or Rome IV criteria for IBS were calculated. Agreement between the Rome III and Rome IV criteria for the presence of IBS was measured using the modified Kappa statistic, where a value  $<0.2$  indicates poor agreement and a value  $>0.8$  indicates excellent agreement beyond chance. The study then examined whether individuals with Rome III-defined IBS were classified into another functional bowel disorder, based on the Rome IV criteria. Finally, the characteristics of individuals meeting the Rome III and Rome IV criteria were compared. Categorical variables, such as sex, ethnicity, impact on activities of daily living, presence of other lower gastrointestinal symptoms, and presence or absence of abnormal anxiety scores, abnormal depression scores, high somatisation scores, high perceived stress scores, and high levels of gastrointestinal symptom-specific anxiety were compared between individuals with Rome III and Rome IV IBS using a  $\chi^2$  test, and continuous data such as age, BMI, and scores for IBS-SSS, HADS, PHQ-15, CPSS, and VSI were compared using an independent samples *t*-test. Due to multiple comparisons a 2-tailed *p* value of  $<0.01$  was considered statistically significant for all analyses. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

### **5.3 Results**

In total, 1375 individuals who self-identified as having IBS were recruited into the study between December 2017 and December 2018. The mean age of recruited subjects was 49.2 years (range 18 to 86 years), 1157 (84.1%) were female, and 1293 (94.0%) of the respondents were White Caucasian. There were 180 (13.1%) individuals who stated that their IBS symptoms commenced after an acute enteric infection. Overall, 1048 (95.5%) of participants stated that they had previously seen their GP with their IBS, and 633 (57.7%) had seen a gastroenterologist.

#### **5.3.1 Proportion of Individuals with IBS Meeting the Rome III and Rome IV Criteria and Level of Agreement**

In total, 1368 individuals with IBS provided complete Rome III data, and 1080 (78.9%) of these met the Rome III criteria for IBS. Overall, 1373 individuals provided complete Rome IV data, of whom 811 (59.1%) met the Rome IV criteria for IBS (Table 5-1). Of those 1080 individuals who met Rome III criteria for IBS, 794 (73.5%) also met Rome IV criteria. Among 811 individuals meeting the Rome IV criteria for IBS, only 17 (2.1%) did not also meet the Rome III criteria. The Kappa statistic for the level of agreement between the Rome III and Rome IV was 0.50, indicating only moderate agreement. When the analysis was restricted to only those who had seen a gastroenterologist, the Kappa statistic for agreement between Rome III and Rome IV was very similar at 0.54.

**Table 5-1. Agreement Between the Rome III and Rome IV Criteria for IBS.**

	<b>Met Rome IV criteria for IBS (n = 811)</b>	<b>Did not Meet Rome IV criteria for IBS (n = 557)</b>
<b>Met Rome III criteria for IBS (n = 1080)</b>	794 (97.9%)	286 (51.3%)
<b>Did not Meet Rome III criteria for IBS (n = 288)</b>	17 (2.1%)	271 (48.7%)

### **5.3.2 Other Functional Bowel Disorder Diagnoses Among Individuals Not Meeting the Rome IV Criteria for IBS**

This study examined whether the 286 individuals who met the Rome III criteria for IBS, but who did not meet Rome IV, satisfied the Rome IV criteria for another functional bowel disorder. Overall, 33 (11.5%) subjects met the Rome IV criteria for functional constipation, 118 (41.3%) functional diarrhoea, 68 (23.8%) functional abdominal bloating or distension, and 67 (23.4%) an unspecified functional bowel disorder. This meant that of those individuals with Rome III IBS who did not meet the Rome IV criteria for IBS, only 11.5% were reclassified into another functional bowel disorder where licensed and evidence-based therapies are available. Reasons for not meeting the Rome IV criteria among those with Rome III IBS overall, and according to other Rome IV-defined functional bowel disorders, are provided in Table 5-2. The commonest reason was not meeting the required symptom frequency threshold for abdominal pain.

**Table 5-2. Reasons for not Meeting the Rome IV Criteria for IBS Among those Meeting the Rome III Criteria.**

	Reported abdominal discomfort, rather than abdominal pain (%)	Reported abdominal pain, but not at the required frequency (%)	Other reasons (%)
<b>Met Rome III criteria, but not Rome IV criteria, for IBS (n = 286)</b>	26 (9.1)	253 (88.5)	7 (2.4)
Rome IV functional constipation (n = 33)	3 (9.1)	29 (87.9)	1 (3.3)
Rome IV functional diarrhoea (n = 118)	9 (7.6)	108 (91.5)	1 (0.8)
Rome IV functional abdominal bloating (n = 68)	6 (8.8)	61 (89.7)	1 (1.5)
Rome IV unspecified functional bowel disorder (n = 67)	8 (11.9)	55 (82.1)	4 (6.0)



### 5.3.3 Characteristics of Individuals with Rome III and Rome IV IBS

The characteristics of the 286 individuals who met the Rome III criteria, but not the Rome IV criteria, for IBS were examined and compared with those of the 811 who met the Rome IV criteria (Table 5-3). Individuals with Rome IV IBS were significantly younger ( $p < 0.001$ ) and less likely to use alcohol ( $p = 0.005$ ), but there were no other differences in demographic characteristics. There was no difference in the proportion of people who had seen a GP with their IBS symptoms, but significantly more of those with Rome IV IBS had seen a gastroenterologist ( $p = 0.001$ ). Those with Rome III IBS were more likely to meet criteria for IBS-M, and those with Rome IV IBS were more likely to have IBS-D or IBS-C ( $p < 0.001$ ). Symptoms were significantly more severe among those with Rome IV IBS, and were more likely to interfere with activities of daily living ( $p < 0.001$ ). Debilitating urgency occurring on most days and faecal incontinence on at least a weekly basis were significantly more frequent, mood and psychological health were significantly worse, and perceived stress levels and gastrointestinal symptom-specific anxiety were higher among those with Rome IV IBS ( $p < 0.001$ ).

**Table 5-3. Characteristics of Individuals Meeting Rome III Criteria, but not Rome IV Criteria for IBS, Compared with those Meeting Rome IV Criteria for IBS.**

	Met Rome III Criteria, but not Rome IV Criteria, for IBS  (n = 286)	Met Rome IV Criteria for IBS  (n= 811)	<i>p</i> value*
Mean age (SD)	51.5 (15.5)	47.4 (15.2)	<0.001
Mean body mass index (SD)	26.9 (8.5)	28.4 (8.3)	0.03
Female gender (%)	231 (80.8)	697 (85.9)	0.04
Tobacco user (%)	12 (4.2)	79 (9.7)	0.01
Alcohol user (%)	187 (65.4)	442 (54.5)	0.005
Married or co-habiting (%)	186 (65.0)	526 (64.9)	1.00
University or postgraduate level of education (%)	72 (25.2)	164 (20.3)	0.10
White Caucasian ethnicity (%)	273 (95.5)	763 (94.3)	0.47
IBS after acute enteric infection (%)	44 (15.4)	106 (13.1)	0.38
Seen a GP with IBS (%)	270 (94.4)	778 (95.9)	0.24
Seen a gastroenterologist with IBS (%)	141 (49.3)	492 (60.7)	0.001
IBS stool subgroup (%)			
IBS-C	33 (11.5)	142 (17.5)	
IBS-D	89 (31.1)	311 (38.3)	
IBS-M	159 (55.6)	331 (40.8)	
IBS-U	5 (1.7)	26 (3.2)	<0.001

<b>IBS-SSS symptom severity (%)</b>			
Remission	17 (6.0)	8 (1.0)	
Mild	117 (41.1)	90 (11.1)	
Moderate	126 (44.2)	333 (41.1)	
Severe	25 (8.8)	379 (46.8)	<0.001
<b>Mean IBS-SSS score (SD)</b>	188.2 (79.2)	292.0 (95.8)	<0.001
<b>IBS limits activities <math>\geq</math>50% of the time (%)</b>	136 (47.6)	573 (70.7)	<0.001
<b>Urgency at least most days (%)</b>	44 (15.4)	233 (28.7)	<0.001
<b>Faecal incontinence at least once a week (%)</b>	26 (9.1)	157 (19.4)	<0.001
<b>HADS-A categories (%)</b>			
Normal	121 (42.3)	202 (24.9)	
Borderline	63 (22.0)	167 (20.6)	
Abnormal	102 (35.7)	442 (54.5)	<0.001
<b>Mean HADS-A score (SD)</b>	8.7 (4.4)	11.0 (4.7)	<0.001
<b>HADS-D categories (%)</b>			
Normal	203 (71.0)	434 (53.5)	
Borderline	52 (18.2)	191 (23.6)	
Abnormal	31 (10.8)	186 (22.9)	<0.001
<b>Mean HADS-D score (SD)</b>	5.6 (4.1)	7.7 (4.5)	<0.001

<b>PHQ-15 categories (%)</b>			
Mild somatisation	8 (2.8)	6 (0.7)	
Low somatisation	71 (24.8)	78 (9.6)	
Medium somatisation	128 (44.8)	270 (33.3)	
High somatisation	79 (27.6)	457 (56.4)	<0.001
<b>Mean PHQ-15 score (SD)</b>	11.8 (4.0)	15.4 (4.9)	<0.001
<b>CPSS tertiles (%)</b>			
Low	131 (45.8)	226 (27.9)	
Medium	98 (34.3)	294 (36.3)	
High	57 (19.9)	290 (35.8)	<0.001
<b>Mean CPSS score (SD)</b>	17.6 (7.8)	21.6 (8.2)	<0.001
<b>VSI tertiles (%)</b>			
Low	141 (49.3)	196 (24.3)	
Medium	94 (32.9)	281 (34.8)	
High	51 (17.8)	331 (41.0)	<0.001
<b>Mean VSI score (SD)</b>	39.5 (16.9)	50.7 (16.8)	<0.001

CPSS, Cohen perceived stress score; HADS, hospital anxiety and depression scale; IBS-SSS, IBS severity scoring system; PHQ-15, patient health questionnaire-15; SD, standard deviation; VSI, visceral sensitivity index.

\**p* value for independent samples *t*-test for continuous data and Pearson  $\chi^2$  for comparison of categorical data.

## 5.4 Discussion

This study has examined the impact of moving from the Rome III criteria for the diagnosis of IBS to Rome IV, in a large cohort of individuals who self-identify as having the condition in the UK. Among more than 1300 participants, almost 80% met the Rome III criteria, but when the Rome IV criteria were used less than 60% still met criteria for IBS. The level of agreement between Rome III and Rome IV criteria for diagnosing IBS was moderate, with almost one-quarter of those meeting the Rome III criteria no longer classed as having IBS when the Rome IV criteria were used. Importantly, among these 286 individuals, almost 90% were reclassified by the Rome IV questionnaire as having functional diarrhoea, functional abdominal bloating or distension, or an unspecified functional bowel disorder. None of these conditions has any licensed or evidence-based therapies available to treat them. Finally, when comparing the characteristics of the 811 individuals with Rome IV-defined IBS with the 286 subjects who met Rome III criteria, there were significantly more individuals with severe symptoms, which had a greater impact on activities of daily living, and higher proportions of participants with low mood, poor psychological health, and high levels of stress and gastrointestinal symptom-specific anxiety among those meeting the Rome IV criteria for IBS. As will be discussed, the findings of this study have implications for future research.

A large number of individuals were recruited into this study, all of whom were in the community and self-identified as having IBS. Some individuals had consulted a GP, some a gastroenterologist, and some had never consulted a physician, meaning the participants are likely to be generalisable to many individuals living with IBS in the UK. This is further supported by the proportion of individuals in the study who stated that their IBS symptoms commenced after an acute enteric infection, which at 13.1% is almost identical to that reported in another recent, large internet survey of subjects with

IBS,<sup>159</sup> and the fact that the proportion with each IBS stool subgroup is similar to other community based surveys.<sup>61, 102</sup> Due to the use of an online questionnaire, data collection was near complete for many of the variables of interest. It is believed that this is the first study to examine the implications of moving from the Rome III to Rome IV criteria for IBS in individuals living with the condition that has actually used the validated Rome III and Rome IV questionnaires side by side in the same study.

Weaknesses of the study include the fact that the diagnosis of IBS was not confirmed in all individuals in this study by looking at their medical records. This means that the study relied on the fact that the people who took part believed that they had IBS as a means of confirming a diagnosis. This may have led to a reduction in performance of both the Rome III and Rome IV criteria. However, given that almost 80% of those who responded did meet the Rome III criteria for IBS, more than 95% had previously seen a GP with their IBS, and almost 60% had seen a gastroenterologist, this is unlikely to have affected the results to any great degree. As the questionnaire was completed online, after visiting a website, it was not possible to assess how many individuals chose not to complete the questionnaire, or whether those who responded are broadly representative of all the people with IBS registered with these three organisations. In addition, because of the setting in which this study was conducted, and the fact that participants had to have internet access and be motivated to participate, the individuals taking part may not be generalisable to patients consulting with a gastroenterologist in secondary or tertiary care. However, this is probably unlikely, as 57.7% had previously consulted in this setting. Finally, there may have been an over-representation of White Caucasians in this study, meaning that the results cannot be extrapolated to individuals with IBS of other ethnicities.

As discussed, previous studies have suggested there may be few implications of moving from the Rome III to the Rome IV criteria for IBS.<sup>40-42</sup> In a study conducted in

a tertiary referral population in Sweden,<sup>40</sup> Aziz *et al.* reported that 85% of patients with Rome III-defined IBS met the Rome IV criteria, but that quality of life was impaired to a greater degree, and symptoms were more severe, among those with Rome IV IBS. Another study, conducted in secondary and tertiary care in the Netherlands demonstrated almost identical findings.<sup>41</sup> More than 85% of individuals meeting Rome III criteria for IBS still met the Rome IV criteria, although symptoms were more severe, and quality of life worse, in those with Rome IV IBS. However, neither of these studies applied the Rome III and IV criteria for IBS simultaneously, but instead used a surrogate for Rome IV, consisting of reporting abdominal pain on  $\geq 2$  days in the last 10 days in one study,<sup>40</sup> or reporting abdominal pain once a week in a diary in the other study.<sup>41</sup> In addition, the consequences of moving from Rome III to Rome IV-defined IBS in those who did not meet Rome IV criteria, in terms of reclassification to another functional bowel disorder, were only examined in one of these studies, with approximately one-third of patients meeting criteria for each of functional constipation, functional diarrhoea, and functional abdominal bloating or distension.<sup>41</sup> A third tertiary care study showed less diagnostic agreement between Rome III and IV criteria, with a Kappa of 0.45, and only 46.5% of those with Rome III-defined IBS meeting the Rome IV criteria.<sup>42</sup> Symptom severity was greater among those with Rome IV IBS, but there were few other differences.

There are likely to be several implications of this study for research and clinical practice. Firstly, moving from the Rome III criteria for IBS to Rome IV means that approximately one-in-four individuals who believe that they have IBS will no longer meet criteria for the condition. Although all these individuals can be reclassified as suffering from another functional bowel disorder according to Rome IV, in almost 90% of individuals in this study this was not one that was treatable. Functional constipation is the only other functional bowel disorder with evidence-based licensed therapies

available to treat it.<sup>283, 388</sup> It is unlikely that those with troublesome gastrointestinal symptoms will be particularly happy to be labelled as having a poorly understood condition, such as functional abdominal bloating or distension, or an unspecified functional bowel disorder, with little in the way of effective therapies. In addition, unlike in IBS where a positive diagnosis is encouraged,<sup>212, 269, 278</sup> functional diarrhoea is a diagnosis of exclusion, due to the higher likelihood that organic conditions, such as bile acid diarrhoea or microscopic colitis may present with similar symptoms. This is likely to have implications for the health service, in terms of costs of investigation.

Secondly, the degree of agreement between Rome III and IV criteria for IBS was only modest, and worse than for any other iterations of the Rome criteria. A previous study demonstrated Kappa values of between 0.74 to 0.95 for the Rome I, II, and III criteria for diagnosing IBS.<sup>34</sup> The main reason for the lack of agreement between Rome III and Rome IV was the increase in the frequency threshold for abdominal pain required to meet Rome IV criteria. This study shows that applying this threshold leads to a substantial number of individuals who believe they have IBS no longer meeting diagnostic criteria for the condition. Finally, the increased severity of symptoms, and higher levels of mood disorder, poor psychological health, perceived stress, and visceral sensitivity seen among those with Rome IV IBS demonstrate that this is the more severe end of the disease spectrum. This is likely to have huge implications for treatment trials in the disorder. Placebo response rates in IBS are high,<sup>318</sup> and most drugs that have been tested in patients with Rome III IBS only have modest efficacy,<sup>292, 293, 297, 298, 335</sup> as has been discussed in the network meta-analyses presented in Chapters 3 and 4. It is therefore possible that moving from Rome III to Rome IV IBS will reduce the likelihood of novel pharmacological therapies demonstrating efficacy in the condition in future RCTs; however, placebo response rates may be lower among a patient cohort with more severe IBS.



In summary, moving from the Rome III to the Rome IV criteria for IBS led to a reclassification of one-in-four individuals who believe they have IBS to another functional bowel disorder. Almost 90% instead met criteria for disorders that are even more poorly understood than IBS and have little in the way of available evidence-based therapies. Most of this reclassification occurred due to the change in the frequency threshold for abdominal pain required by Rome IV. Agreement between Rome III and Rome IV was modest at best. Individuals meeting Rome IV criteria for IBS had more severe symptoms, which impacted more on activities of daily living, and had higher prevalence of abnormal mood, psychological comorbidity, perceived stress, and gastrointestinal symptom-specific anxiety. Understanding the impact of these changes to the diagnostic classification system for IBS on the efficacy of novel therapies for the disorder in future RCTs will be important. The findings of this study, therefore, have important implications for the work presented in Chapters 6 and 7, in which data from the same cohort of individuals will be used to explore novel approaches to subgrouping people with IBS. The clinical and psychological characteristics of people with IBS differ significantly dependent on whether the diagnosis is made using the Rome III or Rome IV criteria, so it will be necessary to evaluate whether different subgrouping models are derived depending on which iteration of the Rome criteria is used to define IBS. In addition, this study highlights that reclassification to another functional bowel disorder occurs in people who no longer meet criteria for IBS, and that this has potentially important clinical ramifications. This will need to be a consideration when evaluating the natural history of the novel subgrouping models in Chapter 7.

## **CHAPTER 6**

### **Using Latent Class Analysis to Identify Distinct and Reproducible Subgroups of People with Irritable Bowel Syndrome Based on Gastrointestinal Symptoms and Psychological Profiles**

## 6.1 Introduction

Earlier discussion has already detailed how people with IBS are subgrouped according to their predominant stool pattern into one of four groups: IBS-C, IBS-D, IBS-M, or IBS-U. These groups are defined by the Rome criteria and have been described in Table 1.3. Although the aims of this classification system are laudable, using it to direct therapy is problematic for several reasons. First, even when people with IBS with these stool subgroups are treated with novel drugs, which have more precise modes of action, only 20% to 30% report symptom improvement,<sup>290, 291, 293, 298, 335, 350</sup> and, as has already been shown in Chapters 3 and 4, there is little to choose between many of the available drugs, in terms of efficacy. Second, predominant stool type in IBS fluctuates over time.<sup>44, 47</sup> Third, almost 50% of patients have IBS-M or IBS-U,<sup>61, 389-391</sup> but most new drugs are tested only in IBS-D or IBS-C, so treatment options for patients with these two subgroups are limited. Finally, and perhaps most importantly, because IBS is a brain-gut disorder, mood and psychological health play an important role in the development and persistence of symptoms.<sup>50-54</sup> Mood disorders are much more common in people with IBS than among healthy individuals.<sup>55</sup> Earlier use of psychological therapies in patients exhibiting substantial psychological comorbidity might change the natural history of IBS. However, access to these is limited and, often, their use is advocated only in patients whose symptoms do not respond adequately to pharmacological treatment,<sup>269</sup> so they tend to be used only as a last resort. Indeed, recent studies have bolstered interest in the use of psychological therapies, such as CBT, as effective treatments for IBS with long-lasting benefits.<sup>308-310</sup> Unfortunately, current approaches to subgrouping patients with IBS offer no clinical guidance regarding who might derive the most benefit from these therapies.

A classification system based on stool pattern alone does not, therefore, reflect the complex composite nature of IBS adequately, nor does it allow equitable access of

patients to either clinical trials of novel drugs, or existing drugs or psychological therapies with an evidence base for efficacy. In acknowledgment of the fact that IBS is a disorder of gut-brain interaction, with biopsychosocial influences, the Rome Foundation developed the MDCP, which has already been described in detail in Table 1.4. To recap, this is a framework that, in addition to clinical symptoms, includes the assessment of psychological factors, and impact of the illness, in order to build a unique clinical profile for each patient.<sup>57</sup> Although intended to help guide treatment, this approach has yet to be utilised in routine clinical practice, and is not incorporated into current diagnostic criteria. If it were possible to classify patients, not only by clinical symptoms, but also by psychological profiles, this may help optimise treatment selection, resulting in better outcomes, and reduced health service and societal costs of IBS.<sup>392</sup>

To date, only a few studies have examined this issue.<sup>26, 27, 59</sup> In two of these studies, conducted by the same group of investigators, distinct subgroups, or clusters, of patients appeared to exist. These subgroups consisted of those whose symptoms were predominantly intestinal, and who had only minimal psychological distress, and those for whom IBS symptoms were part of a broader picture, which included anxiety, depression, or extra-intestinal symptoms.<sup>26, 27</sup> These subgroups were not, however, reproducible across different patient cohorts or different iterations of the Rome criteria, and one study was conducted in only 172 patients in tertiary care.<sup>26</sup> A third study demonstrated clusters distinguished by low or high severity of intestinal and non-intestinal symptoms, which were further differentiated by the extent of impairment in IBS-related quality of life, but combined patients meeting either the Rome II or Rome III criteria together.<sup>59</sup> However, the study reported in Chapter 5 has shown that there are important differences in the clinical and psychological characteristics of people with

IBS depending on how it is defined. Comparing subgroups between different iterations of the Rome criteria is, therefore, important.

In this study, it was hypothesised that it would be possible to derive subgroups of people with IBS that were distinct and reproducible, irrespective of setting or diagnostic criteria. If feasible, these subgroups could change both the classification of, and management strategies for, IBS. For instance, those with predominantly gastrointestinal symptoms may respond best to a drug acting peripherally on the intestine, those with predominantly psychological or extra-intestinal symptoms to a centrally acting drug or psychological therapy, and those with both gastrointestinal and extra-intestinal symptoms to a combination of therapies.

## **6.2 Methods**

### **6.2.1 Participants and Setting**

The study recruited individuals who self-identified as having IBS registered with three UK organisations. Full details of the recruitment methodology have already been discussed in Chapter 5.

### **6.2.2 Data Collection and Synthesis**

#### **6.2.2.1 Demographic and Symptom Data**

Basic demographic data were collected, and respondents were asked to state whether they had seen a GP or a gastroenterologist about their IBS symptoms. Lower gastrointestinal symptom data was captured using the Rome III and Rome IV questionnaires.<sup>379, 380</sup> The severity of IBS symptoms was assessed using the IBS-SSS.<sup>381</sup> Full details of demographic and symptom data collection have already been discussed in Chapter 5.

### **6.2.2.2 Assessment of Mood and Extra-Intestinal Symptoms**

Anxiety and depression data was collected using the HADS.<sup>382</sup> The total HADS score ranges from a minimum of 0 to a maximum of 21 for either anxiety or depression. Data regarding extra-intestinal symptoms was collected using the PHQ-12,<sup>113</sup> derived from the validated PHQ-15.<sup>383</sup> The total PHQ-12 score ranges from a minimum of 0 to a maximum of 24. Full details of the assessment of mood and extra-intestinal symptoms have already been discussed in Chapter 5.

### **6.2.2.3 Assessment of Gastrointestinal Symptom-specific Anxiety and Perceived Stress**

The 15-item VSI<sup>115</sup> was used to measure gastrointestinal symptom-specific anxiety. Perceived stress was assessed using the 10-item version of the CPSS, which is derived from the original 14-item instrument.<sup>385</sup> Full details of the assessment of gastrointestinal symptom-specific anxiety and perceived stress have already been discussed in Chapter 5.

## **6.2.3 Statistical Analysis**

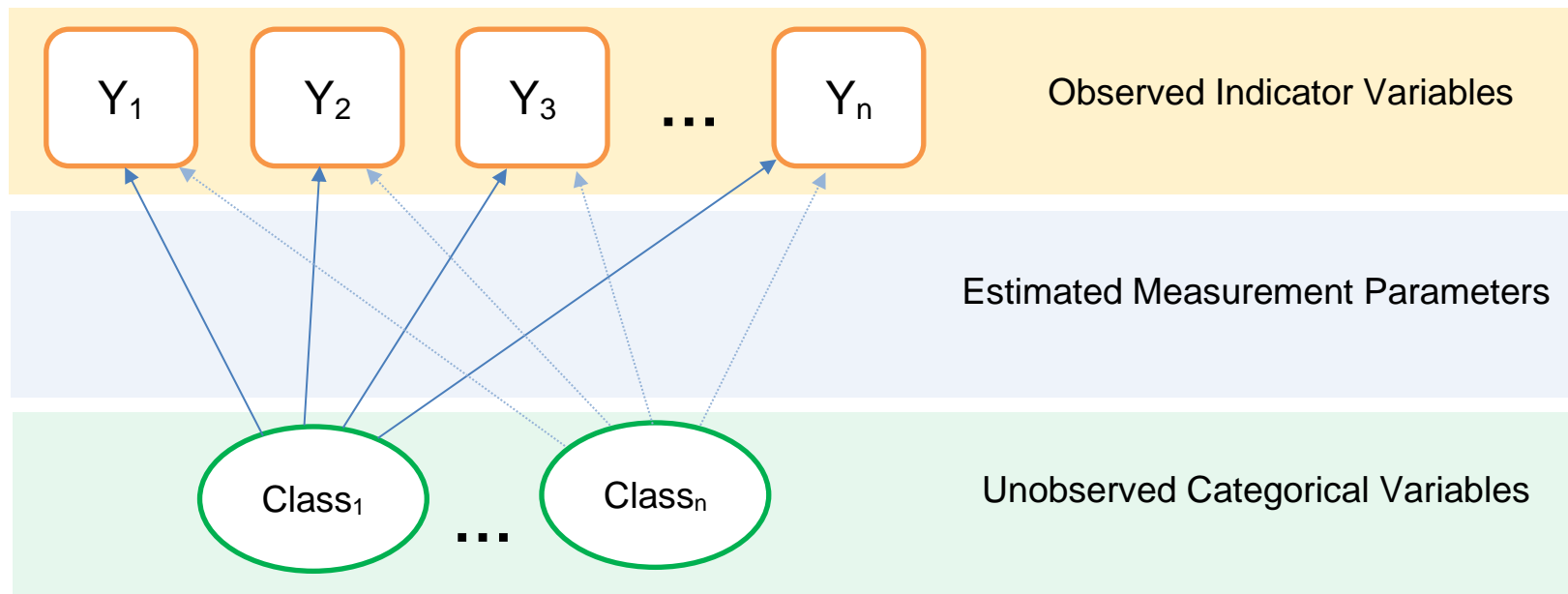
### **6.2.3.1 Rome III and Rome IV Cohorts**

Two cohorts of individuals, who self-identified as having IBS and who met either the Rome III or Rome IV criteria for IBS, were identified. Many participants met both iterations of the diagnostic criteria and were therefore represented in both cohorts. Consequently, the baseline characteristics of these two cohorts were compared using a partially overlapping *t*-test for continuous data, and a partially overlapping *z*-test for comparison of proportions,<sup>393</sup> with the “partiallyoverlapping” package in R (version 3.6.2).<sup>321, 394</sup>

### 6.2.3.2 Latent Class Analysis

Latent class analysis (LCA) was performed in each cohort using LatentGOLD (version 5.1 Statistical Innovations, Belmont, MA, USA).<sup>395</sup> LCA is a method of structural equation modelling used to identify unobserved groups, or latent classes, within observed multivariate data.<sup>396</sup> A statistical model is postulated for the population from which the data sample is obtained, and it is assumed that a mixture of underlying probability distributions generates the data.<sup>397</sup> The use of LCA for this purpose is referred to as model-based clustering (Figure 6-1). LCA is a flexible technique, enabling inclusion of a range of variable types within the same model. Analysis is iterative, whereby, for any given number of clusters, multiple solutions are evaluated to determine the best output.<sup>397</sup> Finally, robust statistical criteria can be used to determine the best fit of the model, and the optimum number of clusters.<sup>398</sup> The Bayesian information criterion of the log-likelihood (BIC(LL)) was used for this purpose, and the cluster solution with the lowest BIC(LL) value was selected as the one that best fit the data. Details of the variables used in the model are provided in Table 6-1.

**Figure 6-1. Principles of Latent Class Analysis.**



The observed indicator variables are chosen directly from the dataset to be used in the model. The unobserved categorical variables are the latent classes, the number of which can be specified. The estimated measurement parameters describe the relationship between the unobserved categorical variables and the observed data. Interpretation of these parameters enables identification and characterisation of clusters, or subgroups, within the dataset that would otherwise be unknown.



**Table 6-1. Variables Used in the Latent Class Analysis.**

	<b>Variable</b>	<b>Type of variable</b>	<b>Scale of Measurement</b>	<b>Reason for including in the model</b>
<b>Gastrointestinal Symptoms</b>	Frequency of abdominal pain (or discomfort*) anywhere in the abdomen in past 3 months	Ordinal	9-point scale from “Never” (0) to “Multiple times per day or all the time” (8)	All of these variables for quantifying gastrointestinal symptoms were taken from Rome Foundation questionnaires. These are the recognised “gold standard” for diagnosing IBS, and are widely used.
	Frequency of abdominal pain being closely related to a bowel movement	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency with which abdominal pain improved or resolved following a bowel movement	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency with which stools became softer or harder than usual in association with abdominal pain	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency with which stools became more or less frequent than usual in association with abdominal pain	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency with which abdominal pain started or got worse after a meal	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency with which abdominal pain restricted usual activities	Ordinal	11-point scale from “0%” (never) to “100%” (always)	
	Frequency of hard or lumpy stools in last 3 months	Ordinal	5-point scale from “0%” (never or rarely) to “100%” (always)	
	Frequency of loose, mushy, or watery stools in the last 3 months	Ordinal	5-point scale from “0%” (never or rarely) to “100%” (always)	
	Frequency of faecal urgency over last 3 months	Ordinal	9-point scale from “Never” (0) to “Multiple times per day or all the time” (8)	
	Frequency of faecal incontinence over last 3 months	Ordinal	9-point scale from “Never” (0) to “Multiple times per day or all the time” (8)	

	Frequency of abdominal bloating or distension over last 3 months	Ordinal	9-point scale from “Never” (0) to “Multiple times per day or all the time” (8)	
<b>Extra-intestinal Symptoms</b>	All individual items of the PHQ-12 and the frequency experienced in the last 4 weeks: Back pain Arm, leg, joint pain Period pain/period problems Headaches Chest pain Dizziness Fainting spells Heart pounding/racing Shortness of breath Pain/problems during sex Feeling tired or low in energy Trouble sleeping	Ordinal	3-point scale: “Never” (0), “A little” (1), or “A lot” (2)	Reporting symptoms referable to multiple body systems, also referred to as somatisation, is recognised as being associated with IBS and other functional gastrointestinal disorders. The PHQ-12 questionnaire is a widely used and validated method for measuring this.
<b>Mood</b>	Presence of anxiety, as measured by the total score of the HADS-Anxiety questionnaire	Ordinal	3-point scale: normal (0), borderline (1), or abnormal (2)	Abnormal mood is well-recognised as being an important factor in IBS. The HADS questionnaire for quantifying the presence of anxiety and/or depression are widely used and validated for this purpose.
	Presence of depression, as measured by the total score of HADS-Depression questionnaire	Ordinal	3-point scale: normal (0), borderline (1), or abnormal (2)	

HADS, hospital anxiety and depression scale; PHQ-12, patient health questionnaire-12.

\* Discomfort was included, in addition to pain, for the Rome III definition of IBS, as per Rome III criteria.

### **6.2.3.3 Description of Cluster Characteristics**

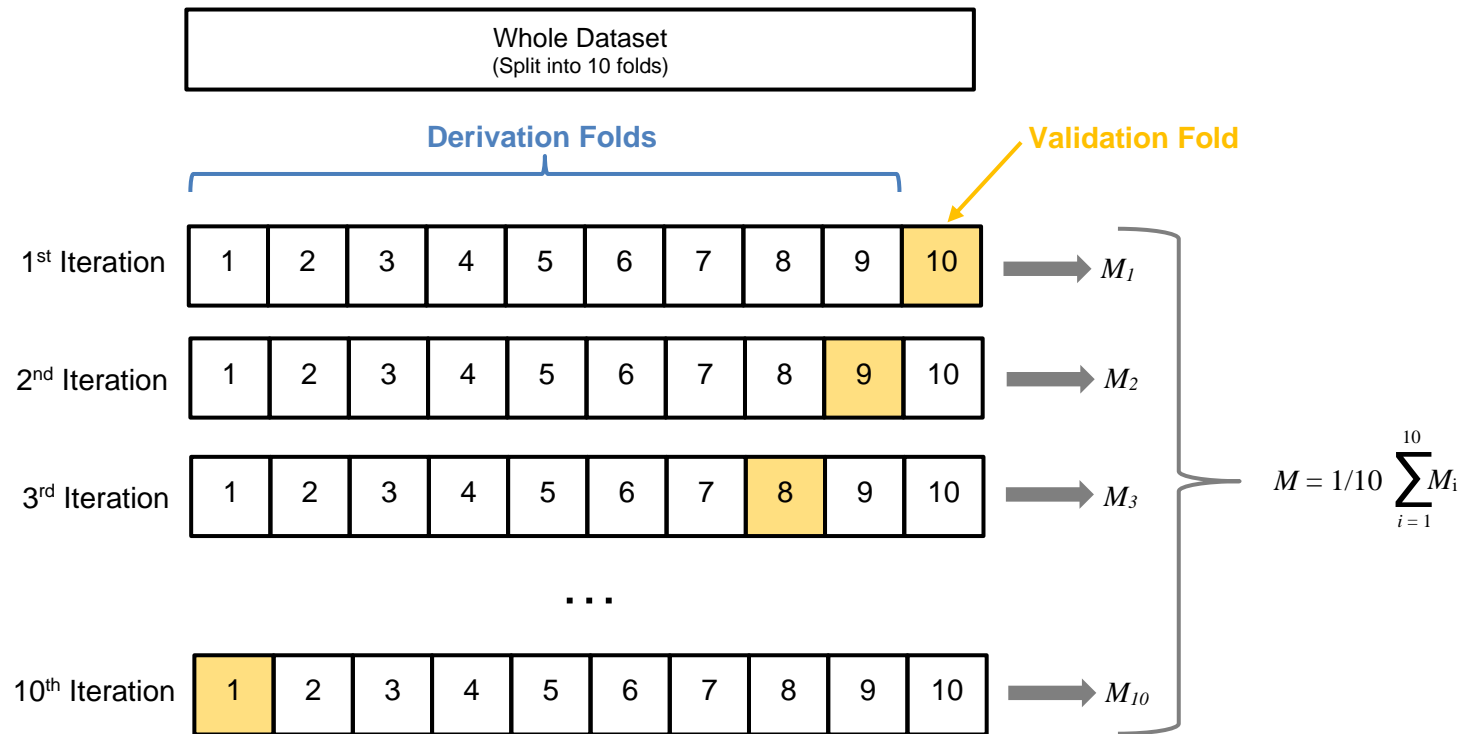
For each cluster, a radar plot was drawn using *z*-values for each variable. These were calculated by adjusting the cluster mean for each variable to the cohort mean and standard deviation (SD) for that variable. The radar plots were compared by visual inspection and the particular characteristics of each cluster were described.

### **6.2.3.4 Validation of Rome III and IV Latent Class Models**

In order to internally validate the analyses, 10-fold cross-validation was performed,<sup>399</sup> for both the Rome III and Rome IV models, using the *n*-validation capability of LatentGOLD. The misclassification statistic for the original model derivation was compared with that obtained from cross-validation, in order to understand how the model would perform if applied to a different dataset.

10-fold cross-validation was also performed manually, by splitting the data randomly into 10 equally-sized groups, or folds. These folds were recombined in all 10 possible permutations, omitting a different fold each time, and LCA was undertaken in each recombined dataset, using the same variables as were included in the original model. The clusters for each derivation were drawn out using radar plots and it was determined, by visual inspection, whether the subgroups appeared similar to those of the original model. Each derivation model was validated by applying it to the fold that had been omitted each time, averaging the misclassification statistic across all 10 validation cycles to determine the overall misclassification statistic for the cross-validation process as a whole. The process of 10-fold cross-validation is illustrated in Figure 6-2.

**Figure 6-2. Principles of 10-Fold Cross-Validation.**



The dataset is split randomly into 10 equally-sized folds. In each iteration, the model is derived in the combined training folds and evaluated in the validation fold in order to calculate a performance metric, in this case the misclassification statistic ( $M$ ). The misclassification statistic is averaged across all 10 iterations in order to calculate the misclassification statistic for the 10-fold cross-validation process as a whole.

### **6.2.3.5 Comparison of Characteristics of Individuals Between Clusters**

The characteristics of individuals in each cluster were compared for both the Rome III and Rome IV cohorts. Categorical variables, such as sex, consultation with a gastroenterologist, high levels of gastrointestinal symptom-specific anxiety or perceived stress, high symptom severity scores, IBS stool subgroup according to the BSFS, and whether IBS onset followed an acute enteric infection, were compared between individuals in each cluster using a  $\chi^2$  test. Differences in continuous variables between clusters were compared using a one-way analysis of variance (ANOVA) test. Due to multiple comparisons, a 2-tailed *p* value of <0.01 was considered as statistically significant for these analyses, which were performed using SPSS for Windows (version 24.0 SPSS Inc., Chicago, IL, USA).

## **6.3 Results**

In total, and as reported in Chapter 5, 1375 individuals who self-identified as having IBS were recruited into the study. The mean age of subjects was 49.2 years (range 18 to 86 years) 1157 (84.1%) were female, and 1293 (94.0%) were White Caucasian. Overall, 180 (13.1%) individuals stated their IBS symptoms commenced after an acute enteric infection, 1048 (95.5%) had previously seen their GP with their IBS, and 633 (57.7%) had seen a gastroenterologist.

### **6.3.1 Characteristics of the Rome IV and Rome III Cohorts**

There were 1373 individuals providing complete Rome IV data, of whom 811 (59.0%) met the Rome IV criteria for IBS. In total, 1368 individuals with IBS provided complete Rome III data, and 1080 (78.9%) met the Rome III criteria for IBS. The two cohorts overlapped, such that of the 1080 individuals who met Rome III criteria for IBS, 794 (73.5%) also met Rome IV criteria. Therefore, among 811 individuals meeting the Rome IV criteria for IBS, only 17 (2.1%) did not also meet Rome III criteria. The Rome

IV cohort were significantly younger ( $p < 0.001$ ), but there was no difference in the proportion of female participants between groups (Table 6-2). In both cohorts, over 95% of individuals had seen a GP with IBS; however, those in the Rome IV cohort were significantly more likely to have seen a gastroenterologist ( $p < 0.001$ ). IBS symptoms were significantly more severe in the Rome IV cohort ( $p < 0.001$ ), and mood and psychological health were significantly worse ( $p < 0.001$ ). CPSS and VSI scores were also significantly higher among those with Rome IV IBS ( $p < 0.001$ ).

**Table 6-2. Comparison of Demographic Data, IBS Symptom Severity, and Psychological Comorbidity Between the Rome III and Rome IV Cohorts.**

	Rome III cohort <sup>*</sup>	Rome IV cohort <sup>†</sup>	<i>p</i> value <sup>‡</sup>
	(n = 1080)	(n = 811)	
Mean age (SD)	48.4 (15.3)	47.4 (15.2)	<0.001
Female (%)	915 (84.7)	697 (85.9)	0.06
IBS after acute enteric infection (%)	147 (13.6)	106 (13.1)	0.40
Seen a GP with IBS (%)	1031 (95.5)	778 (95.9)	0.22
Seen a gastroenterologist with IBS (%)	620 (57.4)	492 (60.7)	<0.001
Mean IBS-SSS score (SD)	265 (102)	292 (96)	<0.001
Mean PHQ-12 score (SD)	9.6 (4.3)	10.3 (4.3)	<0.001
Mean HADS-Anxiety score (SD)	10.4 (4.7)	11.0 (4.7)	<0.001
Mean HADS-Depression score (SD)	7.1 (4.5)	7.6 (4.5)	<0.001
Mean CPSS score (SD)	20.5 (8.3)	21.6 (8.2)	<0.001
Mean VSI score (SD)	47.6 (17.5)	50.7 (16.8)	<0.001

CPSS, Cohen perceived stress scale; HADS, hospital anxiety and depression scale; IBS-SSS, IBS severity scoring system; PHQ-12, patient health questionnaire-12; VSI, visceral sensitivity index; SD, standard deviation.

\*Includes 794 individuals who also met the Rome IV criteria for IBS.

†Includes 17 individuals who did not meet Rome III criteria for IBS.

‡*p* value for overlapping samples *t*-test for continuous data and overlapping samples *z*-test for comparison of proportions.

### 6.3.2 Latent Class Analysis in the Rome IV Cohort

The best LCA solution was achieved with seven clusters, as indicated by the lowest value of the BIC(LL) (Figure 6-3). An overview of the seven-cluster result is provided in Figure 6-4, with descriptions of the clusters and their relative proportions. Each cluster was characterised by specific symptom profiles. Radar plots for each of these clusters are presented in Figure 6-5.

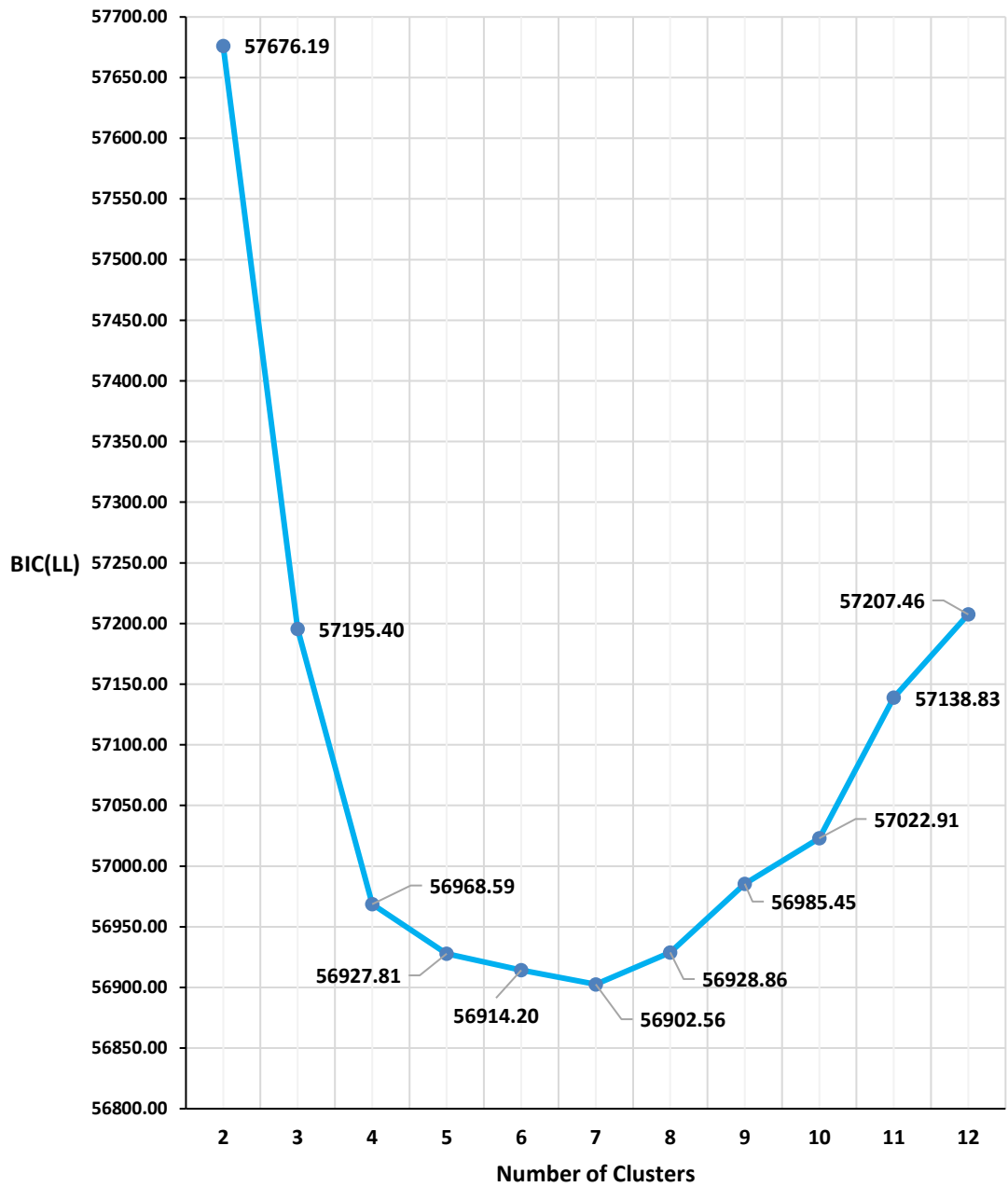
Two clusters were characterised by above-average scores for loose and watery stools and urgency, but were differentiated by the presence of below-average or above-average scores for abdominal pain that was not relieved by defaecation, and for extra-intestinal and mood-related symptoms. Similarly, another two of the clusters were characterised by above-average scores for hard and lumpy stools and bloating, and were again differentiated by the presence of below-average or above-average scores for abdominal pain that was not relieved by defaecation, and for extra-intestinal and mood-related symptoms. These clusters were described as diarrhoea and urgency with low psychological burden (Figure 6-5A), diarrhoea, abdominal pain, and urgency with high psychological burden (Figure 6-5D), constipation and bloating with low psychological burden (Figure 6-5G), and constipation, abdominal pain, and bloating with high psychological burden (Figure 6-5E).

Two clusters were characterised by below-average scores for all gastrointestinal symptoms, and were differentiated by the presence of below-average or above-average scores for extra-intestinal and mood-related symptoms. These clusters were described as low overall gastrointestinal symptom severity with low psychological burden (Figure 6-5C) and low overall gastrointestinal symptom severity with high psychological burden (Figure 6-5B), respectively. The remaining cluster was characterised by a mixed profile of well above-average scores for gastrointestinal symptoms, including diarrhoea, constipation, and abdominal pain, as well as well above-average scores for extra-



intestinal and mood-related symptoms. This cluster was described as high overall gastrointestinal symptom severity with high psychological burden (Figure 6-5F).

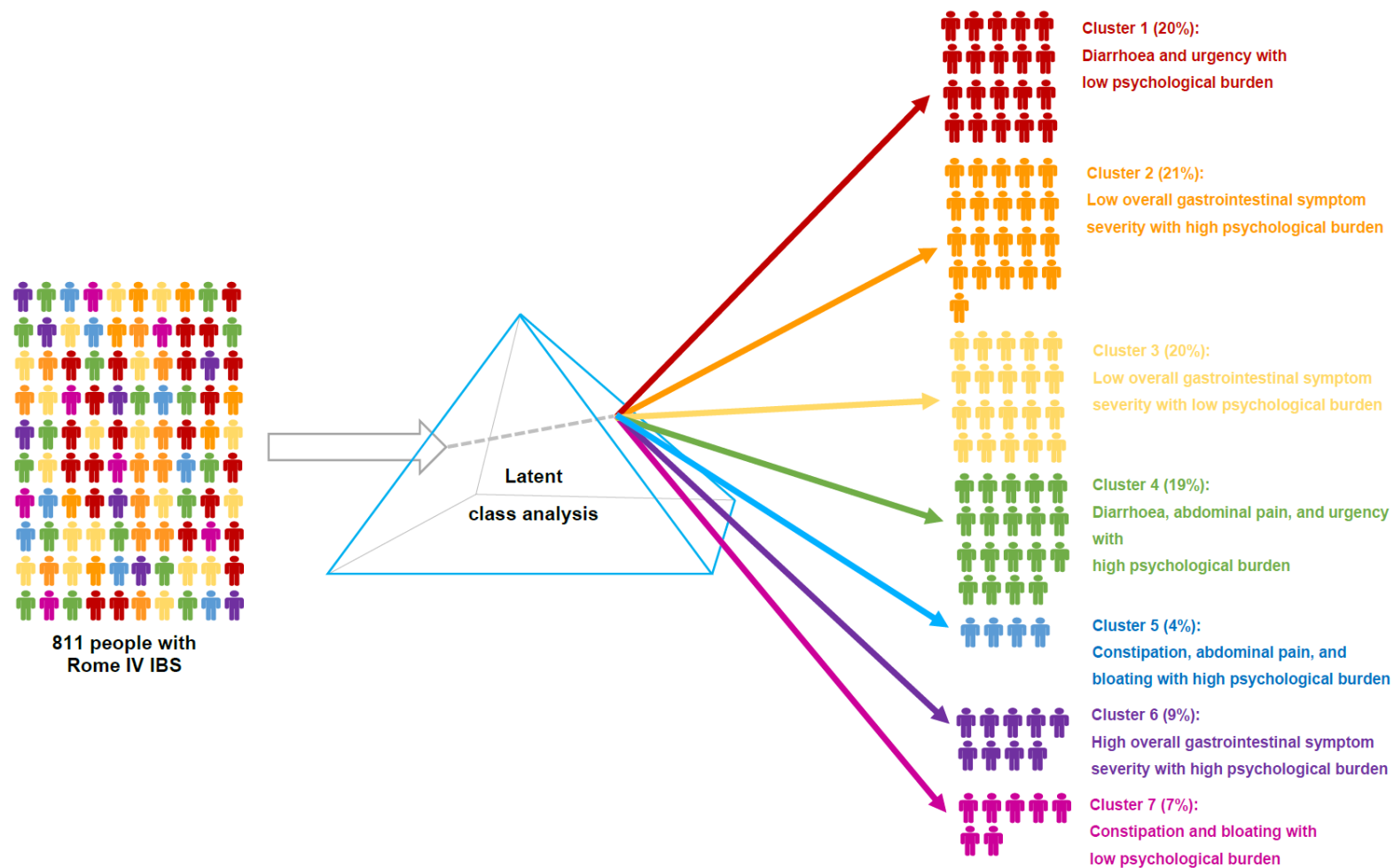
**Figure 6-3. Values of BIC(LL) Plotted for Each Specification of the Number of Clusters in the Rome IV Cohort.**



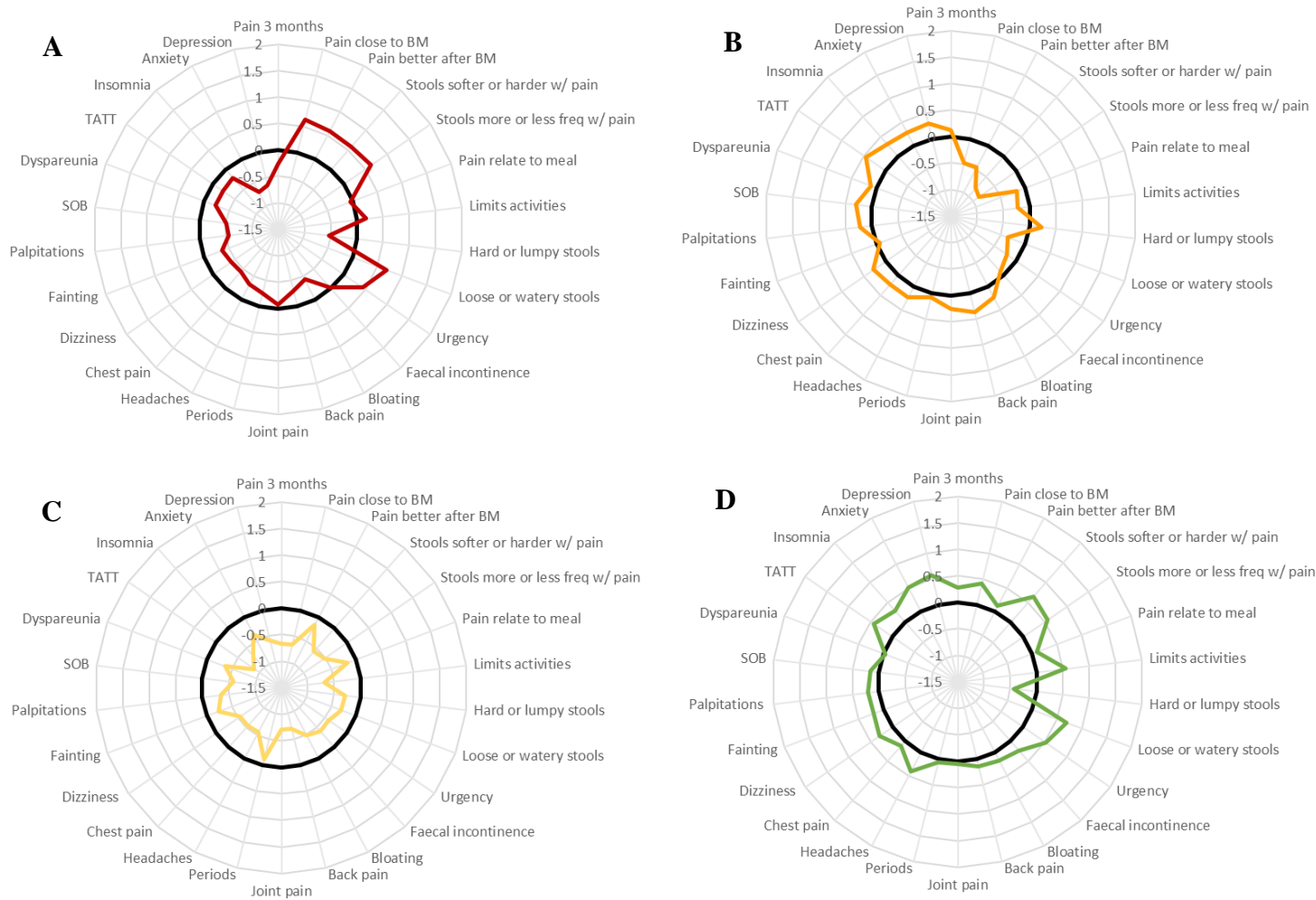
Lowest value of BIC(LL) indicates the optimum number of clusters. The model converges on a 7-cluster solution being the best fit for the model.

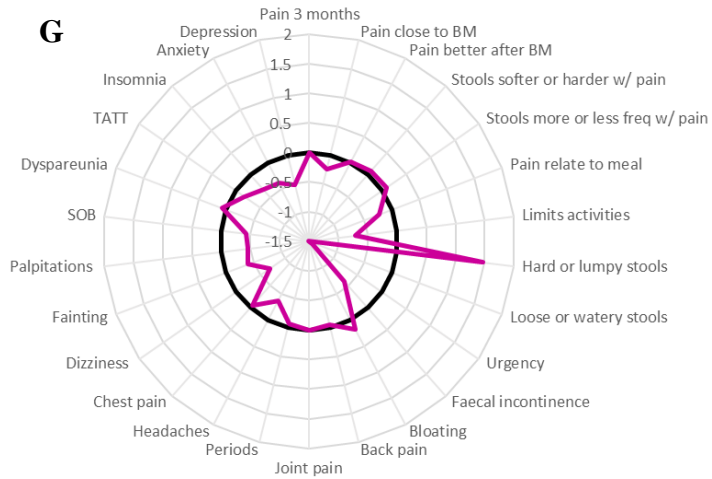
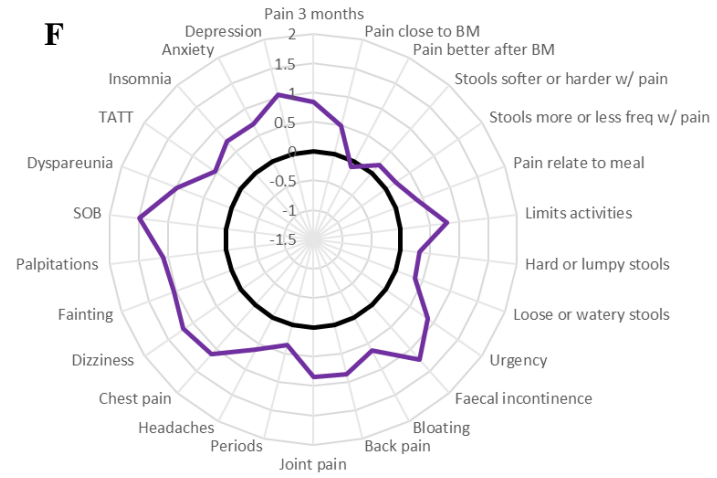
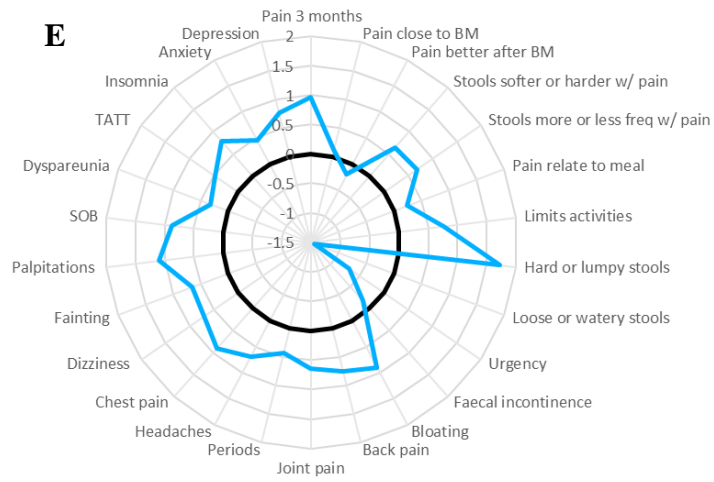
BIC(LL): Bayesian information criterion of the log-likelihood.

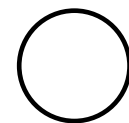
**Figure 6-4. Latent Class Analysis in a Cohort of 811 People with Rome IV IBS.**



**Figure 6-5. Profiles of the Seven Latent Class Clusters Identified in the Rome IV Cohort.**





 = adjusted cohort mean

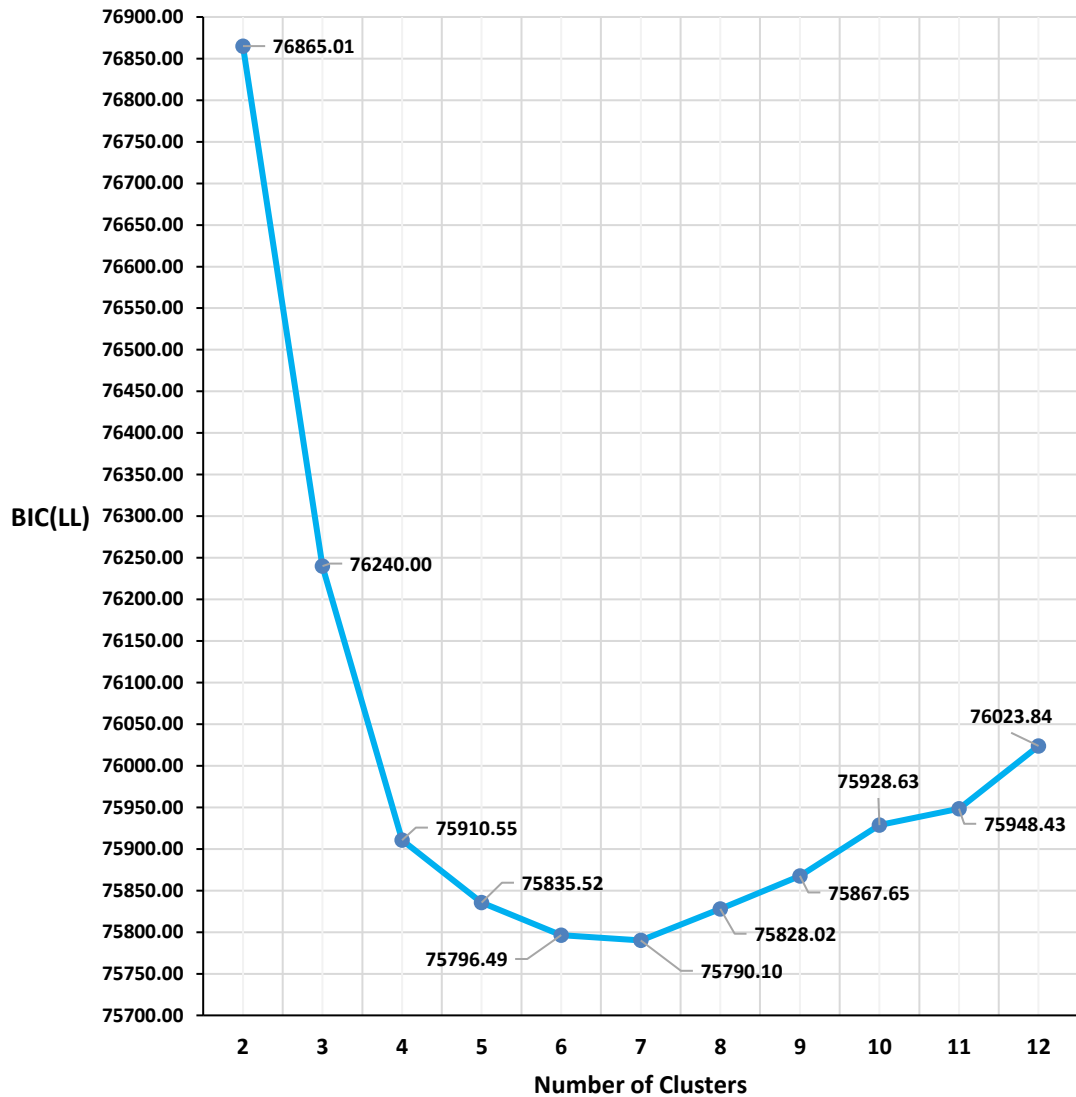
- A. Cluster 1: Diarrhoea and urgency with low psychological burden.
- B. Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.
- C. Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.
- D. Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.
- E. Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.
- F. Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.
- G. Cluster 7: Constipation and bloating with low psychological burden.

BM: bowel movement; SOB: shortness of breath; TATT: tired all the time.

### **6.3.3 Latent Class Analysis in the Rome III Cohort**

In the Rome III cohort, the best LCA solution was again achieved with seven clusters (Figure 6-6). Overall, these clusters were almost identical to those identified in the Rome IV cohort analysis, as shown in Figure 6-7. The symptom profiles that characterised each cluster were essentially identical, and radar plots for each of these clusters are presented in (Figure 6-8).

**Figure 6-6. Values of BIC(LL) Plotted for Each Specification of the Number of Clusters in the Rome III Cohort.**

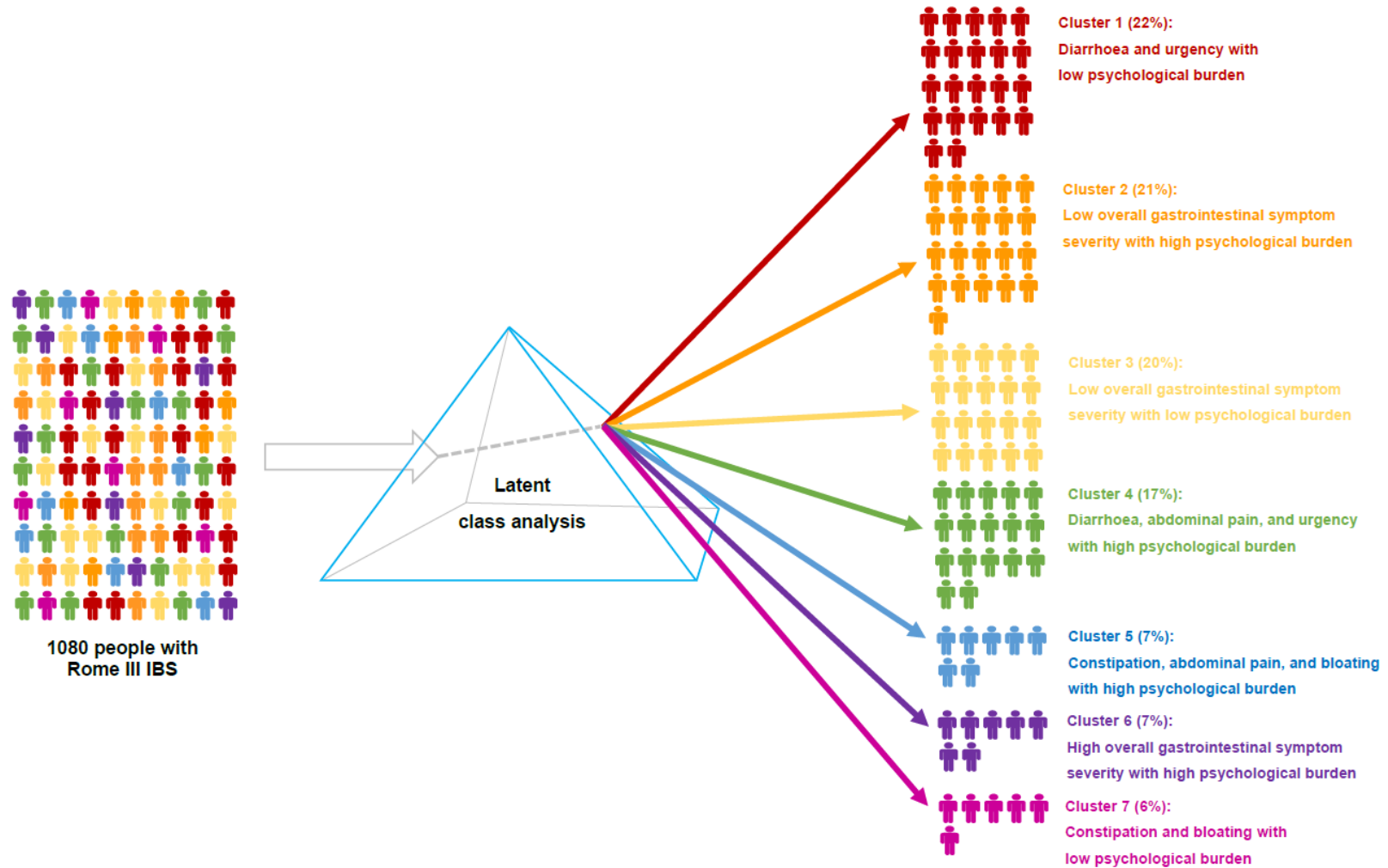


Lowest value of BIC indicates the optimum number of clusters. The model converges on a 7-cluster solution being the best fit for the model.

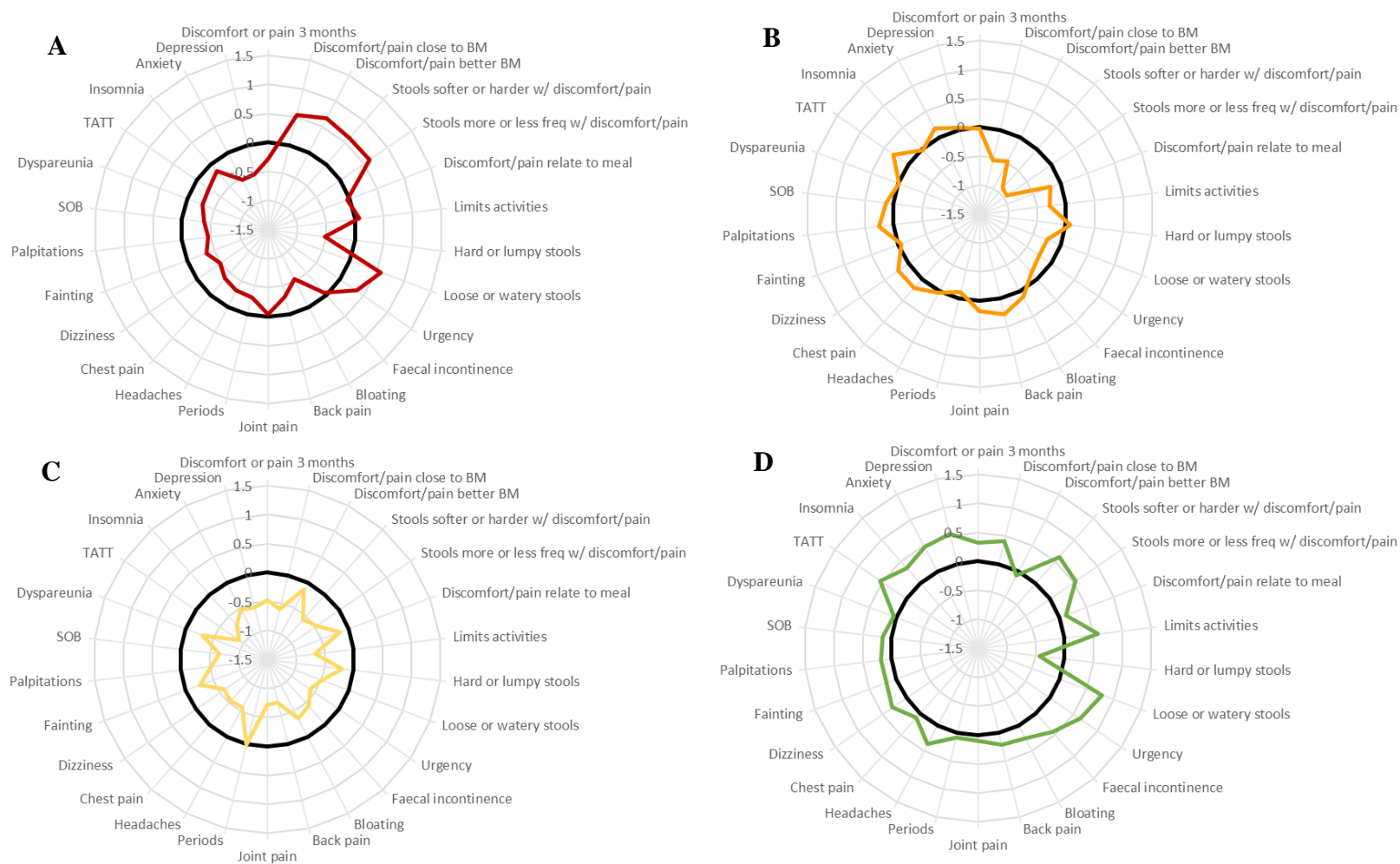
BIC(LL): Bayesian information criterion of the log-likelihood.

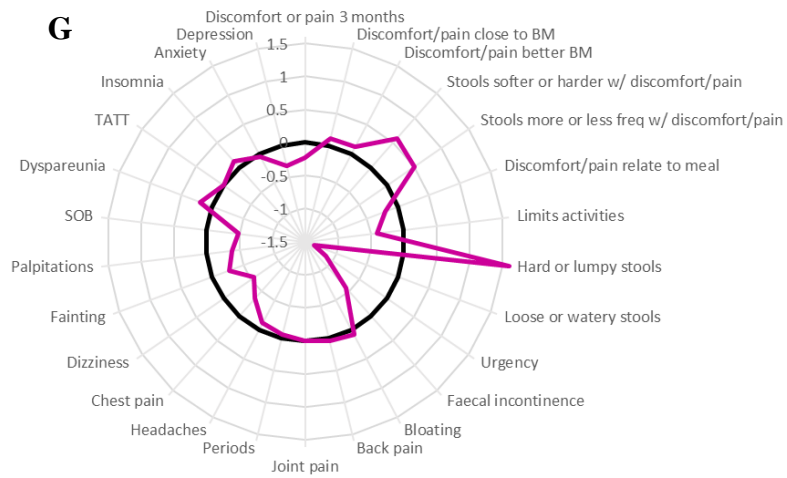
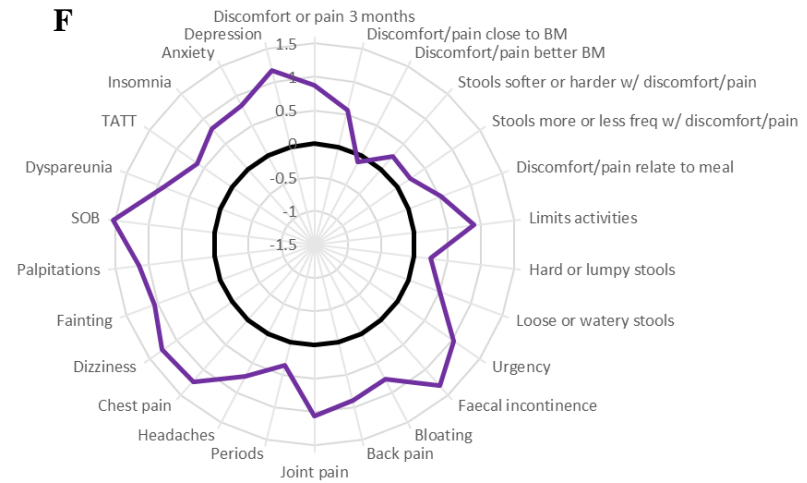
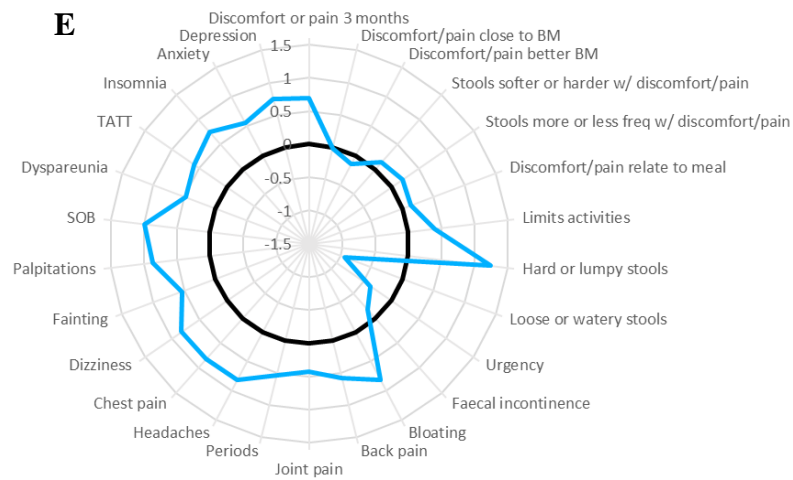


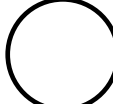
Figure 6-7. Latent Class Analysis in a Cohort of 1080 People with Rome III IBS.



**Figure 6-8. Profiles of the Seven Latent Class Clusters Identified in the Rome III Cohort.**





 = adjusted cohort mean

- A. Cluster 1: Diarrhoea and urgency with low psychological burden.
- B. Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.
- C. Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.
- D. Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.
- E. Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.
- F. Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.
- G. Cluster 7: Constipation and bloating with low psychological burden.

BM: bowel movement; SOB: shortness of breath; TATT: tired all the time.

### **6.3.4 Cluster Assignment Among Those Individuals Not Meeting Rome III or IV Criteria for IBS**

There were 271 individuals who, although they identified as having IBS, met neither the Rome III nor Rome IV criteria for IBS. In the case of Rome IV, this was because, in 235 people (86.7%), their GI symptoms were mild, although 89 (37.9%) of these reported psychological symptoms. When the Rome IV-derived model was applied to these 271 people, 146 (53.9%) were assigned to cluster 3, with low overall gastrointestinal symptoms and low psychological burden, and 89 (32.8%) to cluster 2, with low overall gastrointestinal symptoms and high psychological burden. The findings for the Rome III criteria, and applying the Rome III-derived model, were similar.

### **6.3.5 10-fold Cross-validation for the Rome IV and Rome III Latent Class Analyses**

The misclassification statistic for the Rome IV cohort seven-cluster LCA was 12.2%, compared with 14.8% when 10-fold cross-validation was carried out. This suggests that the model could be expected to perform similarly if applied to a different dataset containing the same variables. When the cross-validation process was undertaken manually and radar plots characterising the clusters resulting from each iteration were drawn out, seven clusters of very similar appearance occurred each time, matching the characteristics of the seven clusters described in the original model analysis. The results from 10-fold cross-validation in the Rome III cohort were broadly similar; the misclassification statistic for the Rome III cohort seven-cluster LCA was 14.4%, compared with 16.4% when 10-fold cross-validation was carried out.

### 6.3.6 Characteristics of the Different Clusters in the Rome IV and Rome III Cohorts

The characteristics of the seven clusters in the Rome IV cohort are shown in Table 6-3. There was a difference in mean age between clusters, with those in cluster 1, defined as diarrhoea, urgency and low psychological burden, being significantly older, and those in cluster 5, defined as constipation, abdominal pain, and high psychological burden, being significantly younger ( $p < 0.001$ ). There was also a difference in sex distribution between clusters, with a significantly higher proportion of men in cluster 3, with low overall gastrointestinal symptoms and low psychological burden ( $p = 0.003$ ). There were no significant differences in terms of the proportion of individuals who had seen a gastroenterologist, or the proportion who reported that their IBS symptoms started after an acute enteric infection. The proportion of participants with high CPSS scores and VSI scores, and the proportion of individuals with severe symptoms were significantly higher in clusters 2, 4, 5, and 6; those characterised by higher psychological burden ( $p < 0.001$ ). Stool subgroup according to the BSFS reflected the symptom-based characteristics of each cluster, and this trend was significant ( $p < 0.001$ ). Clusters 1 and 4, which were those groups with above-average scores for diarrhoea, had the largest proportions of subjects with IBS-D according to the BSFS, with very few having IBS-C, and approximately one-third having IBS-M. Conversely, clusters 5 and 7, which had above-average scores for constipation, had the highest proportion of participants with IBS-C, and contained very few individuals with either IBS-D or IBS-M. The proportion of individuals with IBS-M was highest in clusters 2, 3, and 6; those characterised by a more mixed profile of gastrointestinal symptoms of varying severity. An identical analysis comparing clusters in the Rome III cohort demonstrated broadly similar findings (Table 6-4).

**Table 6-3. Characteristics of Latent Class Clusters in the Rome IV Cohort.**

	<b>Cluster 1</b> <b>Diarrhoea and urgency with low psychological burden</b> <b>(n = 161)</b>	<b>Cluster 2</b> <b>Low overall GI symptom severity with high psychological burden</b> <b>(n = 170)</b>	<b>Cluster 3</b> <b>Low overall GI symptom severity with low psychological burden</b> <b>(n = 165)</b>	<b>Cluster 4</b> <b>Diarrhoea, abdominal pain, and urgency with high psychological burden</b> <b>(n = 154)</b>	<b>Cluster 5</b> <b>Constipation, abdominal pain, and bloating with high psychological burden</b> <b>(n = 31)</b>	<b>Cluster 6</b> <b>High overall GI symptom severity with high psychological burden</b> <b>(n = 71)</b>	<b>Cluster 7</b> <b>Constipation and bloating with low psychological burden</b> <b>(n = 59)</b>	<b>p value*</b>
<b>Mean age (SD)</b>	51.7 (15.5)	44.6 (15.2)	49.3 (16.7)	45.3 (13.1)	40.7 (12.9)	46.9 (13.8)	47.6 (14.3)	<0.001
<b>Female (%)</b>	140 (87.0)	141 (82.9)	129 (78.2)	139 (90.3)	31 (100.0)	62 (87.3)	55 (93.2)	0.003
<b>Seen a gastroenterologist with IBS (%)</b>	92 (57.1)	104 (61.2)	97 (58.8)	98 (63.6)	18 (58.1)	48 (68.6)	35 (59.3)	0.726
<b>High VSI scores (%)</b>	46 (28.6)	80 (47.3)	32 (19.5)	87 (56.5)	23 (74.2)	53 (75.7)	10 (16.9)	<0.001
<b>High CPSS scores (%)</b>	18 (11.2)	81 (47.6)	20 (12.1)	86 (56.2)	18 (58.1)	57 (80.3)	10 (16.9)	<0.001
<b>Severe symptoms on IBS-SSS (%)</b>	63 (39.4)	87 (51.2)	27 (16.4)	90 (58.4)	25 (80.6)	63 (88.7)	24 (40.7)	<0.001

<b>Subgroup on BSFS</b>								
IBS-C (%)	6 (3.7)	37 (21.9)	20 (12.1)	3 (1.9)	26 (83.9)	2 (2.8)	48 (81.4)	
IBS-D (%)	101 (62.7)	40 (23.7)	58 (35.2)	88 (57.1)	2 (6.5)	19 (26.8)	3 (5.1)	
IBS-M (%)	50 (31.1)	87 (51.5)	77 (46.7)	61 (39.6)	3 (9.7)	46 (64.8)	7 (11.9)	
IBS-U (%)	4 (2.5)	5 (3.0)	10 (6.1)	2 (1.3)	0 (0.0)	4 (5.6)	1 (1.7)	<0.001
<b>IBS after acute enteric infection (%)</b>	21 (13.0)	19 (11.2)	30 (18.2)	15 (9.7)	6 (19.4)	12 (17.1)	3 (5.1)	0.083

BSFS: Bristol stool form scale; CPSS: Cohen perceived stress scale; GI: gastrointestinal; IBS-SSS: IBS severity scoring system; SD, standard deviation; VSI: visceral sensitivity index.

\**p* value for Pearson  $\chi^2$  for comparison of categorical data and one-way ANOVA for comparison of means.



**Table 6-4. Characteristics of Latent Class Clusters in the Rome III Cohort.**

	<b>Cluster 1</b> <b>Diarrhoea and urgency with low psychological burden</b> <b>(n = 236)</b>	<b>Cluster 2</b> <b>Low overall GI symptom severity with high psychological burden</b> <b>(n = 225)</b>	<b>Cluster 3</b> <b>Low overall GI symptom severity with low psychological burden</b> <b>(n = 212)</b>	<b>Cluster 4</b> <b>Diarrhoea, abdominal pain, and urgency with high psychological burden</b> <b>(n = 185)</b>	<b>Cluster 5</b> <b>Constipation, abdominal pain, and bloating with high psychological burden</b> <b>(n = 81)</b>	<b>Cluster 6</b> <b>High overall GI symptom severity with high psychological burden</b> <b>(n = 80)</b>	<b>Cluster 7</b> <b>Constipation and bloating with low psychological burden</b> <b>(n = 61)</b>	<i>p</i> value*
<b>Mean age (SD)</b>	53.3 (15.4)	48.6 (15.2)	48.3 (16.4)	46.8 (14.1)	40.0 (13.5)	46.4 (13.6)	47.66 (13.6)	<0.001
<b>Female (%)</b>	202 (85.6)	181 (80.4)	167 (78.8)	161 (87.0)	78 (96.3)	70 (87.5)	56 (91.8)	0.002
<b>Seen a gastroenterologist with IBS (%)</b>	132 (55.9)	136 (60.4)	104 (49.1)	119 (64.3)	40 (49.4)	53 (67.1)	62 (59.0)	0.014
<b>High VSI scores (%)</b>	53 (22.5)	73 (32.6)	27 (12.7)	97 (52.4)	47 (58.8)	60 (75.9)	15 (24.6)	<0.001
<b>High CPSS scores (%)</b>	31 (13.1)	72 (32.0)	21 (9.9)	92 (50.0)	43 (53.1)	66 (82.5)	14 (23.0)	<0.001
<b>Severe symptoms on IBS-SSS (%)</b>	59 (25.2)	73 (32.4)	23 (10.8)	100 (54.3)	55 (67.9)	69 (86.3)	17 (27.9)	<0.001

<b>Subgroup on BSFS</b>								
IBS-C (%)	10 (4.2)	38 (17.0)	49 (23.1)	4 (2.2)	46 (56.8)	3 (3.8)	45 (73.8)	
IBS-D (%)	149 (63.1)	61 (27.2)	70 (33.0)	105 (56.8)	2 (2.5)	26 (32.5)	5 (8.2)	
IBS-M (%)	65 (27.5)	116 (51.8)	81 (38.2)	74 (40.0)	32 (39.5)	47 (58.8)	10 (16.4)	
IBS-U (%)	12 (5.1)	9 (4.0)	12 (5.7)	2 (1.1)	1 (1.2)	4 (5.0)	1 (1.6)	<0.001
<b>IBS after acute enteric infection (%)</b>	34 (14.4)	28 (12.5)	37 (17.5)	24 (13.0)	9 (11.1)	12 (15.2)	3 (4.9)	0.269

BSFS: Bristol stool form scale; CPSS: Cohen perceived stress scale; GI: gastrointestinal; IBS-SSS: IBS severity scoring system; SD, standard deviation; VSI: visceral sensitivity index.

\*  $p$  value for Pearson  $\chi^2$  for comparison of categorical data and one-way ANOVA for comparison of means.

## 6.4 Discussion

This study investigated whether it is possible to subgroup people with IBS using factors beyond stool pattern. The analysis found seven unique clusters of individuals with IBS, distinguished by the pattern of gastrointestinal symptoms, extra-intestinal symptoms, and mood. Two of these were characterised by diarrhoea and were differentiated based on the presence of abdominal pain that was not relieved by defaecation, and high or low psychological burden (Figure 6-5A/6-8A vs. Figure 6-5D/6-8D). Two clusters were characterised by constipation and were again differentiated based on the presence of abdominal pain that was not relieved by defaecation, and high or low psychological burden (Figure 6-5E/6-8E vs. Figure 6-5G/6-8G). A further two clusters exhibited mixed gastrointestinal symptoms of low overall intensity but were differentiated by the presence of high or low psychological burden (Figure 6-5B/6-8B vs. Figure 6-5C/6-8C). The final cluster was characterised by mixed gastrointestinal symptoms of high overall intensity with high psychological burden (Figure 6-5F/6-8F). These seven clusters were reproducible, irrespective of whether IBS was defined according to the Rome III or Rome IV criteria. These models were validated, demonstrating that they would be expected to perform similarly if applied to a different dataset. Comparing additional characteristics between clusters found a significantly higher proportion of men in the cluster with low overall symptoms and low psychological comorbidity. It was also found that groups characterised by high psychological comorbidity had a significantly greater proportion of people with high scores using other measures of psychological health, such as the VSI and CPSS, which were not included in the model itself. Finally, stool subgroup, as defined according to the BSFS, correlated significantly with the gastrointestinal symptom profile of each cluster. These results have the potential to change classification and treatment of IBS.

This study has several strengths. A large number of individuals were recruited, all of whom were in the community and self-identified as having IBS. Some individuals had consulted a GP, some a gastroenterologist, and some had never consulted a physician, meaning the participants are likely to be generalisable to many individuals living with IBS. This is further supported by the proportion of individuals with each IBS stool subgroup, which is similar to other community based surveys.<sup>61, 102</sup> The study used an online questionnaire, meaning data collection was near complete for many of the variables of interest. External validation of the Rome III and Rome IV latent class models in a different cohort of patients was not possible because no suitable data were available. In lieu of this, it was possible to internally validate both models instead, in order to understand how they might apply to other groups of patients with IBS.

Weaknesses of the study include the fact that it was not possible to confirm the diagnosis of IBS in all individuals in this study by looking at their medical records. This means it was necessary to rely on the fact that the people who took part believed that they had IBS as a means of confirming a diagnosis. This may have led to the inclusion of some people with disorders other than IBS, which may have different symptom profiles, and this may have affected the extent to which the results of this LCA are indicative of true IBS subgroups. However, given that almost 80% of those who responded did meet the Rome III criteria for IBS, more than 95% had previously seen a GP with their IBS, and almost 60% had seen a gastroenterologist, it is unlikely that this will have affected the results to any great degree. As the questionnaire was completed online, after visiting a website, it was not possible to assess how many individuals visited the website but chose not to complete the questionnaire, or whether those who responded are broadly representative of all the people with IBS registered with these three organisations. In addition, because of the setting in which the study was conducted, and the fact that participants had to have internet access and be motivated to

participate, they may not be generalisable to patients consulting with a gastroenterologist in secondary or tertiary care. However, given that almost 60% had previously consulted in this setting, this is unlikely.

To date, there have been only four previous studies examining approaches other than stool pattern to subgrouping people with IBS.<sup>26, 27, 59, 60</sup> In the first of these studies, there appeared to be six distinct subgroups of people with Rome III-defined IBS; those whose symptoms were predominantly intestinal, including diarrhoea, constipation, or abdominal pain, and who had only minimal psychological distress, and those for whom IBS symptoms were part of a broader picture, which included anxiety, depression, and extra-intestinal symptom reporting.<sup>26</sup> This Swedish study, however, included only 172 patients in tertiary care, so the findings may not be generalisable to the majority of people with IBS, who are seen in a primary or secondary care setting. In a second study conducted by the same group, again IBS subgroups characterised by a combination of gastrointestinal and extra-intestinal symptoms were identified, but these were not consistent between Rome III and Rome IV criteria.<sup>27</sup> The authors identified seven subgroups for Rome III-defined IBS, but only five with Rome IV. The latter were less distinct, with a preponderance of mixed-symptom profiles. Moreover, and in contrast to this study, it was a population-based cross-sectional survey, which classified participants as having IBS solely based on whether their responses fulfilled the Rome criteria, rather being included because they reported having IBS, or had received a diagnosis of IBS. A third study included 107 patients diagnosed with IBS using the Rome I criteria and conducted a K means cluster analysis using intestinal symptoms, psychological health, and rectal distension thresholds.<sup>60</sup> Three distinct subgroups of patients were observed. Two of these were defined by low rectal distension thresholds and were distinguished by low or high psychological co-morbidity. In contrast, the third subgroup had high rectal distension thresholds, low disease impact, and low

psychological co-morbidity overall. The final study used an advertisement to recruit 332 patients who had received a diagnosis of IBS, and analysis of data concerning gastrointestinal symptoms, extra-intestinal symptoms, and IBS-related quality of life identified four subgroups.<sup>59</sup> Two subgroups had low overall symptoms and were differentiated based on having either good or moderate quality of life. The other two subgroups had high overall symptoms, with or without diarrhoea, and were further differentiated based on having poor or moderate quality of life. This study defined IBS according to either the Rome II or Rome III criteria, but combined all participants together for analysis, so it is unclear how use of these different symptom-based definitions of IBS might have affected the characteristics of the subgroups.

Despite differences in their patient populations, and the variables used to define symptoms, all the studies conducted thus far have demonstrated that people with IBS appear to separate into distinct subgroups based on more than just stool pattern. The number of subgroups, however, and their precise characteristics, differs between studies. In part, this reflects differences in the choice of variables to be included in the model. Choosing different variables will change the results, a limitation of any such modelling analysis, which is why it is important to select relevant variables with a clear rationale. Although distinct IBS subgroups constructed using clinical symptoms, symptom severity, and psychological symptoms appear to exist, whether they are reproducible in other patient cohorts is unknown. This study is the first to demonstrate that the same IBS subgroups are reproducible irrespective of whether IBS is defined according to the Rome III or Rome IV criteria. This might partly reflect the overlap between the Rome III and Rome IV cohorts. However, previous studies, which also had similarly overlapping groups, failed to demonstrate this consistency.<sup>27</sup> Moreover, the subgrouping model was validated, demonstrating it could be expected to perform similarly if it were applied to a different cohort of patients with IBS. This is important

because it suggests that the analysis has not derived a model that is too specific and “overfitted” to the data, a risk in previous studies where model validation has not been undertaken.<sup>26, 27, 59</sup>

As all of these studies are cross-sectional in design, and in the absence of follow-up data, whether these subgroups can be used to guide treatment for the individual patient with IBS is uncertain.<sup>58</sup> Nonetheless, examining the diverse characteristics of the individuals within the seven clusters identified in this study, which look beyond gastrointestinal symptoms, it becomes easier to understand why response to a drug targeted against a predominant stool pattern is so variable in clinical practice. It also supports the MDCP approach proposed by the Rome Foundation, but indicates that, rather than simply acting as a guide to clinicians for managing an individual patient, it could be more effective if incorporated formally into the stratification of all patients with IBS. This view is supported by a recent discussion paper, suggesting that conditions such as IBS should be classified as “functional somatic disorders”, occupying a neutral territory between being considered purely somatic or purely mental.<sup>400</sup> Such a classification system aligns with the aetiological construct that these disorders reflect the complex interaction between brain and body. Indeed, the results of this study indicate that some people are likely to respond well to drugs targeting their most troublesome gastrointestinal symptom, some may benefit from instituting a psychological therapy early on in their disease course and, in others, a combined approach targeting both physical and psychological symptoms may be more effective. People in cluster 3 could be provided with education about the condition and lifestyle advice,<sup>401</sup> cluster 1 or 7 treated with a drug targeting diarrhoea or constipation, respectively, cluster 2 a psychological therapy, such as CBT, cluster 4 or 5 a drug targeting diarrhoea or constipation, in combination with a central neuromodulator or psychological therapy to address pain and mood,<sup>402</sup> and cluster 6 augmentation of a

central neuromodulator with a psychological therapy, a successful strategy in other functional somatic disorders, such as chronic headache and fibromyalgia.<sup>403</sup> This is supported by a recent observational study, which suggested that female patients with high somatisation and depression should be prioritised for gut-brain psychological therapies.<sup>404</sup>

Overall, therefore, stratifying patients into these clusters has the potential to change the management paradigm for IBS, facilitating a more personalised approach to treatment, by allowing clinicians to select the best treatment, or treatments, at the earliest opportunity for any individual patient. There is therefore a need to understand whether these clusters predict underlying pathophysiological mechanisms in IBS and, more importantly, whether they can be used to tailor treatment. The latter could be achieved in collaboration with other investigators by examining clinical trial datasets retrospectively to assess whether these subgroups predict response to a particular drug or psychological therapy. This study also provides guidance for a minimum dataset that future treatment trials in IBS could collect, to identify subgroups of patients who will respond best to a particular treatment.

In summary, this study shows that, irrespective of whether IBS is defined according to the Rome III or Rome IV criteria, people with IBS could be divided into seven distinct and reproducible clusters. These were differentiated according to the presence of certain gastrointestinal symptoms, including stool form or frequency, and abdominal pain that was not relieved by defaecation, as well as by the presence of extra-intestinal symptoms and abnormal mood. If these novel subgroups are reproducible in other settings, and are shown to predict response to specific therapies that are available to treat IBS, they could then be utilised to personalise treatment. This has the potential to change clinical practice by allowing gastroenterologists and patients to select the right therapy based on these subgroups, leading to improved symptom control, higher



levels of patient satisfaction, better quality of life, and reduced health service and societal costs of managing IBS. In addition, for people whose IBS symptoms form part of a broader picture that includes substantial psychological comorbidity, the subgroups could be used to prioritise access to psychological therapies, or to make the decision to institute combined therapy with both a drug and a psychological therapy. Earlier use of psychological therapies in these particular subgroups of people, rather than after pharmacological therapies have failed, as is currently recommended,<sup>269</sup> may alter the clinical course of the condition. To better understand whether these subgroups could be used to personalise the treatment of IBS and change outcomes as described, longitudinal follow-up exploring their natural history and prognostic value is needed, and this is the focus of the study presented in Chapter 7.

**CHAPTER 7**

**Examining the Natural History and Prognostic Value of a Novel  
Classification System for Irritable Bowel Syndrome**

## 7.1 Introduction

In Chapter 6 it has been demonstrated that, irrespective of whether IBS is defined according to the Rome III or Rome IV criteria, people with IBS can be divided into seven distinct and reproducible clusters using latent class analysis. These were characterised by a pattern of gastrointestinal symptoms (predominantly diarrhoea-related, predominantly constipation-related, or mixed symptoms) further differentiated by the presence or absence of abdominal pain not relieved by defaecation, and by the presence of high or low levels of both extra-intestinal symptom reporting and psychological comorbidity. This reflects the principles of the Rome Foundation MDCP framework, which looks beyond the cardinal gastrointestinal symptoms needed to make a diagnosis of IBS and subgrouping patients according to their predominant stool pattern, instead recommending the assessment of additional clinical features, psychological factors, and impact of the illness, in order to build a unique clinical profile for each patient.<sup>57</sup> Nevertheless, directing treatment according to predominant stool pattern alone remains the mainstay of IBS management, even though longitudinal studies demonstrate that IBS stool subgroups are not stable over time,<sup>44, 45, 47-49</sup> with a change in subgroup occurring in up to one-third of people during follow-up.<sup>49</sup> Moreover, in a recent study, fluctuation between IBS stool subgroups did not depend solely on whether a new treatment was initiated, or whether the choice of treatment was deemed appropriate based on IBS stool subgroup at baseline.<sup>49</sup> If, as discussed, gastroenterologists and patients were to personalise their treatment choices based on these novel subgroups instead, for example making earlier use of psychological therapies in clusters with high psychological comorbidity, this has the potential to improve outcomes. To explore this theory further, a longitudinal follow-up study was conducted in order to understand the evolution of IBS according to this novel classification system, and to assess whether these clusters were predictive of differing

disease courses. This study also examined if commencing new treatments was associated with a change in cluster membership.

## **7.2 Methods**

### **7.2.1 Participants and Setting**

This was a 12-month follow-up study of individuals who self-identified as having IBS registered with three organisations in the UK, and who agreed to participate in the previous studies detailed in Chapters 5 and 6. Briefly, participants were contacted via email and post, inviting them to complete an online questionnaire. The questionnaire collected demographic data, and data about lower gastrointestinal symptoms, extra-intestinal symptoms, and psychological health. Invitations were sent out to complete a follow-up questionnaire a minimum of 12 months later, using the same methods. All non-responders were sent a reminder. Although all participants self-identified as having IBS, the baseline data were used to identify two cohorts of people meeting the Rome IV and Rome III diagnostic criteria for IBS. In both cohorts, latent class analysis, a method of model-based clustering, was used to derive novel subgroups of people with IBS, and these models were validated internally. Comprehensive details regarding this methodology are provided in Chapter 6.

The latent class modelling using baseline data identified seven distinct IBS clusters, which were almost identical, in both the Rome IV and Rome III cohorts, and which are detailed in Figure 6-5 and Figure 6-8. To examine the natural history of these clusters, the same model was applied to participant follow-up data, and cluster membership at baseline was compared with that at 12-month follow-up. The University of Leeds research ethics committee approved the study in November 2017 (reference MREC17-018).

## **7.2.2 Data Collection and Synthesis**

### **7.2.2.1 Demographic and Treatment Data**

Demographic data was collected at baseline. At 12 months, participants were asked to record any new treatments (dietary, drugs, and/or psychological, but not complementary or alternative medicines) that they commenced, as well as GP visits, or consultations with a gastroenterologist, after the baseline questionnaire. The questionnaires were otherwise identical at baseline and 12-month follow-up.

### **7.2.2.2 Lower Gastrointestinal Symptom and Psychological Health Data**

Lower gastrointestinal symptom data at baseline and follow-up were captured using both the Rome IV and Rome III questionnaires.<sup>379, 380</sup> The presence or absence of either Rome IV or Rome III-defined IBS was assigned among all individuals according to the scoring algorithms proposed for these questionnaires.<sup>14, 32</sup> Participants who no longer met either Rome IV or Rome III criteria for IBS at 12 months were classified into one of the other functional bowel disorders, including functional constipation, functional diarrhoea, functional abdominal bloating or distension, or unspecified functional bowel disorder.<sup>14</sup> Individuals with the latter diagnosis have lower gastrointestinal symptoms that do not meet criteria for any of the other four functional bowel disorders. Symptom severity was measured using the validated IBS-SSS,<sup>381</sup> and the impact of symptoms, in terms of the proportion of time that they limited normal daily activities, was measured as per the Rome questionnaire. Anxiety and depression data were collected using the HADS,<sup>382</sup> and extra-intestinal symptom data using the PHQ-12,<sup>113</sup> derived from the validated PHQ-15.<sup>383</sup> These same measures were used to assess psychological burden at baseline. Full details of these questionnaires and measures have already been discussed in Chapter 5.

### 7.2.3 Statistical Analysis

Categorical variables were compared between individuals responding to the 12-month questionnaire, and those who did not, using a  $\chi^2$  test. An independent samples *t*-test was used to compare mean age. IBS cluster at baseline was compared with IBS cluster at follow-up in those still meeting criteria for Rome IV-defined IBS and Rome III-defined IBS, respectively. In addition, IBS cluster membership was compared between the two time points stratified according to predominant stool pattern, and level of psychological burden, at baseline. The proportions of individuals with Rome IV or Rome III IBS at baseline who fluctuated to another functional bowel disorder at 12 months was also compared, analysed according to their IBS cluster at baseline. Due to multiple comparisons a 2-tailed *p* value of <0.01 was considered statistically significant for all analyses. The study also examined whether baseline cluster influenced subsequent disease behaviour by comparing proportions of people in each cluster who reported symptoms limiting their activities  $\geq 50\%$  of the time, commenced a new treatment, saw their GP, or consulted a gastroenterologist, using a  $\chi^2$  test, and the mean number of new treatments commenced using a one-way ANOVA. Finally, the study examined what treatments participants received, according to their baseline cluster, and whether commencing new treatment(s) was associated with changing to a different cluster at follow-up. All analyses were performed using SPSS for Windows (version 24.0 SPSS Inc., Chicago, IL, USA).

### 7.3 Results

As detailed in Chapter 6, 1375 individuals who self-identified as having IBS were recruited into the study at baseline with a mean age of 49.2 years (range 18 to 86 years). 1157 (84.1%) were female, and 1293 (94.0%) were White Caucasian. 784 participants (57.0%) were successfully followed up and provided complete data at 12 months. The differences between responders and non-responders related to demographic

characteristics (Table 7-1). There were no differences in the proportion who met either the Rome IV or Rome III criteria at baseline, IBS symptom severity, or psychological comorbidity between those successfully followed up, and those who were not. There was also no difference in the proportion of individuals in each baseline cluster between responders and non-responders. There were 811 participants who met Rome IV criteria for IBS at baseline, of whom 452 (55.7%) responded to the 12-month questionnaire, and 319 (70.6%) of these individuals still met Rome IV criteria for IBS at follow-up. In total, 631 (58.4%) of 1080 participants who met Rome III criteria for IBS at baseline responded to the 12-month questionnaire, and 527 (83.5%) still met the Rome III criteria for IBS at follow-up. Overall, results for the cohort of participants meeting Rome III criteria were very similar to those for the cohort meeting Rome IV criteria.

**Table 7-1. Characteristics of Individuals Responding to the 12-month Questionnaire Compared with Non-responders.**

	<b>Responded to Questionnaire at 12 months (n=784)</b>	<b>Did not Respond to Questionnaire at 12 months (n = 591)</b>	<b><i>p</i> value*</b>
<b>Mean age (SD)</b>	50.7 (14.4)	47.1 (16.4)	<0.001
<b>Female gender (%)</b>	660 (84.2)	497 (84.1)	0.96
<b>Married or co-habiting (%)</b>	535 (68.2)	363 (61.4)	0.009
<b>University or postgraduate level of education (%)</b>	369 (47.1)	218 (37.2)	<0.001
<b>White Caucasian ethnicity (%)</b>	754 (96.2)	539 (91.7)	<0.001
<b>IBS after acute enteric infection (%)</b>	102 (13.0)	78 (13.2)	0.90
<b>Previously seen a GP regarding IBS at study entry (%)</b>	754 (96.2)	548 (92.9)	0.007
<b>Previously seen a gastroenterologist regarding IBS at study entry (%)</b>	475 (60.6)	314 (53.2)	0.006
<b>Rome IV criteria for IBS met (%)</b>	452 (57.7)	359 (60.8)	0.24
<b>Rome III criteria for IBS met (%)</b>	631 (80.7)	449 (76.6)	0.07
<b>IBS stool subgroup (%)</b>			
IBS-C	146 (18.6)	124 (21.0)	
IBS-D	310 (39.5)	207 (35.1)	
IBS-M	296 (37.8)	220 (37.3)	
IBS-U	32 (4.1)	35 (5.9)	0.03



<b>Severity on IBS-SSS (%)</b>			
Remission	27 (3.4)	28 (4.8)	
Mild	183 (23.3)	110 (18.7)	
Moderate	314 (40.1)	231 (39.2)	
Severe	260 (33.2)	220 (37.4)	0.09
<b>HADS anxiety categories (%)</b>			
Normal	251 (32.0)	177 (29.9)	
Borderline	167 (21.3)	118 (20.0)	
Abnormal	366 (46.7)	296 (50.1)	0.46
<b>HADS depression categories (%)</b>			
Normal	480 (61.2)	329 (55.7)	
Borderline	164 (20.9)	130 (22.0)	
Abnormal	140 (17.9)	132 (22.3)	0.07
<b>PHQ-12 severity high (%)</b>	166 (21.2)	142 (24.0)	0.21
<b>Rome IV latent class baseline cluster (%)<sup>†‡</sup></b>			
Cluster 1	135 (17.2)	109 (18.4)	
Cluster 2	167 (21.3)	127 (21.5)	
Cluster 3	277 (35.3)	188 (31.8)	
Cluster 4	105 (13.4)	70 (11.8)	
Cluster 5	14 (1.8)	20 (3.4)	
Cluster 6	34 (4.3)	40 (6.8)	
Cluster 7	52 (6.6)	37 (6.3)	0.15

HADS, hospital anxiety and depression scale; IBS-SSS, IBS severity scoring system;

PHQ-12, patient health questionnaire-12; SD, standard deviation.

\* $p$  value for independent samples  $t$ -test for continuous data and Pearson  $\chi^2$  for comparison of categorical data.

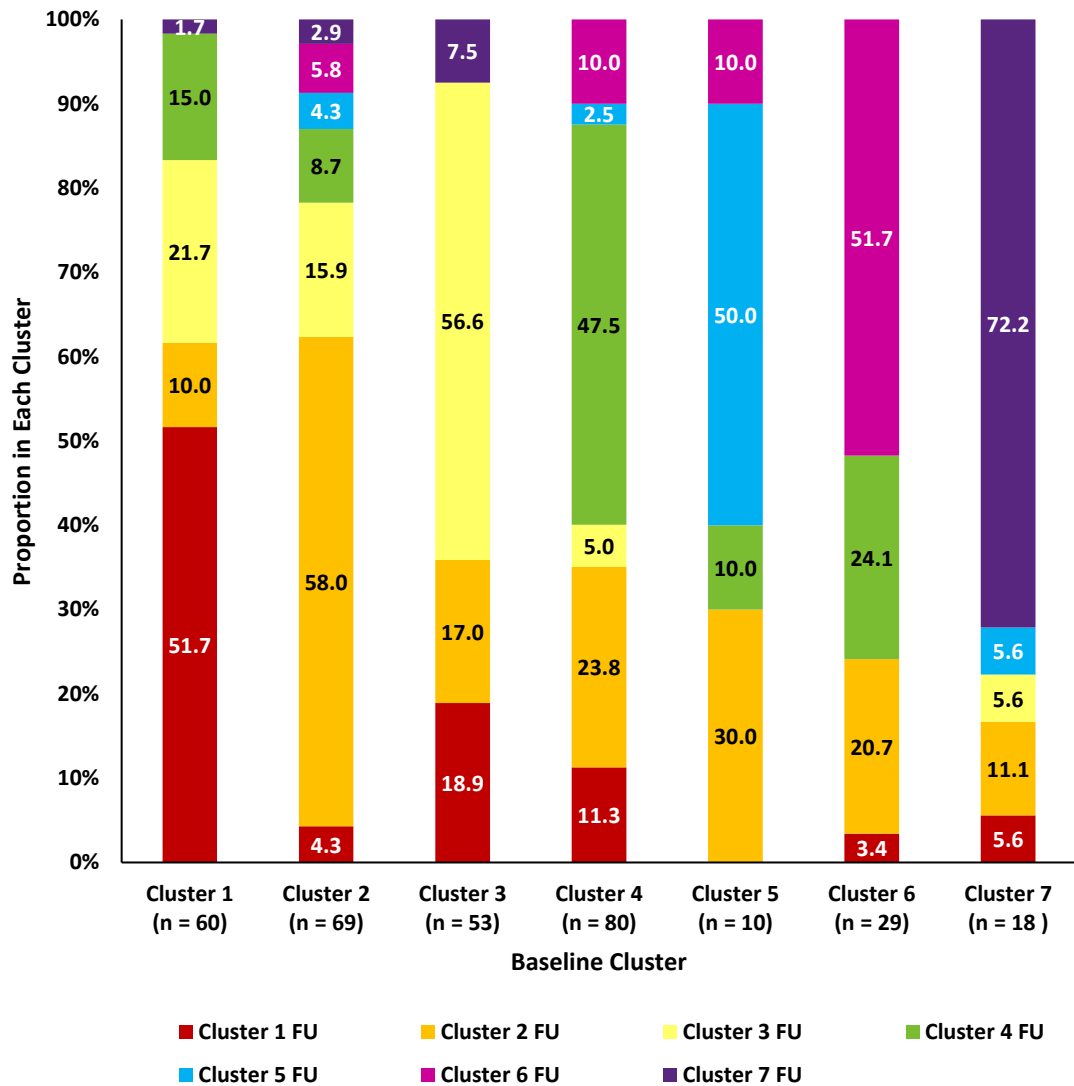
†Based on applying Rome IV model to all participants, not only those with Rome IV IBS.

‡Analysis comparing Rome III Latent Class Baseline Cluster also showed no significant difference between responders and non-responders ( $p = 0.52$ ).

### **7.3.1 Natural History of IBS Clusters Among Individuals Continuing to Meet Rome IV Criteria for IBS at Follow-up**

Of the 319 individuals still meeting Rome IV criteria for IBS at follow-up, 172 (53.9%) remained in the same IBS cluster as at baseline and 147 (46.1%) changed cluster. Fluctuation in each individual cluster is detailed in Figure 7-1. The proportion of people who remained in the same cluster between baseline and follow-up varied from 47.5% for cluster 4 (diarrhoea, abdominal pain, and urgency with high psychological burden) to 72.2% for cluster 7 (constipation and bloating with low psychological burden) ( $p < 0.001$ ).

**Figure 7-1. Comparison of IBS Cluster Membership Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.**



Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

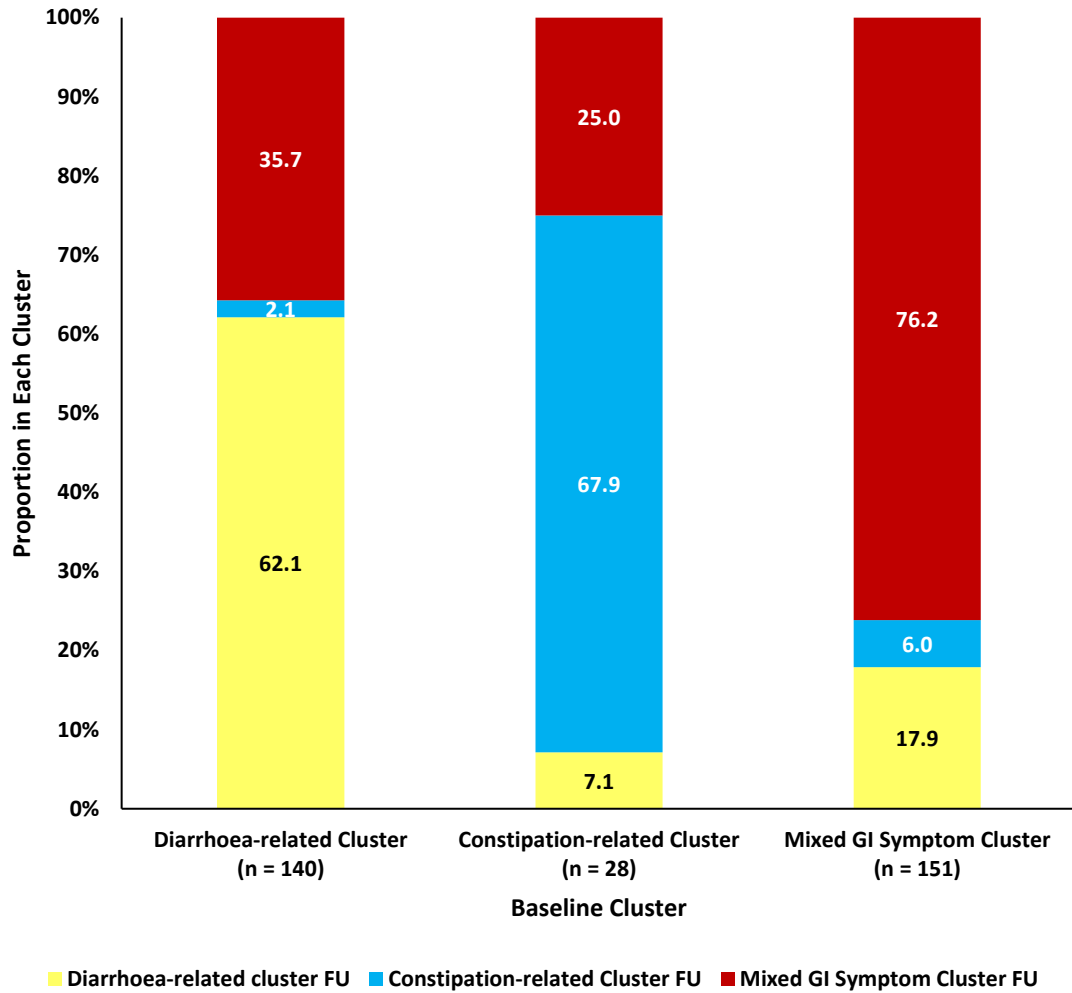
Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.

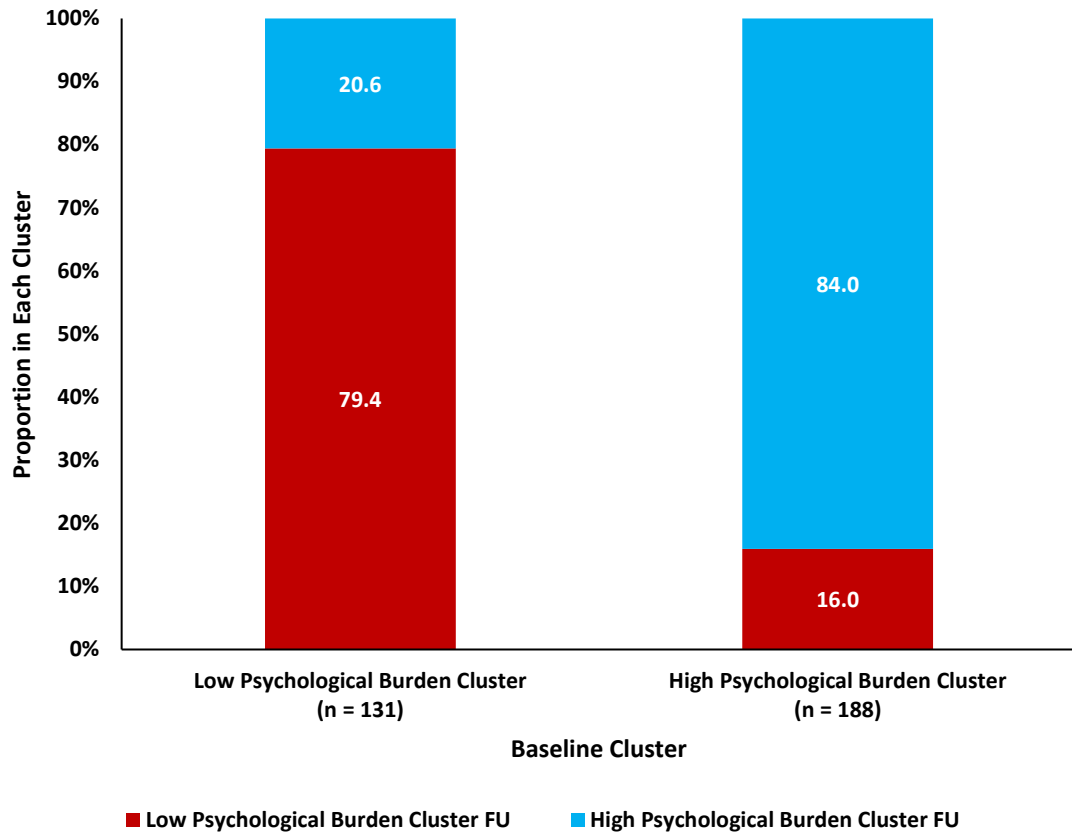
Of the 140 people who were in a diarrhoea-related cluster (clusters 1 or 4) at baseline, 87 (62.1%) remained in a diarrhoea-related cluster at follow-up and 50 (35.7%) moved to a mixed gastrointestinal symptom cluster (clusters 2, 3, or 6), whilst only three individuals (2.1%) moved to a constipation-related cluster (clusters 5 or 7) (Figure 7-2). Similarly, although the number of people was smaller, of 28 individuals in a constipation-related cluster at baseline, 19 (67.9%) remained in a constipation-related cluster at follow-up, seven (25.0%) moved to a mixed gastrointestinal symptom cluster, and only two individuals (7.1%) moved to a diarrhoea-related cluster. Lastly, of the 151 individuals in a mixed gastrointestinal symptom cluster at baseline, 115 (76.2%) remained in a mixed gastrointestinal symptom cluster at follow-up. The proportion of individuals who remained in a mixed gastrointestinal symptom cluster at follow-up was significantly higher than the proportion who remained in either a diarrhoea-related cluster or a constipation-related cluster ( $p < 0.001$ ).

**Figure 7-2. Comparison of IBS Cluster Membership According to Pattern of Gastrointestinal Symptoms Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.**



Of the 131 people who were in a cluster with low psychological burden at baseline (clusters 1, 3, or 7), 104 (79.4%) remained in a cluster with low psychological burden at follow-up (Figure 7-3). Similarly, of the 188 people who were in a cluster with high psychological burden at baseline (clusters 2, 4, 5, or 6), only 30 individuals (16.0%) moved to a cluster with low psychological burden at follow-up. Mean IBS-SSS scores at follow-up were significantly higher in clusters with high psychological burden at baseline assessment ( $p<0.001$ ) (Table 7-2).

**Figure 7-3. Comparison of Cluster Membership According to Degree of Psychological Burden Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.**





**Table 7-2. Symptom Severity, Consultation Behaviour, and Commencement of New Treatment According to Baseline IBS Cluster Assignment Among 319 Individuals with Rome IV IBS.**

	Rome IV IBS latent class cluster at baseline								
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Total	<i>p</i> value
	Diarrhoea and urgency with low psychological burden (n = 60)	Low overall GI symptom severity with high psychological burden (n = 69)	Low overall GI symptom severity with low psychological burden (n = 53)	Diarrhoea, abdominal pain, and urgency with high psychological burden (n = 80)	Constipation, abdominal, and bloating with high psychological burden (n = 10)	High overall GI symptom severity with high psychological burden (n = 29)	Constipation and bloating with low psychological burden (n = 18)	(n = 319)	
Mean IBS-SSS score at follow-up (SD)	278.5 (97.9)	299.2 (93.8)	220.1 (92.9)	315.5 (105.8)	389.0 (76.1)	367.7 (88.1)	285.2 (74.7)	294.5 (104.2)	<0.001

<b>Symptoms limiting activities ≥50% of the time at follow-up (%)</b>	40 (66.7)	45 (65.2)	22 (41.5)	70 (87.5)	9 (90.0)	27 (93.1)	8 (44.4)	221 (69.3)	<0.001
<b>Seen a GP regarding IBS during follow-up (%)</b>	24 (40.0)	31 (44.9)	23 (43.3)	47 (58.8)	9 (90.0)	24 (82.8)	7 (38.9)	165 (51.7)	<0.001
<b>Seen a gastroenterologist regarding IBS during follow-up (%)</b>	12 (20.0)	21 (30.4)	13 (24.5)	28 (35.0)	4 (40.0)	17 (58.6)	3 (16.7)	98 (30.7)	0.007

<b>Any new treatment commenced during follow-up (%)</b>	41 (68.3)	50 (72.5)	32 (60.4)	72 (90.0)	9 (90.0)	23 (79.3)	16 (88.9)	243 (76.2)	0.002
<b>Mean number of new treatments commenced during follow-up (SD)</b>	1.42 (1.37)	1.71 (1.62)	1.08 (1.05)	2.10 (1.38)	2.20 (1.03)	2.21 (1.59)	1.67 (1.09)	1.71 (1.43)	<0.001
<b>Any medication for constipation commenced during follow-up (%)</b>	7 (11.7)	19 (27.5)	7 (13.2)	18 (22.5)	6 (60.0)	10 (34.5)	9 (50.0)	76 (23.8)	<0.001
<b>Laxative (%)</b>	6 (10.0)	17 (24.6)	2 (3.8)	15 (18.8)	4 (40.0)	9 (31.0)	7 (38.9)	60 (18.8)	0.001

<b>Suppositories or enemas (%)</b>	3 (5.0)	7 (10.1)	3 (5.7)	4 (5.0)	3 (30.0)	3 (10.3)	2 (11.1)	25 (7.8)	0.14
<b>Secretagogue (%)</b>	0 (0.0)	3 (4.3)	1 (1.9)	3 (3.8)	1 (10.0)	3 (10.3)	2 (11.1)	13 (4.1)	0.16
<b>Prucalopride (%)</b>	3 (5.0)	2 (2.9)	2 (3.8)	4 (5.0)	1 (10.0)	1 (3.4)	1 (5.6)	14 (4.4)	0.97
<b>Any medication for diarrhoea commenced during follow-up (%)</b>	28 (46.7)	17 (24.6)	14 (26.4)	41 (51.2)	1 (10.0)	10 (34.5)	0 (0.0)	111 (34.8)	<0.001
<b>Anti-diarrhoeal (%)</b>	28 (46.7)	14 (20.3)	14 (26.4)	37 (46.3)	1 (10.0)	9 (31.0)	0 (0.0)	103 (32.3)	<0.001
<b>Ondansetron (%)</b>	0 (0.0)	4 (5.8)	0 (0.0)	4 (5.0)	0 (0.0)	1 (3.4)	0 (0.0)	9 (2.8)	0.26

<b>Any medication for pain and central neuromodulators commenced during follow-up (%)</b>	28 (46.7)	38 (55.1)	24 (45.3)	62 (77.5)	8 (80.0)	20 (69.0)	13 (72.2)	193 (60.5)	0.001
<b>Anti-spasmodic e.g. hyoscine (%)</b>	20 (33.3)	21 (30.4)	17 (32.1)	40 (50.0)	5 (50.0)	11 (37.9)	8 (44.4)	122 (38.2)	0.19
<b>Mebeverine or alverine (%)</b>	10 (16.7)	19 (27.5)	4 (7.5)	21 (26.3)	1 (10.0)	7 (24.1)	2 (11.1)	64 (20.1)	0.07
<b>TCA (%)</b>	2 (3.3)	9 (13.0)	5 (9.4)	12 (15.0)	3 (30.0)	5 (17.2)	3 (16.7)	39 (12.2)	0.15
<b>SSRI (%)</b>	5 (8.3)	14 (20.3)	3 (5.7)	21 (26.3)	2 (20.0)	7 (24.1)	3 (16.7)	55 (17.2)	0.03
<b>SNRI (%)</b>	0 (0.0)	4 (5.8)	1 (1.9)	3 (3.8)	1 (10.0)	4 (13.8)	1 (5.6)	14 (4.4)	0.09

<b>Any psychological therapy commenced during follow-up (%)</b>	8 (13.3)	4 (5.8)	4 (7.5)	4 (5.0)	0 (0.0)	4 (13.8)	1 (5.6)	25 (7.8)	0.40
<b>CBT (%)</b>	6 (10.0)	3 (4.3)	3 (5.7)	3 (3.8)	0 (0.0)	3 (10.3)	1 (5.6)	19 (6.0)	0.62
<b>Hypnotherapy (%)</b>	2 (3.3)	1 (1.4)	2 (3.8)	1 (1.3)	0 (0.0)	1 (3.4)	0 (0.0)	7 (2.2)	0.89

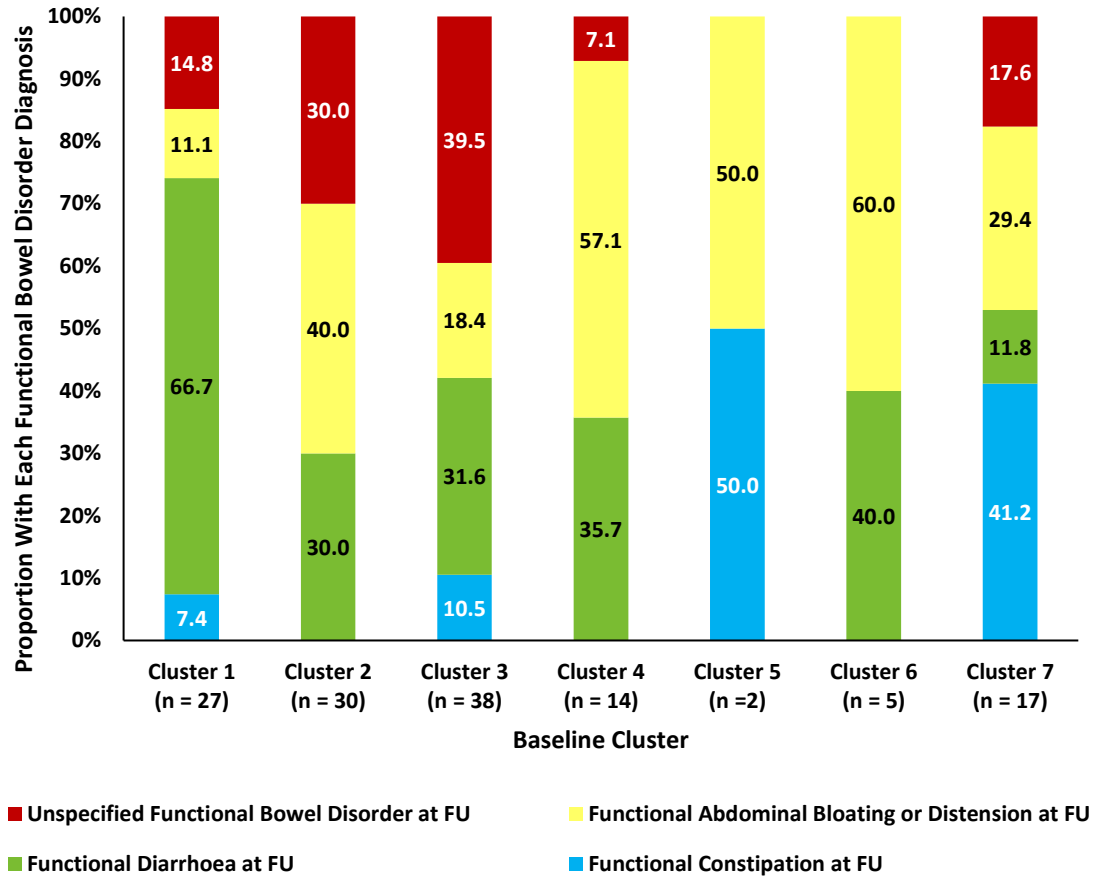
\*Adds up to >100%, as some people commenced more than one treatment during 12-month follow-up.

CBT, cognitive behavioural therapy; IBS-SSS, IBS severity scoring system; GI, gastrointestinal; SD, standard deviation; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

### **7.3.2 Change in Functional Bowel Disorder Diagnosis and IBS Cluster Membership Among Those No Longer Meeting Rome IV Criteria for IBS at Follow-up.**

Among the 133 (29.4%) individuals with Rome IV IBS at baseline who no longer met Rome IV criteria for IBS at 12-month follow-up, 48 (36.1%) met Rome IV criteria for functional diarrhoea, 39 (29.3%) functional abdominal bloating or distension, 32 (24.1%) unspecified functional bowel disorder, and 14 (10.5%) functional constipation. Change in functional bowel disorder diagnosis at 12 months according to baseline IBS cluster is shown in Figure 7-4. Although these individuals no longer met Rome IV criteria for IBS, when the baseline Rome IV cluster model was applied to these individuals at 12 months, 93 (69.9%) were assigned to clusters with low overall gastrointestinal symptoms (clusters 2 or 3), compared with 68 (51.1%) at baseline, reflecting a greater proportion fluctuating to having milder symptoms that, overall, did not meet criteria for IBS.

**Figure 7-4. Change in Functional Bowel Disorder Diagnosis at Follow-up According to Baseline IBS Cluster Among 133 Individuals with Rome IV IBS at Baseline.**



Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.



### 7.3.3 Commencement of New Treatment and Consultation Behaviour

#### According to Baseline IBS Cluster Among Those with Rome IV IBS at Baseline and Follow-up.

Overall, of the 319 individuals who continued to have Rome IV IBS at follow-up, 243 (76.2%) had commenced at least one new treatment during the 12-month follow-up period, of whom 112 (46.1%) changed IBS cluster at follow-up. Similarly, of the 76 people who did not commence any new treatment, 35 (46.1%) changed IBS cluster at follow-up. There was no significant association between commencing a new treatment and changing IBS cluster at follow-up ( $p = 1.00$ ). This remained the case when subcategories of treatment were examined, including commencing any medication for diarrhoea ( $p = 0.23$ ), any medication for constipation ( $p = 1.00$ ), any medication for pain, including a central neuromodulator ( $p = 0.35$ ), or any psychological therapy ( $p = 0.84$ ).

New treatments commenced by baseline IBS cluster are shown in Table 7-2. Only 25 individuals with Rome IV IBS at baseline and follow-up reported receiving any form of psychological therapy, of whom 13 (52%) were in baseline clusters characterised by low psychological burden (clusters 1, 3, or 7). Overall, the mean number of treatments commenced was significantly higher in clusters with a high psychological burden (clusters 2, 4, 5, or 6) ( $p < 0.001$ ), and these clusters also had significantly higher rates of consultation with both GPs and gastroenterologists ( $p < 0.001$  and  $p = 0.007$ , respectively). The impact of symptoms at follow-up, in terms of patients reporting that they limited activities at least 50% of the time, was also significantly greater in clusters with high psychological burden at baseline ( $p < 0.001$ ). Although it was the combination of troublesome gastrointestinal symptoms and high psychological burden that was the most debilitating (clusters 4, 5, and 6), it should be noted that the proportion of individuals with diarrhoea and urgency with low

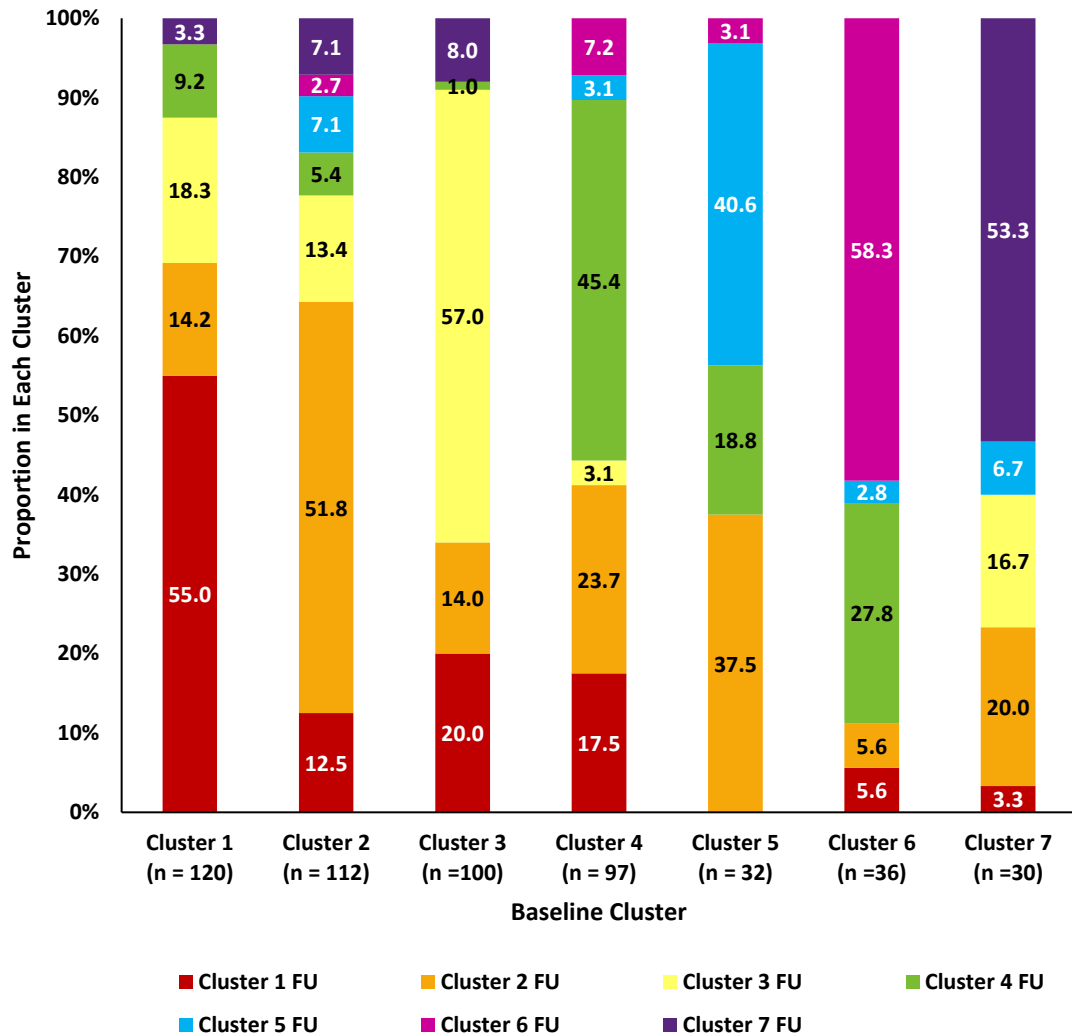
psychological burden (cluster 1) reporting marked limitation of activities was slightly greater than the proportion of those with low overall gastrointestinal symptom severity and high psychological burden (cluster 2), and much greater than the proportion of people with low psychological burden in association with constipation and bloating (cluster 7). Diarrhoea and urgency therefore appear to be important symptoms with respect to the impact they can have on daily life.

As would be expected, a significantly higher proportion of people in clusters with diarrhoea-related symptoms (clusters 1 or 4) commenced medication for diarrhoea ( $p < 0.001$ ) and, similarly, a significantly higher proportion of people in clusters with constipation-related symptoms (clusters 5 or 7) commenced medication for constipation ( $p < 0.001$ ). Finally, a significantly higher proportion of people in clusters characterised by high psychological burden (clusters 2, 4, 5, or 6) commenced medication for pain, including prescription of central neuromodulators ( $p = 0.001$ ).

#### **7.3.4 Natural History of IBS Clusters Among Individuals Continuing to Meet Rome III Criteria for IBS at Follow-up**

Of the 527 individuals still meeting Rome III criteria for IBS at follow-up, 275 (52.2%) remained in the same IBS cluster as at baseline and 252 (47.8%) changed cluster. Fluctuation in each individual cluster is detailed in Figure 7-5. The proportion of people who remained in the same cluster between baseline and follow-up varied from 40.6% for cluster 5 (constipation, abdominal pain, and bloating with high psychological burden) to 58.3% for cluster 6 (high overall gastrointestinal symptom severity with high psychological burden) ( $p < 0.001$ ).

**Figure 7-5. Comparison of IBS Cluster Membership Between Baseline and Follow-up Among 527 Individuals with Rome III IBS.**



Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

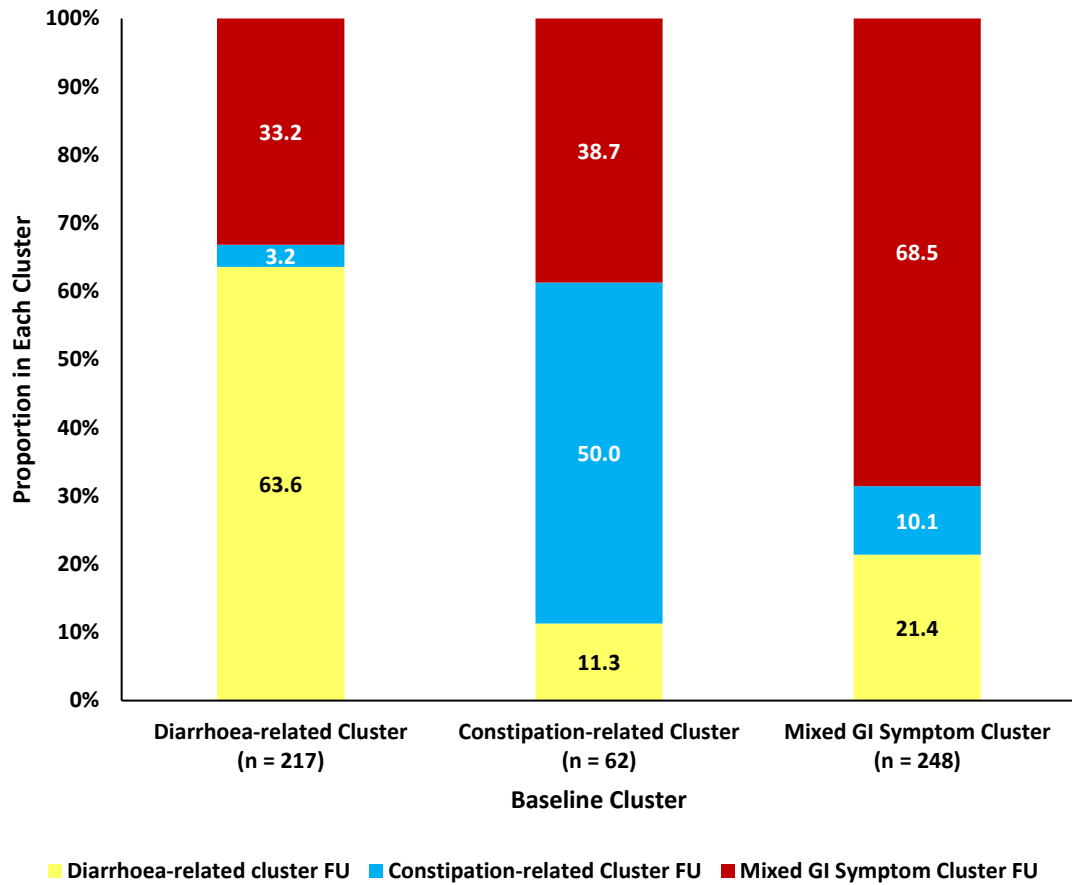
Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.

Of the 217 people who were in a diarrhoea-related cluster (1 or 4) at baseline, 138 (63.6%) remained in a diarrhoea-related cluster at follow-up and 72 (33.2%) moved to a mixed gastrointestinal symptom cluster (2, 3, or 6), whilst only seven individuals (3.2%) moved to a constipation-related cluster (5 or 7) (Figure 7-6). Similarly, although the number of people was smaller, of 62 individuals in a constipation-related cluster at baseline, 31 (50.0%) remained in a constipation-related cluster at follow-up and 24 (38.7%) moved to a mixed gastrointestinal symptom cluster, with only seven individuals (11.3%) moving to a diarrhoea-related cluster. Lastly, of the 248 individuals in a mixed gastrointestinal symptom cluster at baseline, 170 (68.5%) remained in a mixed gastrointestinal symptom cluster at follow-up. The proportion of individuals who remained in a constipation-related cluster at follow-up was significantly lower than the proportion who remained in either a diarrhoea-related cluster or a mixed gastrointestinal symptom cluster ( $p < 0.001$ ).

**Figure 7-6. Comparison of IBS Cluster Membership According to Pattern of Gastrointestinal Symptoms Between Baseline and Follow-up Among 527 Individuals with Rome III IBS.**



Of the 250 people who were in a cluster with low psychological burden at baseline (clusters 1, 3, or 7), 199 (79.6%) remained in a cluster with low psychological burden at follow-up (Figure 7-7). Similarly, of the 277 people who were in a cluster with high psychological burden at baseline (clusters 2, 4, 5, or 6), only 59 individuals (21.3%) moved to a cluster with low psychological burden at follow-up. Mean IBS-SSS scores at follow-up were significantly higher in clusters with high psychological burden at baseline assessment ( $p<0.001$ ) (Table 7-3).

**Table 7-3. Symptom Severity, Consultation Behaviour, and Commencement of New Treatment According to Baseline IBS Cluster Assignment Among 527 Individuals with Rome III IBS.**

	Rome III IBS latent class cluster at baseline								<i>P</i> value
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Total	
	Diarrhoea and urgency with low psychological burden (n = 120)	Low overall GI symptom severity with high psychological burden (n = 112)	Low overall GI symptom severity with low psychological burden (n = 100)	Diarrhoea, abdominal pain, and urgency with high psychological burden (n = 97)	Constipation, abdominal, and bloating with high psychological burden (n = 32)	High overall GI symptom severity with high psychological burden (n = 36)	Constipation and bloating with low psychological burden (n = 30)	(n = 527)	
Mean IBS-SSS score at follow-up (SD)	209.7 (97.7)	251.6 (89.6)	184.0 (86.5)	294.3 (108.8)	336.9 (99.9)	355.9 (94.8)	222.4 (80.3)	247.7 (108.6)	<0.001

<b>Symptoms limiting activities <math>\geq</math>50% of the time at follow-up (%)</b>	71 (59.2)	58 (51.8)	34 (34.0)	79 (81.4)	29 (90.6)	33 (91.7)	11 (36.7)	315 (59.8)	<0.001
<b>Seen a GP regarding IBS during follow-up (%)</b>	40 (33.3)	41 (36.6)	29 (29.0)	51 (52.6)	25 (78.1)	27 (75.0)	10 (33.3)	223 (42.3)	<0.001
<b>Seen a gastroenterologist regarding IBS during follow-up (%)</b>	19 (15.8)	22 (19.6)	17 (17.0)	29 (29.9)	10 (31.3)	20 (55.6)	3 (10.0)	120 (22.8)	<0.001
<b>Any new treatment commenced during follow-up (%)</b>	77 (64.2)	76 (67.9)	61 (61.0)	78 (80.4)	28 (87.5)	29 (80.6)	23 (76.7)	372 (70.6)	0.005
<b>Mean number of new treatments commenced during follow-up (SD) (%)</b>	1.19 (1.13)	1.47 (1.42)	1.09 (1.16)	1.85 (1.46)	2.03 (1.36)	2.19 (1.56)	1.50 (1.17)	1.49 (1.35)	<0.001



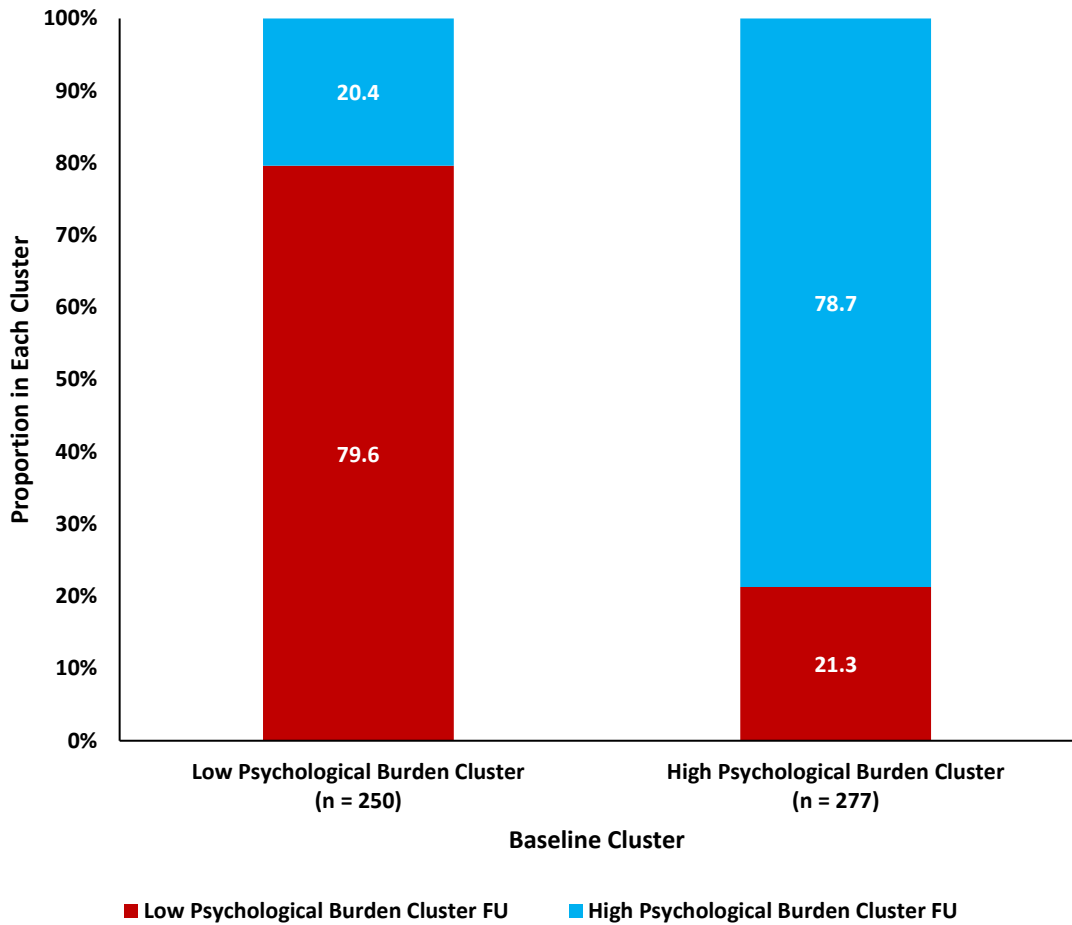
<b>Any medication for constipation commenced during follow-up (%)</b>	11 (9.2)	23 (20.5)	14 (14.0)	21 (21.6)	15 (46.9)	11 (30.6)	17 (56.7)	112 (21.3)	<0.001
<b>Laxative (%)</b>	10 (8.3)	20 (17.9)	9 (9.0)	18 (18.6)	12 (37.5)	10 (27.8)	15 (50.0)	94 (17.8)	<0.001
<b>Suppositories or enemas (%)</b>	4 (3.3)	9 (8.0)	4 (4.0)	6 (6.2)	5 (15.6)	3 (8.3)	5 (16.7)	36 (6.8)	0.052
<b>Secretagogue (%)</b>	1 (0.8)	0 (0.0)	1 (1.0)	2 (2.1)	3 (9.4)	4 (11.1)	2 (6.7)	13 (2.5)	<0.001
<b>Prucalopride (%)</b>	2 (1.7)	3 (2.7)	2 (2.0)	3 (3.1)	2 (6.3)	2 (5.6)	3 (10.0)	17 (3.2)	0.28
<b>Any medication for diarrhoea commenced during follow-up (%)</b>	54 (45.0)	26 (23.2)	26 (26.0)	47 (48.5)	7 (21.9)	12 (33.3)	1 (3.3)	173 (32.8)	<0.001
<b>Anti-diarrhoeal (%)</b>	54 (45.0)	25 (22.3)	26 (26.0)	43 (44.3)	5 (15.6)	11 (30.6)	1 (3.3)	165 (31.3)	<0.001
<b>Ondansetron (%)</b>	0 (0.0)	2 (1.8)	0 (0.0)	4 (4.1)	2 (6.3)	1 (2.8)	0 (0.0)	9 (1.7)	0.064
<b>Any medication for pain and central</b>	56 (46.7)	59 (52.7)	48 (48.0)	62 (63.9)	23 (71.9)	25 (69.4)	14 (46.7)	287 (54.5)	0.013

<b>neuromodulators commenced during follow-up (%)</b>									
<b>Anti-spasmodic e.g. hyoscine (%)</b>	35 (29.2)	30 (26.8)	34 (34.0)	40 (41.2)	13 (40.6)	14 (38.9)	9 (30.0)	175 (33.2)	0.30
<b>Mebeverine or alverine (%)</b>	20 (16.7)	23 (20.5)	13 (13.0)	17 (17.5)	9 (28.1)	10 (27.8)	3 (10.0)	95 (18.0)	0.23
<b>TCA (%)</b>	4 (3.3)	15 (13.4)	7 (7.0)	15 (15.5)	5 (15.6)	6 (16.7)	4 (13.3)	56 (10.6)	0.031
<b>SSRI (%)</b>	7 (5.8)	22 (19.6)	5 (5.0)	21 (21.6)	7 (21.9)	9 (25.0)	2 (6.7)	73 (13.9)	<0.001
<b>SNRI (%)</b>	0 (0.0)	4 (3.6)	0 (0.0)	5 (5.2)	2 (6.3)	4 (11.1)	1 (3.3)	16 (3.0)	0.007
<b>Any psychological therapy commenced during follow-up (%)</b>	6 (5.0)	11 (9.8)	7 (7.0)	5 (5.2)	0 (0.0)	5 (13.9)	0 (0.0)	34 (6.5)	0.11
<b>CBT (%)</b>	4 (3.3)	10 (8.9)	7 (7.0)	4 (4.1)	0 (0.0)	3 (8.3)	0 (0.0)	28 (5.3)	0.18
<b>Hypnotherapy (%)</b>	2 (1.7)	2 (1.8)	1 (1.0)	1 (1.0)	0 (0.0)	2 (5.6)	0 (0.0)	8 (1.5)	0.51

\*Adds up to >100%, as some people commenced more than one treatment during 12-month follow-up.

CBT, cognitive behavioural therapy; GI, gastrointestinal; IBS-SSS, IBS severity scoring system; SD, standard deviation; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

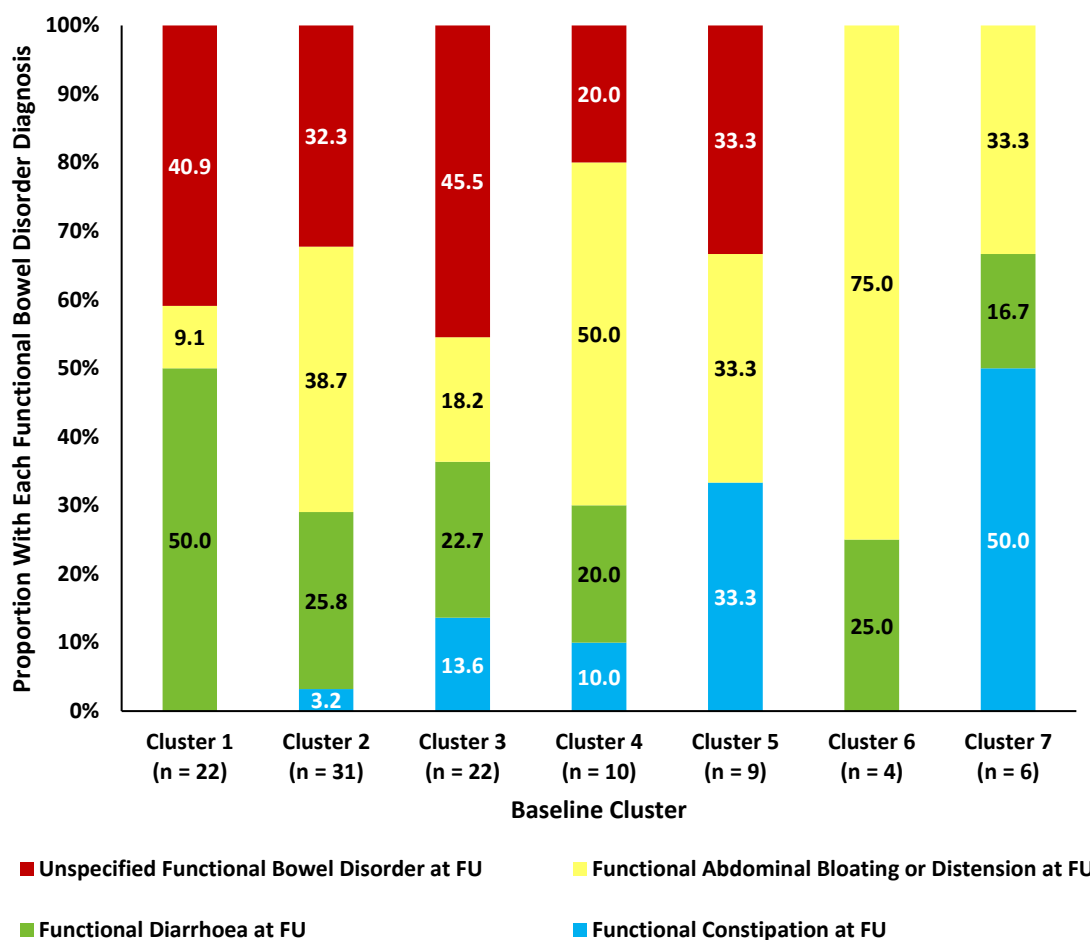
**Figure 7-7. Comparison of IBS Cluster Membership According to Degree of Psychological Burden Between Baseline and Follow-up Among 527 Individuals with Rome III IBS.**



### **7.3.5 Change in Functional Bowel Disorder Diagnosis and IBS Cluster Membership Among Those No Longer Meeting Rome Criteria for IBS at Follow-up.**

Among the 104 individuals (16.5%) with Rome III IBS at baseline who no longer met Rome III criteria for IBS at 12-month follow-up, 34 (32.7%) met criteria for an unspecified functional bowel disorder, 31 (29.8%) functional abdominal bloating or distension, 28 (26.9%) functional diarrhoea, and 11 (10.6%) functional constipation. A comparison of change in functional bowel disorder diagnosis according to baseline IBS cluster is shown in Figure 7-8. When the baseline Rome III cluster model was applied to these individuals at 12-month follow-up, 87 (83.7%) were assigned to clusters with low overall gastrointestinal symptoms (clusters 2 or 3), compared with 53 (51.0%) at baseline.

**Figure 7-8. Change in Functional Bowel Disorder Diagnosis at Follow-up According to Baseline IBS Cluster Among 104 Individuals with Rome III IBS at Baseline.**



Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.

### 7.3.6 Commencement of New Treatment and Consultation Behaviour

#### According to Baseline IBS Cluster Among Those with Rome III IBS at Baseline and Follow-up.

Overall, of the 527 individuals who continued to have Rome III IBS at follow-up, 372 (70.6%) had commenced at least one new treatment during the 12-month follow-up period, of whom 174 (46.8%) changed IBS cluster at follow-up. Similarly, of the 155 people who did not commence any new treatment, 78 (50.3%) also changed IBS cluster at follow-up. Overall, there was no significant association between commencing a new treatment and changing IBS cluster at follow-up ( $p = 0.46$ ). This remained the case when subcategories of treatment were examined, including commencing any medication for diarrhoea ( $p = 0.61$ ), any medication for constipation ( $p = 0.93$ ), any medication for pain, including a central neuromodulator ( $p = 0.40$ ), or any psychological therapy ( $p = 0.93$ ).

New treatments commenced by baseline IBS cluster are shown in Table 7-3. Only 34 individuals with Rome III IBS at baseline and follow-up reported receiving any form of psychological therapy, of whom 13 (38.2%) were in baseline clusters characterised by low psychological burden (clusters 1, 3, or 7). Overall, the mean number of treatments commenced was significantly higher in clusters with a high psychological burden (clusters 2, 4, 5, or 6) ( $p < 0.001$ ), and these clusters also had significantly higher rates of consultation with both GPs and gastroenterologists ( $p < 0.001$ ). The impact of symptoms at follow-up, in terms of patients reporting that they limited activities at least 50% of the time, was also significantly greater in clusters with high psychological burden at baseline ( $p < 0.001$ ).

A significantly higher proportion of people in clusters with diarrhoea-related symptoms (clusters 1 or 4) commenced medication for diarrhoea ( $p < 0.001$ ), and, similarly, a significantly higher proportion of people in clusters with constipation-

related symptoms (clusters 5 or 7) commenced medication for constipation ( $p < 0.001$ ). Finally, a significantly higher proportion of people in clusters characterised by high psychological burden (clusters 2, 4, 5, or 6) commenced medication for pain, including prescription of central neuromodulators ( $p = 0.013$ ).

## 7.4 Discussion

The study reported in Chapter 6 used LCA to derive and validate a model to classify people with IBS into seven novel subgroups, or clusters, based on their pattern of gastrointestinal symptoms, extra-intestinal symptoms, and psychological profiles. The current longitudinal follow-up study has examined the natural history of these subgroups, investigating whether they are of prognostic value, and explored changes in cluster membership, by applying the baseline model to longitudinal data, collected after 12-months, in the same cohort of people. Of those who provided follow-up data, 46% changed cluster at 12 months. Commencing a new treatment was not associated with a change in cluster membership. When cluster membership was stratified according to gastrointestinal symptoms, of those in a diarrhoea-predominant or constipation-predominant cluster at baseline, around two-thirds remained in such a cluster at follow-up. Of those who changed cluster, this was almost exclusively to a mixed-gastrointestinal symptom cluster; transition between diarrhoea-predominant and constipation-predominant clusters, or *vice versa*, was rare. Of those in a mixed gastrointestinal symptoms cluster at baseline, three-quarters remained in such a cluster at follow-up. Cluster membership stratified according to psychological comorbidity was more stable; of those in a cluster with high psychological comorbidity at baseline, 84% remained in a cluster with high psychological comorbidity at follow-up. Findings with respect to those in a cluster with low psychological comorbidity at baseline were similar. This stratification was useful from a prognostic perspective; people in clusters with high psychological burden had more severe symptoms at follow-up, which had a



significantly greater impact on daily activities, commenced a higher mean number of treatments, and were more likely to consult with a doctor about their IBS compared with people in clusters with low psychological burden, irrespective of whether the Rome IV or III criteria were used to define IBS.

This study recruited a large number of individuals in a community setting who self-identified as having IBS. Most had consulted a GP, some a gastroenterologist, and a small proportion had never sought medical advice for their symptoms. This implies that the participants, and the model that was derived from their data, will be generalisable to many individuals living with IBS. Moreover, and in contrast to other subgroup modelling studies in IBS,<sup>26, 27, 59</sup> the model has been validated, as described in Chapter 6, showing that it was likely to perform similarly if applied to other cohorts of patients with IBS. In addition, the questionnaire was completed using a web-based portal meaning that, for most variables of interest, data collection at baseline and 12-months was complete.

Weaknesses include the fact that it was not possible to confirm the diagnosis of IBS in all individuals in this study using medical records. Consequently, because those participating believed that they had IBS, and met diagnostic criteria, it was assumed that they had the condition. It is important to acknowledge that some organic gastrointestinal disorders, such as coeliac disease or inflammatory bowel disease, can mimic IBS;<sup>304, 405-407</sup> however, the community prevalence of these disorders in comparison to IBS is considerably lower. Moreover, over 95% of study subjects had consulted with a doctor regarding their symptoms. It is likely, therefore, that the majority of participants had undergone some investigation, in addition to clinical assessment, to rule out organic disease and did, therefore, genuinely have IBS. The response rate to the 12-month questionnaire was 57%, which is similar to other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame.<sup>408-412</sup> Responders were

older, less likely to smoke, more likely to be married or co-habiting, to have attained a university or postgraduate level of education, to be White Caucasian, and to have seen a doctor about their IBS symptoms. This indicates that the population that was studied at follow-up may not be representative of the original cohort of people that were recruited. However, comparison between responders and the original study participants in terms of symptoms, symptom severity, psychological comorbidity, and baseline cluster membership revealed no significant differences. Moreover, absolute differences in demographic data observed were relatively modest.

Other investigators have also examined the possibility of subgrouping people with IBS using factors beyond stool pattern.<sup>26, 27, 59, 60</sup> Although there is a consensus that people with IBS can be separated into distinct groups using a combination of gastrointestinal symptoms and psychological factors, the specific characteristics and number of subgroups varies between studies. The current treatment paradigm for IBS advocates targeting therapy according to predominant gastrointestinal symptom; however, extra-intestinal symptoms and psychological comorbidity, which are recognised as playing an important role in IBS symptomatology, are not considered as part of the current classification system for the condition. Consequently, knowing how best to tailor multimodal treatment, including use of psychological therapies, to the needs of the individual patient is difficult, and yet it seems likely that the pursuit of more personalised treatment in the care of those with IBS will be increasingly desirable. Crucially, no previous study investigating novel IBS subgroups has examined their natural history, in order to understand the clinical evolution of IBS, or whether they can be used to identify those with a worse disease course. If alternative approaches to subgrouping IBS, such as have been proposed, are to be incorporated into clinical practice and used to guide treatment, understanding these issues is key.

Overall, the findings of this study show that cluster membership changes over time; however, rather than being a disadvantage, this flexibility is a desirable feature of a classification system that could be used to direct treatment. Indeed, one would hope that patients could transition from clusters with a high symptom burden to those with a lower symptom burden, a trend that was observed among those individuals no longer meeting criteria for IBS at follow-up. Nevertheless, the reasons for changes in cluster membership are unclear. There was no association with commencing a new treatment and changes may, therefore, reflect natural fluctuations of symptoms over time. However, it is also important to consider that, due to experiencing improvements in their symptoms, some participants may not have responded to the follow-up questionnaire, and this will have affected assessment of natural history of the clusters. In contrast to studies investigating the stability of IBS stool subgroups alone, which have suggested that IBS-M is the least stable subgroup,<sup>44-46</sup> this study found that the proportion of individuals who remained in a mixed gastrointestinal symptoms cluster between baseline and follow-up was higher than the proportion remaining in either a diarrhoea-predominant or constipation-predominant group, respectively. However, in keeping with the findings of these previous stool subgroup stability studies,<sup>44-46</sup> very few participants transitioned from a diarrhoea-predominant cluster to a constipation-predominant cluster, or *vice versa*.

Changes in cluster membership might have been the consequence of alterations in underlying pathophysiological mechanisms which were not measured in this study. With respect to visceral sensitivity, it has been shown that, although patients with IBS are viscerally hypersensitive at baseline compared with healthy controls, repeated exposure to visceral stimuli over a 12-month period resulted in normalisation of visceral perception.<sup>413</sup> This was accompanied by a reduction in CNS arousal, despite continued activation of neural networks involved in processing visceral nociception. Crucially,

however, these changes notwithstanding, there was no accompanying change in either IBS symptom severity or psychological profiles. Overall, therefore, these findings suggest that changes in visceral sensitivity are unlikely to have played a major role in determining changes in cluster membership and, furthermore, they emphasise that pain perception not only depends on neural nociceptive pathways between gut and brain, but also on psychological factors.<sup>414</sup> Another study conducted an integrated longitudinal analysis of the gut microbiome, metabolome, host epigenome, and transcriptome in patients with IBS compared with healthy controls.<sup>415</sup> Changes in the gut microbiome, and in microbial metabolites, appeared to underlie symptom flares in people with IBS and, therefore, these factors might have been drivers of transition from clusters with less severe gastrointestinal symptoms to those with more severe symptom profiles. Similarly, changes in immune function may also have played a role; symptom flares in people with IBS-D have been shown to be associated with significant reductions in both T-helper cell proliferation and concentrations of interferon gamma in peripheral blood samples.<sup>416</sup>

Treatments commenced appeared broadly appropriate for each cluster, but, interestingly, were not associated with a change in cluster membership. It is important to emphasise, however, that, although it is possible to examine treatment according to cluster, it was not directed in this way. Instead it was prescribed by the participants own clinicians, or obtained over the counter, presumably according to predominant gastrointestinal symptoms. Of note, a previous study investigating the effect of treatment on IBS stool subgroup stability specifically, in the same cohort, found that there was no association.<sup>49</sup> Moreover, because this study only collected data at two distinct time points, it is not possible to assess the temporal relationship between treatment and symptoms, or cluster membership. It is also difficult to assess the appropriateness of treatment for any individual, and whether this influences a change in

cluster membership. Some participants who were in a baseline cluster with diarrhoea, for example, received secretagogue drugs for constipation. This seems an inappropriate choice of drug therapy, but an individual's symptoms might have changed from baseline to the point of commencing this treatment. In addition, it is difficult to assess the effects of different combinations of treatment.

Regarding psychological comorbidity, it is interesting to note that those individuals in a cluster characterised by high psychological comorbidity at baseline largely remained in such a cluster at follow-up. Compared with a change in cluster membership stratified by gastrointestinal symptoms, cluster membership stratified by level of psychological comorbidity was more stable, and predicted higher numbers of subsequent treatments, as well as consultation behaviour and disease impact. Of note, despite there being 188 people in a cluster with high psychological comorbidity at baseline, the number of people receiving psychological therapies was very low, the emphasis being mainly on first line drug therapies, such as antidiarrhoeals and laxatives. This might partly reflect difficulties accessing these therapies, particularly for those individuals managed solely in a primary care setting. Nevertheless, these findings raise the question of whether addressing psychological health needs earlier, in conjunction with physical symptoms, might prove to be a more effective approach, which could have resulted in changes to cluster membership and reduced consumption of medical resources.

In summary, this study has explored the natural history and prognostic value of a novel method of subgrouping people with IBS, described in Chapter 6, which uses a combination of gastrointestinal symptoms, extra-intestinal symptoms, and psychological comorbidity. Overall, although approximately half of those responding to the follow-up questionnaire changed cluster, further analysis revealed that there was little transition with respect to psychological comorbidity. Most people who were in a cluster with high

psychological burden at baseline remained in such as cluster at follow-up, and these appeared to predict disease course. Despite this, very few people reported receiving psychological therapies. To better understand whether formal approaches to subgrouping patients with IBS using factors beyond stool are helpful in directing treatment, a prospective study is needed. Such a study would allocate patients to a cluster at baseline using the model, which is a mathematical equation that can be easily applied in clinical practice, and then randomise them to receive targeted treatment according to cluster, or conventional physician-directed management according to the patient's predominant symptoms, with symptoms, quality of life, and resource use compared between groups. Clusters with low gastrointestinal symptoms and high psychological burden would likely receive a psychological therapy, clusters with high gastrointestinal symptoms and low psychological burden a peripherally acting drug, and clusters with high gastrointestinal symptoms and high psychological burden a combination of psychological therapy and drugs, including centrally acting neuromodulators. Further investigation of this potential approach for the management of IBS is warranted as clinicians strive for ways to deliver high-quality and high-value personalised care, with the potential to improve outcomes, for people suffering with this chronic, and frequently debilitating, condition.

**CHAPTER 8**  
**Conclusions**

Over the last 30 years, the Rome Foundation have sought to standardise and refine the definition of IBS used in clinical and research practice by creating symptom-based diagnostic criteria called the Rome criteria. The most recent iteration, Rome IV, were published in 2016 and characterise IBS as the presence of abdominal pain in association with a change in stool frequency, stool form, or both.<sup>14</sup> In addition to making a diagnosis of IBS, the Rome criteria also stipulate that patients should be subgrouped according to their predominant stool pattern, be that IBS-C, IBS-D, or IBS-M, as a means of directing symptom-specific treatments, such as dietary modifications, antidiarrhoeal drugs, or laxatives.

Although gastrointestinal symptoms are central to making a diagnosis of IBS, they are not the only important consideration. Indeed, the Rome IV process reclassified IBS, and all other functional gastrointestinal disorders, as disorders of gut-brain interaction. This was in recognition of the complex interplay of biological, psychological, and social factors underpinning these disorders.<sup>417</sup> However, although a broad range of pathophysiological mechanisms and risk factors have been identified in IBS, including psychological comorbidities, alterations in visceral sensitivity, genetic factors, and changes in the gut microbiome, no single factor is universal to all patients. Moreover, it is likely that even among people with identical gastrointestinal symptoms, the underlying pathophysiology responsible for causing them varies, and this may be important for determining an individual's response to certain drug therapies, or for predicting prognosis. Unfortunately, however, with the exception of psychological health, which can be assessed relatively easily using validated questionnaires, measurement of other factors is complicated both by the need for invasive testing, such as that required to evaluate visceral sensitivity, and by uncertainty regarding the clinical interpretation of results, a problem with respect to profiling the gut microbiome in IBS, for example. Nevertheless, whatever the deficits in current knowledge, subgrouping



patients and directing treatment according to gastrointestinal symptoms in isolation is almost certainly too simplistic, ignoring both the evidently multifaceted nature of IBS and failing to highlight patients liable to benefit from psychological therapies, for example.

These issues are addressed to some extent by the Rome Foundation MDCP, a framework that encourages physician-led appraisal of a broader range of factors, including psychological health and the impact of illness, in addition to gastrointestinal symptoms during the assessment and treatment of anyone with IBS.<sup>57</sup> However, the MDCP is intended for use on a case-by-case basis only, and is not currently incorporated into diagnostic criteria for IBS. This thesis has therefore firstly examined the merits of directing treatment according to predominant stool pattern in isolation, by investigating the relative efficacy of drugs specifically designed for treating stool pattern abnormalities, among patients who were subgrouped in this way using the Rome criteria. It has subsequently investigated whether it is possible to subgroup people with IBS by including factors other than stool pattern alone, and whether differences exist depending on which iteration of the Rome criteria is used to define IBS. Finally, it has explored the natural history of these novel subgroups, including whether they are of prognostic value, in order to evaluate if this approach could lead to more personalised management of the condition.

Over the past 15 years, a number of second-line drugs have been developed specifically for the treatment of IBS-C. These so-called secretagogues, such as lubiprostone, linaclotide, plecanatide, and tenapanor, which share common mechanisms of action, have all been shown to be effective in placebo-controlled trials. Likewise, for the treatment of IBS-D and IBS-M, a range of drug therapies have been developed with proven efficacy, and, although they differ in their pharmacology, they are all usually reserved as second-line treatments. Examples of these include alosetron, ramosetron,

eluxadoline, and rifaximin. Overall, the relative efficacy of these treatments remains unknown due to a lack of head-to-head trials and therefore two network meta-analyses were undertaken, one for treatments in IBS-C, and one for treatments in IBS-D or IBS-M, to resolve this uncertainty. Both of these studies showed that the efficacy of these drugs is modest overall, with little to choose between individual treatments. This is despite them having been developed specifically to target stool pattern abnormalities in IBS and tested in patient populations that are homogeneous with respect to gastrointestinal symptoms, having been recruited using the Rome criteria. One possible explanation for these findings is that trial participants were differentiated by other factors, such as psychological comorbidities, which were not measured, but which might have had a bearing on clinical response to a peripherally acting drug. These two studies therefore reinforced the hypothesis that novel approaches to subgrouping people with IBS, which include these additional factors, may better reflect the complexities of the condition, and enable a more targeted approach to treatment, which might predict clinical response.

In order to explore this further, a study was undertaken to recruit a large cohort of people in the community who self-identified as having IBS, and whose data were used to conduct cluster modelling to derive new IBS subgroups. Participants were evaluated according to both the Rome III and Rome IV criteria for IBS simultaneously.<sup>14, 32</sup> This provided an opportunity to investigate whether there were differences in the clinical and psychological characteristics of people with IBS depending on how the disorder was defined. Indeed, the Rome IV criteria for IBS were made more restrictive than Rome III in order to increase their diagnostic specificity. Previous studies suggested that these changes had few implications;<sup>40-42</sup> however, two studies were unable to apply the full criteria simultaneously, and instead used a retrospective surrogate measure to approximate the Rome IV criteria.<sup>40, 41</sup> In contrast,

the study conducted as part of this thesis used both the Rome IV and III questionnaire side-by-side, and showed that people with Rome IV-defined IBS had more severe symptoms, which had a greater impact on daily life, and higher levels of psychological comorbidity, compared with people with Rome III-defined IBS. These findings highlighted that it would be necessary to evaluate whether different subgrouping models would be derived depending on which iteration of the Rome criteria was used to define IBS.

Subsequently, LCA was used in the same cohort to investigate novel approaches to subgrouping people with IBS using factors beyond stool pattern alone. Only three studies had examined this issue previously,<sup>26, 27, 59</sup> and these had important limitations which this new study aimed to address. One study had included only a small number of patients recruited in a tertiary care setting thereby limiting generalisability,<sup>26</sup> and another used outdated definitions of IBS.<sup>59</sup> The third study recruited people who met Rome criteria for IBS in a population-based cross-sectional survey, rather than including them because they reported having IBS, or had received a diagnosis of IBS.<sup>27</sup> Crucially, no study validated the subgrouping models they proposed, meaning it was unclear whether the models were applicable to other people with IBS, or were specific only to the cohorts in which they were derived.

The LCA study reported in this thesis found that people with IBS could be divided into seven unique subgroups, or clusters. These were differentiated according to the presence of certain gastrointestinal symptoms, including stool pattern, and abdominal pain that was not relieved by defaecation, as well as by the presence of extra-intestinal symptoms and abnormal mood. Despite the aforementioned differences in diagnostic criteria, these seven clusters were reproducible, irrespective of whether IBS was defined according to the Rome III or Rome IV criteria. The subgrouping models were validated internally, demonstrating that they would be expected to perform

similarly if applied to a different dataset. Moreover, a large number of individuals were included in the LCA, all of whom were in the community and self-identified as having IBS. Some individuals had consulted in primary care, some in secondary care, and some had never seen a doctor, meaning that the clusters were likely to be generalisable to many individuals living with IBS.

The characteristics of the seven IBS clusters were diverse. These differences might explain why response to a drug targeted at predominant stool pattern in IBS is so variable in clinical practice. A more personalised approach to management, which addresses psychological health needs in conjunction with gastrointestinal symptoms, may therefore be needed. In order to explore this further, a longitudinal follow-up study was undertaken, examining the natural history of these novel subgroups and assessing their prognostic value. Overall, this showed that, of those who responded to the request for follow-up data at 12-months, around half changed cluster; however, cluster membership stratified according to psychological burden was more stable. Indeed, of those in a cluster with high psychological burden at baseline, over 80% remained in such a cluster at follow-up. Moreover, from a prognostic perspective, people in clusters with high psychological burden at baseline had more severe symptoms at follow-up, which had a significantly greater impact on daily activities, commenced a higher mean number of treatments, and were more likely to consult with a doctor about their IBS, compared with people in clusters with low psychological burden, irrespective of whether the Rome IV or III criteria were used to define IBS. Theoretically, directing treatment according to these clusters, including earlier use of psychological therapies, might alter disease course and improve outcomes in IBS.

The work undertaken in this thesis has highlighted several areas that could be the focus of further research. Firstly, although it can be speculated that using these new subgrouping models to personalise the management of IBS may improve outcomes,

additional studies are needed to test this hypothesis. As discussed, a prospective study could allocate people with IBS to a cluster at baseline using the model, and then randomise them to receive targeted treatment according to cluster using a predefined algorithm, or conventional physician-directed management according to the patient's predominant symptoms. Clinical outcomes, in terms of improvements in gastrointestinal symptoms, psychological health, and quality of life, could be compared between groups, as could use of healthcare resources. Second, if future treatment trials are able to collect the data necessary to enable the application of these models for subgrouping participants, secondary analyses could be conducted to examine whether there is any difference in clinical outcomes between clusters with individual treatments tested. Third, although the subgrouping model in this thesis has included measures of psychological health in addition to gastrointestinal symptoms, if it were also possible to incorporate data regarding other pathophysiologies or risk factors, this might improve the ability of the model to describe the complex nature of IBS, and provide further insights into factors responsible for governing treatment response and prognosis. Gathering pathophysiological data from large cohorts of people is likely to be logistically challenging; however, smaller hypothesis-generating pilot studies could be conducted, which start by cross-tabulating pathophysiological data using the existing seven subgroup model in order to explore possible trends and associations. Finally, although IBS is among the most prevalent of the functional gastrointestinal disorders, it is one of over 30 such conditions that have been categorised by the Rome Foundation. Like IBS, these other conditions, such as functional dyspepsia or functional constipation, are also defined using symptom-based criteria, and are considered to be disorders of gut-brain interaction, with a complex pathophysiology.<sup>417</sup> Exploration of novel approaches to subgrouping people with these other disorders should be considered, and may reveal common themes, such as the relevance of psychological

health, which may change, fundamentally, the way these disorders are categorised and managed in the future.

In summary, this thesis has investigated new approaches to subgrouping people with IBS that look beyond stool pattern alone. It has been demonstrated that people with IBS can be divided into seven unique subgroups based on a combination of gastrointestinal symptoms, extra-intestinal symptoms, and mood. The diversity of these subgroups highlight the complex nature of IBS, and might partly explain why the clinical response to drugs targeted at predominant stool form in isolation is relatively modest, as has been summarised in two complementary network meta-analyses. These novel subgroups were reproducible, irrespective of whether IBS is defined according to the Rome III or Rome IV criteria. This is despite analysis showing that gastrointestinal symptoms are more severe, and psychological health is poorer, among individuals with Rome IV-defined IBS compared with those with Rome III-defined IBS. Longitudinal follow-up over 12 months demonstrated little transition between subgroups with respect to psychological burden, and these appeared to predict a more severe disease course. Directing treatment according to these novel subgroups, including earlier use of psychological therapies, might improve outcomes in IBS, and should be a focus for future research.

**CHAPTER 9**  
**Bibliography**

1. Powell R. On Certain Painful Affections of the Intestinal Canal. *Med Trans Coll Physicians*. 1820;6:106-17.
2. Forbes J, Tweedie A, Conolly J. *The Cyclopaedia of Practical Medicine: Comprising Treatises on the Nature of Treatment of Diseases, Materia Medica and Therapeutics etc. etc.* Philadelphia: Lea and Blanchard; 1849. 655 p.
3. Osler W. *The Principles and Practice of Medicine*. Edinburgh and London: Young J. Pentland; 1892. 396-7 p.
4. Clark A. London Hospital.: Clinical Illustrations of Mucous Disease of the Colon, from Notes of Various Cases. *Lancet*. 1859;74(Dec):614-5.
5. Da Costa JM. Membranous Enteritis. *Am J Med Sci*. 1871;62(Oct):321-38.
6. White H. A Study of 60 Cases of Membranous Colitis. *Lancet*. 1905;2(Oct):1229-35.
7. Bockus H, Bank J, Wilkinson SA. Neurogenic Mucous Colitis. *Am J Med Sci*. 1928;176(6):813-29.
8. Christensen J. Pathophysiology of the irritable bowel syndrome. *Lancet*. 1992;340(8833):1444-7.
9. Ryle J. An Address on the Chronic Spasmodic Affections of the Colon and the Diseases Which They Simulate. *Lancet*. 1928;2(Dec):1115-9.
10. White BV, Cobb S, Jones CM. Mucous Colitis: A Psychological Study of Sixty Cases. *Psychosom Med*. 1939;Monograph 1:1-103.
11. Jordan SM, Kiefer ED. The Irritable Colon. *JAMA*. 1929;93(8):592-5.
12. Peters G, Barger J. The irritable bowel syndrome. *Gastroenterology*. 1944;3:399-402.
13. Chaudhary NA, Truelove SC. The irritable colon syndrome. A study of the clinical features, predisposing causes, and prognosis in 130 cases. *Q J Med*. 1962;31(123):307-22.
14. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel Disorders. *Gastroenterology*. 2016;150(6):1393-407.
15. Lim SJ, Gracie DJ, Kane JS, Mumtaz S, Scarsbrook AF, Chowdhury FU, et al. Prevalence of, and predictors of, bile acid diarrhea in outpatients with chronic diarrhea: A follow-up study. *Neurogastroenterol Motil*. 2019;31(9):e13666.
16. Aziz I, Mumtaz S, Bholah H, Chowdhury FU, Sanders DS, Ford AC. High prevalence of idiopathic bile acid diarrhea among patients with diarrhea-predominant irritable bowel syndrome based on Rome III criteria. *Clin Gastroenterol Hepatol*. 2015;13(9):1650-5.e2.



17. Hofmann AF. The syndrome of ileal disease and the broken enterohepatic circulation: choleric enteropathy. *Gastroenterology*. 1967;52(4):752-7.
18. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J*. 1978;2(6138):653-4.
19. Kruis W, Thieme C, Weinzierl M, Schussler P, Holl J, Paulus W. A diagnostic score for the irritable bowel syndrome. Its value in the exclusion of organic disease. *Gastroenterology*. 1984;87(1):1-7.
20. Bellentani S, Baldoni P, Petrella S, Tata C, Armocida C, Marchegiano P, et al. A simple score for the identification of patients at high risk of organic diseases of the colon in the family doctor consulting room. The Local IBS Study Group. *Fam Pract*. 1990;7(4):307-12.
21. Frigerio G, Beretta A, Orsenigo G, Tadeo G, Imperiali G, Minoli G. Irritable bowel syndrome. Still far from a positive diagnosis. *Dig Dis Sci*. 1992;37(2):164-7.
22. Doğan UB, Unal S. Kruis scoring system and Manning's criteria in diagnosis of irritable bowel syndrome: is it better to use combined? *Acta Gastroenterol Belg*. 1996;59(4):225-8.
23. Ford AC, Talley NJ, Veldhuyzen van Zanten SJ, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? *JAMA*. 2008;300(15):1793-805.
24. Ballou S, Lembo A. Editorial: latent class analysis to improve confidence in the diagnosis of IBS. *Aliment Pharmacol Ther*. 2017;45(9):1267-8.
25. Sood R, Gracie DJ, Gold MJ, To N, Pinto-Sanchez MI, Bercik P, et al. Derivation and validation of a diagnostic test for irritable bowel syndrome using latent class analysis. *Aliment Pharmacol Ther*. 2017;45(6):824-32.
26. Polster A, Van Oudenhove L, Jones M, Ohman L, Tornblom H, Simren M. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. *Aliment Pharmacol Ther*. 2017;46(5):529-39.
27. Polster AV, Palsson OS, Tornblom H, Ohman L, Sperber AD, Whitehead WE, et al. Subgroups of IBS patients are characterized by specific, reproducible profiles of GI and non-GI symptoms and report differences in healthcare utilization: A population-based study. *Neurogastroenterol Motil*. 2019;31(1):e13483.

28. Whitehead WE, Crowell MD, Bosmajian L, Zonderman A, Costa PT, Jr., Benjamin C, et al. Existence of irritable bowel syndrome supported by factor analysis of symptoms in two community samples. *Gastroenterology*. 1990;98(2):336-40.
29. Talley NJ, Phillips SF, Melton LJ, Mulvihill C, Wiltgen C, Zinsmeister AR. Diagnostic value of the Manning criteria in irritable bowel syndrome. *Gut*. 1990;31(1):77-81.
30. Drossman DA, Grant Thompson W, Talley N, Funch-Jensen P, Janssens J, Whitehead W. Identification of sub-groups of functional gastrointestinal disorders. *Gastroenterology Intl*. 1990;3:159-72.
31. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(Suppl 2):43-7.
32. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480-91.
33. Palsson OS, Whitehead WE, van Tilburg MAL, Chang L, Chey W, Crowell MD, et al. Development and validation of the Rome IV diagnostic questionnaire for adults. *Gastroenterology*. 2016;150(6):1481-91.
34. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology*. 2013;145(6):1262-70.e1.
35. Sood R, Gracie DJ, Law GR, Ford AC. Systematic review with meta-analysis: the accuracy of diagnosing irritable bowel syndrome with symptoms, biomarkers and/or psychological markers. *Aliment Pharmacol Ther*. 2015;42(5):491-503.
36. Sood R, Camilleri M, Gracie DJ, Gold MJ, To N, Law GR, et al. Enhancing diagnostic performance of symptom-based criteria for irritable bowel syndrome by additional history and limited diagnostic evaluation. *Am J Gastroenterol*. 2016;111(10):1446-54.
37. Black CJ, Craig O, Gracie DJ, Ford AC. Comparison of the Rome IV criteria with the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gut*. 2020;doi: 10.1136/gutjnl-2020-322519.
38. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. 2004;329(7458):168.

39. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Fluctuation of gastrointestinal symptoms in the community: A 10-year longitudinal follow-up study. *Aliment Pharmacol Ther.* 2008;28(8):1013-20.
40. Aziz I, Törnblom H, Palsson OS, Whitehead WE, Simrén M. How the change in IBS criteria from Rome III to Rome IV impacts on clinical characteristics and key pathophysiological factors. *Am J Gastroenterol.* 2018;113(7):1017-25.
41. Vork L, Weerts Z, Mujagic Z, Kruimel JW, Hesselink MAM, Muris JWM, et al. Rome III vs Rome IV criteria for irritable bowel syndrome: A comparison of clinical characteristics in a large cohort study. *Neurogastroenterol Motil.* 2018;30(2):e13189.
42. Bai T, Xia J, Jiang Y, Cao H, Zhao Y, Zhang L, et al. Comparison of the Rome IV and Rome III criteria for IBS diagnosis: A cross-sectional survey. *J Gastroenterol Hepatol.* 2017;32(5):1018-25.
43. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32(9):920-4.
44. Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. *Gastroenterology.* 2005;128(3):580-9.
45. Garrigues V, Mearin F, Badía X, Balboa A, Benavent J, Caballero A, et al. Change over time of bowel habit in irritable bowel syndrome: a prospective, observational, 1-year follow-up study (RITMO study). *Aliment Pharmacol Ther.* 2007;25(3):323-32.
46. Ersryd A, Posserud I, Abrahamsson H, Simrén M. Subtyping the irritable bowel syndrome by predominant bowel habit: Rome II versus Rome III. *Aliment Pharmacol Ther.* 2007;26(6):953-61.
47. Palsson OS, Baggish JS, Turner MJ, Whitehead WE. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: implications for treatment. *Am J Gastroenterol.* 2012;107(2):286-95.
48. Palsson OS, Baggish J, Whitehead WE. Episodic nature of symptoms in irritable bowel syndrome. *Am J Gastroenterol.* 2014;109(9):1450-60.
49. Barberio B, Houghton LA, Yiannakou Y, Savarino EV, Black CJ, Ford AC. Symptom stability in Rome IV vs Rome III irritable bowel syndrome. *Am J Gastroenterol.* 2021;116(2):362-71.

50. Koloski NA, Boyce PM, Talley NJ. Somatization an independent psychosocial risk factor for irritable bowel syndrome but not dyspepsia: A population-based study. *Eur J Gastroenterol Hepatol*. 2006;18(10):1101-9.
51. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. *Gut*. 2012;61(9):1284-90.
52. Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: A 1-year population-based prospective study. *Aliment Pharmacol Ther*. 2016;44(6):592-600.
53. Jones MP, Tack J, Van Oudenhove L, Walker MM, Holtmann G, Koloski NA, et al. Mood and anxiety disorders precede development of functional gastrointestinal disorders in patients but not in the population. *Clin Gastroenterol Hepatol*. 2017;15(7):1014-20.e4.
54. Clevers E, Tack J, Tornblom H, Ringstrom G, Luyckx K, Simren M, et al. Development of irritable bowel syndrome features over a 5-year period. *Clin Gastroenterol Hepatol*. 2018;16(8):1244-51.e1.
55. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2019;50(2):132-43.
56. Simren M, Tornblom H, Palsson OS, van Tilburg MAL, Van Oudenhove L, Tack J, et al. Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. *Gut*. 2018;67(2):255-62.
57. Drossman DA. The multidimensional clinical profile for functional gastrointestinal disorders. 2nd ed ed. Raleigh, NC: Rome Foundation; 2016.
58. Black CJ, Ford AC. Editorial: subgroups in irritable bowel syndrome-more than just diarrhoea and constipation? *Aliment Pharmacol Ther*. 2017;46(7):697.
59. Han CJ, Pike K, Jarrett ME, Heitkemper MM. Symptom-based latent classes of persons with irritable bowel syndrome. *Res Nurs Health*. 2019;42(5):382-91.
60. Guthrie E, Creed F, Fernandes L, Ratcliffe J, Van Der Jagt J, Martin J, et al. Cluster analysis of symptoms and health seeking behaviour differentiates subgroups of patients with severe irritable bowel syndrome. *Gut*. 2003;52(11):1616-22.

61. Lovell RM, Ford AC. Global prevalence of, and risk factors for, irritable bowel syndrome: A meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712-21.
62. Sperber AD, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut*. 2017;66(6):1075-82.
63. Palsson OS, Whitehead W, Tornblom H, Sperber AD, Simren M. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology*. 2020;158(5):1263-73.e3.
64. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation global study. *Gastroenterology*. 2020;doi:10.1053/j.gastro.2020.04.014.
65. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5(10):908-17.
66. Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: Systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(7):991-1000.
67. Gwee KA, Ghoshal UC, Chen M. Irritable bowel syndrome in Asia: Pathogenesis, natural history, epidemiology, and management. *J Gastroenterol Hepatol*. 2018;33(1):99-110.
68. Wigington WC, Johnson WD, Minocha A. Epidemiology of irritable bowel syndrome among African Americans as compared with whites: a population-based study. *Clin Gastroenterol Hepatol*. 2005;3(7):647-53.
69. Kang JY. Systematic review: the influence of geography and ethnicity in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2005;21(6):663-76.
70. Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. *Am J Gastroenterol*. 1998;93(10):1816-22.
71. Gwee KA, Wee S, Wong ML, Png DJ. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an asian urban community. *Am J Gastroenterol*. 2004;99(5):924-31.
72. Rajendra S, Alahuddin S. Prevalence of irritable bowel syndrome in a multi-ethnic Asian population. *Aliment Pharmacol Ther*. 2004;19(6):704-6.

73. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. *Am J Gastroenterol*. 2008;103(5):1229-39.
74. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ, 3rd. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol*. 1992;136(2):165-77.
75. Halder SL, Locke GR, 3rd, Schleck CD, Zinsmeister AR, Melton LJ, 3rd, Talley NJ. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. *Gastroenterology*. 2007;133(3):799-807.
76. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Bjornsson E, Thjodleifsson B. Natural history of functional gastrointestinal disorders: comparison of two longitudinal population-based studies. *Dig Liver Dis*. 2012;44(3):211-7.
77. Agreus L, Svardsudd K, Talley NJ, Jones MP, Tibblin G. Natural history of gastroesophageal reflux disease and functional abdominal disorders. *Am J Gastroenterol*. 2001;96(10):2905-14.
78. Locke III GR, Zinsmeister AR, Fett SL, Melton III LJ, Talley NJ. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol Motil*. 2005;17(1):29-34.
79. Petersen MW, Schröder A, Jørgensen T, Ørnbøl E, Meinertz Dantoft T, Eliassen M, et al. Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD. *Sci Rep*. 2020;10(1):3273.
80. Hyland ME, Bacon AM, Lanario JW, Davies AF. Symptom frequency and development of a generic functional disorder symptom scale suitable for use in studies of patients with irritable bowel syndrome, fibromyalgia syndrome or chronic fatigue syndrome. *Chronic Dis Transl Med*. 2019;5(2):129-38.
81. Aziz I, Palsson OS, Tornblom H, Sperber AD, Whitehead WE, Simren M. The prevalence and impact of overlapping Rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: A cross-sectional general population study in three countries. *Am J Gastroenterol*. 2018;113(1):86-96.
82. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: A multivariate analysis. *Gastroenterology*. 2004;126(7):1665-73.

83. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*. 2000;119(3):654-60.
84. Frank L, Kleinman L, Rentz A, Ciesla G, Kim JJ, Zacker C. Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases. *Clin Ther*. 2002;24(4):675-89.
85. Singh P, Staller K, Barshop K, Dai E, Newman J, Yoon S, et al. Patients with irritable bowel syndrome-diarrhea have lower disease-specific quality of life than irritable bowel syndrome-constipation. *World J Gastroenterol*. 2015;21(26):8103-9.
86. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes*. 2017;15(1):35.
87. Ballou S, McMahon C, Lee HN, Katon J, Shin A, Rangan V, et al. Effects of irritable bowel syndrome on daily activities vary among subtypes based on results from the IBS in America survey. *Clin Gastroenterol Hepatol*. 2019;17(12):2471-8.e3.
88. Bushnell DM, Martin ML, Ricci JF, Bracco A. Performance of the EQ-5D in patients with irritable bowel syndrome. *Value Health*. 2006;9(2):90-7.
89. Drossman DA, Chang L, Schneck S, Blackman C, Norton WF, Norton NJ. A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. *Dig Dis Sci*. 2009;54(7):1532-41.
90. Lacy BE, Everhart KK, Weiser KT, DeLee R, Strobel S, Siegel C, et al. IBS patients' willingness to take risks with medications. *Am J Gastroenterol*. 2012;107(6):804-9.
91. Drossman DA, Morris CB, Schneck S, Hu YJ, Norton NJ, Norton WF, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *J Clin Gastroenterol*. 2009;43(6):541-50.
92. Canavan C, West J, Card T. Change in quality of life for patients with irritable bowel syndrome following referral to a gastroenterologist: A cohort study. *PLoS One*. 2015;10(10):e0139389.
93. Weerts Z, Vork L, Mujagic Z, Keszthelyi D, Hesselink MAM, Kruijmel J, et al. Reduction in IBS symptom severity is not paralleled by improvement in quality

- of life in patients with irritable bowel syndrome. *Neurogastroenterol Motil.* 2019;31(8):e13629.
94. Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Arch Intern Med.* 2004;164(16):1773-80.
  95. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther.* 2014;40(9):1023-34.
  96. Zhang F, Xiang W, Li CY, Li SC. Economic burden of irritable bowel syndrome in China. *World J Gastroenterol.* 2016;22(47):10450-60.
  97. Muller-Lissner SA, Pirk O. Irritable bowel syndrome in Germany. A cost of illness study. *Eur J Gastroenterol Hepatol.* 2002;14(12):1325-9.
  98. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm.* 2013;19(9):755-64.
  99. Flacco ME, Manzoli L, De Giorgio R, Gasbarrini A, Cicchetti A, Bravi F, et al. Costs of irritable bowel syndrome in European countries with universal healthcare coverage: a meta-analysis. *Eur Rev Med Pharmacol Sci.* 2019;23(7):2986-3000.
  100. Tack J, Stanghellini V, Mearin F, Yiannakou Y, Layer P, Coffin B, et al. Economic burden of moderate to severe irritable bowel syndrome with constipation in six European countries. *BMC Gastroenterol.* 2019;19(1):69.
  101. Akehurst RL, Brazier JE, Mathers N, O'Keefe C, Kaltenthaler E, Morgan A, et al. Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting. *Pharmacoeconomics.* 2002;20(7):455-62.
  102. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther.* 2003;17(5):643-50.
  103. Frandemark A, Tornblom H, Jakobsson S, Simren M. Work Productivity and Activity Impairment in Irritable Bowel Syndrome (IBS): A Multifaceted Problem. *Am J Gastroenterol.* 2018;113(10):1540-9.
  104. Cash B, Sullivan S, Barghout V. Total costs of IBS: employer and managed care perspective. *Am J Manag Care.* 2005;11(1 Suppl):S7-16.
  105. Leong SA, Barghout V, Birnbaum HG, Thibeault CE, Ben-Hamadi R, Frech F, et al. The economic consequences of irritable bowel syndrome: a US employer perspective. *Arch Intern Med.* 2003;163(8):929-35.



106. Poulsen CH, Eplöv LF, Hjorthøj C, Hastrup LH, Eliassen M, Dantoft TM, et al. Irritable bowel symptoms, use of healthcare, costs, sickness and disability pension benefits: A long-term population-based study. *Scand J Public Health*. 2018;47(8):867-75.
107. Wong RK, Drossman DA, Weinland SR, Morris CB, Leserman J, Hu Y, et al. Partner burden in irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11(2):151-5.
108. Van Oudenhove L, Crowell MD, Drossman DA, Halpert AD, Keefer L, Lackner JM, et al. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. *Gastroenterology*. 2016;150(6):1355-67.
109. Quigley EMM. The Gut-Brain Axis and the Microbiome: Clues to Pathophysiology and Opportunities for Novel Management Strategies in Irritable Bowel Syndrome (IBS). *J Clin Med*. 2018;7(1):6.
110. Patel P, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P, et al. Irritable bowel syndrome is significantly associated with somatisation in 840 patients, which may drive bloating. *Aliment Pharmacol Ther*. 2015;41(5):449-58.
111. Bourke JH, Langford RM, White PD. The common link between functional somatic syndromes may be central sensitisation. *J Psychosom Res*. 2015;78(3):228-36.
112. van Tilburg MA, Palsson OS, Whitehead WE. Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. *J Psychosom Res*. 2013;74(6):486-92.
113. Spiller RC, Humes DJ, Campbell E, Hastings M, Neal KR, Dukes GE, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. *Aliment Pharmacol Ther*. 2010;32(6):811-20.
114. Grinsvall C, Törnblom H, Tack J, Van Oudenhove L, Simrén M. Relationships between psychological state, abuse, somatization and visceral pain sensitivity in irritable bowel syndrome. *United European Gastroenterol J*. 2018;6(2):300-9.
115. Labus JS, Bolus R, Chang L, Wiklund I, Naesdal J, Mayer EA, et al. The Visceral Sensitivity Index: Development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther*. 2004;20(1):89-97.

116. Labus JS, Mayer EA, Chang L, Bolus R, Naliboff BD. The central role of gastrointestinal-specific anxiety in irritable bowel syndrome: further validation of the visceral sensitivity index. *Psychosom Med.* 2007;69(1):89-98.
117. Jerndal P, Ringström G, Agerforz P, Karpefors M, Akkermans LM, Bayati A, et al. Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterol Motil.* 2010;22(6):646-e179.
118. Lackner JM, Gudleski GD, Ma CX, Dewanwala A, Naliboff B. Fear of GI symptoms has an important impact on quality of life in patients with moderate-to-severe IBS. *Am J Gastroenterol.* 2014;109(11):1815-23.
119. Black CJ, Yiannakou Y, Houghton LA, Shuweihdi F, West R, Guthrie E, et al. Anxiety-related factors associated with symptom severity in irritable bowel syndrome. *Neurogastroenterol Motil.* 2020;32(8):e13872.
120. Drossman DA. Abuse, trauma, and GI illness: is there a link? *Am J Gastroenterol.* 2011;106(1):14-25.
121. Drossman DA. Irritable bowel syndrome and sexual/physical abuse history. *Eur J Gastroenterol Hepatol.* 1997;9(4):327-30.
122. Drossman DA, Leserman J, Nachman G, Li ZM, Gluck H, Toomey TC, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. *Ann Intern Med.* 1990;113(11):828-33.
123. Talley NJ, Fett SL, Zinsmeister AR. Self-reported abuse and gastrointestinal disease in outpatients: association with irritable bowel-type symptoms. *Am J Gastroenterol.* 1995;90(3):366-71.
124. Delvaux M, Denis P, Allemand H. Sexual abuse is more frequently reported by IBS patients than by patients with organic digestive diseases or controls. Results of a multicentre inquiry. French Club of Digestive Motility. *Eur J Gastroenterol Hepatol.* 1997;9(4):345-52.
125. Bradford K, Shih W, Videlock EJ, Presson AP, Naliboff BD, Mayer EA, et al. Association between early adverse life events and irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2012;10(4):385-90.e1-3.
126. Park SH, Videlock EJ, Shih W, Presson AP, Mayer EA, Chang L. Adverse childhood experiences are associated with irritable bowel syndrome and gastrointestinal symptom severity. *Neurogastroenterol Motil.* 2016;28(8):1252-60.

127. Koloski NA, Talley NJ, Boyce PM. A history of abuse in community subjects with irritable bowel syndrome and functional dyspepsia: the role of other psychosocial variables. *Digestion*. 2005;72(2-3):86-96.
128. Talley NJ, Boyce PM, Jones M. Is the association between irritable bowel syndrome and abuse explained by neuroticism? A population based study. *Gut*. 1998;42(1):47-53.
129. Saito YA, Petersen GM, Larson JJ, Atkinson EJ, Fridley BL, de Andrade M, et al. Familial aggregation of irritable bowel syndrome: a family case-control study. *Am J Gastroenterol*. 2010;105(4):833-41.
130. Waehrens R, Ohlsson H, Sundquist J, Sundquist K, Zoller B. Risk of irritable bowel syndrome in first-degree, second-degree and third-degree relatives of affected individuals: a nationwide family study in Sweden. *Gut*. 2015;64(2):215-21.
131. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology*. 2001;121(4):799-804.
132. Bengtson MB, Ronning T, Vatn MH, Harris JR. Irritable bowel syndrome in twins: genes and environment. *Gut*. 2006;55(12):1754-9.
133. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in irritable bowel syndrome: a twin study. *Am J Gastroenterol*. 2005;100(6):1340-4.
134. Jin DC, Cao HL, Xu MQ, Wang SN, Wang YM, Yan F, et al. Regulation of the serotonin transporter in the pathogenesis of irritable bowel syndrome. *World J Gastroenterol*. 2016;22(36):8137-48.
135. Zhu Y, Zheng G, Hu Z. Association between SERT insertion/deletion polymorphism and the risk of irritable bowel syndrome: A meta-analysis based on 7039 subjects. *Gene*. 2018;679:133-7.
136. Garcia-Etxebarria K, Zheng T, Bonfiglio F, Bujanda L, Dlugosz A, Lindberg G, et al. Increased Prevalence of Rare Sucrase-isomaltase Pathogenic Variants in Irritable Bowel Syndrome Patients. *Clin Gastroenterol Hepatol*. 2018;16(10):1673-6.
137. Verstraelen TE, Ter Bekke RM, Volders PG, Masclee AA, Kruijmel JW. The role of the SCN5A-encoded channelopathy in irritable bowel syndrome and other gastrointestinal disorders. *Neurogastroenterol Motil*. 2015;27(7):906-13.

138. Bonfiglio F, Henstrom M, Nag A, Hadizadeh F, Zheng T, Cenit MC, et al. A GWAS meta-analysis from 5 population-based cohorts implicates ion channel genes in the pathogenesis of irritable bowel syndrome. *Neurogastroenterol Motil.* 2018;30(9):e13358.
139. Bonfiglio F, Zheng T, Garcia-Etxebarria K, Hadizadeh F, Bujanda L, Bresso F, et al. Female-specific association between variants on chromosome 9 and self-reported diagnosis of irritable bowel syndrome. *Gastroenterology.* 2018;155(1):168-79.
140. Norcliffe-Kaufmann L, Slaugenhaupt SA, Kaufmann H. Familial dysautonomia: History, genotype, phenotype and translational research. *Prog Neurobiol.* 2017;152:131-48.
141. Komuro H, Sato N, Sasaki A, Suzuki N, Kano M, Tanaka Y, et al. Corticotropin-releasing hormone receptor 2 gene variants in irritable bowel syndrome. *PLoS One.* 2016;11(1):e0147817.
142. Sato N, Suzuki N, Sasaki A, Aizawa E, Obayashi T, Kanazawa M, et al. Corticotropin-releasing hormone receptor 1 gene variants in irritable bowel syndrome. *PLoS One.* 2012;7(9):e42450.
143. Bohn L, Storsrud S, Tornblom H, Bengtsson U, Simren M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol.* 2013;108(5):634-41.
144. Simren M, Mansson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion.* 2001;63(2):108-15.
145. Pauls RN, Max JB. Symptoms and dietary practices of irritable bowel syndrome patients compared to controls: results of a USA national survey. *Minerva Gastroenterol Dietol.* 2019;65(1):1-10.
146. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut.* 2004;53(10):1459-64.
147. Ali A, Weiss TR, McKee D, Scherban A, Khan S, Fields MR, et al. Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial. *BMJ Open Gastroenterol.* 2017;4(1):e000164.

148. Fritscher-Ravens A, Pflaum T, Mosinger M, Ruchay Z, Rocken C, Milla PJ, et al. Many patients with irritable bowel syndrome have atypical food allergies not associated with immunoglobulin E. *Gastroenterology*. 2019;157(1):109-18.e5.
149. Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The Microbiome and Irritable Bowel Syndrome - A Review on the Pathophysiology, Current Research and Future Therapy. *Frontiers in microbiology*. 2019;10:1136.
150. Kassinen A, Krogius-Kurikka L, Makivuokko H, Rinttila T, Paulin L, Corander J, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133(1):24-33.
151. Parthasarathy G, Chen J, Chen X, Chia N, O'Connor HM, Wolf PG, et al. Relationship between microbiota of the colonic mucosa vs feces and symptoms, colonic transit, and methane production in female patients with chronic constipation. *Gastroenterology*. 2016;150(2):367-79.e1.
152. Tap J, Derrien M, Tornblom H, Brazeilles R, Cools-Portier S, Dore J, et al. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. *Gastroenterology*. 2017;152(1):111-23.e8.
153. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. *Nat Rev Dis Primers*. 2016;2:16014.
154. Hugerth LW, Andreasson A, Talley NJ, Forsberg AM, Kjellström L, Schmidt PT, et al. No distinct microbiome signature of irritable bowel syndrome found in a Swedish random population. *Gut*. 2020;69(6):1076-84.
155. Quigley EMM. Gut microbiome as a clinical tool in gastrointestinal disease management: are we there yet? *Nat Rev Gastroenterol Hepatol*. 2017;14(5):315-20.
156. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut*. 2015;64(1):93-100.
157. Black CJ, Ford AC. How effective are antibiotics for the treatment of irritable bowel syndrome? *Expert Opin Pharmacother*. 2020;doi: 10.1080/14656566.2020.1808623.
158. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2009;136(6):1979-88.

159. Card T, Enck P, Barbara G, Boeckxstaens GE, Santos J, Azpiroz F, et al. Post-infectious IBS: Defining its clinical features and prognosis using an internet-based survey. *United European Gastroenterol J.* 2018;6(8):1245-53.
160. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ.* 1997;314(7083):779-82.
161. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther.* 2007;26(4):535-44.
162. Wadhwa A, Al Nahhas MF, Dierkhising RA, Patel R, Kashyap P, Pardi DS, et al. High risk of post-infectious irritable bowel syndrome in patients with *Clostridium difficile* infection. *Aliment Pharmacol Ther.* 2016;44(6):576-82.
163. Ghoshal UC, Rahman MM. Post-infection irritable bowel syndrome in the tropical and subtropical regions: *Vibrio cholerae* is a new cause of this well-known condition. *Indian J Gastroenterol.* 2019;38(2):87-94.
164. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. *Gut.* 2002;51(3):410-3.
165. Schwille-Kiuntke J, Enck P, Zendler C, Krieg M, Polster AV, Klosterhalfen S, et al. Postinfectious irritable bowel syndrome: follow-up of a patient cohort of confirmed cases of bacterial infection with *Salmonella* or *Campylobacter*. *Neurogastroenterol Motil.* 2011;23(11):e479-88.
166. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ.* 1999;318(7183):565-6.
167. Zanini B, Ricci C, Bandera F, Caselani F, Magni A, Laronga AM, et al. Incidence of post-infectious irritable bowel syndrome and functional intestinal disorders following a water-borne viral gastroenteritis outbreak. *Am J Gastroenterol.* 2012;107(6):891-9.
168. Marshall JK, Thabane M, Borgaonkar MR, James C. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. *Clin Gastroenterol Hepatol.* 2007;5(4):457-60.
169. Hanevik K, Wensaas KA, Rortveit G, Eide GE, Morch K, Langeland N. Irritable bowel syndrome and chronic fatigue 6 years after giardia infection: a controlled prospective cohort study. *Clin Infect Dis.* 2014;59(10):1394-400.

170. Wensaas KA, Langeland N, Hanevik K, Morch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. *Gut*. 2012;61(2):214-9.
171. Svendsen AT, Bytzer P, Engsbro AL. Systematic review with meta-analyses: does the pathogen matter in post-infectious irritable bowel syndrome? *Scand J Gastroenterol*. 2019;54(5):546-62.
172. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk Factors, and outcomes of irritable bowel syndrome after infectious enteritis: A systematic review and meta-analysis. *Gastroenterology*. 2017;152(5):1042-54.e1.
173. Rahman MM, Ghoshal UC, Sultana S, Kibria MG, Sultana N, Khan ZA, et al. Long-term gastrointestinal consequences are frequent following sporadic acute infectious diarrhea in a tropical country: A prospective cohort study. *Am J Gastroenterol*. 2018;113(9):1363-75.
174. Parida PK, Mishra D, Pati GK, Nath P, Dash KR, Behera SK, et al. A prospective study on incidence, risk factors, and validation of a risk score for post-infection irritable bowel syndrome in coastal eastern India. *Indian J Gastroenterol*. 2019;38(2):134-42.
175. Youn YH, Kim HC, Lim HC, Park JJ, Kim JH, Park H. Long-term clinical course of post-infectious irritable bowel syndrome after shigellosis: A 10-year follow-up study. *J Neurogastroenterol Motil*. 2016;22(3):490-6.
176. Hiatt RB, Katz L. Mast cells in inflammatory conditions of the gastrointestinal tract. *Am J Gastroenterol*. 1962;37:541-5.
177. Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol*. 2016;13(10):613-21.
178. Matricon J, Meleine M, Gelot A, Piche T, Dapoigny M, Muller E, et al. Review article: Associations between immune activation, intestinal permeability and the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2012;36(11-12):1009-31.
179. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol*. 2011;46(4):421-31.
180. Walker MM, Warwick A, Ung C, Talley NJ. The Role of Eosinophils and Mast Cells in Intestinal Functional Disease. *Current Gastroenterology Reports*. 2011;13(4):323-30.

181. Wouters MM, Vicario M, Santos J. The role of mast cells in functional GI disorders. *Gut*. 2016;65(1):155-68.
182. Zhang L, Song J, Hou X. Mast Cells and Irritable Bowel Syndrome: From the Bench to the Bedside. *J Neurogastroenterol Motil*. 2016;22(2):181-92.
183. Burns G, Carroll G, Mathe A, Horvat J, Foster P, Walker MM, et al. Evidence for Local and Systemic Immune Activation in Functional Dyspepsia and the Irritable Bowel Syndrome: A Systematic Review. *Am J Gastroenterol*. 2019;114(3):429-36.
184. Martin-Viñas JJ, Quigley EM. Immune response in irritable bowel syndrome: A systematic review of systemic and mucosal inflammatory mediators. *J Dig Dis*. 2016;17(9):572-81.
185. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol*. 2001;19:683-765.
186. Brennan FM, Green P, Amjadi P, Robertshaw HJ, Alvarez-Iglesias M, Takata M. Interleukin-10 regulates TNF-alpha-converting enzyme (TACE/ADAM-17) involving a TIMP-3 dependent and independent mechanism. *Eur J Immunol*. 2008;38(4):1106-17.
187. Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. *Cytokine Growth Factor Rev*. 2014;25(4):453-72.
188. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-Line pharmacotherapies for patients with moderate to severely active ulcerative colitis: An updated network meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(10):2179-91.e6.
189. Bashashati M, Rezaei N, Bashashati H, Shafieyoun A, Daryani NE, Sharkey KA, et al. Cytokine gene polymorphisms are associated with irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2012;24(12):1102-e566.
190. Black CJ, Ford AC. Rational investigations in irritable bowel syndrome. *Frontline Gastroenterol*. 2020;11(2):140-7.
191. Zihni C, Mills C, Matter K, Balda MS. Tight junctions: from simple barriers to multifunctional molecular gates. *Nat Rev Mol Cell Biol*. 2016;17(9):564-80.
192. Mu Q, Kirby J, Reilly CM, Luo XM. Leaky gut as a danger signal for autoimmune diseases. *Front Immunol*. 2017;8:598.



193. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, et al. Intestinal permeability--a new target for disease prevention and therapy. *BMC Gastroenterol.* 2014;14:189.
194. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol.* 2012;303(7):G775-85.
195. Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter* enteritis and in post-dysenteric irritable bowel syndrome. *Gut.* 2000;47(6):804-11.
196. Marshall JK, Thabane M, Garg AX, Clark W, Meddings J, Collins SM. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario. *Aliment Pharmacol Ther.* 2004;20(11-12):1317-22.
197. Dunlop SP, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol.* 2006;101(6):1288-94.
198. Piche T, Barbara G, Aubert P, Bruley des Varannes S, Dainese R, Nano JL, et al. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. *Gut.* 2009;58(2):196-201.
199. Turcotte JF, Kao D, Mah SJ, Claggett B, Saltzman JR, Fedorak RN, et al. Breaks in the wall: increased gaps in the intestinal epithelium of irritable bowel syndrome patients identified by confocal laser endomicroscopy (with videos). *Gastrointest Endosc.* 2013;77(4):624-30.
200. Fritscher-Ravens A, Schuppan D, Ellrichmann M, Schoch S, Röcken C, Brasch J, et al. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology.* 2014;147(5):1012-20.e4.
201. Ohsawa S, Vaughen J, Igaki T. Cell Extrusion: A Stress-Responsive Force for Good or Evil in Epithelial Homeostasis. *Dev Cell.* 2018;44(3):284-96.
202. Gu Y, Rosenblatt J. New emerging roles for epithelial cell extrusion. *Curr Opin Cell Biol.* 2012;24(6):865-70.
203. Bednarska O, Walter SA, Casado-Bedmar M, Ström M, Salvo-Romero E, Vicario M, et al. Vasoactive Intestinal Polypeptide and Mast Cells Regulate

- Increased Passage of Colonic Bacteria in Patients With Irritable Bowel Syndrome. *Gastroenterology*. 2017;153(4):948-60.e3.
204. Bertiaux-Vandaële N, Youmba SB, Belmonte L, Lecleire S, Antonietti M, Gourcerol G, et al. The expression and the cellular distribution of the tight junction proteins are altered in irritable bowel syndrome patients with differences according to the disease subtype. *Am J Gastroenterol*. 2011;106(12):2165-73.
205. Black CJ, Ford AC. Chronic idiopathic constipation in adults: epidemiology, pathophysiology, diagnosis and clinical management. *Med J Aust*. 2018;209(2):86-91.
206. Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transit times using radioopaque markers. *Gut*. 1969;10(10):842-7.
207. Staller K, Barshop K, Ananthakrishnan AN, Kuo B. Number of retained radiopaque markers on a colonic transit study does not correlate with symptom severity or quality of life in chronic constipation. *Neurogastroenterol Motil*. 2018;30(5):e13269.
208. Shim L, Talley NJ, Boyce P, Tennant C, Jones M, Kellow JE. Stool characteristics and colonic transit in irritable bowel syndrome: evaluation at two time points. *Scand J Gastroenterol*. 2013;48(3):295-301.
209. Törnblom H, Van Oudenhove L, Sadik R, Abrahamsson H, Tack J, Simrén M. Colonic transit time and IBS symptoms: what's the link? *Am J Gastroenterol*. 2012;107(5):754-60.
210. Agrawal A, Houghton LA, Reilly B, Morris J, Whorwell PJ. Bloating and distension in irritable bowel syndrome: the role of gastrointestinal transit. *Am J Gastroenterol*. 2009;104(8):1998-2004.
211. Midenfjord I, Polster A, Sjövall H, Friberg P, Törnblom H, Simrén M. Associations among neurophysiology measures in irritable bowel syndrome (IBS) and their relevance for IBS symptoms. *Sci Rep*. 2020;10(1):9794.
212. Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*. 2007;56(12):1770-98.
213. Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. *Gastroenterology*. 1990;98(5 Pt 1):1208-18.

214. Schmidt T, Hackelsberger N, Widmer R, Meisel C, Pfeiffer A, Kaess H. Ambulatory 24-hour jejunal motility in diarrhea-predominant irritable bowel syndrome. *Scand J Gastroenterol.* 1996;31(6):581-9.
215. Simrén M, Castedal M, Svedlund J, Abrahamsson H, Björnsson E. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBS) [correction of (IBD)]. *Dig Dis Sci.* 2000;45(11):2151-61.
216. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology.* 2002;123(6):2108-31.
217. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci.* 1980;25(6):404-13.
218. Caballero-Plasencia AM, Valenzuela-Barranco M, Herrerías-Gutiérrez JM, Esteban-Carretero JM. Altered gastric emptying in patients with irritable bowel syndrome. *Eur J Nucl Med.* 1999;26(4):404-9.
219. Stanghellini V, Tosetti C, Barbara G, De Giorgio R, Cogliandro L, Cogliandro R, et al. Dyspeptic symptoms and gastric emptying in the irritable bowel syndrome. *Am J Gastroenterol.* 2002;97(11):2738-43.
220. Hendrix TR, Atkinson M, Clifton JA, Ingelfinger FJ. The effect of 5-hydroxytryptamine on intestinal motor function in man. *Am J Med.* 1957;23(6):886-93.
221. Camilleri M. Serotonin in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes.* 2009;16(1):53-9.
222. Houghton LA, Atkinson W, Lockhart C, Whorwell PJ, Keevil B. Sigmoid-colonic motility in health and irritable bowel syndrome: a role for 5-hydroxytryptamine. *Neurogastroenterol Motil.* 2007;19(9):724-31.
223. Dunlop SP, Coleman NS, Blackshaw E, Perkins AC, Singh G, Marsden CA, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2005;3(4):349-57.
224. Shekhar C, Monaghan PJ, Morris J, Issa B, Whorwell PJ, Keevil B, et al. Rome III Functional Constipation and Irritable Bowel Syndrome With Constipation Are Similar Disorders Within a Spectrum of Sensitization, Regulated by Serotonin. *Gastroenterology.* 2013;145(4):749-57.
225. Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology.* 2006;130(1):34-43.

226. Gunn D, Garsed K, Lam C, Singh G, Lingaya M, Wahl V, et al. Abnormalities of mucosal serotonin metabolism and 5-HT<sub>3</sub> receptor subunit 3C polymorphism in irritable bowel syndrome with diarrhoea predict responsiveness to ondansetron. *Aliment Pharmacol Ther.* 2019;50(5):538-46.
227. Camilleri M, Chey WY, Mayer EA, Northcutt AR, Heath A, Dukes GE, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med.* 2001;161(14):1733-40.
228. Garsed K, Chernova J, Hastings M, Lam C, Marciani L, Singh G, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut.* 2014;63(10):1617-25.
229. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. *Gut.* 1973;14(2):125-32.
230. Bouin M, Plourde V, Boivin M, Riberdy M, Lupien F, Laganier M, et al. Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology.* 2002;122(7):1771-7.
231. Andresen V. Visceral sensitivity testing. *Best Pract Res Clin Gastroenterol.* 2009;23(3):313-24.
232. Mujagic Z, Jonkers D, Ludidi S, Keszthelyi D, Hesselink MA, Weerts Z, et al. Biomarkers for visceral hypersensitivity in patients with irritable bowel syndrome. *Neurogastroenterol Motil.* 2017;29(12):e13137.
233. Kanazawa M, Palsson OS, Thiwan SI, Turner MJ, van Tilburg MA, Gangarosa LM, et al. Contributions of pain sensitivity and colonic motility to IBS symptom severity and predominant bowel habits. *Am J Gastroenterol.* 2008;103(10):2550-61.
234. van der Veek PP, Van Rood YR, Masclee AA. Symptom severity but not psychopathology predicts visceral hypersensitivity in irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2008;6(3):321-8.
235. Posserud I, Syrous A, Lindstrom L, Tack J, Abrahamsson H, Simren M. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. *Gastroenterology.* 2007;133(4):1113-23.
236. Sabate JM, Veyrac M, Mion F, Siproudhis L, Ducrotte P, Zerbib F, et al. Relationship between rectal sensitivity, symptoms intensity and quality of life in

- patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 2008;28(4):484-90.
237. Dorn SD, Palsson OS, Thiwan SI, Kanazawa M, Clark WC, van Tilburg MA, et al. Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity. *Gut.* 2007;56(9):1202-9.
238. Harraf F, Schmulson M, Saba L, Niazi N, Fass R, Munakata J, et al. Subtypes of constipation predominant irritable bowel syndrome based on rectal perception. *Gut.* 1998;43(3):388-94.
239. Gladman MA, Lunniss PJ, Scott SM, Swash M. Rectal hyposensitivity. *Am J Gastroenterol.* 2006;101(5):1140-51.
240. Halpert A, Godena E. Irritable bowel syndrome patients' perspectives on their relationships with healthcare providers. *Scand J Gastroenterol.* 2011;46(7-8):823-30.
241. Bertram S, Kurland M, Lydick E, Locke GR, 3rd, Yawn BP. The patient's perspective of irritable bowel syndrome. *J Fam Pract.* 2001;50(6):521-5.
242. Harvey JM, Sibelli A, Chalder T, Everitt H, Moss-Morris R, Bishop FL. Desperately seeking a cure: Treatment seeking and appraisal in irritable bowel syndrome. *Br J Health Psychol.* 2018;23(3):561-79.
243. Halpert A, Dalton CB, Palsson O, Morris C, Hu Y, Bangdiwala S, et al. Irritable bowel syndrome patients' ideal expectations and recent experiences with healthcare providers: a national survey. *Dig Dis Sci.* 2010;55(2):375-83.
244. Lacy BE, Weiser K, Noddin L, Robertson DJ, Crowell MD, Parratt-Engstrom C, et al. Irritable bowel syndrome: patients' attitudes, concerns and level of knowledge. *Aliment Pharmacol Ther.* 2007;25(11):1329-41.
245. Bradley S, Alderson S, Ford AC, Foy R. General practitioners' perceptions of irritable bowel syndrome: a Q-methodological study. *Fam Pract.* 2018;35(1):74-9.
246. Casiday RE, Hungin AP, Cornford CS, de Wit NJ, Blell MT. GPs' explanatory models for irritable bowel syndrome: a mismatch with patient models? *Fam Pract.* 2009;26(1):34-9.
247. Dixon-Woods M, Critchley S. Medical and lay views of irritable bowel syndrome. *Fam Pract.* 2000;17(2):108-13.

248. Zulman DM, Haverfield MC, Shaw JG, Brown-Johnson CG, Schwartz R, Tierney AA, et al. Practices to Foster Physician Presence and Connection With Patients in the Clinical Encounter. *JAMA*. 2020;323(1):70-81.
249. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann Intern Med*. 1995;122(2):107-12.
250. British Dietetic Association (BDA). Irritable Bowel Syndrome and Diet: Food Fact Sheet 2019 [Available from: <https://www.bda.uk.com/resource/irritable-bowel-syndrome-diet.html>].
251. Cockerell KM, Watkins AS, Reeves LB, Goddard L, Lomer MC. Effects of linseeds on the symptoms of irritable bowel syndrome: a pilot randomised controlled trial. *J Hum Nutr Diet*. 2012;25(5):435-43.
252. de Vries J, Miller PE, Verbeke K. Effects of cereal fiber on bowel function: A systematic review of intervention trials. *World J Gastroenterol*. 2015;21(29):8952-63.
253. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, glucose homeostasis and metabolic health: Modulation by dietary fibers. *Nutrients*. 2018;10(3):275.
254. Algera J, Colomier E, Simrén M. The dietary management of patients with irritable bowel syndrome: A narrative review of the existing and emerging evidence. *Nutrients*. 2019;11(9):2162.
255. Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109(9):1367-74.
256. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. *Lancet*. 1994;344(8914):39-40.
257. Jeffery IB, O'Toole PW, Ohman L, Claesson MJ, Deane J, Quigley EM, et al. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*. 2012;61(7):997-1006.
258. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2018;48(10):1044-60.

259. Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, et al. Physical activity and incident depression: A meta-analysis of prospective cohort studies. *Am J Psychiatry*. 2018;175(7):631-48.
260. McDowell CP, Dishman RK, Gordon BR, Herring MP. Physical activity and anxiety: A systematic review and meta-analysis of prospective cohort studies. *Am J Prev Med*. 2019;57(4):545-56.
261. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541-56.
262. Strid H, Simren M, Storsrud S, Stotzer PO, Sadik R. Effect of heavy exercise on gastrointestinal transit in endurance athletes. *Scand J Gastroenterol*. 2011;46(6):673-7.
263. Villoria A, Serra J, Azpiroz F, Malagelada JR. Physical activity and intestinal gas clearance in patients with bloating. *Am J Gastroenterol*. 2006;101(11):2552-7.
264. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain axis. *Gut Microbes*. 2019;10(5):555-68.
265. Daley AJ, Grimmett C, Roberts L, Wilson S, Fatek M, Roalfe A, et al. The effects of exercise upon symptoms and quality of life in patients diagnosed with irritable bowel syndrome: a randomised controlled trial. *Int J Sports Med*. 2008;29(9):778-82.
266. Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol*. 2011;106(5):915-22.
267. Johannesson E, Ringstrom G, Abrahamsson H, Sadik R. Intervention to increase physical activity in irritable bowel syndrome shows long-term positive effects. *World J Gastroenterol*. 2015;21(2):600-8.
268. Zhou C, Zhao E, Li Y, Jia Y, Li F. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. *Neurogastroenterol Motil*. 2019;31(2):e13461.
269. Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ*. 2015;350:h701.
270. Dancey CP, Taghavi M, Fox RJ. The relationship between daily stress and symptoms of irritable bowel: a time-series approach. *J Psychosom Res*. 1998;44(5):537-45.

271. Blanchard EB, Lackner JM, Jaccard J, Rowell D, Carosella AM, Powell C, et al. The role of stress in symptom exacerbation among IBS patients. *J Psychosom Res.* 2008;64(2):119-28.
272. Whelan K, Martin LD, Staudacher HM, Lomer MCE. The low FODMAP diet in the management of irritable bowel syndrome: an evidence-based review of FODMAP restriction, reintroduction and personalisation in clinical practice. *J Hum Nutr Diet.* 2018;31(2):239-55.
273. Dionne J, Ford AC, Yuan Y, Chey WD, Lacy BE, Saito YA, et al. A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(9):1290-300.
274. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J.* 2019;7(5):583-613.
275. Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol.* 2011;106(3):508-14.
276. Shahbazkhani B, Sadeghi A, Malekzadeh R, Khatavi F, Etemadi M, Kalantri E, et al. Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial. *Nutrients.* 2015;7(6):4542-54.
277. Ford AC, Talley NJ, Spiegel BMR, Foxx-Orenstein AE, Schiller L, Quigley EMM, et al. Effect of fibre, antispasmodics, and peppermint oil in irritable bowel syndrome: Systematic review and meta-analysis. *BMJ.* 2008;337:1388-92.
278. Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, et al. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(Suppl 2):1-18.
279. Atarodi S, Rafieian S, Whorwell PJ. Faecal incontinence-the hidden scourge of irritable bowel syndrome: a cross-sectional study. *BMJ Open Gastroenterol.* 2014;1(1):e000002.



280. Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome--a double-blind placebo controlled study. *Scand J Gastroenterol Suppl.* 1987;130:77-80.
281. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl.* 1987;130:81-4.
282. Lacy BE, Chey WD, Cash BD, Lembo AJ, Dove LS, Covington PS. Eluxadoline efficacy in IBS-D patients who report prior loperamide use. *Am J Gastroenterol.* 2017;112(6):924-32.
283. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut.* 2011;60(2):209-18.
284. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis.* 2010;12(11):1131-8.
285. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol.* 2013;108(9):1508-15.
286. Ford AC, Lacy BE, Harris LA, Quigley EM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: An updated systematic review and meta-analysis. *Am J Gastroenterol.* 2019;114(1):21-39.
287. Vahedi H, Merat S, Momtahan S, Kazzazi AS, Ghaffari N, Olfati G, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* 2008;27(8):678-84.
288. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev.* 2018;2(2):Cd010292.
289. Lewis-Fernández R, Lam P, Lucak S, Galfalvy H, Jackson E, Fried J, et al. An Open-Label Pilot Study of Duloxetine in Patients With Irritable Bowel Syndrome and Comorbid Major Depressive Disorder. *J Clin Psychopharmacol.* 2016;36(6):710-5.
290. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel

- syndrome--results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther.* 2009;29(3):329-41.
291. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol.* 2012;107(11):1714-24.
292. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol.* 2012;107(11):1702-12.
293. Brenner DM, Fogel R, Dorn SD, Krause R, Eng P, Kirshoff R, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. *Am J Gastroenterol.* 2018;113(5):735-45.
294. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 12-Week, Placebo-Controlled Phase 3 Trial (T3MPO-1). *Am J Gastroenterol.* 2020;115(2):281-93.
295. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2009;7(12):1279-86.
296. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364(1):22-32.
297. Lembo A, Pimentel M, Rao SS, Schoenfeld P, Cash B, Weinstock LB, et al. Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. *Gastroenterology.* 2016;151(6):1113-21.
298. Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, et al. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. *N Engl J Med.* 2016;374(3):242-53.
299. Brenner D, Gutman C, Jo E. Efficacy and safety of eluxadoline in IBS-D patients who report inadequate symptom control with prior loperamide use: A phase 4, multicenter, multinational, randomized, placebo-controlled, double-blinded study (RELIEF). *Am J Gastroenterol.* 2018;113 (supplement):S254-5.

300. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT<sub>3</sub> antagonists and 5-HT<sub>4</sub> agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol.* 2009;104(7):1831-43.
301. Olden KW, Chey WD, Shringarpure R, Paul Nicandro J, Chuang E, Earnest DL. Alosetron versus traditional pharmacotherapy in clinical practice: effects on resource use, health-related quality of life, safety and symptom improvement in women with severe diarrhea-predominant irritable bowel syndrome. *Curr Med Res Opin.* 2019;35(3):461-72.
302. Zheng Y, Yu T, Tang Y, Xiong W, Shen X, Jiang L, et al. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2017;12(3):e0172846.
303. Plasse TF, Barton G, Davidson E, Abramson D, Kalfus I, Fathi R, et al. Bimodal release ondansetron improves stool consistency and symptomatology in diarrhea-predominant irritable bowel syndrome: A randomized, double-blind, trial. *Am J Gastroenterol.* 2020;115(9):1466-73.
304. Slattery SA, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther.* 2015;42(1):3-11.
305. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology.* 2003;125(1):19-31.
306. Vollmer A, Blanchard EB. Controlled comparison of individual versus group cognitive therapy for irritable bowel syndrome. *Behavior Therapy.* 1998;29(1):19-33.
307. Boyce PM, Talley NJ, Balaam B, Koloski NA, Truman G. A randomized controlled trial of cognitive behavior therapy, relaxation training, and routine clinical care for the irritable bowel syndrome. *Am J Gastroenterol.* 2003;98(10):2209-18.
308. Lackner JM, Jaccard J, Keefer L, Brenner DM, Firth RS, Gudleski GD, et al. Improvement in gastrointestinal symptoms after cognitive behavior therapy for refractory irritable bowel syndrome. *Gastroenterology.* 2018;155(1):47-57.
309. Everitt HA, Landau S, O'Reilly G, Sibelli A, Hughes S, Windgassen S, et al. Assessing telephone-delivered cognitive-behavioural therapy (CBT) and web-

- delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): a multicentre randomised trial. *Gut*. 2019;68(9):1613-23.
310. Everitt HA, Landau S, O'Reilly G, Sibelli A, Hughes S, Windgassen S, et al. Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. *Lancet Gastroenterol Hepatol*. 2019;4(11):863-72.
311. Simren M, Ringstrom G, Bjornsson ES, Abrahamsson H. Treatment with hypnotherapy reduces the sensory and motor component of the gastrocolonic response in irritable bowel syndrome. *Psychosom Med*. 2004;66(2):233-8.
312. Galovski TE, Blanchard EB. The treatment of irritable bowel syndrome with hypnotherapy. *Appl Psychophysiol Biofeedback*. 1998;23(4):219-32.
313. Lindfors P, Unge P, Arvidsson P, Nyhlin H, Bjornsson E, Abrahamsson H, et al. Effects of gut-directed hypnotherapy on IBS in different clinical settings-results from two randomized, controlled trials. *Am J Gastroenterol*. 2012;107(2):276-85.
314. Palsson OS, Turner MJ, Whitehead WE. Hypnosis home treatment for irritable bowel syndrome: a pilot study. *Int J Clin Exp Hypn*. 2006;54(1):85-99.
315. Flik CE, Laan W, Zuithoff NPA, van Rood YR, Smout A, Weusten B, et al. Efficacy of individual and group hypnotherapy in irritable bowel syndrome (IMAGINE): a multicentre randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2019;4(1):20-31.
316. Bijkerk CJ, de Wit NJ, Muris JW, Whorwell PJ, Knottnerus JA, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. *BMJ*. 2009;339:b3154.
317. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J Clin Epidemiol*. 2011;64:163-71.
318. Ford AC, Moayyedi P. Meta-analysis: Factors affecting placebo response rate in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2010;32(2):144-58.
319. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions: Version 5.1.0 2009* [Available from: [www.cochrane-handbook.org](http://www.cochrane-handbook.org)].
320. Rucker G, Krahn U, Konig J, Efthimiou O, Schwarzer G. *netmeta: Network meta-analysis using frequentist methods*. R package version 1.2-1 2018 [Available from: <https://cran.r-project.org/web/packages/netmeta/index.html>].

321. R.Core.Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2020 [Available from: <https://www.R-project.org/>].
322. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-84.
323. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res*. 2008;17:279-301.
324. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3:80-97.
325. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8:e76654.
326. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3:98-110.
327. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
328. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15:58.
329. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2008;27(8):685-96.
330. Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome and constipation. *Gastroenterology*. 2010;139(6):1877-86.
331. Yang Y, Fang J, Guo X, Dai N, Shen X, Yang Y, et al. Linaclotide in irritable bowel syndrome with constipation: A phase 3 randomized trial in China and other regions. *J Gastroenterol Hepatol*. 2018;33(5):980-9.
332. Fukudo S, Nakajima A, Fujiyama Y, Kosako M, Nakagawa A, Akiho H, et al. Determining an optimal dose of linaclotide for use in Japanese patients with

- irritable bowel syndrome with constipation: A phase II randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil.* 2018;30(5):e13275.
333. Anonymous. Phase III study of ASP0456 - A double-blind, placebo-controlled, parallel-group, comparative study and long-term study in patients with irritable bowel syndrome With constipation (IBS-C) 2018 [Available from: <https://astellasclinicalstudyresults.com/hcp/study.aspx?ID=207>].
334. Miner P, De Luca R, La Portilla M, Padila E, Koltun W, Wiltz O, et al. Plecanatide, a novel urogunaylin analog: A 12-week randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C). *Am J Gastroenterol.* 2014;109 (supplement 2s):S541.
335. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: A phase 2, randomized, placebo-controlled efficacy and safety trial. *Am J Gastroenterol.* 2017;112(5):763-74.
336. Ardelyx reports successful phase 3 T3MPO-1 trial of tenapanor in patients with IBS-C 2018 [Available from: <http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-reports-successful-phase-3-t3mpo-1-trial-tenapanor>].
337. Ardelyx's pivotal phase 3 study of tenapanor for IBS-C hits primary and all secondary endpoints to support NDA submission in 2018 2018 [Available from: <http://ir.ardelyx.com/news-releases/news-release-details/ardelyxs-pivotal-phase-3-study-tenapanor-ibs-c-hits-primary-and-all-secondary-endpoints-to-support-NDA-submission-in-2018>].
338. Chang L, Chey WD, Drossman D, Losch-Beridon T, Wang M, Lichtlen P, et al. Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther.* 2016;44(10):1114-22.
339. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med.* 2013;159(2):130-7.
340. Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ.* 2001;323(7303):42-6.
341. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: A systematic review and meta-analysis. *Am J Gastroenterol.* 2018;113(3):329-38.

342. Griffin PH. Comment on meta-analysis by Shah *et al.* *Am J Gastroenterol.* 2018;113(9):1395.
343. Fisher M, Walker A, Falques M, Moya M, Rance M, Taylor D, et al. Cost-effectiveness of linaclotide compared to antidepressants in the treatment of irritable bowel syndrome with constipation in Scotland. *Eur J Health Econ.* 2016;17(9):1091-100.
344. Cinca R, Chera D, Gruss HJ, Halphen M. Randomised clinical trial: Macrogol/PEG 3350+electrolytes versus prucalopride in the treatment of chronic constipation - a comparison in a controlled environment. *Aliment Pharmacol Ther.* 2013;37(9):876-86.
345. Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT<sub>3</sub> receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. *Aliment Pharmacol Ther.* 2000;14(6):775-82.
346. Min YW, Rhee PL. The clinical potential of ramosetron in the treatment of irritable bowel syndrome with diarrhea (IBS-D). *Therap Adv Gastroenterol.* 2015;8(3):136-42.
347. Delvaux M, Louvel D, Mamet JP, Campos-Oriola R, Frexinos J. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 1998;12(9):849-55.
348. Kane JS, Ford AC. Rifaximin for the treatment of diarrhea-predominant irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol.* 2016;10(4):431-42.
349. Barshop K, Staller K. Eluxadoline in irritable bowel syndrome with diarrhea: Rationale, evidence and place in therapy. *Ther Adv Chronic Dis.* 2017;8(11):153-60.
350. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364(1):22-32.
351. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. *Lancet.* 2000;355(9209):1035-40.
352. Fukudo S, Kinoshita Y, Okumura T, Ida M, Akiho H, Nakashima Y, et al. Ramosetron reduces symptoms of irritable bowel syndrome with diarrhea and improves quality of life in women. *Gastroenterology.* 2016;150(2):358-66.
353. Camilleri M, Mayer EA, Drossman DA, Heath A, Dukes GE, McSorley D, et al. Improvement in pain and bowel function in female irritable bowel patients with

- alosectron, a 5-HT<sub>3</sub> receptor antagonist. *Aliment Pharmacol Ther.* 1999;13(9):1149-59.
354. Chey WD, Chey WY, Heath AT, Dukes GE, Carter EG, Northcutt AR, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2004;99(11):2195-203.
355. Chang L, Ameen VZ, Dukes GE, McSorley D, Carter EG, Mayer EA. A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol.* 2005;100(1):115-23.
356. Lembo T, Wright RA, Lotronex Investigator T, Bagby B, Decker C, Gordon S, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2001;96(9):2662-70.
357. Krause R, Ameen V, Gordon SH, West M, Heath AT, Perschy T, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. *Am J Gastroenterol.* 2007;102(8):1709-19.
358. Matsueda K, Harasawa S, Hongo M, Hiwatashi N, Sasaki D. A randomized, double-blind, placebo-controlled clinical trial of the effectiveness of the novel serotonin type 3 receptor antagonist ramosetron in both male and female Japanese patients with diarrhea-predominant irritable bowel syndrome. *Scand J Gastroenterol.* 2008;43(10):1202-11.
359. Matsueda K, Harasawa S, Hongo M, Hiwatashi N, Sasaki D. A phase II trial of the novel serotonin type 3 receptor antagonist ramosetron in Japanese male and female patients with diarrhea-predominant irritable bowel syndrome. *Digestion.* 2008;77(3-4):225-35.
360. Fukudo S, Ida M, Akiho H, Nakashima Y, Matsueda K. Effect of ramosetron on stool consistency in male patients with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol.* 2014;12(6):953-9.e4.
361. Fukudo S, Matsueda K, Haruma K, Ida M, Hayase H, Akiho H, et al. Optimal dose of ramosetron in female patients with irritable bowel syndrome with diarrhea: A randomized, placebo-controlled phase II study. *Neurogastroenterol Motil.* 2017;29(6):e13023.



362. Dove LS, Lembo A, Randall CW, Fogel R, Andrae D, Davenport JM, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology*. 2013;145(2):329-38.e1.
363. Cash BD, Lacy BE, Rao T, Earnest DL. Rifaximin and eluxadoline - newly approved treatments for diarrhea-predominant irritable bowel syndrome: What is their role in clinical practice alongside alosetron? *Expert Opin Pharmacother*. 2016;17(3):311-22.
364. Camilleri M, Krause R, Deveze S, Rao T, Earnest D. Evaluation of alosetron using the new FDA composite endpoint demonstrates strong treatment effect in females with severe irritable bowel syndrome with diarrhea. *Am J Gastroenterol*. 2014;109 (suppl 2):S535.
365. Acosta A, Camilleri M, Shin A, Linker Nord S, O'Neill J, Gray AV, et al. Effects of rifaximin on transit, permeability, fecal microbiome, and organic acid excretion in irritable bowel syndrome. *Clin Transl Gastroenterol*. 2016;7(5):e173.
366. Pimentel M, Chang C, Chua KS, Mirocha J, DiBaise J, Rao S, et al. Antibiotic treatment of constipation-predominant irritable bowel syndrome. *Dig Dis Sci*. 2014;59(6):1278-85.
367. Tong K, Nicandro JP, Shringarpure R, Chuang E, Chang L. A 9-year evaluation of temporal trends in alosetron postmarketing safety under the risk management program. *Therap Adv Gastroenterol*. 2013;6(5):344-57.
368. Cole JA, Cook SF, Sands BE, Ajene AN, Miller DP, Walker AM. Occurrence of colon ischemia in relation to irritable bowel syndrome. *Am J Gastroenterol*. 2004;99(3):486-91.
369. Treatment of irritable bowel syndrome with diarrhoea using titrated ondansetron trial (TRITON) 2019 [Available from: <https://clinicaltrials.gov/ct2/show/NCT03555188?term=ondansetron&cond=Irritable+Bowel+Syndrome&rank=1>].
370. Jones RH, Holtmann G, Rodrigo L, Ehsanullah RSB, Crompton PM, Jacques LA, et al. Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients. *Aliment Pharmacol Ther*. 1999;13(11):1419-27.
371. Lee KJ, Kim NY, Kwon JK, Huh KC, Lee OY, Lee JS, et al. Efficacy of ramosetron in the treatment of male patients with irritable bowel syndrome with

- diarrhea: a multicenter, randomized clinical trial, compared with mebeverine. *Neurogastroenterol Motil.* 2011;23(12):1098-104.
372. Houghton LA, Fell C, Whorwell PJ, Jones I, Sudworth DP, Gale JD. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut.* 2007;56(9):1218-25.
373. Iturrino J, Camilleri M, Busciglio I, Burton D, Zinsmeister AR. Effect of the  $\alpha 2\delta$  ligand, pregabalin, on colonic sensory and motor functions in healthy adults. *Am J Physiol Gastrointest Liver Physiol.* 2011;301(2):G377-84.
374. Saito YA, Almazar AE, Tilkes KE, Choung RS, Van Norstrand MD, Schleck CD, et al. Randomised clinical trial: pregabalin vs placebo for irritable bowel syndrome. *Aliment Pharmacol Ther.* 2019;49(4):389-97.
375. Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology.* 2002;123(2):425-32.
376. Berman SM, Chang L, Suyenobu B, Derbyshire SW, Stains J, Fitzgerald L, et al. Condition-specific deactivation of brain regions by 5-HT<sub>3</sub> receptor antagonist Alosetron. *Gastroenterology.* 2002;123(4):969-77.
377. Naliboff BD, Derbyshire SW, Munakata J, Berman S, Mandelkern M, Chang L, et al. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. *Psychosom Med.* 2001;63(3):365-75.
378. Jarcho JM, Chang L, Berman M, Suyenobu B, Naliboff BD, Lieberman MD, et al. Neural and psychological predictors of treatment response in irritable bowel syndrome patients with a 5-HT<sub>3</sub> receptor antagonist: a pilot study. *Aliment Pharmacol Ther.* 2008;28(3):344-52.
379. Whitehead WE, and the Validation Working Team Committee in association with the Rome Questionnaire C. Development and validation of the Rome III diagnostic questionnaire. In: Drossman DA, editor *Rome III: The functional gastrointestinal disorders*, 3rd edition Virginia: Degnon Associates Inc. 2006:835-53.
380. Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. *Gastroenterology.* 2016;150(6):1481-91.
381. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: A simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther.* 1997;11(2):395-402.

382. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-70.
383. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med.* 2002;64(2):258-66.
384. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA.* 1999;282(18):1737-44.
385. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24(4):385-96.
386. Cohen S, Williamson GM. Perceived stress in a probability sample in the United States. In: Oskamp SSS, editor. *The social psychology of health.* Oxford: Newbury Park, CA; 1988. p. 31-67.
387. Graff LA, Walker JR, Lix L, Clara I, Rawsthorne P, Rogala L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol.* 2006;4(12):1491-501.
388. Nelson AD, Camilleri M, Chirapongsathorn S, Vijayvargiya P, Valentin N, Shin A, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: A systematic review and network meta-analysis. *Gut.* 2017;66(9):1611-22.
389. Andrews EB, Eaton SC, Hollis KA, Hopkins JS, Ameen V, Hamm LR, et al. Prevalence and demographics of irritable bowel syndrome: Results from a large web-based survey. *Aliment Pharmacol Ther.* 2005;22(10):935-42.
390. Khoshkrood-Mansoori B, Pourhoseingholi MA, Safaee A, Moghimi-Dehkordi B, Sedigh-Tonekaboni B, Pourhoseingholi A, et al. Irritable bowel syndrome: A population based study. *J Gastrointestin Liver Dis.* 2009;18(4):413-8.
391. Lee S, Wu J, Ma YL, Tsang A, Guo WJ, Sung J. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: A community study. *Aliment Pharmacol Ther.* 2009;30(6):643-51.
392. Boeckxstaens GE, Drug V, Dumitrascu D, Farmer AD, Hammer J, Hausken T, et al. Phenotyping of subjects for large scale studies on patients with IBS. *Neurogastroenterol Motil.* 2016;28(8):1134-47.

393. Derrick B, Dobson-McKittrick A, Toher D, White P. Tests for Comparing Two Proportions With Partially Overlapping Samples. *Journal of Applied Quantitative Methods*. 2015;10(3):1-14.
394. Derrick B. Partiallyoverlapping: Partially Overlapping Samples Tests. R package version 2.0. 2018 [Available from: <https://CRAN.R-project.org/package=Partiallyoverlapping>].
395. Magidson J, Vermunt J. Latent Class Models for Clustering: A Comparison with K Means. *Canadian Journal of Marketing Research*. 2002;20:37-44.
396. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. *Prev Sci*. 2013;14(2):157-68.
397. Magidson J. Latent class cluster analysis. In: Hagenaars JaM, AL,; editor. *Advances in Latent Class Analysis*. Cambridge: Cambridge University Press; 2002.
398. Vrieze SI. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). *Psychol Methods*. 2012;17(2):228-43.
399. Stone M. Cross-Validatory Choice and Assessment of Statistical Predictions. *Journal of the Royal Statistical Society Series B (Methodological)*. 1974;36(2):111-47.
400. Burton C, Fink P, Henningsen P, Löwe B, Rief W. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. *BMC Med*. 2020;18(1):34.
401. Ringström G, Störsrud S, Posserud I, Lundqvist S, Westman B, Simrén M. Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: a randomized controlled study. *Eur J Gastroenterol Hepatol*. 2010;22(4):420-8.
402. Drossman DA, Tack J, Ford AC, Szigethy E, Tornblom H, Van Oudenhove L. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. *Gastroenterology*. 2018;154(4):1140-71.e1.
403. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA*. 2001;285(17):2208-15.

404. Riehl ME, Kinnucan JA, Chey WD, Stidham RW. Nuances of the psychogastroenterology patient: A predictive model for gastrointestinal quality of life improvement. *Neurogastroenterol Motil.* 2019;31(9):e13663.
405. Kamp EJ, Kane JS, Ford AC. Irritable bowel syndrome and microscopic colitis: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2016;14(5):659-68.
406. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: An updated systematic review and meta-analysis. *Am J Gastroenterol.* 2017;112(1):65-76.
407. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: Systematic review and meta-analysis. *Am J Gastroenterol.* 2012;107(10):1474-82.
408. Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of brain-gut interactions in patients with inflammatory bowel disease. *Gastroenterology.* 2018;154(6):1635-46.e3.
409. Gracie DJ, Hamlin PJ, Ford AC. Longitudinal impact of IBS-type symptoms on disease activity, healthcare utilization, psychological health, and quality of life in inflammatory bowel disease. *Am J Gastroenterol.* 2018;113(5):702-12.
410. Nicholl BI, Halder SL, MacFarlane GJ, Thompson DG, O'Brien S, Musleh S, et al. Psychosocial risk markers for new onset irritable bowel syndrome - Results of a large prospective population-based study. *Pain.* 2008;137(1):147-55.
411. Bolling-Sternevald E, Aro P, Ronkainen J, Storskrubb T, Talley NJ, Junghard O, et al. Do gastrointestinal symptoms fluctuate in the short-term perspective? The Kalixanda study. *Dig Dis.* 2008;26(3):256-63.
412. Wong RK, Palsson O, Turner MJ, Levy RL, Feld AD, Von Korff M, et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. *Am J Gastroenterol.* 2010;105(10):2228-34.
413. Naliboff BD, Berman S, Suyenobu B, Labus JS, Chang L, Stains J, et al. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. *Gastroenterology.* 2006;131(2):352-65.
414. Aziz Q. Visceral hypersensitivity: fact or fiction. *Gastroenterology.* 2006;131(2):661-4.

415. Mars RAT, Yang Y, Ward T, Houtti M, Priya S, Lekatz HR, et al. Longitudinal Multi-omics Reveals Subset-Specific Mechanisms Underlying Irritable Bowel Syndrome. *Cell*. 2020;182(6):1460-73.e17.
416. Mavrangelos C, Campaniello MA, Andrews JM, Bampton PA, Hughes PA. Longitudinal analysis indicates symptom severity influences immune profile in irritable bowel syndrome. *Gut*. 2018;67(2):398-9.
417. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology*. 2016;150(6):1257-61.