1 **Title:** Irritable Bowel Syndrome.

2

3 **Short running head:** Irritable Bowel Syndrome.

4

5 **Authors:** Professor Alexander C. Ford MD[1,2], Professor Ami D. Sperber MD.[3], Maura

6 Corsetti PhD[4,5], Professor Michael Camilleri MD[6].

7

8 [1]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

9 [2]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

10 [3]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

11 [4]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS

12 Trust, UK.

13 [5]University of Nottingham and Nottingham Digestive Diseases Centre, School of Medicine,

14 University of Nottingham, Nottingham, UK.

15 [6]Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.),

16 Mayo Clinic, Rochester, MN, USA.

17

18	**Abbreviations:**	5-HT	5-hydroxytryptamine
19		CBT	cognitive behavioural therapy
20		CI	confidence interval
21		CRC	colorectal cancer
22		cGMP	Cyclic GMP
23		EMA	European Medicines Agency
24		FDA	Food and Drug Administration

25		FODMAPs	fermentable oligo-, di-, and mono-saccharides and
26			polyols
27		IBD	inflammatory bowel disease
28		IBS	irritable bowel syndrome
29		IBS-C	irritable bowel syndrome with constipation
30		IBS-D	irritable bowel syndrome with diarrhoea
31		IBS-M	irritable bowel syndrome with mixed stool pattern
32		IBS-U	irritable bowel syndrome unclassified
33		MC	microscopic colitis
34		OR	odds ratio
35		PI-IBS	post-infection IBS
36		RCT	randomised controlled trial
37		RR	relative risk
38		SeHCAT	23-seleno-25-homotaurocholic acid
39		SSRI	selective serotonin reuptake inhibitor
40		SIBO	small intestinal bacterial overgrowth
41		TCA	tricyclic antidepressant

42

43 **Correspondence:** Professor Alexander C. Ford

44 Leeds Gastroenterology Institute

45 Room 125

46 4th Floor

47 Bexley Wing

48 St. James's University Hospital

49 Beckett Street

50   Leeds

51   United Kingdom

52   LS9 7TF

53   Email: alexf12399@yahoo.com

54   Telephone: +441132684963

55

58

59   **Word count:**   5102

60

61   **ABSTRACT**

62   Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder whose symptoms

63   include abdominal pain associated with a change in stool form or frequency. The condition

64   affects between 5% and 10% of otherwise healthy individuals in the community at any one

65   point in time and, in most people, runs a relapsing and remitting course. The best described

66   risk factor is acute enteric infection, but IBS is also more common in people with

67   psychological co-morbidity, and in young adult females. The pathophysiology of IBS

68   remains incompletely understood, but it is well established that there is disordered

69   communication between the gut and the brain, leading to motility disturbances, visceral

70   hypersensitivity, and altered central nervous system processing. Other less reproducible

71   mechanisms may include genetic associations, alterations in gastrointestinal microbiota, and

72   disturbances in mucosal and immune function. In most people the diagnosis can be made

73   based on the clinical history, with limited, judicious, use of investigations, unless alarm

74   symptoms such as weight loss or rectal bleeding are present, or there is a family history of

75   inflammatory bowel disease or coeliac disease. Once the diagnosis is made, an empathetic

76   approach is key, and can improve quality of life and symptoms, and reduce health care

77   expenditure. The mainstays of treatment include patient education about the condition,

78   dietary changes, soluble fibre, and antispasmodic drugs. Other treatments tend to be reserved

79   for those with more severe symptoms; these include central neuromodulators, intestinal

80   secretagogues, drugs acting on 5-hydroxytryptamine or opioid receptors, or minimally

81   absorbed antibiotics (all of which are selected according to predominant bowel habit), and

82   psychological therapies. The increased understanding of the pathophysiology of IBS in the

83   last 10 years has led to a healthy pipeline of novel drugs in development.

84

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that has a substantial impact on quality of life and social functioning. [1,2] The pathophysiology of IBS is only partially understood. [3] It affects between and 5% and 10% of the general population, [4] and is characterised by recurrent abdominal pain in association with abnormal stool form or frequency. [5] Treatment aims to improve both abdominal pain and bowel habit, but often is targeted towards the most troublesome symptom. First-line therapies include dietary changes, soluble fibre, and antispasmodic drugs; in patients with more severe symptoms, treatments include central neuromodulators, including low-dose tricyclic antidepressants (TCAs), intestinal secretagogues, drugs acting on opioid or 5-hydroxytryptamine (5-HT) receptors, antibiotics, and psychological therapies. [6] The annual direct and indirect costs related to IBS are estimated to be up to €8 billion in Europe, [7] ¥123 billion in China, [8] and in excess of $10 billion in the USA. [9]

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the medical literature using MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials during the last 10 years with the terms "irritable bowel syndrome", "epidemiology", "prevalence", "incidence", "aetiology", "pathophysiology", "diagnosis", "investigation", "management", "therapy", and "treatment" in order to identify pertinent articles. In addition, we searched clinicaltrials.gov for unpublished trials. We included only publications in English, and selected those articles whose findings were, in our view, of the greatest importance, favouring randomised controlled trials, meta-analyses, and network meta-analyses.

110 **EPIDEMIOLOGY**

111   The most recent symptom-based diagnostic criteria for IBS, the Rome IV criteria,

112 were developed by consensus among experts in functional gastrointestinal disorders. The

113 criteria consist of abdominal pain associated with an alteration in either stool form or

114 frequency, occurring for at least 6 months. [5] Patients are subgrouped according to

115 predominant stool pattern, using the Bristol stool form scale: [10] IBS with diarrhoea (IBS-D),

116 IBS with constipation (IBS-C), IBS with mixed stool pattern (IBS-M), and IBS unclassified

117 (IBS-U) (Table 1). Methodological limitations make it difficult to obtain reliable estimates of

118 prevalence, [11] particularly because, in the absence of universally accepted biomarkers of

119 disease, the diagnosis relies on self-reported symptom clusters. However, as organic

120 gastrointestinal disease in the community is relatively rare, and a diagnosis of IBS is made

121 based on the presence of typical symptoms, population-based epidemiological studies provide

122 a close approximation of true prevalence, which is between 5% and 10% in most

123 geographical regions (Figure 1). [4]

124   Various iterations of these symptom-based diagnostic criteria have resulted in

125 differences in reported prevalence, but disease impact is substantial even in people felt to

126 have IBS, but not meeting such criteria. [12] In addition, both symptom interpretation and

127 reporting are influenced by cultural factors, and can vary among ethnic groups.[11] Prior to

128 publication of the Rome IV criteria in 2016, [5] two systematic reviews examining global

129 prevalence of IBS were conducted. [4,13] The first reported a pooled prevalence of 11.2% (95%

130 confidence interval (CI) 9.8% to 12.8%), [13] ranging from 1.1% in Iran, using the Rome III

131 criteria, to 45% in Pakistan using Rome II. The second review reported a global prevalence of

132 8.8% (95% CI 8.7% to 8.9%). [4] Prevalence varied widely, from 1.1% in France using the

133 Rome II criteria, and Iran using Rome III, to 35.5% in Mexico using Rome II. [14] Thus,

134   despite commonly accepted prevalence ranges, variation in estimates between studies is

135   large, partly due to methodological heterogeneity.

136   Findings from a Rome Foundation 33-nation cross-sectional survey, examining

137   worldwide prevalence and burden of functional gastrointestinal disorders in over 73,000

138   individuals in 26 countries, were published in 2020. [15] Using Rome IV criteria, prevalence

139   rates ranged between 2% and 6%, with a pooled prevalence of 4.1%. In countries where both

140   Rome III and IV criteria were applied, pooled prevalence fell from 10.1% with Rome III to

141   3.8% for Rome IV. However, there remains a dearth of prevalence data from Africa, Eastern

142   Europe, and the Middle East.

143

144   **RISK FACTORS**

145   In two systematic reviews, rates of IBS were significantly higher in females [4,13] and,

146   when 14 studies were pooled, prevalence was lower in those aged ≥50 (odds ratio (OR) 0.75;

147   95% CI 0.62 to 0.92) compared with those aged <50 years. [13] There are no reliable data on

148   IBS and socio-economic status. IBS is more common in patients with functional somatic

149   syndromes, such as fibromyalgia and chronic fatigue. [16] Many other psychosocial, biological,

150   and environmental factors are associated with IBS, and may influence symptom severity

151   (Figure 2). However, it is unclear if these are genuine risk factors; most studies are cross-

152   sectional, and lack the temporal element needed to determine cause and effect.

153   Perhaps the best-recognised risk factor for IBS, observed in approximately 10% of

154   patients, [17] is prior acute enteric infection. This is termed post-infection IBS (PI-IBS), and

155   can occur after bacterial, viral, or protozoal infection. [18] In one retrospective cohort study,

156   even non-specific gastrointestinal infections, which comprised the vast majority of cases,

157   were associated with an equally high risk of PI-IBS to culture-confirmed bacterial or viral

158   infections. [19] A meta-analysis of 45 observational studies reported a four-fold increase in

159   odds of developing IBS in exposed individuals 12 months post-infection (OR 4.2; 95% CI 3.1

160   to 5.7). [18] Risk factors for development of PI-IBS included female sex, antibiotic exposure,

161   psychological distress preceding the illness, and severity of infection. [18] Prognosis may be

162   better than in those with a non-infectious cause although, in one longitudinal follow-up study,

163   15% of those with PI-IBS remained symptomatic 8 years later. [20]

164

165   **PATHOPHYSIOLOGY**

166   The biopsychosocial model to explain symptoms of abdominal pain and disordered

167   bowel habit in IBS conceptualised a genetic predisposition, where adverse events in early

168   life, psychological factors, or gastrointestinal infections then trigger alterations in the enteric

169   nervous system, which controls gastrointestinal motor, sensory, mucosal barrier, and

170   secretory responses (Figure 3). [21]

171

172   **"Traditional" Mechanisms: The Brain-gut Axis, Stress, Visceral Hypersensitivity, and**

173   **Altered Motility**

174   In addition to the psychological component of IBS, [22] gut-brain communication is

175   bidirectional. Prospective longitudinal studies demonstrate that a subset of patients

176   experience gastrointestinal symptoms first, [23,24] and psychological distress later.

177   Gastrointestinal infection and psychological disorders appear to be distinct risk factors,

178   contributing additively to the development of both PI-IBS and the extra-intestinal symptoms

179   frequently linked to IBS, such as chronic fatigue. [19]

180   Altered visceral sensation in IBS is characterised by central abnormalities in sensory,

181   emotional arousal, and prefrontal cortical regions of the brain. Alterations in the descending

182   pathways modulating sensation, and peripheral mechanisms are also involved in the

183   pathogenesis of visceral pain. [25] On average, about 60% of patients exhibit increased

184   sensitivity of the gut to different physiological stimuli. [26,27] Disordered motility in IBS is

185   manifested by abnormal colonic myoelectric activity, [28] repetitive contractions of the small

186   intestine and colon, associated with abdominal pain, and alterations in gastrointestinal or

187   colonic transit. [29,30] Accumulation of different mechanisms (psychological, sensory, and

188   motor) increases both gastrointestinal and non-gastrointestinal symptom severity, as well as

189   impairments in quality of life. [31,32]

190

191   **The Gut Microenvironment**

192   As many IBS patients report that their symptoms are associated with eating, or

193   eliminating, certain foods, [33] it has been assumed that diet and, more recently, gastrointestinal

194   microbiota are involved in pathophysiology.

195

196   Dietary FODMAPs and Disaccharide Maldigestion

197   Fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) are present

198   in high levels in some fruits, artificial sweeteners, legumes, and green vegetables, and are

199   poorly absorbed in all individuals. They have fermentative and osmotic effects, which may

200   contribute to symptoms in some patients. [34] Although randomised controlled trials (RCTs)

201   have confirmed that dietary modification can affect IBS symptoms, so far, they have not

202   confirmed symptom generation by a specific food. Patients with IBS exhibit comparable

203   increases in small intestinal water content and colonic volume to FODMAPs to those seen in

204   healthy individuals, but symptomatic responses are greater in IBS, supporting the role of

205   visceral hypersensitivity. [35] Dietary disaccharide maldigestion may induce symptoms

206   secondary to osmotic diarrhoea and gas production following fermentation of unabsorbed

207   sugars, [36,37] due to disaccharidase deficiency, classically lactase or, as more recently

208   demonstrated in 4% of patients with IBS, [38,39] sucrase-isomaltase, which digests sucrose and

209   starch.

210

211   The Microbiome

212   Although some studies demonstrate that patients with IBS have a different

213   gastrointestinal microbiome, compared with healthy controls, [40,41] the role of the microbiota

214   is still questioned, particularly because what constitutes a "healthy" microbiome remains

215   unclear. A systematic review demonstrated few consistent findings in IBS (possibly because

216   age, sex, race, diet, and antibiotic intake were not controlled for in included studies), and

217   certainly no microbiome signature differentiating IBS subgroups. [42] Antibiotics change the

218   intestinal microbiome, and have been associated with development of IBS. [43] Small intestinal

219   bacterial overgrowth (SIBO), has also been implicated, [44] but its role is controversial due, in

220   large part, to limitations of available diagnostic tests, such as glucose and lactulose breath

221   tests [45] and culture of jejunal aspirates. [46]

222

223   Bile Acids

224   Up to 25% of patients who meet criteria for IBS-D have idiopathic bile acid

225   diarrhoea, demonstrated by abnormal retention following 23-seleno-25-homotaurocholic acid

226   (SeHCAT) scanning, [47] or total 48-hour faecal bile acid levels. [48] The latter correlated with

227   stool number and form, and colonic transit, in one case series of patients. [49] Excess faecal bile

228   acids in IBS-D appeared to be associated with dysbiosis, specifically a Clostridia-rich

229   microbiota, in a case-control study. [50]

230

231

232

233   Barrier Function and Immune Activation

234   Acute gastrointestinal infections induce changes in intestinal permeability and the

235   microbiome. [51] This may promote activation of immune cells, including T-lymphocytes and

236   mast cells, in the gastrointestinal epithelium, [52] leading to cytokine release, which can modify

237   neural control of gastrointestinal motor, sensory, and secretory functions. Pathophysiological

238   alterations can last for years. For example, in PI-IBS neuronal signalling remained sensitised

239   2 years after the infection. [53] Other investigators have reported increased gastrointestinal

240   permeability and elevated immune cell counts, even in patients with IBS without an infective

241   aetiology. [54,55]

242

243   **Genetics**

244   Although research into the genetics of IBS lags behind other conditions, like

245   inflammatory bowel disease (IBD), genome-wide association studies have provided

246   associations with variants on chromosome 9 (9q31.2 locus) that are linked to the functions of

247   diverse ion channels and autonomic dysfunction, [56] and mutations in the sucrase-isomaltase

248   gene, [38,39] as previously discussed. In addition, approximately 2% of IBS patients carry

249   missense mutations in *SCN5A*, [57] which alters the function of the voltage-gated

250   mechanosensitive Na^+ channel $Na_v1.5$, and affects smooth muscle function and mechanical

251   sensitivity. In twin studies, concordance of a diagnosis of IBS is commoner in monozygotic,

252   compared with dizygotic twins; however, having a parent with IBS is a stronger predictor,

253   suggesting that environmental factors such as learned illness behaviour are more important. [58]

254

255   **CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS**

256   Although IBS is a multifactorial and heterogeneous disorder, there are some typical

257   features. The condition is most common among females aged 20 to 40 years, [4,13] although in

258   some countries appears more prevalent in males. [59] It can occur at any age; [15] the average age

259   of participants in clinical trials of novel drugs in IBS is around 45 years, illustrating the broad

260   age range of patients. Coexistent mood problems and extra-intestinal symptoms, including

261   back pain, gynaecological and bladder symptoms, headache, and fatigue are common, [60,61] as

262   is overlap with other functional gastrointestinal disorders. [62] The presence of abdominal pain

263   is essential to the definition of IBS. Accordingly, the differential diagnosis is broad, but other

264   features help narrow this down. Firstly, as IBS is a chronic disorder, causes of acute

265   abdominal pain are ruled out. Secondly, the pain is recurrent, but it is intermittent rather than

266   continuous. Thirdly, pain is usually in the lower abdomen, although Asian patients may

267   report upper abdominal pain. [63] Finally, and most critically, pain in IBS is associated with

268   defaecation, and occurs at the time when the patient experiences alterations in stool frequency

269   or consistency. [5] Although IBS is subgrouped according to predominant stool pattern, [5] this

270   fluctuates in many patients. [64] Abdominal bloating is not a cardinal symptom but is very

271   common, and supports the diagnosis, particularly if it is diurnal. It is often accompanied by

272   visible abdominal distension. [65]

273   In order to understand the precise meaning of terms such as diarrhoea or constipation,

274   as well as the impact of the disorder on social functioning and wellbeing, a thorough history

275   is essential. The Bristol stool form scale is a useful tool to assess stool consistency in the

276   clinic, and can be used to direct treatment, which is discussed later. A detailed history helps

277   differentiate between IBS and other disorders characterised by abdominal pain in association

278   with altered bowel habit, including coeliac disease, IBD, colorectal cancer (CRC), and

279   microscopic colitis (MC). These are considered below.

280

281

282

283   **INVESTIGATIONS**

284   Although there is no universally accepted biomarker for IBS, exhaustive investigation

285   to exclude an organic cause for the symptoms is discouraged, as this is expensive, and many

286   patients are not reassured by such an approach. [66] Once a clinical diagnosis of IBS is made, it

287   is unlikely to be revised, even during extended follow-up. [67] Guidelines recommend a

288   "positive" diagnosis using symptom-based diagnostic criteria, such as the Rome criteria, and

289   minimising investigations (Figure 4). [6] Although the Rome IV criteria have yet to be

290   validated independently, in secondary care sensitivity of the Rome III criteria was 68.8%,

291   specificity 79.5%, and positive and negative likelihood ratios 3.35 and 0.39, respectively. [68]

292   The addition of other features from the clinical history, including absence of nocturnal stools,

293   presence of anxiety, depression, or extra-intestinal symptoms, and a normal full blood count

294   and C-reactive protein enhances the diagnostic performance of the Rome III criteria. [69]

295   There is little evidence to support a routine panel of blood tests, other than full blood

296   count, C-reactive protein, and serological screening for coeliac disease, which has a

297   prevalence of 1% in most Western countries, and is an important differential diagnosis. A

298   meta-analysis demonstrated an almost three-fold higher odds of positive coeliac serology in

299   patients with symptoms suggestive of IBS (OR 2.75; 95% CI 1.35 to 5.61), compared with

300   healthy controls, irrespective of predominant stool pattern. [70]

301   Whether any further investigations are required in a patient with new onset symptoms

302   depends, to some extent, on bowel habit, unless alarm symptoms or signs (Table 2) are

303   present. [71] The latter are an indication for urgent colonoscopy. Colonoscopy should also be

304   performed if the patient is aged ≥50 years and has not already had age-related CRC

305   screening. In addition, unexplained rectal bleeding or iron-deficiency anaemia needs

306   investigation, regardless of age. A family history of coeliac disease, IBD, or CRC is also

307   relevant. In a patient with IBS-C, the diagnosis is secure, unless there are obstructive

308   symptoms (excessive straining, sense of incomplete rectal evacuation, or digitation of the

309   anus to facilitate defaecation) or digital rectal examination suggests a defaecatory disorder, [72]

310   which is the result of incoordination of the normal functions required for rectal evacuation. If

311   present, anorectal manometry with balloon expulsion testing may be helpful, as the treatment

312   of choice for these conditions is biofeedback, [73] rather than dietary or drug therapy.

313   In a patient with diarrhoea, there may be greater concern for a missed organic

314   diagnosis. Faecal calprotectin, which is a cytosol protein released by neutrophils, can

315   differentiate between IBS and IBD, [74,75] avoiding the need for colonoscopy, for which the

316   yield is low. In a cross-sectional survey of almost 500 patients with IBS, only 0.4% of

317   patients were found to have IBD at colonoscopy, 1.5% MC, and there were no cases of CRC.

318   [76] MC is more common in females over the age of 45 years. There are other clues to MC as a

319   cause of symptoms, rather than IBS, which should lead to consideration of colonoscopy to

320   obtain colonic biopsies. These include the fact that the presence of abdominal pain is

321   variable, duration of symptoms tends to be shorter, and patients often have coexistent

322   autoimmune disease, report nocturnal diarrhoea and weight loss, or are taking drugs, such as

323   a non-steroidal anti-inflammatory drug or a proton pump inhibitor. [77,78]

324   Bile acid diarrhoea is another important differential in patients presenting with IBS-D,

325   as its estimated population prevalence is 1%. It can be diagnosed using SeHCAT scanning, a

326   fasting serum 7α-hydroxy-4-cholesten-3-one, fibroblast growth factor-19, or 48-hour faecal

327   bile acid excretion, [79] but these are not universally available. A therapeutic trial of a bile acid

328   sequestrant as a surrogate diagnostic test is an alternative, although it is unclear what dose

329   should be used, and problems with medication compliance may compromise its utility. [80]

330   The reported association between SIBO and IBS is contentious. [44] Investigations to

331   exclude SIBO should only be considered in patients with clear risk factors, such as previous

332   gastric or intestinal surgery, or known structural abnormalities, including jejunal

333   diverticulosis. Hydrogen breath tests may be falsely positive, as they are a marker for rapid

334   transit. [45] Instead, culture of jejunal aspirates should be considered if SIBO is suspected. [81]

335

336   **NATURAL HISTORY AND IMPACT**

337   The typical course in IBS consists of fluctuating symptoms, in terms of bowel habit. [64]

338   Incidence of new-onset IBS was approximately 1.5% to 2.5% per year, over 10 to 12 years, in

339   three longitudinal studies. [82-84] However, prevalence remains stable, because the number of

340   people developing new symptoms is matched by the number whose symptoms disappear or

341   fluctuate to another functional gastrointestinal disorder. [83,84] IBS causes morbidity, but not

342   mortality, [85] and affects quality of life [1] to the same degree as organic gastrointestinal

343   disorders such as Crohn's disease. [86]

344   It also impacts work productivity, [1,2] social integration, and psychosocial factors, such

345   as general and gut-related anxiety, depression, and somatisation. [60,87] Some of these

346   associations are bidirectional, [23,24] so that psychosocial factors can exacerbate IBS symptoms,

347   and the illness experience, and vice versa. One cross-sectional survey showed the impact on

348   daily activity differs according to stool pattern; those with IBS-D avoided travel or leaving

349   the house, due to concerns about toilet access, and those with IBS-C avoided sexual

350   intercourse and reported difficulty concentrating. [88] Associations with severity include

351   overlap with other functional gastrointestinal disorders, [62] and consulter status. [89] However,

352   those who consult with symptoms also have poorer quality of life, increased rates of

353   psychological symptoms, and reduced coping. [89] There is a direct correlation between number

354   of overlapping functional gastrointestinal disorders, reduced quality of life, and increased

355   health care utilisation and gastrointestinal surgery. [62] Patients are willing to accept a 1%

356   median risk of sudden death in return for a 99% chance of cure of their symptoms with a

357   hypothetical medication. [90]

358   **MANAGEMENT**

359   As no medical therapy is proven to alter the natural history of IBS, and the majority of

360   RCTs are only conducted over a 12-week period meaning that their long-term efficacy is

361   unknown, an empathetic approach is key. This can improve quality of life and symptoms, [91]

362   reduce health care visits, and enhance adherence to treatment. [92,93] Management should

363   commence with explanation of the disorder, its pathophysiology, and natural history. In fact,

364   structured patient education about the condition led to a significantly greater improvement in

365   symptoms, compared with written information, in one RCT. [94] Treatment is directed towards

366   the predominant symptom, with a realistic discussion of the limitations of available therapies,

367   in order to manage expectations, as most improve symptoms in only 25% to 30% of patients

368   (Table 3), and have only been tested in referral populations. The final decision as to the

369   choice of treatment should be the patient's, after they receive full information on available

370   options in a dialogue with the doctor.

371

372   **Lifestyle, Diet, and Probiotics**

373   The effect of lifestyle changes in IBS has not been well studied; in a small RCT of

374   physiotherapist-administered exercise, symptoms improved significantly, compared with a

375   control arm with no changes to physical activity. [95] Traditionally, patients with IBS were told

376   to increase dietary fibre intake. However, bran may exacerbate symptoms, [96] although

377   ispaghula husk was more efficacious than placebo in a meta-analysis of seven RCTs (relative

378   risk (RR) of remaining symptomatic 0.83; 95% CI 0.73 to 0.94). [97] Several RCTs

379   demonstrate that FODMAP restriction leads to an improvement in IBS symptoms, compared

380   with habitual diet. [98,99] However, other RCTs suggest that "traditional" dietary advice to eat

381   small regular meals, avoid known trigger foods, and reduce alcohol and caffeine, is as

382   effective as a low FODMAP diet. [100,101] Long-term FODMAP restriction may lead to

383 deleterious alterations in the microbiome. [102] FODMAPs should, therefore, be reintroduced to

384 tolerance after a limited period of restriction, but RCTs conducted to date only examine the

385 effect on symptoms during FODMAP elimination. There is little evidence to support benefit

386 of a gluten-free diet in IBS. [103] However, as wheat contains fructans, which is a FODMAP, it

387 incorporates elements of a low FODMAP diet; some patients may, therefore, adapt a low

388 FODMAP diet to one that instead avoids gluten. [104] There have been numerous RCTs of

389 probiotics in IBS but, although some trials show positive results, ability to make

390 recommendations as to which combination, species, or strain is effective is limited due to the

391 wide variety of products studied, and the conflicting results among individual trials. [105]

392

393 **First-line Medical Therapies**

394   Laxatives, antidiarrhoeals, and antispasmodics are all used first-line in IBS. Most

395 RCTs of these drugs are old, and are hampered by suboptimal methodology and

396 heterogeneous patient selection, meaning that efficacy according to predominant stool pattern

397 is uncertain. In addition, efficacy endpoints do not meet current recommendations from the

398 Food and Drug Administration (FDA) or European Medicines Agency (EMA). Although

399 osmotic and stimulant laxatives are efficacious in chronic constipation, [106] there is little

400 evidence for their use in IBS. A placebo-controlled trial of polyethylene glycol in 139

401 patients with IBS-C demonstrated an increased number of bowel movements, but no

402 improvement in abdominal pain. [107] Similarly, there are only a few small RCTs of

403 antidiarrhoeals, such as loperamide. [6] Nevertheless, some patients find laxatives or

404 antidiarrhoeals useful. Antispasmodic drugs were more efficacious than placebo in a meta-

405 analysis of 26 trials (RR of remaining symptomatic 0.65; 95% CI 0.56 to 0.76), although side

406 effects were more common (RR 1.60; 95% CI 1.15 to 2.21). [6] In terms of individual drugs,

407 otilonium, cimetropium, pinaverium, and hyoscine had the most evidence for efficacy;

408   availability is an issue in some countries. A 4-week RCT of pinaverium, recruiting 427

409   Chinese patients with IBS-D, and which used FDA-recommended endpoints, demonstrated a

410   significant benefit of the drug over placebo for both abdominal pain and diarrhoea, [108]

411   suggesting antispasmodics may be efficacious in IBS-D. Peppermint oil also appeared

412   superior to placebo in a meta-analysis of seven RCTs (RR of remaining symptomatic 0.54;

413   95% CI 0.39 to 0.76), [6] although a subsequent placebo-controlled trial of small intestinal or

414   ileocolonic-release formulations did not demonstrate efficacy for either FDA or EMA-

415   recommended endpoints. [109]

416

417   **Second-line Medical Therapies**

418   Given the accepted role of the gut-brain axis in IBS, the use of antidepressant drugs

419   and CNS targeted medications, or central neuromodulators, as a potential therapy is logical.

420   There is some evidence for efficacy of TCAs; a meta-analysis of 12 RCTs reported a RR of

421   remaining symptomatic of 0.65 (95% CI 0.55 to 0.77) compared with placebo, but trial

422   quality was low and in most RCTs patients were not recruited according to predominant stool

423   pattern. [110] Adverse events were more common (RR 1.56; 95% CI 1.23 to 1.98). TCAs have

424   neuromodulatory properties and also slow gastrointestinal transit, [111] so may be best for

425   patients with predominant pain and/or diarrhoea. Evidence for efficacy of selective serotonin

426   reuptake inhibitors (SSRIs) in the same meta-analysis was less convincing. [110] A 12-week

427   placebo-controlled trial of pregabalin in 85 patients failed to demonstrate adequate relief of

428   symptoms, but there were significant improvements in global symptoms, pain, diarrhoea, and

429   bloating. [112] All other second-line therapies are licensed and are used based on predominant

430   stool pattern.

431   5-HT_4 receptor agonists accelerate gastrointestinal transit. Tegaserod was more

432   efficacious than placebo in IBS-C, [113] but was withdrawn due to a small excess number of

433   cerebrovascular and cardiovascular ischaemic events. It was reintroduced in the USA in 2018

434   for female patients <65 years without existing cardiovascular disease. Prucalopride, another

435    $5-HT_4$ agonist, was superior to placebo in chronic constipation;[106] there are no RCTs in IBS-

436   C. Intestinal secretagogues, such as lubiprostone, linaclotide, plecanatide, and tenapanor act

437   on ion channels in enterocytes, leading to water efflux, thereby accelerating gastrointestinal

438   transit and improving stool consistency. Placebo-controlled trials have demonstrated efficacy

439   of these drugs in IBS-C;[114-117] there have been no head-to-head trials. A network meta-

440   analysis of 15 RCTs demonstrated similar efficacy for all drugs, but linaclotide was ranked

441   first for improvements in global symptoms, abdominal pain, and stool frequency; tenapanor

442   ranked first for improvement in bloating.[118] Diarrhoea was the most common adverse event

443   with all drugs except lubiprostone, which causes nausea in up to 20% of patients.[118]

444   Licensed therapies for IBS-D include the $5-HT_3$ antagonists alosetron and ramosetron,

445   a peripherally acting mixed opioid receptor agonist/antagonist eluxadoline, and the minimally

446   absorbed antibiotic rifaximin. $5-HT_3$ antagonists and eluxadoline slow gastrointestinal transit

447   and reduce visceral hypersensitivity.[119] $5-HT_3$ antagonists also alter rectal compliance.[120]

448   Rifaximin has been tested on the basis that alterations in the gastrointestinal microbiota and

449   SIBO may, in part, be responsible for symptoms in IBS; the exact mechanism of action

450   remains uncertain.[121] Although all these drugs have demonstrated efficacy over placebo,

451   [113,122-124] again there have been no head-to-head trials. A network meta-analysis of 18 RCTs

452   demonstrated that $5-HT_3$ receptor antagonists ranked first for improvement in global

453   symptoms, abdominal pain, and stool consistency.[125] All drugs, except rifaximin, were more

454   likely to cause constipation than placebo. A crossover placebo-controlled trial of

455   ondansetron, another $5-HT_3$ antagonist, in 120 patients with IBS-D demonstrated significant

456   improvements in stool consistency and urgency, but not pain;[126] a large RCT is ongoing.[127]

457   Figure 5 outlines the spectrum of medications available for pain, constipation, and

458   diarrhoea in IBS, as well as drugs in development. Overall, there is a plethora of choices for

459   diarrhoea or constipation, but still an unmet clinical need for relief of pain.

460

461   **Psychological Therapies**

462   Similar to central neuromodulators, psychological therapies may exert not only

463   central effects on mood, but also peripheral effects on pain perception, visceral

464   hypersensitivity, and gastrointestinal motility. [128,129] A meta-analysis of 36 RCTs

465   demonstrated that cognitive behavioural therapy (CBT), gut-directed hypnotherapy,

466   relaxation therapy, multi-component psychological therapy, and dynamic psychotherapy were

467   all more effective than a control intervention. [110] Some have evidence for efficacy out to 12

468   months of follow-up. [130] These may be intensive, in terms of hours of therapist contact, but

469   subsequent RCTs demonstrate that minimal contact CBT, CBT via the telephone, and group

470   gut-directed hypnotherapy are also effective, even for patients whose symptoms are

471   refractory to medical therapy. [131-133] Whether earlier intervention with psychological

472   therapies can change the natural history of IBS, or whether augmentative therapy with a

473   psychological therapy and a central neuromodulator has additive benefit, is unclear.

474

475   **FUTURE DIRECTIONS AND CONTROVERSIES**

476   Reasons for the difference in prevalence of IBS across different countries, remain

477   uncertain, and prevalence data from certain regions are lacking. Our understanding of the

478   epidemiology is likely to increase as the Rome Foundation global cross-sectional survey

479   database of 73,076 participants is mined further. [15] Despite considerable efforts, a biomarker

480   for IBS remains elusive. A validation study of antibodies to bacterial toxins and host cell

481   adhesion proteins performed only modestly in distinguishing IBS from health. [134] A case-

482 control study reported distinct faecal and urinary metabolomic profiles in those with IBS, [135]

483 which might allow the development of microbe-based treatments. The efficacy of probiotics

484 and faecal microbiota transplantation is inconsistent, [105,136] although a RCT of faecal

485 microbiota transplantation using a single, healthy, well-characterised donor demonstrated

486 efficacy. [137] However, more than 50% of patients in this trial continued to have moderate to

487 severe symptoms. With the discovery of actionable biomarkers to identify the mechanisms

488 underlying symptoms the hope is that, in the future, IBS therapy will move away from drugs

489 targeting the predominant symptom, or symptoms, towards one where patients are stratified

490 based on underlying pathophysiology, using these biomarkers, in order to facilitate

491 individualised treatment. [138]

492   Other pharmacological therapies are in development (Figure 5). Drugs that reduce

493 uptake of sodium ions from the lumen, via transporters expressed in the intestine, result in

494 water retention in the lumen and looser stools. These include mizagliflozin, a sodium-glucose

495 cotransporter-1 inhibitor, and DRAinh-A250, an inhibitor of the solute carrier 26A3. In a

496 phase 2 placebo-controlled trial of mizagliflozin in patients with chronic constipation,

497 response rates were significantly higher with 5mg and 10mg doses, and the medication

498 appeared safe, [139] albeit after only 1 week of treatment. When administered intraluminally,

499 DRAinh-A250 blocked fluid absorption in mouse colonic loops and reversed loperamide-

500 induced constipation; [140] there are no human studies to date.

501   Bile acids are physiological laxatives, and are implicated in the pathophysiology of

502 IBS. [48] Inhibition of the ileal bile acid transporter by elobixibat accelerated colonic transit in

503 patients with constipation, [141] and a trial in Japan demonstrated that a 10mg dose was

504 efficacious in patients with constipation, including IBS-C. [142] Although the drug is licensed in

505 Japan, adverse events occurred in 30% of patients, particularly diarrhoea and abdominal pain,

506 and this was only a 2-week trial.

507   Novel analgesic approaches include further refinements of existing secretagogues.

508   Cyclic GMP (cGMP) production in enterocytes is stimulated by some of these drugs, such as

509   linaclotide. When transported into the extracellular space at the basolateral membrane, [143]

510   cGMP leads to decreased conduction of submucosal afferent nociceptive neurons, attenuating

511   visceral pain. [144] A preliminary RCT of targeted colonic delivery of linaclotide in patients

512   with IBS-C demonstrated pain relief, without effects on constipation, [145] suggesting that

513   cGMP release from enterocytes reduces the function of peripheral visceral afferents.

514   When conventional opioids bind to μ-opioid receptors, they induce analgesia through

515   activation of G protein-mediated pathways, but they also activate β-arrestin, which inhibits

516   gastrointestinal motility and depresses central functions, such as cognition and respiration.

517   New biased μ-opioid receptor ligands activate the G protein pathway exclusively, leading to

518   analgesia with reduced gastrointestinal dysfunction. [146] Oliceridine is a biased μ-opioid

519   receptor ligand with comparable analgesic effects to morphine although there are, as yet, no

520   human studies in visceral pain. [147] The cannabinoid type-2 receptor agonist, olorinab, has the

521   potential to alter immune function, as well as sensation, given expression of cannabinoid

522   type-2 receptors in the brain, peripheral nervous system, and gastrointestinal tract. In an

523   open-label trial in patients with quiescent Crohn's disease, it reduced abdominal pain and

524   improved bowel movements. [148] Clinical trials are being conducted in IBS. [149] The histamine-

525      $_1$ receptor antagonist ebastine appears to attenuate visceral hypersensitivity *in vitro* [150] and, in

526   a RCT of 45 patients, led to significant improvements in both global symptoms and

527   abdominal pain compared with placebo; [150] a larger trial is in progress. [151]

528   In summary, the greater understanding of pathophysiological mechanisms in IBS has

529   ushered in the development of novel treatment strategies to manage patients, particularly the

530   abdominal pain component of IBS, for which central neuromodulators or psychological

531   therapies are currently the main approaches. The diverse molecular mechanisms to which

532   drugs in development are targeted augurs for substantial impact in the management of IBS in

533   the foreseeable future. Nevertheless, a strong doctor-patient relationship with attention to the

534   clinical history, an appreciation of the impact of symptoms on the patient's life, together with

535   an explanation of the condition and its natural history, and shared decision-making, remain

536   key to effective management.

537

538   **Contributors**

539   ACF, ADS, MC, and MC did the literature search, wrote the manuscript, and drafted the

540   figures. ACF and MC revised the initial manuscript. All authors critically revised subsequent

541   versions of the manuscript and approved the final version of the manuscript.

542

543   **Declaration of Interests**

544   ACF has no conflicts of interest. ADS has no conflicts of interest. MC has acted as a

545   consultant to Allergan outside the submitted work. MC reports grant from Allergan, grant

546   from Novartis, grant from Takeda, and other from Allergan, Ironwood, Arena, Takeda

547   (consulting with fees going to employer, Mayo Clinic), outside the submitted work.

548

549   **REFERENCES**
550
551   1.   Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity,

552   and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual*

553   *Life Outcomes* 2017; **15**: 35.

554   2.   Frandemark A, Tornblom H, Jakobsson S, Simren M. Work productivity and activity

555   impairment in irritable bowel syndrome (IBS): A multifaceted problem. *Am J Gastroenterol*

556   2018; **113**: 1540-9.

557   3.   Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome.

558   *Lancet Gastroenterol Hepatol* 2016; **1**: 133-46.

559   4.   Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults

560   remains elusive due to the heterogeneity of studies: A Rome Foundation working team

561   literature review. *Gut* 2017; **66**: 1075-82.

562   5.   Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology* 2016; **150**:

563   1393-407.

564   6.   Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology

565   monograph on management of irritable bowel syndrome. *Am J Gastroenterol* 2018; **113**

566   **(Suppl 2)**: 1-18.

567   7.   Flacco ME, Manzoli L, De Giorgio R, et al. Costs of irritable bowel syndrome in

568   European countries with universal healthcare coverage: A meta-analysis. *Eur Rev Med*

569   *Pharmacol Sci* 2019; **23**: 2986-3000.

570 8. Zhang F, Xiang W, Li CY, Li SC. Economic burden of irritable bowel syndrome in

571 China. *World J Gastroenterol* 2016; **22**: 10450-60.

572 9. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver,

573 and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 2019; **156**: 254-

574 72.e11.

575 10. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time.

576 *Scand J Gastroenterol* 1997; **32**: 920-4.

577 11. Sperber AD, Gwee KA, Hungin AP, et al. Conducting multinational, cross-cultural

578 research in the functional gastrointestinal disorders: Issues and recommendations. A Rome

579 Foundation working team report. *Aliment Pharmacol Ther* 2014; **40**: 1094-102.

580 12. Van den Houte K, Carbone F, Pannemans J, et al. Prevalence and impact of self-

581 reported irritable bowel symptoms in the general population. *United European Gastroenterol*

582 *J* 2019; **7**: 307-15.

583 13. Lovell RM, Ford AC. Global prevalence of, and risk factors for, irritable bowel

584 syndrome: A meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 712-21.

585 14. Schmulson M, Ortiz O, Santiago-Lomeli M, et al. Frequency of functional bowel

586 disorders among healthy volunteers in Mexico City. *Dig Dis* 2006; **24**: 342-7.

587 15. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden

588 of functional gastrointestinal disorders, results of Rome Foundation global study.

589 *Gastroenterology* 2020; **doi:10.1053/j.gastro.2020.04.014**.

590 16. Petersen MW, Schröder A, Jørgensen T, et al. The unifying diagnostic construct of

591 bodily distress syndrome (BDS) was confirmed in the general population. *J Psychosom Res*

592 2020; **128**: 109868.

593 17. Card T, Enck P, Barbara G, et al. Post-infectious IBS: Defining its clinical features

594 and prognosis using an internet-based survey. *United European Gastroenterol J* 2018; **6**:

595 1245-53.

596 18. Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, risk factors, and outcomes of

597 irritable bowel syndrome after infectious enteritis: A systematic review and meta-analysis.

598 *Gastroenterology* 2017; **152**: 1042-54.e1.

599 19. Donnachie E, Schneider A, Mehring M, Enck P. Incidence of irritable bowel

600 syndrome and chronic fatigue following GI infection: A population-level study using

601 routinely collected claims data. *Gut* 2018; **67**: 1078-86.

602 20. Marshall JK, Thabane M, Garg AX, et al. Eight year prognosis of postinfectious

603 irritable bowel syndrome following waterborne bacterial dysentery. *Gut* 2010; **59**: 605-11.

604 21. Ringel Y, Sperber AD, Drossman DA. Irritable bowel syndrome. *Annu Rev Med*

605 2001; **52**: 319-38.

606   22.   Drossman DA. Presidential address: Gastrointestinal illness and the biopsychosocial

607   model. *Psychosom Med* 1998; **60**: 258-67.

608   23.   Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain--gut

609   pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective

610   population-based study. *Gut* 2012; **61**: 1284-90.

611   24.   Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-

612   to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: A 1-year

613   population-based prospective study. *Aliment Pharmacol Ther* 2016; **44**: 592-600.

614   25.   Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions

615   activated during rectal distension in irritable bowel syndrome. *Gastroenterology* 2011; **140**:

616   91-100.

617   26.   Posserud I, Syrous A, Lindstrom L, Tack J, Abrahamsson H, Simren M. Altered rectal

618   perception in irritable bowel syndrome is associated with symptom severity.

619   *Gastroenterology* 2007; **133**: 1113-23.

620   27.   Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the

621   irritable colon syndrome. *Gut* 1973; **14**: 125-32.

622   28.   Sullivan MA, Cohen S, Snape WJ, Jr. Colonic myoelectrical activity in irritable-

623   bowel syndrome. Effect of eating and anticholinergics. *N Engl J Med* 1978; **298**: 878-83.

624 29. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is

625 correlated with symptoms. *Gastroenterology* 1987; **92**: 1885-93.

626 30. Spiller RC, Brown ML, Phillips SF. Emptying of the terminal ileum in intact humans.

627 Influence of meal residue and ileal motility. *Gastroenterology* 1987; **92**: 724-9.

628 31. Camilleri M, McKinzie S, Busciglio I, et al. Prospective study of motor, sensory,

629 psychologic, and autonomic functions in patients with irritable bowel syndrome. *Clin*

630 *Gastroenterol Hepatol* 2008; **6**: 772-81.

631 32. Simren M, Tornblom H, Palsson OS, Van Oudenhove L, Whitehead WE, Tack J.

632 Cumulative effects of psychologic distress, visceral hypersensitivity, and abnormal transit on

633 patient-reported outcomes in irritable bowel syndrome. *Gastroenterology* 2019; **157**: 391-

634 402.e2.

635 33. Bohn L, Storsrud S, Tornblom H, Bengtsson U, Simren M. Self-reported food-related

636 gastrointestinal symptoms in IBS are common and associated with more severe symptoms

637 and reduced quality of life. *Am J Gastroenterol* 2013; **108**: 634-41.

638 34. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal

639 symptoms in patients with irritable bowel syndrome: Randomized placebo-controlled

640 evidence. *Clin Gastroenterol Hepatol* 2008; **6**: 765-71.

641 35. Major G, Pritchard S, Murray K, et al. Colon hypersensitivity to distension, rather

642 than excessive gas production, produces carbohydrate-related symptoms in individuals with

643 irritable bowel syndrome. *Gastroenterology* 2017; **152**: 124-33.e2.

644   36.   Thingholm L, Ruhlemann M, Wang J, et al. Sucrase-isomaltase 15Phe IBS risk

645   variant in relation to dietary carbohydrates and faecal microbiota composition. *Gut* 2019; **68**:

646   177-8.

647   37.   Zheng T, Eswaran S, Photenhauer AL, Merchant JL, Chey WD, D'Amato M.

648   Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying sucrase-isomaltase

649   (SI) hypomorphic variants. *Gut* 2020; **69**: 397-8.

650   38.   Henstrom M, Diekmann L, Bonfiglio F, et al. Functional variants in the sucrase-

651   isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut* 2018; **67**: 263-

652   70.

653   39.   Garcia-Etxebarria K, Zheng T, Bonfiglio F, et al. Increased prevalence of rare

654   sucrase-isomaltase pathogenic variants in irritable bowel syndrome patients. *Clin

655   Gastroenterol Hepatol* 2018; **16**: 1673-6.

656   40.   Jalanka-Tuovinen J, Salojarvi J, Salonen A, et al. Faecal microbiota composition and

657   host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel

658   syndrome. *Gut* 2014; **63**: 1737-45.

659   41.   Sundin J, Rangel I, Fuentes S, et al. Altered faecal and mucosal microbial

660   composition in post-infectious irritable bowel syndrome patients correlates with mucosal

661   lymphocyte phenotypes and psychological distress. *Aliment Pharmacol Ther* 2015; **41**: 342-

662   51.

663   42.   Pittayanon R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel

664   syndrome: A systematic review. *Gastroenterology* 2019; **157**: 97-108.

665   43.   Krogsgaard LR, Engsbro AL, Bytzer P. Antibiotics: A risk factor for irritable bowel

666   syndrome in a population-based cohort. *Scand J Gastroenterol* 2018; **53**: 1027-30.

667   44.   Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth

668   reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000; **95**: 3503-6.

669   45.   Yu D, Cheeseman F, Vanner S. Combined oro-caecal scintography and lactulose

670   hydrogen breath testing demonstrate that breath testing detects oro-caecal transit , not small

671   intestinal bacterial overgrowth in patients with IBS. *Gut* 2011; **60**: 334-40.

672   46.   Posserud I, Stotzer PO, Bjornsson ES, Abrahamsson H, Simren M. Small intestinal

673   bacterial overgrowth in patients with irritable bowel syndrome. *Gut* 2007; **56**: 802-8.

674   47.   Slattery SA, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-

675   analysis: The prevalence of bile acid malabsorption in the irritable bowel syndrome with

676   diarrhoea. *Aliment Pharmacol Ther* 2015; **42**: 3-11.

677   48.   Shin A, Camilleri M, Vijayvargiya P, et al. Bowel functions, fecal unconjugated

678   primary and secondary bile acids, and colonic transit in patients with irritable bowel

679   syndrome. *Clin Gastroenterol Hepatol* 2013; **11**: 1270-5.

680   49.   Camilleri M, Busciglio I, Acosta A, et al. Effect of increased bile acid synthesis or

681   fecal excretion in irritable bowel syndrome-diarrhea. *Am J Gastroenterol* 2014; **109**: 1621-

682   30.

683   50.   Zhao L, Yang W, Chen Y, et al. A Clostridia-rich microbiota enhances bile acid

684   excretion in diarrhea-predominant irritable bowel syndrome. *J Clin Invest* 2020; **130**: 438-50.

685   51.   Marshall JK, Thabane M, Garg AX, Clark W, Meddings J, Collins SM. Intestinal

686   permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute

687   gastroenteritis in Walkerton, Ontario. *Aliment Pharmacol Ther* 2004; **20**: 1317-22.

688   52.   Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological

689   features of postinfective irritable bowel syndrome. *Am J Gastroenterol* 2003; **98**: 1578-83.

690   53.   Balemans D, Mondelaers SU, Cibert-Goton V, et al. Evidence for long-term

691   sensitization of the bowel in patients with post-infectious-IBS. *Sci Rep* 2017; **7**: 13606.

692   54.   Gecse K, Roka R, Sera T, et al. Leaky gut in patients with diarrhea-predominant

693   irritable bowel syndrome and inactive ulcerative colitis. *Digestion* 2012; **85**: 40-6.

694   55.   Bashashati M, Moossavi S, Cremon C, et al. Colonic immune cells in irritable bowel

695   syndrome: A systematic review and meta-analysis. *Neurogastroenterol Motil* 2018; **30**: doi:

696   10.1111/nmo.13192.

697   56.   Bonfiglio F, Zheng T, Garcia-Etxebarria K, et al. Female-specific association between

698   variants on chromosome 9 and self-reported diagnosis of irritable bowel syndrome.

699   *Gastroenterology* 2018; **155**: 168-79.

700   57.   Beyder A, Mazzone A, Strege PR, et al. Loss-of-function of the voltage-gated sodium

701   channel NaV1.5 (channelopathies) in patients with irritable bowel syndrome.

702   *Gastroenterology* 2014; **146**: 1659-68.

703   58.   Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel

704   syndrome in twins: Heredity and social learning both contribute to etiology.

705   *Gastroenterology* 2001; **121**: 799-804.

706   59.   Jafri W, Yakoob J, Jafri N, Islam M, Masroor Ali Q. Irritable bowel syndrome and

707   health seeking behaviour in different communities of Pakistan. *J Pak Med Assoc* 2007; **57**:

708   285-7.

709   60.   Patel P, Bercik P, Morgan DG, et al. Irritable bowel syndrome is significantly

710   associated with somatisation in 840 patients, which may drive bloating. *Aliment Pharmacol*

711   *Ther* 2015; **14**(10): 13074.

712   61.   Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: The

713   prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment*

714   *Pharmacol Ther* 2019; **50**: 132-43.

715   62.   Aziz I, Palsson OS, Tornblom H, Sperber AD, Whitehead WE, Simren M. The

716   prevalence and impact of overlapping Rome IV-diagnosed functional gastrointestinal

717   disorders on somatization, quality of life, and healthcare utilization: A cross-sectional general

718   population study in three countries. *Am J Gastroenterol* 2018; **113**: 86-96.

719   63.   Gwee KA, Wee S, Wong ML, Png DJ. The prevalence, symptom characteristics, and

720   impact of irritable bowel syndrome in an Asian urban community. *Am J Gastroenterol* 2004;

721   **99**: 924-31.

722   64.   Palsson OS, Baggish JS, Turner MJ, Whitehead WE. IBS patients show frequent

723   fluctuations between loose/watery and hard/lumpy stools: Implications for treatment. *Am J*

724   *Gastroenterol* 2012; **107**: 286-95.

725   65.   Houghton LA, Lea R, Agrawal A, Reilly B, Whorwell PJ. Relationship of abdominal

726   bloating to distention in irritable bowel syndrome and effect of bowel habit.

727   *Gastroenterology* 2006; **131**: 1003-10.

728   66.   Spiegel BM, Gralnek IM, Bolus R, et al. Is a negative colonoscopy associated with

729   reassurance or improved health-related quality of life in irritable bowel syndrome?

730   *Gastrointest Endosc* 2005; **62**: 892-9.

731   67.   Adeniji OA, Barnett CB, Di Palma JA. Durability of the diagnosis of irritable bowel

732   syndrome based on clinical criteria. *Dig Dis Sci* 2004; **49**: 572-4.

733   68.   Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P.

734   Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary

735   care. *Gastroenterology* 2013; **145**: 1262-70.

736   69.   Sood R, Camilleri M, Gracie DJ, et al. Enhancing diagnostic performance of

737   symptom-based criteria for irritable bowel syndrome by additional history and limited

738   diagnostic evaluation. *Am J Gastroenterol* 2016; **111**: 1446-554.

739   70.   Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel

740   syndrome: An updated systematic review and meta-analysis. *Am J Gastroenterol* 2017; **112**:

741   65-76.

742   71.   Suspected cancer: recognition and referral.

743   https://www.nice.org.uk/guidance/ng12/chapter/Introduction#lower-gastrointestinal-tract-

744   cancers 2015. Accessed 14th December 2019

745   72.   Brandler J, Camilleri M. Pretest and post-test probabilities of diagnoses of rectal

746   evacuation disorders based on symptoms, rectal exam, and basic tests: A systematic review.

747   *Clin Gastroenterol Hepatol* 2019; **doi: 10.1016/j.cgh.2019.11.049**.

748   73.   Rao SS, Valestin J, Brown CK, Zimmerman B, Schulze K. Long-term efficacy of

749   biofeedback therapy for dyssynergic defecation: Randomized controlled trial. *Am J

750   Gastroenterol* 2010; **105**: 890-6.

751   74.   The new faecal calprotectin care pathway.

752   *https://www.nice.org.uk/sharedlearning/the-new-faecal-calprotectin-care-pathway* 2018.

753   Accessed 14th December 2019

754   75.   Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility

755   of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin

756 to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015; **110**:

757 444-54.

758 76. Chey WD, Nojkov B, Rubenstein JH, Dobhan R, Greenson JK, Cash BD. The yield of

759 colonoscopy in patients with non-constipated irritable bowel syndrome: Results from a

760 prospective, controlled US trial. *Am J Gastroenterol* 2010; **105**: 859-65.

761 77. Macaigne G, Lahmek P, Locher C, et al. Microscopic colitis or functional bowel

762 disease with diarrhea: a French prospective multicenter study. *Am J Gastroenterol* 2014; **109**:

763 1461-70.

764 78. Kane JS, Rotimi O, Everett SM, Samji S, Michelotti F, Ford AC. Development and

765 validation of a scoring system to identify patients with microscopic colitis. *Clin

766 Gastroenterol Hepatol* 2015; **13**: 1125-31.

767 79. Vijayvargiya P, Camilleri M. Current practice in the diagnosis of bile acid diarrhea.

768 *Gastroenterology* 2019; **156**: 1233-8.

769 80. Orekoya O, McLaughlin J, Leitao E, Johns W, Lal S, Paine P. Quantifying bile acid

770 malabsorption helps predict response and tailor sequestrant therapy. *Clin Med (Lond)* 2015;

771 **15**: 252-7.

772 81. Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of

773 chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut* 2018; **67**:

774 1380-99.

775 82. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Irritable bowel syndrome:

776 A 10-year natural history of symptoms, and factors that influence consultation behavior. *Am J*

777 *Gastroenterol* 2008; **103**: 1229-39.

778 83. Halder SLS, Locke III GR, Schleck CD, Zinsmeister AR, Melton III LJ, Talley NJ.

779 Natural history of functional gastrointestinal disorders: A 12-year longitudinal population-

780 based study. *Gastroenterology* 2007; **133**: 799-807.

781 84. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Bjornsson E, Thjodleifsson B. Natural

782 history of functional gastrointestinal disorders: Comparison of two longitudinal population-

783 based studies. *Dig Liver Dis* 2012; **44**: 211-7.

784 85. Chang JY, Locke III GR, McNally MA, et al. Impact of functional gastrointestinal

785 disorders on survival in the community. *Am J Gastroenterol* 2010; **105**: 822-32.

786 86. Pace F, Molteni P, Bollani S, et al. Inflammatory bowel disease versus irritable bowel

787 syndrome: A hospital-based, case-control study of disease impact on quality of life. *Scand J*

788 *Gastroenterol* 2003; **38**: 1031-8.

789 87. Black CJ, Yiannakou Y, Houghton LA, Ford AC. Epidemiological, clinical, and

790 psychological characteristics of individuals with self-reported irritable bowel syndrome based

791 on the Rome IV vs Rome III criteria. *Clin Gastroenterol Hepatol* 2020; **18**: 392-8.

792 88. Ballou S, McMahon C, Lee HN, et al. Effects of irritable bowel syndrome on daily

793 activities vary among subtypes based on results from the IBS in America survey. *Clin*

794 *Gastroenterol Hepatol* 2019; **17**: 2471-8.e3.

795   89.   Ringstrom G, Abrahamsson H, Strid H, Simren M. Why do subjects with irritable

796   bowel syndrome seek health care for their symptoms? *Scand J Gastroenterol* 2007; **42**: 1194-

797   203.

798   90.   Lacy BE, Everhart KK, Weiser KT, et al. IBS patients' willingness to take risks with

799   medications. *Am J Gastroenterol* 2012; **107**: 804-9.

800   91.   Hulme K, Chilcot J, Smith MA. Doctor-patient relationship and quality of life in

801   irritable bowel syndrome: An exploratory study of the potential mediating role of illness

802   perceptions and acceptance. *Psychol Health Med* 2018; **23**: 674-84.

803   92.   Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: Long-term

804   prognosis and the physician-patient interaction. *Ann Intern Med* 1995; **122**: 107-12.

805   93.   Drossman DA. 2012 David Sun lecture: Helping your patient by helping yourself--

806   how to improve the patient-physician relationship by optimizing communication skills. *Am J*

807   *Gastroenterol* 2013; **108**: 521-8.

808   94.   Ringström G, Störsrud S, Posserud I, Lundqvist S, Westman B, Simrén M. Structured

809   patient education is superior to written information in the management of patients with

810   irritable bowel syndrome: A randomized controlled study. *Eur J Gastroenterol Hepatol* 2010;

811   **22**: 420-8.

812   95.   Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves

813   symptoms in irritable bowel syndrome: A randomized controlled trial. *Am J Gastroenterol*

814   2011; **106**: 915-22.

815   96.   Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal.

816   *Lancet* 1994; **344**: 39-40.

817   97.   Moayyedi P, Quigley EM, Lacy BE, et al. The effect of fiber supplementation on

818   irritable bowel syndrome: A systematic review and meta-analysis. *Am J Gastroenterol* 2014;

819   **109**: 1367-74.

820   98.   Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs

821   reduces symptoms of irritable bowel syndrome. *Gastroenterology* 2014; **146**: 67-75.

822   99.   Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction

823   reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel

824   syndrome. *J Nutr* 2012; **142**: 1510-8.

825   100.   Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled

826   trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-

827   D. *Am J Gastroenterol* 2016; **111**: 1824-32.

828   101.   Bohn L, Storsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of

829   irritable bowel syndrome as well as traditional dietary advice: A randomized controlled trial.

830   *Gastroenterology* 2015; **149**: 1399-407.e2.

831   102.   Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets

832   that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* 2015;

833   **64**: 93-100.

834   103.   Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating

835   the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of irritable

836   bowel syndrome. *Am J Gastroenterol* 2018; **113**: 1290-300.

837   104.   O'Keeffe M, Jansen C, Martin L, et al. Long-term impact of the low-FODMAP diet

838   on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization

839   in irritable bowel syndrome. *Neurogastroenterol Motil* 2018; **30**: doi: 10.1111/nmo.13154.

840   105.   Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with

841   meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable

842   bowel syndrome. *Aliment Pharmacol Ther* 2018; **48**: 1044-60.

843   106.   Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic

844   idipathic constipation: Systematic review and meta-analysis. *Gut* 2011; **60**: 209-18.

845   107.   Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial:

846   Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated

847   with irritable bowel syndrome. *Am J Gastroenterol* 2013; **108**: 1508-15.

848   108.   Zheng L, Lai Y, Lu W, et al. Pinaverium reduces symptoms of irritable bowel

849   syndrome in a multi-center, randomized controlled trial. *Clin Gastroenterol Hepatol* 2015;

850   **13**: 1285-92.

851   109.   Weerts ZZRM, Masclee AAM, Witteman BJM, et al. Efficacy and safety of

852   peppermint oil in a randomized double-blind trial of patients with irritable bowel syndrome.

853   *Gastroenterology* 2020; **158**: 123-36.

854   110.   Ford AC, Lacy BE, Harris LA, Quigley EM, Moayyedi P. Effect of antidepressants

855   and psychological therapies in irritable bowel syndrome: An updated systematic review and

856   meta-analysis. *Am J Gastroenterol* 2019; **114**: 21-39.

857   111.   Gorard DA, Libby GW, Farthing MJ. Effect of a tricyclic antidepressant on small

858   intestinal motility in health and diarrhea-predominant irritable bowel syndrome. *Dig Dis Sci*

859   1995; **40**: 86-95.

860   112.   Saito YA, Almazar AE, Tilkes KE, et al. Randomised clinical trial: Pregabalin vs

861   placebo for irritable bowel syndrome. *Aliment Pharmacol Ther* 2019; **49**: 389-97.

862   113.   Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy

863   of 5-HT 3 antagonists and 5-HT 4 agonists in irritable bowel syndrome: Systematic review

864   and meta-analysis. *Am J Gastroenterol* 2009; **104**: 1831-43.

865   114.   Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: Lubiprostone in patients

866   with constipation-associated irritable bowel syndrome - results of two randomized, placebo-

867   controlled studies. *Aliment Pharmacol Ther* 2009; **29**: 329-41.

868   115.   Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with

869   constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate

870   efficacy and safety. *Am J Gastroenterol* 2012; **107**: 1702-12.

871   116.   Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with

872   constipation-predominant irritable bowel syndrome: A phase 2, randomized, placebo-

873   controlled efficacy and safety trial. *Am J Gastroenterol* 2017; **112**: 763-74.

874   117.   Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide

875   in patients with irritable bowel syndrome with constipation: Results of two phase 3

876   randomized clinical trials *Am J Gastroenterol* 2018; **113**: 735-45.

877   118.   Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of

878   secretagogues in patients with irritable bowel syndrome with constipation: Systematic review

879   and network meta-analysis. *Gastroenterology* 2018; **155**: 1753-63.

880   119.   Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT3 receptor antagonist,

881   delays colonic transit in patients with irritable bowel syndrome and healthy volunteers.

882   *Aliment Pharmacol Ther* 2000; **14**: 775-82.

883   120.   Thumshirn M, Coulie B, Camilleri M, Zinsmeister AR, Burton DD, Van Dyke C.

884   Effects of alosetron on gastrointestinal transit time and rectal sensation in patients with

885   irritable bowel syndrome. *Aliment Pharmacol Ther* 2000; **14**: 869-78.

886   121.   Acosta A, Camilleri M, Shin A, et al. Effects of rifaximin on transit, permeability,

887   fecal microbiome, and organic acid excretion in irritable bowel syndrome. *Clin Transl*

888   *Gastroenterol* 2016; **7**: e173.

889   122.   Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and

890   effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology*

891   2016; **151**: 1113-21.

892   123.   Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome

893   with diarrhea. *N Engl J Med* 2016; **374**: 242-53.

894   124.   Fukudo S, Kinoshita Y, Okumura T, et al. Ramosetron reduces symptoms of irritable

895   bowel syndrome with diarrhea and improves quality of life in women. *Gastroenterology*

896   2016; **150**: 358-66.

897   125.   Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in

898   patients with IBS with diarrhoea or mixed stool pattern: Systematic review and network

899   meta-analysis. *Gut* 2020; **69**: 74-82.

900   126.   Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the

901   treatment of irritable bowel syndrome with diarrhoea. *Gut* 2014; **63**: 1617-25.

902   127.   Gunn D, Fried R, Lalani R, et al. Treatment of irritable bowel syndrome with

903   diarrhoea using titrated ondansetron (TRITON): Study protocol for a randomised controlled

904   trial. *Trials* 2019; **20**: 517.

905   128.   Lowen MB, Mayer EA, Sjoberg M, et al. Effect of hypnotherapy and educational

906   intervention on brain response to visceral stimulus in the irritable bowel syndrome. *Aliment*

907   *Pharmacol Ther* 2013; **37**: 1184-97.

908   129.   Simren M, Ringstrom G, Bjornsson ES, Abrahamsson H. Treatment with

909   hypnotherapy reduces the sensory and motor component of the gastrocolonic response in

910   irritable bowel syndrome. *Psychosom Med* 2004; **66**: 233-8.

911   130.   Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy

912   of psychological therapies for irritable bowel syndrome: Systematic review and network

913   meta-analysis. *Gut* 2020; **doi: 10.1136/gutjnl-2020-321191**.

914   131.   Lackner JM, Jaccard J, Keefer L, et al. Improvement in gastrointestinal symptoms

915   after cognitive behavior therapy for refractory irritable bowel syndrome. *Gastroenterology*

916   2018; **155**: 47-57.

917   132.   Everitt HA, Landau S, O'Reilly G, et al. Assessing telephone-delivered cognitive-

918   behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable

919   bowel syndrome (ACTIB): A multicentre randomised trial. *Gut* 2019; **68**: 1613-23.

920   133.   Flik CE, Laan W, Zuithoff NPA, et al. Efficacy of individual and group hypnotherapy

921   in irritable bowel syndrome (IMAGINE): A multicentre randomised controlled trial. *Lancet*

922   *Gastroenterol Hepatol* 2019; **4**: 20-31.

923   134.   Pimentel M, Morales W, Rezaie A, et al. Development and validation of a biomarker

924   for diarrhea-predominant irritable bowel syndrome in human subjects. *PLoS One* 2015; **10**:

925   e0126438.

926   135.   Jeffery IB, Das A, O'Herlihy E, et al. Differences in fecal microbiomes and

927   metabolomes of people with vs without irritable bowel syndrome and bile acid

928   malabsorption. *Gastroenterology* 2020; **158**: 1016-28.

929   136.   Ianiro G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic

930   review with meta-analysis: Efficacy of faecal microbiota transplantation for the treatment of

931   irritable bowel syndrome. *Aliment Pharmacol Ther* 2019; **50**: 240-8.

932   137.   El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy

933   of faecal microbiota transplantation for patients with irritable bowel syndrome in a

934   randomised, double-blind, placebo-controlled study. *Gut* 2020; **69**: 859-67.

935   138.   Camilleri M, Shin A, Busciglio I, et al. Validating biomarkers of treatable

936   mechanisms in irritable bowel syndrome. *Neurogastroenterol Motil* 2014; **26**: 1677-85.

937   139.   Fukudo S, Endo Y, Hongo M, et al. Safety and efficacy of the sodium-glucose

938   cotransporter 1 inhibitor mizagliflozin for functional constipation: A randomised, placebo-

939   controlled, double-blind phase 2 trial. *Lancet Gastroenterol Hepatol* 2018; **3**: 603-13.

940   140.   Haggie PM, Cil O, Lee S, et al. SLC26A3 inhibitor identified in small molecule

941   screen blocks colonic fluid absorption and reduces constipation. *JCI insight* 2018; **3**.

942   141.   Wong BS, Camilleri M, McKinzie S, Burton D, Graffner H, Zinsmeister AR. Effects

943   of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females

944   with functional constipation. *Am J Gastroenterol* 2011; **106**: 2154-64.

945   142.   Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic

946   constipation: Results from a randomised, double-blind, placebo-controlled, phase 3 trial and

947   an open-label, single-arm, phase 3 trial. *Lancet Gastroenterol Hepatol* 2018; **3**: 537-47.

948   143.   Tchernychev B, Ge P, Kessler MM, et al. MRP4 modulation of the guanylate cyclase-

949   C/cGMP pathway: Effects on linaclotide-induced electrolyte secretion and cGMP efflux. *J

950   Pharmacol Exp Ther* 2015; **355**: 48-56.

951   144.   Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors

952   and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-

953   monophosphate. *Gastroenterology* 2013; **145**: 1334-46.e1-11.

954   145.   Chey WD, Chamberlin P, Bochenek W, et al. Targeted delivery of linaclotide to

955   specific areas of the intestine affects clinical efficacy in patients with irritable bowel

956   syndrome with constipation (IBS-C). *Gastroenterology* 2017; **152 (suppl 1)**: S1314-S5.

957   146.   DeWire SM, Yamashita DS, Rominger DH, et al. A G protein-biased ligand at the

958   mu-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory

959   dysfunction compared with morphine. *J Pharmacol Exp Ther* 2013; **344**: 708-17.

960   147.   Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, Singla N. APOLLO-1: A

961   randomized placebo and active-controlled phase III study investigating oliceridine (TRV130),

962   a G protein-biased ligand at the micro-opioid receptor, for management of moderate-to-

963   severe acute pain following bunionectomy. *J Pain Res* 2019; **12**: 927-43.

964   148.   Yacyshyn B, Ginsberg DC, Gilder K, et al. Safety and efficacy of olorinab, a

965   peripherally restricted, highly selective, cannabinoid receptor 2 agonist in a phase 2A study in

966   chronic abdominal pain associated with Crohn's Disease. *Gastroenterology* 2019; **156 (suppl**

967   **1)**: S-665.

968   149.   Olorinab in IBS-C and IBS-D (CAPTIVATE).

969   *https://clinicaltrials.gov/ct2/show/NCT04043455* Accessed 14th December 2019

970   150.   Wouters MM, Balemans D, Van Wanrooy S, et al. Histamine receptor H1-mediated

971   sensitization of TRPV1 mediates visceral hypersensitivity and symptoms in patients with

972   irritable bowel syndrome. *Gastroenterology* 2016; **150**: 875-87.e9.

973   151.   Peripheral histamine 1 receptor blockade in IBS: Multicenter trial.

974   *https://clinicaltrials.gov/ct2/show/NCT01908465* Accessed 14th December 2019

975

976 **FIGURE LEGENDS.**

977 **Figure 1. Global Prevalence of Irritable Bowel Syndrome According to the Rome III**

978 **Criteria*.**

979 ***Note, the prevalence data reported here are taken from studies using the Rome III**

980 **criteria for IBS, summarised in references 4, 13, and 15.**

981 **Figure 2. Factors Affecting Symptom Severity in Irritable Bowel Syndrome.**

982 **Figure 3. Pathophysiological Mechanisms Involved in Irritable Bowel Syndrome.**

983 ***Genome-wide association studies have demonstrated associations with variants of**

984 **chromosome 9 (reference 56), and mutations in the sucrase-isomaltase gene (references**

985 **37 and 38), and studies have shown approximately 2% of IBS patients carry mutations**

986 **in *SCN5A* (reference 57), which alters the function of the voltage-gated**

987 **mechanosensitive Na$^+$ channel Na$_v$1.5.**

988 **†See references 17 to 20.**

989 **±Gastrointestinal symptoms include abdominal pain, abnormal stool form and/or**

990 **frequency, and bloating (reference 5); non-gastrointestinal symptoms include back pain,**

991 **gynaecological and bladder symptoms, headache, and fatigue (reference 60).**

992 **Figure 4. Suggested Diagnostic Algorithm for Patients with Suspected Irritable Bowel**

993 **Syndrome.**

994 ***Abdominal pain, related to defaecation, associated with change in stool form or stool**

995 **frequency (reference 5).**

996 **†Full blood count and C-reactive protein/erythrocyte sedimentation rate**

997 **±See Table 2.**

998 **§Including family history of inflammatory bowel disease, coeliac disease, or colorectal**

999 **cancer, or features suggestive of microscopic colitis (female, age ≥50 years; co-existent**

1000 **autoimmune disease; proton pump inhibitor or non-steroidal anti-inflammatory drug**

1001   **use; duration of diarrhoea < 12 months; weight loss; or nocturnal diarrhoea (references**

1002   **77 and 78)).**

1003   **‡Consider measuring SeHCAT retention, serum 7α-hydroxy-4-cholesten-3-one, serum**

1004   **fibroblast growth factor-19, or 48-hour faecal bile acid excretion, where available, or a**

1005   **trial of a bile acid sequestrant, to exclude bile acid diarrhoea.**

1006   ****If the initial faecal calprotectin level is within the abnormal range the suspicion for**

1007   **inflammatory bowel disease is high, proceed to colonoscopy (reference 74); if the initial**

1008   **faecal calprotectin level is indeterminate according to local laboratory values, repeat the**

1009   **test off non-steroidal anti-inflammatory drugs and refer for colonoscopy if the repeat**

1010   **test remains indeterminate or is within the abnormal range.**

1011   **††If features suggestive of a defaecatory disorder, including obstructive symptoms (such**

1012   **as a feeling of incomplete evacuation or the need to digitate during defaecation) or**

1013   **paradoxical anal contraction on straining during digital rectal examination, are present**

1014   **consider anorectal manometry with balloon expulsion testing.**

1015   **Figure 5. Current and Emerging Treatment Options for Irritable Bowel Syndrome.**

1016

1017   **Table 1. The Rome IV Criteria for Irritable Bowel Syndrome*.**

Rome IV IBS Diagnostic Criteria			
1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following: a. Related to defaecation; b. Associated with a change in frequency of stool; c. Associated with a change in stool form. **AND** **2.** Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis			
IBS-C	**IBS-D**	**IBS-M**	**IBS-U**
≥25% of bowel movements of Bristol stool form types 1 or 2, and <25% of Bristol stool form types 6 or 7.	≥25% of bowel movements of Bristol stool form types 6 or 7, and <25% of Bristol stool form types 1 or 2.	≥25% of bowel movements of Bristol stool form types 1 or 2, and ≥25% of bowel movements of Bristol stool form types 6 or 7.	Patients who meet criteria for IBS, but who do not fall into one of the other three subgroups according to Bristol stool form type.

1018   ***Adapted from reference 5.**

1019

1020   **Table 2. Lower Gastrointestinal Alarm Symptoms and Signs (Based on the UK's NICE**

1021   **Guidance*).**

Definite Referral Criteria
• Aged ≥40 years with unexplained weight loss and abdominal pain.
• Aged ≥50 years with unexplained rectal bleeding.
• Aged ≥60 years with change in bowel habit, a positive faecal occult blood test, or iron deficiency anaemia.

1022   ***Adapted from reference 71.** Regardless of age, adults with unexplained rectal bleeding or

1023   iron-deficiency anaemia (especially if accompanied by abdominal pain, change in bowel

1024   habit, or weight loss), or an abdominal or rectal mass, need investigation to exclude other

1025   gastrointestinal disorders, including cancer.

1026

Table 3. Summary of Evidence for Efficacy of Treatment Approaches for Irritable Bowel Syndrome*.

Therapy	Specific Intervention†	IBS Subgroup Studied	Efficacy	Quality of Data	Adverse Events	Limitations of Data
Diet, lifestyle, and probiotics	Soluble fibre (e.g. ispaghula 20 - 30g/day)	No specific IBS subgroup recruited	Effective	Moderate	Total adverse events no more common with soluble fibre in three RCTs	Only one RCT at low risk of bias; only a small number of patients in existing RCTs
	Low FODMAP diet	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events rarely reported	All RCTs at high risk of bias; heterogeneity between study designs; imprecision in estimate of effect; impact of FODMAP reintroduction not studied within the design
	Exercise	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events not reported	Only two RCTs, which were at high risk of bias; inconsistent effects on symptoms
	Probiotics	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events no more common with probiotics in a meta-analysis of 36 RCTs	Heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual probiotic, meaning that it is difficult to know which species or strain is effective
First-line therapies	Peppermint oil (200mg three times daily)	No specific IBS subgroup recruited	Effective	Low	Total adverse events no more common with peppermint oil in a meta-analysis of six RCTs	Only two RCTs at low risk of bias; heterogeneity between studies; trials used very specific formulations so data cannot be extrapolated to other available products; heartburn may be an issue
	Laxatives (e.g. polyethylene glycol 13.8g once daily and titrated)	Patients with IBS-C	Unclear efficacy	Low	Rates of abdominal pain numerically higher with polyethylene glycol in one RCT	Only two RCTs; both RCTs unclear risk of bias; effect on abdominal pain unclear
	Antidiarrhoeals (e.g. loperamide 4mg as required)	Patients with IBS-D and IBS-M	Unclear efficacy	Very low	Total adverse events no more common with antidiarrhoeals in two RCTs	Only two RCTs; both RCTs unclear risk of bias; not all patients met criteria for IBS; no significant effect on IBS symptoms when data pooled; constipation may be an issue

	Antispasmodics (e.g. cimetropium 50mg three times daily, hyoscine 10-20 mg three times daily, otilonium20-40mg three times daily, or pinaverium 50mg three times daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	May be effective	Very low	Total adverse events significantly more common with antispasmodics in a meta-analysis of 26 RCTs, particularly dry mouth, dizziness, and blurred vision	Only two RCTs at low risk of bias; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual antispasmodic
Second-line therapies	5-HT$_4$ agonists (e.g. tegaserod 6mg twice daily)	IBS-C	Effective	High	Diarrhoea significantly more common with tegaserod in a meta-analysis of six RCTs	Concerns regarding small excess of cardiovascular and cerebrovascular events led to withdrawal of tegaserod, reintroduced in 2018 but only for specific patients; no RCTs of prucalopride
	Linaclotide (290mcg once daily)	IBS-C	Effective	High	Diarrhoea significantly more common with linaclotide in a meta-analysis of three RCTs	None
	5-HT$_3$ antagonists (e.g. alosetron 0.5-1mg twice daily, ramosetron 2.5-5mcg once daily, or ondansetron 4mg once daily and titrated)	IBS-D and IBS-M	Effective	High	Constipation significantly more common with alosetron in a meta-analysis of three RCTs	All RCTs of ramosetron conducted in Japan; serious adverse events with alosetron included ischaemic colitis and severe constipation leading to restricted use; ramosetron is safer, although constipation is still more common with active therapy
	TCAs (e.g. amitriptyline 10-30mg at night or desipramine 50mg at night)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	Effective	Moderate	Total adverse events significantly more common with TCAs in a meta-analysis of six RCTs, particularly dry mouth and drowsiness	Only three RCTs at low risk of bias; possible publication bias; some atypical trials included
	Lubiprostone (8mcg twice daily)	IBS-C	Effective	Moderate	Nausea significantly more common with lubiprostone in a meta-analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	Plecanatide (3-6mg once daily)	IBS-C	Effective	Moderate	Diarrhoea significantly more common with plecanatide in a meta-analysis of two RCTs	Only a modest benefit over placebo in published RCTs

	Tenapanor (50mg twice daily)	IBS-C	Effective	Moderate	Rates of diarrhoea numerically higher with tenapanor	Awaiting publication of all phase 3 trial data
	Eluxadoline (100mg twice daily)	IBS-D	Effective	Moderate	Rates of constipation, nausea, and vomiting numerically higher with eluxadoline in a pooled analysis of two RCTs	Heterogeneity between studies; only a modest benefit over placebo in published RCTs; no benefit over placebo in terms of abdominal pain; serious adverse events include acute pancreatitis and sphincter of Oddi spasm
	Rifaximin (550mg three times daily)	IBS-D and IBS-M	Effective	Moderate	Total adverse events no more common with rifaximin in a pooled analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	SSRIs (e.g. fluoxetine 20mg once daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-C	May be effective	Low	Total adverse events no more common with SSRIs	Only one RCT at low risk of bias; heterogeneity between studies
	Pregabalin (225mg twice daily)	No specific IBS subgroup recruited	May be effective	Low	Total adverse events numerically higher with pregabalin, particularly blurred vision, dizziness, and altered sensation	Only one single-centre RCT although global symptoms, abdominal pain, diarrhoea, and bloating improved significantly
Psychological therapies	CBT or gut-directed hypnotherapy	No specific IBS subgroup recruited	Effective	Very low	Adverse events not reported in individual RCTs, precluding their assessment in a meta-analysis of 36 RCTs	All RCTs at high risk of bias due to the nature of the interventions studied; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each intervention; time consuming due to need for therapist contact; limited availability in some countries

*Data adapted from reference 6.

†**Most drugs should be trialled for 3 months, with their efficacy then reviewed, with the exception of rifaximin, which is a 2-week treatment course. A low FODMAP diet should not be maintained long-term; the restriction phase in RCTs to date has been a maximum of 3 to 4 weeks.**