GUIDELINES

Guidelines on the irritable bowel syndrome: mechanisms and practical management

R Spiller, Q Aziz, F Creed, A Emmanuel, L Houghton, P Hungin, R Jones, D Kumar, G Rubin, N Trudgill, P Whorwell

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Background: IBS affects 5–11% of the population of most countries. Prevalence peaks in the third and fourth decades, with a female predominance.
Aim: To provide a guide for the assessment and management of adult patients with irritable bowel syndrome.
Methods: Members of the Clinical Services Committee of The British Society of Gastroenterology were allocated particular areas to produce review documents. Literature searching included systematic searches using electronic databases such as Pubmed, EMBASE, MEDLINE, Web of Science, and Cochrane databases and extensive personal reference databases.
Results: Patients can usefully be classified by predominant bowel habit. Few investigations are needed except when diarrhoea is a prominent feature. Alarm features may warrant further investigation. Adverse psychological features and somatisation are often present. Ascertaining the patients' concerns and explaining symptoms in simple terms improves outcome. IBS is a heterogeneous condition with a range of treatments, each of which benefits a small proportion of patients. Treatment of associated anxiety and depression often improves bowel and other symptoms. Randomised placebo controlled trials show benefit as follows: cognitive behavioural therapy and psychodynamic interpersonal therapy improve coping; hypnotherapy benefits global symptoms in otherwise refractory patients; antispasmodics and tricyclic antidepressants improve pain; ispaghula improves pain and bowel habit; 5-HT_3 antagonists improve global symptoms, diarrhoea, and pain but may rarely cause unexplained colitis; 5-HT_4 agonists improve global symptoms, constipation, and bloating; selective serotonin reuptake inhibitors improve global symptoms.
Conclusions: Better ways of identifying which patients will respond to specific treatments are urgently needed.

1 SCOPE AND PURPOSE

1.1 Aims

These guidelines were compiled at the request of the Chairman of the Clinical Services Committee of the British Society of Gastroenterology. The committee's aim was to provide a guide for the assessment and management of adult patients with irritable bowel syndrome (IBS). These patients comprise such a large proportion of gastroenterology outpatients that their streamlined and effective management would have a favourable effect on any gastroenterology department's overall performance, and hence improve the management of all gastrointestinal diseases. There are many questions to be addressed (box 1).

These guidelines are designed to be applied to adults with IBS, though they are also likely to apply to most adolescents.

The guideline committee was chosen from members of the British Society of Gastroenterology, aiming to include individuals with a longstanding interest and expertise in the topics to be discussed. Members were chosen to be representative of the spectrum of individuals likely to see such patients, including general practitioners, gastroenterologists from district general hospitals and university hospitals, surgeons and clinical physiologists.

People who suffer from IBS and members of the United Kingdom based IBS Network were also shown this document and their comments have influenced the final version.

The guidelines are aimed primarily at consultant gastroenterologists and trainees in gastroenterology, together with general practitioners with a special interest in gastroenterology. A summary form of this document is available with ''when to refer'' advice for use in primary care (see page 82) which is available online at the Journal website (http://gut.bmj.com/supplemental).

1.2 Development of guidelines

Members of the committee were allocated particular areas to produce review documents for. Literature searching included systematic searches using electronic databases such as Pubmed, EMBASE, MEDLINE, Web of Science, and Cochrane databases and extensive personal reference databases. Citation of the literature is however selective and in particular many low quality studies were discounted. Special attention was paid to high quality studies which used established methodology and substantial patient numbers with clearly defined entry criteria. For trials of treatment, randomisation and placebo control were considered essential. These documents were collated and edited by the Chairman, and the resulting document discussed at a one day face to face meeting. Detailed internal review by members of the committee was followed by revision and teleconferences to establish a consensus. These documents were sent out to patient groups and for external independent review,

Abbreviations: CBT, cognitive behavioural therapy; CCK, cholecystokinin; CRF, corticotropin releasing factor; CRH, corticotrophin releasing hormone; EMA, endomysial antibodies; fMRI, functional magnetic resonance imaging; HPA, hypothalamo-pituitary-adrenal; IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhoea predominant IBS; IBS-M, IBS with mixed bowel pattern; MMC, migrating motor complex; NNT, number needed to treat; PIT, psychodynamic interpersonal therapy; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor

both nationally through the BSG Clinical Services Committee and Council and internationally. The final document represents the consensus of the committee, adjusted in response to reviewers' and patients' comments.

1.3 Link between supporting evidence and recommendations

Evidence was graded according to the type of evidence, giving greatest emphasis to randomised, placebo controlled trials (RCTs). These grades were decreased if there were serious limitations to study quality, important inconsistencies between different studies, or uncertainty about the relevance of the particular study population for the group of patients under consideration. The grade was considered to be further reduced if data were sparse or there was a suggestion of reporting bias, but increased if the evidence of association was strong or if there was clear evidence of a dose–response gradient. Combining the elements of study design, study quality, consistency, and directness, we followed the GRADE working group advice[1] and categorised the quality of evidence as follows:

- *High*—further research is very unlikely to change our confidence in the estimate of effect.
- *Moderate*—further research is likely to have an important effect on our confidence in the estimated effect and may change the estimate.
- *Low*—further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate.
- *Very low*—estimate of effect is very uncertain.

In making recommendations for any intervention, we then considered the trade-off between benefit and harm, categorised as follows:

- *Net benefit*—the intervention clearly does more good than harm.
- *Trade-off*—there are important trade-offs between the benefits and harm.
- *Uncertain trade-off*—it is not clear whether the intervention does more good than harm.
- *No net benefits*—the intervention clearly does not do more good than harm.

Our final recommendations are characterised slightly differently from the GRADE systems in that we classified as ''definitive'' a judgment that most informed people would make, and as ''qualified'', a judgment that the majority of well informed clinicians would make but a substantial minority would not.

It should be noted that many aspects of medical practice have not been formally evaluated using robust methodology; however, the committee still recommended some behaviours such as taking a careful history and listening to the patients complaints as being not only self evident, but also part of the obligations of being a medical practitioner.

Finally, we considered whether the intervention was likely to be cost-effective and what barriers there might be to its use in clinical practice.

Box 1

Main questions to be addressed

- What is the best way to identify IBS patients?
- What are the minimum number of relevant investigations?
- What is the optimum management? (This may include lifestyle adjustments, psychological treatments, dietary modification, and pharmacological treatments.)

1.4 Scheduled review of these guidelines

These guidelines are presented on the BSG website and are freely available to all. They should be reviewed and revised within four years, depending on changes in evidence and clinical practice. Comments on the guidelines should be sent to the authors or posted on the BSG notice board.

1.5 Editorial independence

This document represents a consensus view of the members of the working party and incorporates their response to reviewers' comments. All members completed conflict of interest statements.

2 EPIDEMIOLOGY

2.1 Introduction

IBS is a chronic, relapsing gastrointestinal problem, characterised by abdominal pain, bloating, and changes in bowel habit. While the precise prevalence and incidence depends on the criteria used, all studies agree that it is a common disorder, affecting a substantial proportion of individuals in the general population and presenting frequently to general practitioners and to specialists. IBS is troublesome, with a significant negative impact on quality of life and social functioning in many patients,[2–5] but it is not known to be associated with the development of serious disease or with excess mortality. IBS generates significant health care costs, both direct, because of IBS symptoms and associated disorders, and indirect, because of time off work.

2.2 Definitions

The first attempt to establish diagnostic criteria to define IBS was made in the 1970s by Manning and colleagues.[6] The Manning criteria (box 2) were identified by comparing symptoms in patients with abdominal pain who turned out either to have or not to have organic disease.

Over the past 10 years considerably more attention has been paid to IBS, and the successive Rome working parties have elaborated more detailed, accurate, and useful definitions of the syndrome. The Rome I criteria, which were published in 1990,[7] adopted most of the Manning criteria but subsequent factor analysis indicated that items 1–3 clustered well together while 4–6 did not.[8 9] The Rome II criteria which appeared in 1999[10] took account of this fact but also recognised that pain might be associated with hard as well as loose stools. The Rome III criteria in 2006[11] are shown in box 3. The majority of studies quoted below used Rome II criteria. Rome III modifies Rome II slightly by being more precise, specifying that pain must be present for three or more days a month in the past three months and that criteria need to be fulfilled for the past three months for the patient to be considered as currently having IBS. However, comparative studies suggest these subtle changes will have little effect on prevalence.

The Rome III committee also advised that ''in pathophysiology research and clinical trials a pain/discomfort frequency of at least two days a week is recommended for subject eligibility.''

2.3 Classification

Recently attempts have been made to subclassify IBS according to the predominant bowel habit. Most studies report that around one third of patients have diarrhoea predominant IBS (IBS-D) and one third have constipation predominant IBS

(IBS-C), the remainder having a mixed bowel pattern (IBS-M) with both loose and hard stools.[12–14] However, most of the published data on the incidence, prevalence, and natural history of IBS do not distinguish these subtypes. Furthermore some individuals—now called ''alternators''[11]—switch subtype over time, mostly those with IBS-D or IBS-C switching to a mixed pattern, though in one study a change from IBS-D to IBS-C occurred in 29% over a one year period.[14]

2.4 Prevalence

Most of our knowledge of the descriptive epidemiology of IBS has been obtained from the use of validated postal questionnaires, employing either the Manning or the Rome criteria, completed by individuals in the general population. We were able to identify 37 epidemiological studies of acceptable quality (table 1). Prevalence appears generally higher and more variable using Manning criteria, while Rome I and II yield comparable but less variable results. The number of Manning criteria (one to six) strongly influences the prevalence estimates, which range from 2.5% to 37%. Studies which require three criteria give prevalences of around 10%. The incidence is similar in many countries in spite of substantial differences in lifestyle—for example, the incidence in Mexico is very similar to that in the USA.[45]

2.5 Predictors of health care seeking

Consultation behaviour is likely to be an important determinant of the prevalence of clinically diagnosed IBS. It appears that 33–90% of sufferers do not consult, and that a proportion of consulters meeting IBS criteria are not labelled as having IBS by their clinicians. Although the prevalence of IBS is relatively similar across Europe and the USA (Italy being an exception, with a higher incidence than the rest), the rate of undiagnosed IBS shows a wider variation, with the majority being undiagnosed in all countries except for Italy and the United Kingdom, where around 50% are diagnosed. Most data on prevalence and health care seeking behaviour are from community based samples, indicating that health care seeking behaviour is greater in this population and not just in the group of IBS patients with severe or longstanding symptoms. The main predictors of health care seeking are abdominal pain or distension, pain severity, and symptoms conforming to the Rome II criteria, although psychological and social factors also play a key role in the decision to seek medical advice.[53–57] Overall, health care seeking is greater in IBS patients than in non-IBS patients.[16 17 58–62]

The frequency of IBS symptoms peaks in the third and fourth decades, and in most surveys there is a female predominance of approximately 2:1 in the 20s and 30s, although this bias is less apparent in older patients.[63] IBS symptoms persist beyond middle life, and continue to be reported by a substantial proportion of individuals in their seventh and eighth decades.[24]

Box 2

Manning criteria

1. Pain relieved by defecation
2. More frequent stools at onset of pain
3. Looser stools at onset of pain
4. Visible abdominal distension
5. Passage of mucus per rectum
6. Sense of incomplete evacuation

2.6 Natural history and prognosis

Few studies have assessed the incidence of new cases of IBS, but those that have provide widely varying estimates of incidence (2–70/1000 patient years).[40 64–66] Most current IBS patients will have had symptoms for some years, the mean durations in recent clinical trials being 5, 11, and 13 years, depending on the source of the patients.[67–69] Such patients rarely develop other gastroenterological diseases, though the exact manifestations and stool pattern may change over the years. Once the diagnosis has been made, new diagnoses are rare and are likely to be coincidental.[70] Few studies have examined the progression of IBS over time. One study in Scandinavia studied the ''stability'' of the diagnoses of dyspepsia and IBS in the population over one and seven year periods.[65] This showed that 55% still had IBS at seven years, 13% were completely symptom-free, while 21% had lesser symptoms, no longer meeting the Rome I criteria.

It appears that IBS is not associated with the long term development of any serious disease[71 72] and there is no evidence that IBS is linked to excess mortality, although it has been shown that patients with IBS are more likely to undergo certain surgical operations, including hysterectomy and cholecystectomy, than matched non-IBS controls.[18] Prognosis depends on the length of history, those with a long history being less likely to improve.[73–76]

The other key prognostic factor is chronic ongoing life stress which virtually precluded recovery in one study in which no patient with ongoing life stresses recovered over a 16 month follow up, compared with 41% without such stresses.[77]

3 CLINICAL FEATURES OF IBS

The key features are chronic, recurring abdominal pain or discomfort associated with disturbed bowel habit, or both, in the absence of structural abnormalities likely to account for these symptoms. Symptoms should be present for at least six months to distinguish them from those caused by other conditions such as infections, where the effects are often transient, or progressive diseases such as bowel cancer, which are usually diagnosed within six months of symptom onset.

3.1 Symptoms

As the Rome III criteria indicate (see 2.1), the key features are abdominal pain or discomfort which is clearly linked to bowel function, being either relieved by defecation (suggesting a colonic origin) or associated with change in stool frequency or consistency (suggesting a link to changes in intestinal transit,

Box 3

Rome III diagnostic criteria* for irritable bowel syndrome

Recurrent abdominal pain or discomfort† at least 3 days a month in the past 3 months, associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

*Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis.
†''Discomfort'' means an uncomfortable sensation not described as pain.

Table 1 Prevalence of irritable bowel syndrome in the United Kingdom and in other Western and Eastern populations, using Manning, Rome I, and Rome II diagnostic criteria

		Prevalence and criteria used (%)			
Country	Sample size	Manning	Rome I	Rome II	Reference
UK	301	13.6			Thomson & Heaton, 1980[15]
UK	1620	22			Jones & Lydeard, 1992[16]
UK	1896	9.5			Heaton *et al*, 1992[17]
UK	3179	16.7			Kennedy & Jones, 2000[18]
UK	3111 (PC*)	2.5			Thomson *et al*, 2000[19]
UK	4807		10.5		Wilson *et al*, 2005[20]
USA	789	17.1			Drossman *et al*, 1982[21]
USA	566	15.0			Sandler *et al*, 1984[22]
USA	835	8.7 to 17.0			Talley *et al*, 1991[23]
USA	325	4.9 to 10.9			Talley *et al*, 1992[24]
USA	5430		11.6		Drossman *et al*, 1993[25]
USA	3022	20.0			Talley *et al*, 1995[26]
USA	643	8.6 to 20.4			Saito *et al*, 2000[27]
USA	643		6.8	4.7	Saito *et al*, 2003[28]
USA	5009	14.1			Hungin *et al*, 2005[29]
Canada	1149		13.5	13.1	Thompson *et al*, 2002[30]
Canada	437			2.5	Li *et al*, 2003[31]
Australia	2910	16.7			Boyce *et al*, 2000[32]
New Zealand	980	18.8		3.3	Barbezat *et al*, 2002[33]
Netherlands	438	5.8			Boekema *et al*, 2001[34]
Spain	2000	4.4 to 13.6			Mearin *et al*, 2001[35]
Italy	533	8.5			Gaburri *et al*, 1989[36]
France	20,000			4.7	Coffin *et al*, 2004[37]
Denmark	4581	6.6			Agreus *et al*, 1995[38]
Finland	3631	9.7 to 16.2	5.5	5.1	Hillila & Farkkila, 2004[39]
Sweden	1290	14.0			Kay *et al*, 1994[40]
Iran	4762			5.8	Hoseini-Asl & Amra, 2003[41]
Turkey	998			19.1	Karaman *et al*, 2003[42]
Turkey	1766			6.3	Celebi *et al*, 2004[43]
Bangladesh	2426			8.5	Masud *et al*, 2001[44]
Hong Kong	1000			6.6	Kwan *et al*, 2002[46]
Hong Kong	1298	17.4		3.7	Lau *et al*, 2002[47]
Japan	231	25.0			Schlemper *et al*, 1993[48]
Singapore	696	2.3			Ho *et al*, 1998[49]
South China	4178	13.0			Xiong *et al*, 2004[50]
Singapore	2276	11.0	10.4	8.6	Gwee *et al*, 2004[51]
Malaysia	949			15.7	Rajendra & Alahuddin, 2004[52]

*PC, primary care patients.

which might reflect changes in either motor patterns or secretion).

Symptoms that are common in IBS but not part of the diagnostic criteria include those originally described by Manning[6]—namely, bloating, abnormal stool form (hard and/or loose), abnormal stool frequency (<3×/week or >3×/day), straining at defecation, urgency, feeling of incomplete evacuation, and the passage of mucus per rectum. Most patients experience symptoms intermittently, with flares lasting two to four days followed by periods of remission.[78 79] One important exception is the subgroup of patients with pain which is felt continuously. The diagnosis in this case is usually ''functional abdominal pain'', an unusual and particularly severe condition which needs early recognition, as such patients respond poorly to conventional treatment and often have severe underlying psychological disturbances.[80]

Box 4

Helpful diagnostic behavioural features of irritable bowel syndrome in general practice:

- Symptoms present for more than 6 months
- Frequent consultations for non-gastrointestinal symptoms
- Previous medically unexplained symptoms
- Patient reports that stress aggravates symptoms

IBS is considered a painful condition and those with painless bowel dysfunction are labelled as having ''functional constipation'' or ''functional diarrhoea'', though it is likely that some share underlying pathology with their respective IBS subtypes.

3.2 Stool patterns

These vary widely and are the source of some confusion. The Rome II classification used a complex multidimensional set of criteria which included stool frequency, stool consistency, urgency, and straining. Unfortunately these features do not correlate well. Thus both straining and urgency can be seen with both hard and loose stools, which can also be associated with both frequent and infrequent defecation.[12] The Rome III subclassification is based solely on stool consistency[11] and is hence easier to apply. Patients with hard stools more than 25% of the time and loose stools less than 25% of the time are defined as ''IBS with constipation'' (IBS-C) while ''IBS with diarrhoea'' (IBS-D) patients have loose stools more than 25% of the time and hard stools less than 25% of the time. About one third to one half of IBS patients are ''IBS-mixed'' (IBS-M), who describe both hard and soft stools more than 25% of the time, with a small (4%) unclassified (IBS-U), with neither loose nor hard stools more than 25% of the time.[12] Those whose bowel habit changes from one subtype to another during follow up over months and years are termed ''alternators'' (see 2.3).

These simple categorisations miss some important details about bowel habits. One pattern, familiar to most clinicians but rarely studied, is repeated defecation in the morning (morning

Box 5

Alarm features in irritable bowel syndrome

- Age >50 years
- Short history of symptoms
- Documented weight loss
- Nocturnal symptoms
- Male sex
- Family history of colon cancer
- Anaemia
- Rectal bleeding
- Recent antibiotic use

rush), when stool consistency changes from an initial formed stool to a progressively looser stool as the colonic contents are cleared from left to right. This may best be thought of as an exaggerated colonic response to the stress of waking and starting the day. Regrettably these patterns have not been studied in detail and there is no evidence that such features are more characteristic of those with stress. Although 60% of IBS patients believe that stress aggravates their symptoms, this is also true of organic disease in 40%,[19] so this is not helpful diagnostically in clinical practice.

3.3 Food related symptoms

Many patients believe their symptoms are aggravated by meals and in this respect there is considerable overlap with functional dyspepsia, which is reported in from 42% to 87% of IBS patients.[38 81–84] Thus epigastric pain, nausea, vomiting, weight loss, and early satiety are also common. Furthermore, as the criteria originally developed by Manning[6] were those that distinguished IBS from other gastrointestinal complaints including dyspepsia, aggravation by eating was excluded as a symptom from the definition. However, when symptoms were systematically investigated using a detailed diary, Ragnarsson found that, although 50% of patients said that defecation relieved their pain, in practice this only occurred within 30 minutes of defecation on 10% of occasions, whereas on 50% of occasions pain was aggravated within 90 minutes of eating.[85] This may represent either symptoms originating in the small intestine or an exaggerated colonic response to food, which has been described in IBS by some[86] but not all[87] investigators. It may also reflect the increased sensitivity to intestinal distension induced by eating, an effect particularly obvious after fat ingestion.[88]

3.4 Limitations of the Rome criteria

Several studies suggest that few clinicians systematically use the Rome II criteria[89] but instead tend to rely more on a holistic approach which takes note of features beyond the gut. Primary care physicians are particularly well placed to make such assessments, while specialists, trained to focus solely on gastrointestinal symptoms, are in danger of missing these important clues.

3.5 Associated non-gastrointestinal symptoms

Associated non-gastrointestinal symptoms include lethargy, backache, headache, urinary symptoms such as nocturia, frequency and urgency of micturition, incomplete bladder emptying, and in women, dyspareunia.[90] These are important because they can result in patients being referred to other specialties, where they may receive inappropriate investigation or even treatment (see 2.6).[91 92] Furthermore, there is evidence that these symptoms can be used clinically to improve diagnostic accuracy.[93] A large study in primary care in the United Kingdom suggested that consultation style (see box 4) was also predictive of a final diagnosis of IBS.[19]

3.6 Comorbidity with other diseases

Between 20% and 50% of IBS patients also have fibromyalgia[94 95]; conversely IBS is common in several other chronic pain disorders,[96] being found in 51% of patients with chronic fatigue syndrome, in 64% with temporomandibular joint disorder, and in 50% with chronic pelvic pain.[97–99] The lifetime rates of IBS in patients with these syndromes are even higher, being 77% in fibromyalgia, 92% in chronic fatigue syndrome, and 64% in temporomandibular joint disorder.[100] Those with overlap syndromes tend to have more severe IBS.[95] IBS patients in primary care with numerous other somatic complaints report higher levels of mood disorder, health anxiety, neuroticism, adverse life events, and reduced quality of life, and increased health care seeking.[101] Systematic questioning to identify these comorbid disorders is helpful in identifying patients who are likely to have severe IBS and associated psychiatric disorder.

3.7 Psychological features

At least half the IBS patients can be described as depressed, anxious, or hypochondriacal.[64 96 102–104] While previous studies suggested that this proportion was increased in secondary and tertiary care, more recent large population based surveys suggest that even non-consulters have increased psychological distress[64 96 103] compared with people who do not have IBS. Studies from tertiary care suggest that up to two thirds have a psychiatric disorder—most commonly anxiety or depressive disorder.[102 104 105] The polysymptomatic nature of IBS suggests that hypochondriasis and somatisation[106] may play a role in some patients. Recognising this will help, as it should indicate that focusing on specific bowel symptoms may not be profitable; thus avoiding endless investigation of new symptoms.

The effectiveness of antidepressants and the response to anxiolytic treatment and some psychological treatments also argue for an important psychological component to IBS symptomatology in some patients.[96]

Symptoms may in many cases be caused by altered cerebral interpretation of gastrointestinal symptoms. These often subside during sleep. Waking from sleep with pain or diarrhoea is usually an indication that other diagnosis should be considered.

3.8 Alarm features

While IBS should and can be diagnosed by its characteristic features, recognising when a patient does not have IBS is equally important.

Several studies suggest that alarm features (box 5) improve the predictive value of the Rome criteria substantially in the outpatient setting.

A follow up observational study lasting 24 months[107] found that, in the absence of alarm features and after a full history, examination, and investigation, no IBS patients meeting the Rome II criteria had another diagnosis. By contrast, a substantial number of those not meeting the Rome II criteria were left with a final diagnosis of IBS, suggesting that the Rome criteria in the absence of alarm symptoms were highly specific but not particularly sensitive. A more recent study which looked at a range of alarm features found that age over 50 years at onset of symptoms, male sex, blood mixed in the stool, and blood on the toilet paper were all predictors of an organic diagnosis.[108] Characteristic features of IBS in this study were pain on more than six occasions in the past year, pain that radiated outside the abdomen, and pain associated with looser bowel movements, all of which were much commoner in IBS than in patients with organic disease.[108] Other features commoner in IBS than in organic lower gastrointestinal disease

included incomplete evacuation, nausea, acid regurgitation, bloating, and a history of abdominal pain in childhood, which was found in a quarter of subjects.

Broad spectrum antibiotics lead to transient diarrhoea in around 10% of cases, which if severe and persistent should lead to consideration of testing for *C difficile* toxin or sigmoidoscopy to exclude pseudomembranous colitis. This recommendation is based on expert opinion, as there are no data on the cost-effectiveness of such an approach.

3.9 Assessment of severity

It is characteristic of IBS patients that the pain is reported as severe and debilitating and yet there are no abnormal physical findings. The patient has not lost weight and may look anxious but otherwise well. Several attempts have been made to assess severity.[109 110] The functional bowel disorder severity index (FBDSI) uses severity of abdominal pain, the diagnosis of chronic functional abdominal pain, and the number doctor visits in the past six months to calculate an index which correlates reasonably well with physician rating of severity. The other index, the IBS severity scoring system (IBS SSS), also uses a visual analogue scale to measure severity of abdominal pain but includes an assessment of pain frequency, bloating, dissatisfaction with bowel habit, and interference with life. The score obtained with the IBS SSS can assess change over a relatively short period and has been used to assess response to treatment for audit purposes and in clinical trials.[111 112] The patient's view of severity is important. This is not related to the severity of symptoms but is associated with a degree to which the symptoms interfere with daily life.[113]

4 MECHANISMS OF IRRITABLE BOWEL SYNDROME

4.1 Genetics and family learning

Clinicians have long been aware that a family history of IBS is of value in establishing the diagnosis of this condition.[114] IBS clearly aggregates within families. First degree relatives of IBS patients are twice as likely to have IBS as the relatives of the IBS patient's spouse.[115] Such studies cannot, however, distinguish the influence of genetic and shared environmental factors.

4.1.1 Twin studies

These assume that monozygotic (MZ) and dizygotic (DZ) twin pairs are exposed to the same family environment and therefore any greater similarity or concordance between MZ twins is caused by genetic influences. Two studies have reported higher concordance rates for diagnosed functional bowel disorders among MZ twins, suggesting a genetic contribution to IBS.[116 117] However, Levy *et al* noted that among DZ twins, parent/child concordance was greater than concordance between the twins.[117] As a parent and child share a similar number of genes to a pair of DZ twins, this strongly suggests that parent–child interactions are more important than genetic influences. A recent study of IBS symptoms using the Rome II criteria found no difference in concordance rates in MZ and DZ twins, suggesting no significant genetic contribution to IBS.[118] In summary, twin studies suggest a strong environmental contribution to IBS and possibly a minor genetic contribution.

4.1.2 Parental influences

Parental reinforcement of illness behaviour and children modelling their parent's behaviour are likely to contribute to the development of IBS. Children of IBS patients make more health care visits,[119] complain of more gastrointestinal and non-gastrointestinal symptoms, and have more school absences.[120] Parental encouragement of the sick role during menstruation or colds is associated with more absenteeism and more menstrual and non-gynaecological symptoms, respectively.[121]

4.1.3 Candidate genes

Associations between various candidate genes and IBS have been studied. Polymorphisms of the serotonin transporter 5-HTT, α adrenergic receptor, interleukin (IL)-10, and tumour necrosis factor α (TNFα) genes have been associated with some forms of IBS.[122 123] The most intriguing of these studies found that 5-HTT polymorphisms were linked to a greater slowing of colonic transit in response to the 5-hydroxytryptamine 3 (5-HT_3) antagonist alosetron.[124] However, published candidate gene studies often have small sample sizes and are therefore underpowered to detect what is likely to be a small effect. This is exacerbated by inadequate stratification for ethnicity and inherent difficulties in defining phenotype in IBS[122 125] which lead to inconsistent results.[126] Reported associations with 5-HTT polymorphisms may plausibly relate not to an association with IBS per se but rather to confounding by the recognised association of the polymorphisms with anxiety or somatisation.[127] Somatisation also explains most of the reported familial aggregation,[115] is largely genetically determined,[128 129] and may be responsible for the genetic contribution to IBS noted in some twin studies.[116–118] Interpretation of genetic polymorphism studies is also hampered by the frequently poor replication of such associations, particularly from small studies.[126]

Familial aggregation of IBS appears from available evidence to result largely from environmental influences, such as parental–child interactions. Genetic factors may make a minor contribution but future studies of this heterogeneous disease must establish IBS phenotypes more clearly and in particular allow for confounding because of psychological factors.

4.2 Disturbances of gastrointestinal motility

Antecedent terms used to describe the clinical entity now known as IBS include ''spastic colon'' and ''irritable colon''. These terms indicate that clinicians of the day thought that this condition reflected an underlying motility disorder. This perception is further supported by routine prescription of antispasmodic agents in the clinical management of IBS patients, though as we shall see in section 7, their efficacy is limited.

Although motor disturbances do occur in IBS, these vary between patient subtypes[130] and, as around one quarter of IBS patients change their bowel habit predominance at least once within a year,[14] it is likely that motility patterns may also change with time.

4.2.1 Alterations of gastric motility

A proportion of IBS patients have delayed gastric emptying, particularly of solids.[82 131–135] This appears is especially noticeable in patients with constipation[133] or those with overlapping dyspeptic symptoms.[82] Disturbed gastric emptying correlates highly with a lack of a postprandial increase in electrogastrography (EGG) amplitude ($r = 0.8$; $p<0.005$).[136] Furthermore, emotions such as anger suppress antral contractility in IBS patients but increase it in healthy volunteers.[137]

4.2.2 Abnormalities of small bowel motility

While various abnormalities of small bowel motor activity have been demonstrated in IBS under study conditions, none appears to be specific for the condition. Small bowel motility shows marked diurnal variability and hence consistent results can only be obtained with prolonged (at least 24 hour) recordings and large numbers of subjects. This may account for some inconsistencies in published reports, as many studies have been small and of short duration. Small bowel motor disturbances reported include: increased frequency and duration of discrete cluster contractions,[138–141] increased frequency of the migrating motor complex (MMC),[140–142] more retrograde

duodenal and jejunal contractions,[140 143] and an exaggerated motor response to meal ingestion,[140 142] ileal distension, and cholecystokinin (CCK).[142] Corticotrophin releasing hormone (CRH) has been reported to increase the number of discrete cluster contractions.[144] These observations appear more relevant to IBS patients with diarrhoea than with constipation.[139–142] Small bowel transit is faster in IBS patients with diarrhoea than with constipation[145] and, in contrast to healthy controls, colonic distension does not appear to reduce duodenal motility in IBS patients, suggesting an impaired intestino-intestinal inhibitory reflex.[146]

4.2.3 Colonic response to feeding and emotion

As the predominant symptom in IBS is a change in defecatory habit, colonic dysmotility was initially thought to be the likely cause. The most consistent motor abnormality recorded in the colon is an exaggerated motility response to meal ingestion.[105 130 147–151] Enhanced colonic motility in response to emotional stress,[152] CRH,[144] CCK[151 153] and recto-sigmoid balloon distension has also been reported in IBS.[154] However, not all studies have reproduced these findings[155–159] and studies under fasting conditions are even more variable.[151 160–163]

Some of this confusion might be explained because earlier studies failed to distinguish subtypes of IBS, yet we now know that IBS patients with diarrhoea appear to have increased colonic motility—particularly the number of high amplitude propagating contractions (HAPCs)[151 154]—and accelerated colonic transit,[145 164] while those with constipation have reduced motility, fewer HAPCs, and delayed transit.[145 154 165–167] The significance of bowel habit is further emphasised by the recent observations that postprandial platelet-depleted plasma 5-HT concentrations—a possible mediator of colonic motility[168]—are increased in patients with diarrhoea but reduced in those with constipation predominant IBS.[169] Interestingly, postprandial distal colonic tone has been shown to be reduced in patients with both constipation[170] and diarrhoea[171 172] but not to differ significantly from healthy controls under fasting conditions.[173]

4.2.4 Rectal compliance and tension

Rectal motor physiology has been mainly studied with respect to compliance and tension, with some[174–177] but not all studies[154 177–182] reporting lower rectal compliance or increased tension, or both, in patients with IBS. This has been proposed as a possible mechanism for enhanced visceral sensation to balloon distension in IBS.[183]

4.2.5 Relation between motor patterns and symptoms

Whether the above changes in gastrointestinal motility account for the symptoms of IBS continues to be debated, but one study has shown that over 90% of HAPCs coincide with abdominal pain or cramps, while 40% of postprandial HAPCs occurred immediately before defecation in IBS patients with diarrhoea.[151] Small bowel disturbances, such as discrete cluster contractions, are also associated with pain,[138 139 141 142] while higher rates of duodenal retrograde contractions during phase II of the MMC directly correlate with worsening gastrointestinal symptoms in IBS patients with diarrhoea.[140] Gastric dysmotility may be associated with dyspeptic symptoms in some patients with IBS,[82 184] although not all studies have found such a correlation.[131]

Finally, it must be recalled that many of the phasic motor events described above occur in healthy subjects, albeit at a lower incidence, and are not associated with concomitant symptomatology, suggesting that in IBS heightened visceral sensation may also play an important role in the perception of these motor events (see 4.3). A comprehensive summary of all the above studies on motility in IBS is provided in appendix 1, which is available on the journal website (http://www.gutjnl.-com/supplemental).

4.3 Visceral hypersensitivity

Abdominal pain and discomfort cause considerable morbidity in IBS patients and are essential components of the diagnostic criteria.[10 11] Approximately two thirds of the patients show enhanced pain sensitivity to experimental gut stimulation, a phenomenon known as visceral hypersensitivity. Visceral hypersensitivity is thought to play an important role in the development of chronic pain and discomfort in IBS patients.[185 186]

4.3.1 Mechanisms of visceral hypersensitivity

Both animal and human studies suggest that visceral hypersensitivity is caused by a combination of factors that involve heightened sensitivity of both the peripheral and the central nervous system. Mechanisms that lead to heightened nervous system sensitivity have been well described in models of inflammation or injury to tissues, and these will be briefly outlined.

4.3.1.1 Peripheral sensitisation

During tissue injury and inflammation, peripheral nociceptor terminals are exposed to a mixture of immune and inflammatory mediators such as prostaglandins, leukotrienes, serotonin, histamine, cytokines, neurotrophic factors, and reactive metabolites.[187 188] These inflammatory mediators act on nociceptor terminals, leading to the activation of intracellular signalling pathways, which in turn upregulate their sensitivity and excitability. This phenomenon has been termed peripheral sensitisation. Peripheral sensitisation is believed to cause pain hypersensitivity at the site of injury or inflammation, also known as primary hyperalgesia (increased sensitivity to painful stimuli) and allodynia (non-painful stimuli perceived as painful).[189 190]

4.3.1.2 Central sensitisation

A secondary consequence of peripheral sensitisation is the development of an area of hypersensitivity in the surrounding uninjured tissue (secondary hyperalgesia/allodynia). This phenomenon occurs because of an increase in the excitability and receptive fields of spinal neurones and results in recruitment and amplification of both non-nociceptive and nociceptive inputs from the adjacent healthy tissue.[191]

4.3.2 Evidence of sensitisation in IBS

Depending on the setting, between 6% and 17% of patients with IBS report that their symptoms began with an episode of gut inflammation related to gastroenteritis.[192] Furthermore, an increase in mucosal T lymphocytes has been reported by several investigators in subjects with postinfectious IBS (see 4.5). Therefore the environment of nociceptor terminals in the gut of IBS patients is likely to be altered, suggesting a role for peripheral sensitisation.

Evidence for central sensitisation as an important mechanism for the development of visceral hypersensitivity in IBS patients comes from three main observations. First, in response to colonic stimulation, patients with IBS have greater radiation of pain to somatic structures in comparison with healthy subjects.[193] Second, some IBS patients also suffer from fibromyalgia, a condition characterised by somatic hyperalgesia.[194] Finally, patients with IBS also often show hypersensitivity of more proximal regions of the gut.[186] These observations may be explained by the fact that the innervation of different gut organs overlaps and converges with that of the somatic structures at the level of the spinal cord. Therefore the

sensitisation of proximal organs in IBS patients, and greater radiation of pain to somatic structures in response to visceral stimulation in patients who also have fibromyalgia, could all be explained by the phenomenon of central sensitisation of the spinal segments that demonstrate this viscero-visceral and viscero-somatic convergence.

4.3.3 Central pain processing

Peripheral and central sensitisation are by no means the only mechanisms that can explain the development of visceral hypersensitivity observed in IBS patients. This is because the perception of pain in humans involves processing of sensory inputs in various cortical and subcortical brain structures. Our understanding of the brain processing of visceral sensation has improved significantly because of the availability of functional brain imaging techniques such as cortical evoked potentials, magnetoencephalography, functional magnetic resonance imaging (fMRI), and positron emission tomography (PET).

These functional brain imaging studies have shown that, like somatic sensation, visceral sensation is represented in both the primary (S1) and the secondary somatosensory cortex (S2), and this representation most probably mediates the sensory discriminative aspects of sensation. Furthermore, visceral sensation is also represented in the paralimbic and limbic structures such as the anterior insula, anterior cingulate, and prefrontal cortices.[195 196] These areas are likely to mediate the affective and cognitive components of visceral sensation. Activation of subcortical regions such as the thalamus and periaqueductal grey matter in response to rectal stimulation has also been demonstrated.[196]

4.3.4 Descending and spinal modulation of pain processing

Animal studies have shown that stimulation of the periaqueductal grey matter in the midbrain inhibits behavioural responses to noxious stimulation because of inhibition of spinal neurones.[197] The periaqueductal grey matter receives direct inputs from the hypothalamus and the limbic cortex and controls spinal nociceptive transmission through descending pathways. These selectively target the dorsal horn laminae that house the nociceptive relay neurones. This circuit can therefore selectively modulate nociceptive transmission by its anatomical proximity to central ends of the primary afferent nociceptor terminals and dorsal horn neurones that respond to noxious stimulation.

Furthermore, some neurones in the dorsal horn of the spinal cord are strongly inhibited when a nociceptive stimulus is applied to any part of the body, distinct from their excitatory receptive fields. This phenomenon is termed diffuse noxious inhibitory control (DNIC)[198] and refers to a neurophysiological mechanism that underlies the long established clinical phenomenon of counterirritation, in which application of an acute aversive stimulus provides temporary relief of chronic and recurrent pain.[199] Several animal and human studies have assessed the role of spinal nociceptive processes using DNIC paradigms and have demonstrated hyperexcitability of spinal nociceptive processes in a subgroup of IBS patients associated with failure of descending inhibitory control.[200]

4.3.5 Altered central processing

Brain imaging studies have begun to address the possible neural mechanisms of hypersensitivity in IBS patients, and a common finding has been that, compared with healthy controls, patients with IBS show altered or enhanced activation of regions involved in pain processing, such as the anterior cingulate cortex, thalamus, insula, and prefrontal cortex, in response to experimental rectal pain.[201–203] However, variable activation patterns in IBS patients have been reported, and the role of these functional brain imaging studies is not clearly established in helping us to understand the mechanism of visceral hypersensitivity in IBS patients.[204] The main reason for this is that most of the functional brain imaging techniques used so far in assessing the brain processing of visceral sensation in IBS patients have relied on techniques such as fMRI and PET. These techniques image minute changes in cortical blood flow in response to a stimulus and, because of the very small effects being measured, require group studies to detect significant differences. As visceral hypersensitivity in IBS patients may be caused by a variety of mechanisms, unless the groups under study consist of a very homogeneous population with similar mechanisms, significant differences are hard to detect. In contrast, studies using neurophysiological techniques such as cortical evoked potentials and magnetoencephalography rely on identifying electromagnetic fields generated in response to a peripheral stimulus and can be used to study individual patients. Recently, cortical evoked potentials have been used in non-cardiac chest pain patients and the results suggest that it may be possible to differentiate visceral hypersensitivity caused by sensitisation of afferent nerves from that caused by psychological influences.[205]

4.3.6 Summary

Patients with IBS characteristically complain of abdominal pain. A proportion of these patients display heightened pain sensitivity to experimental gut stimulation (visceral hypersensitivity). Chronic pain in these patients can occur through various central and peripheral mechanisms. The challenge for the future is to be able to differentiate between these mechanisms so that patients can be treated more specifically.

4.4 Stress response

4.4.1 The hypothalamo-pituitary-adrenal axis

The response of an organism to external stressors is mediated through the integration of the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic branch of the autonomic nervous system with the host immune system.[206] A potential novel aetiopathological model for IBS combines the classical observation of high levels of anxiety in IBS patients and the demographic similarity between patients with IBS and other functional disorders (such as fibromyalgia and chronic fatigue syndrome). The model proposes altered central stress circuits, in predisposed individuals, which are triggered by external stressors resulting in the development of gut and extraintestinal symptoms. The HPA axis is part of that circuit: in the hypothalamus, paraventricular nucleus neurones release corticotropin releasing factor (CRF), which stimulates anterior pituitary secretion of adrenocorticotropin hormone (ACTH). This in turn acts on the adrenal medulla, resulting in cortisol secretion into the circulation. Release of CRF is dependent on input from the limbic structures in the brain and from peripheral feedback by ACTH and cortisol. The production and release of CRF is therefore under multiple control systems, reflecting the pluripotent role of this peptide in controlling autonomic, immunological, and emotional responses to stress.[207] Circulating peripheral levels of CRF do not reflect levels released into the hypophyseal circulation, so HPA axis activity is traditionally assessed by ACTH and cortisol measurements.

4.4.2 Neuroimmune interactions

The emerging recognition that a distinct subgroup of IBS patients develops postinfectious IBS has led to the speculation that altered HPA axis activity may be causally involved in generating symptoms. The persistence of chronic inflammatory

mucosal changes and enterochromaffin cell hyperplasia that persists after eradication of the infectious organism[208] are consistent with an inadequate physiological response to acute gut inflammation, in particular an inadequate cortisol or altered sympathetic response. The key interplay between the autonomic nervous system and the HPA axis in regulating gut mucosal immunology has led to a rapidly emerging body of work looking at how the stress response, which activates both these effector systems, may be aetiologically important in IBS. The stress response may thus be of central pathophysiological importance in uniting the sensory, motor, immunological, and possibly even genetic abnormalities that have been observed in IBS. Epidemiological observations have pointed to the importance of environmental stressors both in predisposing towards developing IBS and in perpetuating the symptoms of IBS. Previous life stressors[209–211] and past exposure to childhood abuse[212] predispose to the risk of developing IBS in later life. Psychiatric illness episodes or anxiety-provoking situations preceded the onset of bowel symptoms in two thirds of IBS patients attending outpatients,[213] and IBS patients report significantly more negative life events than matched peptic ulcer patients.[210] Additionally, psychological traits such as hypochondriasis,[214] anxiety, and depression predispose previously healthy individuals who develop gastroenteritis to developing symptoms of IBS.[215]

4.4.3 Abnormalities of emotional motor system

Allied to the evidence from animal experiments, clinical observations, and brain imaging studies, these epidemiological data have led to the development of the notion of a central ''emotional motor system''.[216] The outputs from this system probably involve the HPA, which is the key endocrine stress system in humans.[217 218] The inputs to this system involve both altered visceral sensory input[178 219] and altered visceral perception.[220 221] It is likely that the autonomic nervous system is of prime importance to these input and output circuits, given its neuroanatomical and neurophysiological connections, and there is increasing evidence of autonomic dysfunction in IBS.[144 222 223] In terms of motor change, diarrhoea predominant IBS seems to be associated with sympathetic adrenergic dysfunction while constipation predominant IBS seems to be associated with parasympathetic dysfunction.[224 225] Approximately three quarters of patients report that stress leads to acute abdominal pain and changes in stool pattern.[21] In terms of sensory change, recent evidence has pointed to a dissociation between visceral sensitivity and autonomic function in IBS patients in response to acute physical and psychological stress.[223] This would suggest involvement of a different regulatory mechanism (either central or peripheral) in IBS patients in response to stress. That this mechanism may be endocrine is suggested by the finding that a subgroup of IBS patients has an exaggerated endocrine stress response, as shown by a heightened release of ACTH and cortisol in response to exogenous CRF administration.[217 226] This exaggerated stress HPA response seems to be associated with mucosal immune activation.[226]

4.4.4 Imaging the stress response

An additional way to study the stress response in IBS has been to employ functional brain imaging techniques. The ventral portion of the anterior cingulate cortex and, to a lesser extent, the medial prefrontal cortex have repeatedly been shown to be differentially activated by rectal balloon distension in IBS patients compared with controls.[196] This activation is heightened by acute stress.[227] Taken together with established neuroanatomical knowledge, it has been proposed that the response to acute stress is coordinated by the amygdala, locus coeruleus, and hypothalamus.[228] These structures are closely interconnected and it is suggested that the amygdala processes the emotional component of the response to stress, the locus coeruleus the autonomic response, and the hypothalamus the endocrine response.[227]

4.4.5 Implications for treatment

This ever increasing understanding offers the potential for manipulating the stress response to provide novel treatments for IBS. Potential mechanisms include non-specific approaches, such as with tricyclic antidepressants,[227] or the use of selective compounds, such as the CRF antagonists. The potential for these latter drugs is enormous, given the core role of CRF in modulating the stress response.[229]

4.5 Postinfective IBS

A small subgroup of IBS patients relate the onset of their symptoms to a bout of infectious gastroenteritis and these have proved a useful model in helping to understand other non-postinfectious types of IBS. The prevalence of postinfective IBS varies from 17% in primary care in the United Kingdom to as little as 6% in tertiary care in the USA.[192] Population surveys indicate a relative risk of 11.1[230] to 11.9[231] of developing IBS in the year following a bout of gastroenteritis. Such IBS patients are an attractive group in whom to study the mechanisms underlying IBS as they represent ''nature's experiment'', with less confounding by psychological factors and a clearly defined start date.

4.5.1 Risk factors

Known risk factors in order of importance include the severity of the initial illness, bacterial toxigenicity,[232] female sex, a range of adverse psychological factors including neuroticism, hypochondriasis,[233] anxiety, and depression,[215] and adverse life events[214] (for a review see Spiller[208]). Postinfective IBS has been reported after shigella,[234] salmonella,[235 236] and campylobacter[215] infections and does not appear specific to any particular organism.[237]

4.5.2 Mucosal abnormalities

Histological studies indicate that postinfective IBS is characterised by increased lymphocyte numbers in mucosal biopsies,[215 234] an effect which is seen throughout the colon.[234] Where the terminal ileum has been biopsied, increased mast cells have also been noted.[234] Another change following inflammation is enterochromaffin cell hyperplasia, a feature which, as animal models demonstrate, is dependent on functioning T cells.[238] While in most subjects this change resolves over the ensuing three months, in postinfective IBS levels of both lymphocytes and enteroendocrine cells remain raised.[215] Failure of resolution of inflammation has also been documented in several studies showing persistent elevation of interleukin-1β mRNA expression, implying impairment of downregulation of inflammation.[234 239] Increased enterochromaffin cell numbers are associated with an increase in postprandial 5-HT release, an abnormality shown both in postinfective IBS[240] and in diarrhoea predominant IBS without an obvious postinfective origin.[169] Immediately after gastroenteritis affecting the small bowel there may be transient lactose intolerance which is particularly obvious in young children. However, in adults with postinfective IBS, who by definition have had symptoms for over six months, the incidence of lactose malabsorption is no different from uninfected controls.[241]

4.5.3 Gut permeability

Another abnormality found in most individuals suffering from bacterial gastroenteritis is increased gut permeability.[242]

Moreover, persistently increased gut permeability is seen in those who develop postinfective IBS, as was reported in the Walkerton health study.[243] In that study of 105 new cases of IBS following infection with *E coli* and *Campylobacter jejuni*, a lactulose/mannitol ratio of >0.02 was seen in 35% of IBS cases compared with just 13% of non-IBS controls.[243] This increased permeability, which would allow access of bacterial products to the lamina propria, could be a mechanism for perpetuating chronic inflammation.

4.5.4 Neuroimmune mechanisms

As stress and mucosal abnormalities are known to interact and contribute equally to the development of postinfective IBS,[214 215] it is possible that stress, by activating mast cells, may contribute to persistently increased gut permeability and hence to immune activation. This stress effect has been demonstrated in numerous animal models.[244 245] Recent studies suggest that, regardless of bowel habit subtype, IBS patients may show evidence of an ongoing immune activation.[246] A genetic tendency to underproduce IL-10 might pre-dispose to this, as an abnormally small number of high IL-10 producing genotypes has been reported in IBS[247] (though a recent smaller study has failed to confirm this[248]).

4.6 Bloating

Abdominal bloating is reported by up to 96% of patients with IBS, is more common in female patients, and is often ranked as their most bothersome symptom.[249] However, its presence in other functional disorders—such as functional dyspepsia and chronic constipation, and indeed even in healthy subjects—means that it is not considered a diagnostic criterion but a supportive symptom of IBS.[11] Sufferers typically report a worsening of bloating as the day progresses, particularly after meals, with the symptom usually improving or disappearing overnight, which helps to distinguish if from more sinister causes of abdominal swelling such as ascites or an ovarian cyst.[250 251] This increase in the sensation of bloating may or may not be associated with an increase in abdominal girth (that is, distension), which if present can reach 12 cm.[251] Distension only correlates with bloating in IBS-C patients, who suffer from this more frequently (60%) than those with IBS-D (40%).[251] Men do not appear to complain of bloating or distension as often as women, although this may partly reflect the fact that they often describe the symptom in different language, referring to it as ''tightness'' or ''hardness'' of the abdomen.

4.6.1 Mechanisms

While many patients attribute their bloating to ''trapped wind'', studies have generally failed to show excessive intra-abdominal gas.[249 252–254] Indeed in studies where 10 times the normal amount of gas present in the gut was infused into the intestine, it resulted in less than half the mean increase in abdominal distension seen in IBS (that is, <2 cm).[252] Thus abnormal gas volume cannot be the sole cause of distension and bloating, although there is evidence of impaired gas transit in these patients.[252 255 256] The observation that bloating only strongly correlates with distension in patients with IBS-C[251] suggests that the pathophysiology is likely to be multifactorial and may differ between the bowel habit subtypes. Indeed there is evidence that small bowel transit[257] may be delayed in IBS patients with bloating and subjective reports of distension. This is supported by recent objective measures of girth using the validated technique of abdominal inductance plethysmography,[258 259] which showed that IBS-C patients with delayed large bowel transit distended significantly more than IBS-C patients with normal transit.[260] Using this technique it has also been shown that, compared with healthy subjects, patients with bloating alone have lower sensory thresholds, whereas those with bloating and distension have normal or slightly higher sensory thresholds.[261] Thus bloating alone—which tends to be commoner in IBS-D—may be more of a sensory problem, whereas bloating with distension—which tends to be commoner in IBS-C—may be more of a mechanical problem. However, computed tomography of the abdomen in distended IBS patients has shown that distension is not caused by voluntary protrusion of the abdomen or exaggerated lumbar lordosis.[254] Moreover, electromyographic assessment of the anterior abdominal musculature in distended and healthy subjects revealed no differences.[262] However, rectal infusion of gas was shown to be associated with paradoxical relaxation of the internal oblique muscle in patients with distension compared with an increase seen in healthy volunteers,[263] suggesting an abnormality in an abdominal accommodation reflex irrespective of its strength.

5 CLINICAL HISTORY AND INVESTIGATION

Appropriate management is highly dependent on the information obtained at the time of the initial consultation and in almost all cases the diagnosis of IBS can be made on the basis of clinical history alone, integrating the many features listed below to come to a final conclusion.

5.1 History of symptoms

The patient should be allowed to tell their story in their own words to ensure that they feel the doctor has understood their concerns, as previous consultations may have been unsatisfactory in this respect. The clinician should make an effort to understand the psychosocial factors which might have led the patient to seek help at this particular time. Modern medical education emphasises the benefits of optimal consultation techniques designed to elicit a therapeutic alliance between patient and physician. These include optimal eye contact, body language which conveys empathy, and open ended questioning designed to elicit the patient's ideas and thus ensure their concerns and expectations are met. While much of this is based on cultural expectations, there is some evidence that such practice can reduce reconsultation rates.[264] Approximately half the consulting patients believe they have serious disease such as cancer.[265] Disease or death in close relatives is a frequent cause of health anxieties, and understanding the patient's concerns will make it much easier to reassure them and to achieve a satisfactory consultation. It may then be appropriate to make a more specific inquiry about the chronology of key symptoms and possible precipitating factors such as gastroenteritis.

5.1.1 Features of pain

Key symptoms include the pattern of pain or discomfort, the nature of the associated bowel disturbance, and abnormalities of defecation. Pain relieved by defecation or associated with changes in stool consistency or frequency is usually intestinal in origin. Pain without these associations should lead to careful consideration of other conditions including neoplasms and inflammatory bowel, urogenital, or musculoskeletal diseases.

5.1.2 Constant pain

Constant unrelieved pain may reflect neoplastic pain or be due to functional abdominal pain syndrome.[80] This is a particularly difficult syndrome to manage, commonly associated with complex psychiatric problems including possible personality disorder.

5.1.3 Disordered bowel habit

Clarification of exactly what the patient means by the terms ''diarrhoea'' and ''constipation'' is vital, and the Bristol stool form score is an easy way to do this without misunderstanding.[266] It should be recognised that the patient may experience both loose and hard stools within a short period, and around half fit the category of ''mixed'' bowel habit rather than either ''diarrhoea'' or ''constipation''.[11]

Other features that may trouble the patient are bloating (see 4.6), straining, incomplete evacuation, passage of mucus per rectum, urgency, and sometimes incontinence. In addition to inquiring about individual symptoms, their severity should be ascertained, as different patients rank different symptoms—including extracolonic features—as the most intrusive aspect of their problem. The recognition of the association of extracolonic symptoms with IBS is important as already discussed (see 3.5), as this can avoid unnecessary investigation as well as inappropriate referral to other specialties. Patients are often relieved to know about the association of these features with IBS, as they frequently feel that underlying pathology is being overlooked. Indeed it may be helpful to point out that having multiple somatic complaints makes it more likely that they have a ''functional'' rather than an ''organic'' disorder.

5.2 Psychological factors

Approximately two thirds of IBS patients referred to secondary care show some form of psychological distress, most commonly anxiety. This may not necessarily be easily recognised, as some patients are reluctant to expose their feelings, whereas normal anxiety about unexplained symptoms may be mistakenly judged as abnormal. Hostility may be apparent, particularly in patients who feel dissatisfied with previous consultations with doctors, whom they felt expressed little sympathy. It is vital that any ongoing severe stress, especially of a domestic nature, is identified, as it has been shown this impairs the response to treatment.[77] Multiple unexplained physical symptoms are common in IBS[19] and can be a manifestation of somatisation disorder. This complicates the interpretation of symptoms and response to treatment in IBS (see 5.8.2).

5.3 Family history

It is also important to inquire about a family history of inflammatory bowel disease or colon cancer, particularly below the age of 50, as this will influence patients' concerns and expectations and should correctly lower the threshold for investigation.

5.4 Dietary considerations

Almost all patients with IBS will have tried some form of dietary manipulation and in some instances this can lead to the adoption of bizarre diets that may be nutritionally inadequate. It should be remembered that favourite foods or foods that are taken regularly without the chance of observing the effects of withdrawal are more likely to be causing trouble, so a careful history is worthwhile to identify ingestion of abnormal amounts of fruit, caffeine, dairy products, and dietary fibre, particularly bran. It has been shown that a tendency to an eating disorder is quite common in female IBS patients and the two conditions can therefore exacerbate each other (the role of dietary manipulations is dealt with in section 7.1).

5.5 Precipitating and exacerbating factors

A small proportion of patients, varying from 17% in primary care in the United Kingdom to 6% in a university outpatient clinic in the USA,[192] will date their IBS to an episode of gastroenteritis or ''food poisoning''. Other events that might cause problems, even in normal individuals, tend to cause an exaggerated response in IBS. Thus menstruation or the administration of drugs such as antibiotics,[267] non-steroidal anti-inflammatory drugs (NSAIDs), or statins may exacerbate symptoms. IBS symptoms can also be exacerbated by stress. Smoking or alcohol in moderation do not seem to affect the course of IBS. If an analgesic is required, paracetamol is preferred to opiates or NSAIDs as it is less likely to disturb bowel function.

5.6 Physical examination

Physical examination usually reveals no relevant abnormality. General examination for signs of systemic disease should be followed by abdominal examination. This includes asking the patient to demonstrate the area of pain. Note should be made of whether pain is diffuse (expressed by an outstretched hand) or localised (pointing with a finger). Visceral pain is poorly localised, so pain which is well localised is atypical and should suggest possible alternative diagnoses. Abdominal wall pain originating from hernia, local muscle injury, or trapped nerves can be readily identified by Carnett's test. This involves asking the patient to fold their arms across their chest and raise their head off the pillow against gentle resistance from the physician's hand. Exacerbation of the pain is a positive Carnett's test. A recent study showed that abdominal wall pain is a secure diagnosis which rarely needs to be revised.[268] Pain localised to the rib cage can also be a source of confusion. The painful rib syndrome, characterised by point tenderness and pain on springing the rib cage, has a benign course and its recognition can save much unnecessary and futile testing.[269 270] Examination of the perianal region and rectum will be appropriate in most cases, especially those with diarrhoea, rectal bleeding, or disordered defecation. Those with rectal bleeding or diarrhoea should also have an endoscopic examination to exclude local pathology including colitis, haemorrhoids, or rectal cancer. This can either be a limited sigmoidoscopy in the clinic or as a planned procedure soon after. Those with a family history of colorectal cancer or those over 50 with recent onset of symptoms (less than six months), including a change in bowel habit, should also be considered for colonoscopy (see 5.8.3).

5.7 Alarm features (see box 5)

Rectal bleeding, anaemia, weight loss, nocturnal symptoms, a family history of colon cancer, abnormal physical examination, recent antibiotic use, age of onset more than 50 years, and a short history of symptoms should all lead to careful evaluation before a diagnosis of IBS is made[108 271] because of the possibility of an inflammatory or neoplastic cause. However, it should be recognised that minor bleeding from the anus, usually combined with anal discomfort, is extremely common and should not exclude an IBS diagnosis, even though an examination may be needed to reassure the patient and clinician. The Association of Coloproctologists of Great Britain and Ireland guidelines on management of colorectal cancer recommend that rectal bleeding combined with a change in bowel habit and in the absence of anal symptoms should be fully investigated, as a significant number will have colorectal cancer (www.acpgbi.org.uk/download/GUIDELINES-bowelcancer.pdf). A large recent study in an unselected gastroenterology outpatient clinic in Australia indicated that age over 50 years and rectal bleeding of any type were significantly commoner in those with a final diagnosis of organic disease, and should therefore lead to full evaluation before a final diagnosis of IBS is made (see 5.6).[108]

5.8 Investigations

5.8.1 Initial laboratory investigations

The concept that IBS is a diagnosis of exclusion is no longer tenable and in a straightforward case of IBS in a young person, investigations—particularly those involving irradiation—should be kept to a minimum. The yield in those with established IBS is low but not zero.[272] The patients should be warned therefore from the outset that investigations are likely to be normal, thus avoiding the possibility that negative results will lead to the demand for ever more invasive and unnecessary tests. A full blood count (FBC) should be ordered in all older patients at first presentation, and an FBC plus erythrocyte sedimentation rate (ESR) and C reactive protein in all those with recent onset D-IBS. Endomysial or tissue transglutaminase antibodies show high sensitivity and specificity in distinguishing patients with coeliac disease from healthy controls, but in IBS—where the incidence is low (0–3%)[273 274]—sensitivity is lower at 79%, with a specificity of 98%.[274] However, many clinicians working in areas of high incidence such as the United Kingdom undertake these tests because the diagnosis of coeliac disease radically alters treatment over a lifetime and may otherwise easily be missed. It should be emphasised that this section deals with IBS and not painless diarrhoea, for which there are separate guidelines (see guidelines for the investigation of chronic diarrhoea on the BSG website at http://www.bsg.org.uk).

5.8.2 Psychological investigation

Given the frequency of anxiety and depression it is useful to assess these features objectively. The hospital anxiety and depression scale (HADS) is a simple 14 item questionnaire that can be used even in a busy outpatient clinic to provide an objective measure of anxiety and depression. The 15 item patient health questionnaire (PHQ 15)[275] may also be helpful in difficult cases, as it clearly identifies the presence of multiple somatic symptoms (somatisation) which may otherwise be missed in a busy consultation. While there are no randomised studies showing benefit, there are several studies showing that somatisation is common in IBS outpatients,[276] correlates with impaired quality of life,[276] and predicts dissatisfaction[106] with treatment and increased health care use (see 7.2.2).

5.8.3 Second level investigations including endoscopy and imaging

Second level investigations are based on the likely differential diagnosis (box 6). Given the high frequency of colonic cancer in the population at large, an examination of the colon is advisable for a change in bowel habit over the age of 50 (earlier if there is a first degree relative affected by colorectal cancer when aged less than 45 years, or two affected first degree relatives[277]). As IBS patients have no increased risk of colon cancer, advice on screening for this is no different from the general population.

Patients with IBS-D tend to require more in the way of investigation than IBS-C, because of the overlap with other diarrhoeal diseases including coeliac and inflammatory bowel disease. It needs to be recalled that microscopic colitis now accounts for 20% of unexplained diarrhoea in the over 70s age group in countries where colonoscopy is freely available.[278] Tests for malabsorption or small bowel bacterial overgrowth are not undertaken in straightforward cases of IBS but those with difficult diarrhoea—particularly if associated with defecation which disturbs sleep—may warrant further tests (see guidelines for the investigation of chronic diarrhoea on the BSG website at http://www.bsg.org.uk). Giardiasis should be excluded by stool examination or duodenal biopsy in those with acute onset of diarrhoea as symptoms can be long lasting. Adult acquired lactose intolerance, which can be identified by a lactose breath hydrogen test, can cause IBS-type symptoms and should be considered, especially in racial groups with a high incidence of this feature, which worldwide is the norm rather than the exception.[279] A simple screen for this is to ask the patient to undertake a ''milk challenge'' of one pint of skimmed milk which contains approximately 25 g of lactose. If no symptoms result then lactose intolerance is unlikely. A positive result should be followed by objective confirmation using a formal lactose breath hydrogen test, as the milk challenge lacks specificity. It should be noted that these recommendations are based on expert opinion and experience as there are no published data.

Sudden onset of severe diarrhoea, especially if it is of large volume with nocturnal disturbance, should suggest bile acid malabsorption, which can be diagnosed by the SeCHAT test.[280] It should be noted that only those with severe malabsorption (less than 5% of labelled bile acid retained at seven days) respond predictably to cholestyramine.[281] Constant upper abdominal pain, particularly if it radiates to the back, should lead one to consider pancreatic disease, best investigated by means of abdominal spiral computed tomography. Right upper quadrant pain with biliary features may indicate the need for ultrasound investigation and, rarely, consideration of sphincter of Oddi dysfunction, especially if pain is associated with a rise in liver enzymes or amylase.[282] These investigations should be restricted to those with typical meal provoked symptoms, as IBS patients with asymptomatic gall stones are in danger of being subjected to an unnecessary cholecystectomy without benefit to their pain.

Box 6

Differential diagnosis of diarrhoea predominant irritable bowel syndrome

- Microscopic colitis
- Coeliac disease
- Giardiasis
- Lactose malabsorption
- Tropical sprue
- Small bowel bacterial overgrowth
- Bile salt malabsorption
- Colon cancer

Table 2 Summary of the recommendations for investigating irritable bowel syndrome

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation
• Take a symptom history	Low	Net benefit	Definitive
• Assess psychosocial factors	Low	Net benefit	Definitive
• Physical examination	Low	Net benefit	Definitive
• Check for alarm symptoms	Moderate	Net benefit	Definitive
• Investigations			
FBC	Moderate	Net benefit	Definitive
EMA	Moderate	Trade-offs	Qualified
Lactose breath hydrogen test	Moderate	Net benefit	Qualified
Colonoscopy	Moderate	Trade-offs	Qualified
Abdominal ultrasound	Low	Trade-offs	Qualified

EMA, endomysial antibodies; FBC, full blood count.

5.9 Recommendations

A summary of the recommendations for investigating IBS is given in table 2.

6 DIAGNOSIS AND INITIAL MANAGEMENT OF IBS IN PRIMARY CARE

Adult patients who present to their general practitioner with lower gastrointestinal tract disorders often pose a difficult diagnostic problem. They account for one in 20 of all general practice consultations[19] and yet their symptoms are frequently ill defined. Although functional disorders such as IBS are the most prevalent, the possibility of colorectal cancer or inflammatory bowel disease may create diagnostic uncertainty and reluctance on the part of the doctor to attribute the symptoms to a specific diagnosis.[283]

6.1 Differences between primary and secondary care

Primary care differs from specialist care because the general practitioner's greater familiarity with the patient, and their previous consultations and behaviours, enable current complaints to be seen in context rather than in isolation. Furthermore, it involves the first contact for care of problems and diseases at a stage when they are likely to be poorly differentiated. Lastly, it is characterised by a model of patient care that is longitudinal and comprehensive, and takes account of the biopsychosocial context of the person's problem.

These characteristics become particularly important when considering chronic disorders, such as IBS, where patients place high priority on continuity of care[19] and where the doctor's relationship with the patient can be therapeutic in itself. Time is frequently used as both a diagnostic and a therapeutic tool in primary care.

6.1.1 Diagnosis in primary care

Existing diagnostic criteria for IBS are based on specific symptoms of defined duration and frequency and have been derived from the characteristics of patients in secondary care. Their applicability to clinical practice has been challenged as unnecessarily restrictive,[32] with one study finding that only a minority of those diagnosed with IBS in primary care fulfilled the Rome II criteria.[35] This may be because their restrictive approach is at odds with the diagnostic process used in primary care. Here the diagnosis is based on risk estimations that start from the prevalence of symptoms in primary care, balancing the perceived relative risks of serious (notably cancer) and non-serious disease, and combining this with a limited number of investigations. In this diagnostic process, symptoms, history, psychosocial background, disease patterns, previous disease history, and consultation behaviour play important roles. At the same time, the patient's ideas, concerns (notably about cancer, see 5.1), and expectations are also addressed.

6.1.2 Diagnostic decision making in primary care

GPs (primary care physicians) tend to make a positive diagnosis of IBS when the risk profile for that condition is high, the characteristics of the patient fit the profile for functional disease, and the risk of serious bowel disease is low.[284] This profiling approach to diagnosis is quite distinct from a criterion based approach, though its key features and their relative importance are unknown. Most surveys suggest that similar strategies are used in secondary care, as very few specialists use formal diagnostic criteria for IBS.

6.1.3 Diagnosing IBS in primary care

In a rigorous consensus development exercise using a nominal group technique,[285] European GPs identified alteration in bowel habit and bloating or distension, with symptom-free intervals, as characteristics essential for the diagnosis of IBS.[286] Abdominal pain per se was not an essential characteristic, though participants described as essential a feature of "disordered abdominal sensation", which included pain, discomfort, and annoyance. This reflected differences in expression according to culture and language. Symptom characteristics and interrelationships—such as relief of abdominal pain/discomfort/annoyance with defecation—were considered supportive of the diagnosis. Measures of frequency and persistence of symptoms were considered relevant but without consensus on specific figures.[286]

Consultation style, notably frequent consultation, somatisation, and abnormal illness behaviours in response to stress are key contextual features supporting the diagnosis of IBS in general practice. Inappropriate consultations for minor illness and multiple somatic complaints have been described for IBS by Whitehead and Bosmajian.[287]

Extracolonic symptoms, however, have less prominence in making the diagnosis, and in most instances there was no consensus on their significance among GPs. Apart from being associated with IBS, symptoms such as tiredness, urinary frequency, and backache are commonly encountered in general practice and may be perceived as lacking specificity, while others such as history of abuse lack sensitivity

Mood assessment can be done rapidly using three questions[288] (box 7). In general practice the diagnosis of depression after these three questions have been answered has a sensitivity of 79% and a specificity of 94%.[288]

6.1.4 Investigations in primary care

The consensus group considered only a limited number of investigations to be essential for the diagnosis of IBS. Rectal examination confirms the consistency of the stool and identifies anal conditions and low rectal masses, but has a low sensitivity as a diagnostic test for rectal cancer.[289] A full blood count should be ordered in all older patients at first presentation and an FBC and ESR/CRP in all those with new IBS-D. Faecal occult blood testing cannot be recommended as it lacks the required sensitivity and specificity. The value of serological tests for coeliac disease (endomysial antibodies (EMA) or tissue transglutaminase (TTG) antibodies) in patients with IBS-D depends on the population and is generally considered cost-effective if the incidence of coeliac disease is above 1%.[290] It may therefore be worthwhile in the United Kingdom, where up to 3% of cases of IBS-D in primary care have coeliac disease.[291]

6.1.5 When to refer

Patients with alarm symptoms (see Box 5), those in whom there is genuine uncertainty about the diagnosis, and those whose concerns have not been successfully allayed in their consultations with the GP should be referred for a specialist opinion. Twenty per cent of patients with non-specific abdominal complaints present over a 12 month period were referred to secondary care in one Dutch study.[74]

Box 7

Questions for assessing mood in primary care

- During the past month have you often been bothered by feeling down, depressed, or hopeless?
- During the past month have you often been bothered by little interest or pleasure in doing things?
- Is this something you would like help with?

Table 3 Recommendations for diagnosing irritable bowel syndrome in primary care

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation
• Take a symptom history	Moderate	Net benefit	Definitive
• Assess previous consultations	Low	Net benefit	Definitive
• Screening questions for depression	Good	Net benefit	Definitive
• Assess psychosocial factors	Moderate	Net benefit	Definitive
• Check for alarm symptoms	Moderate	Net benefit	Definitive
• Investigations			
FBC	Moderate	Net benefit	Definitive
EMA/TTG	Good	Trade-offs	Qualified

EMA, endomysial antibodies; FBC, full blood count; TTG, tissue transglutaminase.

6.2 Recommendations

A summary of the recommendations for diagnosing IBS in primary care is given in table 3.

7 TREATMENT OF IBS

Treatments should be safe and proportionate. Safety is a high priority as IBS is non-fatal, though it should be recognised that for some patients symptoms markedly reduce the quality of life. Furthermore, as IBS is very common, cost-effectiveness is also important for health care providers.

7.1 Dietary treatment

7.1.1 Alterations in fibre intake

Fruit and vegetable contain substantial amounts of both soluble (pectins, hemicelluloses) and insoluble (cellulose, lignin) non-starch polysaccharide commonly referred to under the umbrella term ''fibre'', while cereals and especially bran contains mainly insoluble fibre. Although the commonest dietary recommendation made to patients with IBS is to increase the intake of dietary fibre, with particular emphasis on cereal bran, there are few data to support this approach. A survey based on secondary care patients actually suggested that cereal fibre makes the symptoms worse in around 55% of cases, with only 11% reporting any benefit.[292] Other forms of fibre, especially the soluble varieties, were not so detrimental. Psyllium and ispaghula—though they are soluble gum-forming mucilages—are relatively poorly fermented, which may give them unique advantages. These have been demonstrated in RCTs.[293 294] It is also interesting to note that the majority of therapeutic trials examining the effect of fibre in IBS have failed to show much benefit, and have suffered from the flaw that they were not designed to detect a negative effect. A recent systematic review of 17 clinical trials concluded that the benefits of fibre in IBS were marginal and that insoluble fibre can make the condition worse.[294] It is important to point out that none of these studies was undertaken in primary care, where, it could be argued, response to alteration of fibre intake may be more encouraging. It is therefore worthwhile trying a period of cereal fibre exclusion, especially in those patients in whom consumption is excessive. However, if it is felt that fibre supplementation is needed and this cannot be achieved by diet alone, then the soluble varieties (ispaghula, sterculia, or methyl cellulose) are probably the best choice.

7.1.2 Role of food allergy

The symptoms of IBS are often made worse by eating, and this leads many patients to conclude that they are suffering from some form of dietary ''allergy''. There is little evidence to suggest that immediate type IgE mediated reactions are particularly important in IBS as a whole, although in those who suffer from diarrhoea and also exhibit atopy, this mechanism may be more important[295] and oral sodium cromoglycate has been recommended.[296–298] However, it should be noted that the trials that support this—which were completed a decade ago within a single country—did not use the standard randomised placebo controlled design. In clinical practice this treatment is rarely used, indicating that these studies need to be repeated with more rigorous study designs before any definite conclusions can be drawn. There seems little doubt, however, that some patients do show some form of food intolerance, but the mechanisms involved in such reactions are not known. Currently the most robust way of identifying food intolerance is by double blind food challenge, although this is time consuming and labour intensive. In a study involving 21 patients with diarrhoea predominant IBS, it was shown that in approximately 66% of cases food intolerance could be identified by using an exclusion diet followed serial reintroduction of individual foods.[299] In some of these patients the validity of the intolerance was confirmed by a double blind challenge.[299] There has been a systematic review of seven studies attempting to reproduce these results, which showed response rates varying from 15% to 71%, and it was concluded that there is insufficient evidence to recommend this approach routinely.[300] Nevertheless, there is no doubt that some patients do respond to dietary exclusion, and this may be worth trying in the more refractory patients. It is important to realise that dietary exclusion can become problematic if the diet becomes so restricted as to be nutritionally inadequate, so it is best if this process can be supervised by a dietician.

Dietary exclusion would be much easier if there was a simple test that could be used to predict which food, or foods, are likely to be causing problems. A wide variety of food intolerance tests is available ''over the counter'' but none of these has any evidence base and they are therefore of dubious value. However, there is some preliminary evidence that the measurement of circulating IgG antibodies to food may be successfully used as a guide to which foods should be eliminated from the diet in order to improve symptoms.[301–303] Interestingly, the foods identified by using IgG antibodies or an exclusion diet differ somewhat, suggesting that the two approaches might be detecting different mechanisms of intolerance.

7.1.3 Carbohydrate intolerance

This has been extensively investigated in IBS,[304–313] with varying levels of lactose, fructose, and sorbitol intolerance being reported. However, the prevalence of lactose intolerance shows considerable geographical fluctuation, which partly reflects racial differences in the incidence of the mutant gene that causes lactase persistence, which appears to have originated in NW Europe. Thus the incidence of adult hypolactasia is just 10% in people of north western European origin but approximately 40% in those of Mediterranean origin, 60% in Asians, and 90% in Chinese.[279] In addition, in some studies the prevalence of malabsorption of carbohydrates in IBS does not greatly exceed that observed in controls, although their exclusion from the diet undoubtedly benefits some patients. It is also worth remembering that IBS patients often show fat intolerance and it has been shown that lipid can induce greater gas retention[256] and increase visceral hypersensitivity[314] in patients with IBS than in healthy controls.

In the absence of a specific test on which dietary advice can be based, an empirical approach is still necessary. Adjusting the intake of fibre, carbohydrate, and fat is relatively easy before embarking on more complex strategies which involve excluding a wide range of foods and then systematically reintroducing

them one by one until intolerances can be identified.[315] When this has been done, 38–41% showed specific benefit,[315 316] the commonest intolerances being to dairy and wheat products. It should also be remembered that even normal individuals often have one or two foods that ''upset'' them, and IBS subjects are no exception to this rule. When undertaking a trial of dietary manipulation patients should be warned that the effect of this may take a few days to become apparent, because whole gut transit may range from one to five days in normal individuals and possibly much longer when there is constipation. Likewise, responses to offending foods may also be delayed by many hours.

7.1.4 Recommendations

A summary of the recommendations for the dietary treatment of IBS is given in table 4.

7.2 Psychological treatment

7.2.1 Introduction

The role of psychological factors in the onset and progress of irritable bowel syndrome (IBS) is complex, and remains controversial, ranging from subtle modulations of enteric nervous system function and maladaptive behaviour to overt co-morbidity with anxiety, depression, or somatisation disorder. Unsurprisingly a range of psychological approaches to managing IBS has been developed and—because of significant challenges in terms of study design, patient selection, and the interpretation of results—some uncertainty still remains about the roles of psychological therapies in management.

7.2.2 Psychological approach to management

Most patients with IBS are managed in primary care, where the mainstay of treatment is explanation and reassurance in terms understandable to the patient, coupled with sensible advice about lifestyle, including diet and stresses and, when possible, symptom control. A psychological approach to management should be integrated into the first consultation. Eliciting the patient's reason for consulting and their views on the causes of their symptoms is essential. Fears of cancer or other serious illnesses are common, and are important reasons for seeking medical attention.[59] Patients who attribute their symptoms to physical illness rather than to stress are more likely to be referred from primary to secondary care and consult their general practitioner more often.[19 317]

In secondary care the patient who fears serious illness is more likely to be reassured if the doctor has correctly determined, at the first interview, whether the symptoms are attributed to stress or to physical illness.[318] Interestingly, marked fears of serious illness do not appear to be allayed by numerous investigations or consultations, whereas seeing the same doctor at different consultations does seem to be important.[318]

A 30 minute standardised gastroenterology consultation, which includes a positive diagnosis, patient education using a leaflet, and explicit reassurance about the absence of serious illness, may be followed by a reduced number of consultations for gastrointestinal symptoms and less pain.[319] Such management does not, however, appear to be followed by improvement in health related quality of life or reduced anxiety about numerous bodily symptoms.[319] This is important, because when anxiety, depression, or somatisation disorder are present, patients are not reassured by normal investigations,[320] they consult more frequently, and have an impaired quality of life.[321–323] It is important that psychological co-morbidity is detected and effectively treated in IBS, as discussed later.

Table 4 Summary of recommendations for the dietary treatment of irritable bowel syndrome

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation
1. Take a careful dietary history to identify potential causes of symptoms	Very low	Net benefit	Qualified
2. Assess dietary fibre intake and consider recommending an increase or decrease accordingly	Low	Net benefit	Qualified
3. Trial of exclusion of wheat bran or lactose	Low	Trade-offs	Qualified
4. Consider systematic modification of diet to identify intolerances	Low	Trade-offs	Qualified

7.2.3 Evidence for psychological therapies

Two recent systematic reviews of psychological treatment in IBS provide a useful summary of most relevant studies.[324 325] One is guarded in its support for psychological treatments,[324] pointing to major design issues with many trials, including the robustness of the control groups and the blindness of assessments. Eight studies[326–333] were identified as being of acceptable methodological quality in both reviews, and four of these showed a clear benefit to patients in terms of IBS symptoms and included studies of cognitive behavioural therapy (CBT), psychotherapy, and multicomponent behaviour therapy.[307 308 312 333] The second review, adopting careful and innovative methodology to select and analyse the studies, found that psychological treatments were significantly superior to controls in terms of improvement in abdominal pain, bowel dysfunction, depression, and anxiety.[334] The meta-analyses were not entirely satisfactory because two thirds of the trials had been undertaken at the same centre in the USA, at which a waiting list control was used rather than a true attention control. This review concluded that there was overall evidence of efficacy for psychological treatments, with little to choose between the various forms.

Three larger trials employing more rigorous methodology have subsequently been published,[112 335 336] adding further support for the efficacy of CBT and psychotherapy, either alone or in conjunction with antidepressant drug treatment. Interpretation of these trials is made difficult by the fact that they have been conducted in different settings, including the general population,[326] primary care,[112] gastroenterology clinics,[335] and in patients with chronic or treatment resistant IBS.[336] It is likely that patients recruited after failure of short term treatment in primary care[112] have less severe IBS than those recruited from gastroenterology clinics, who have failed to respond to the usual treatments.[336] In spite of this there is some evidence that psychological treatment for different types of somatic complaints (including IBS) is more effective when delivered to patients in tertiary care than in community settings.[337]

7.3.4 The psychological therapies

Anxiety and depression are common in IBS,[105] and patients report a close relation between stress and hassles and their gut symptoms,[338] providing a pragmatic rationale for psychological therapy.

7.3.4.1 Relaxation training

This is useful when stress causes exacerbation of symptoms, which can be relieved by progressive muscle relaxation, biofeedback, and transcendental or yoga meditations,[339 340]

although it is unclear how much of the benefit is the result of the non-specific factor of increased attention from a therapist.[341–343]

7.3.4.2 Cognitive behavioural therapy

CBT is also based on the assumption that IBS symptoms are a response to stressful life events or daily hassles, producing maladaptive behaviour and inappropriate symptom attributions. Treatment involves identifying the triggers for symptom exacerbation, understanding the patient's response to symptoms, and teaching more adaptive ways of responding. The evidence for the efficacy of CBT remains controversial,[112 327 335 344] with the most recent study in primary care—in which CBT was combined with mebeverine—showing symptom improvement at up to three months, and improved work and social adjustment up to one year. A larger study in secondary care found little effect on abdominal pain or IBS-specific quality of life, although satisfaction and global well-being were improved.[335] Both studies suggest that CBT may help patients cope with their symptoms without necessarily abolishing them.

7.3.4.3 Psychodynamic interpersonal therapy

Psychodynamic interpersonal therapy (PIT) attempts to provide the patient with insights into why symptoms developed in the context of difficulties or changes in key relationships. As well as helping the patient understand how emotional state is related to stress, the link between emotions and bowel symptoms may also become clearer.[345] When successful, this treatment may lead to significant life changes as well as to an improvement in emotional state and IBS symptoms.[328 333 345]

Two studies of PIT compared with ''supportive listening'' with the same therapist, showed significant improvements compared with the comparison groups, and a large cost-effectiveness trial has shown that short term PIT is widely acceptable and leads to a significant improvement in health related quality of life and a reduction in health care costs.[336]

Hypnotherapy, which is an important psychological treatment, is described later (7.4).

7.3.5 Choosing patients for psychotherapy

Patients with constant as opposed to intermittent abdominal pain and constipation tend to do poorly with PIT—the large trials of CBT and PIT in secondary care reported no improvement in patients with depression.[323 335] PIT was particularly successful in patients who reported a history of sexual abuse.[336 346] In the primary care CBT trial,[112] a poor response to therapy was found in men who believed in a physical cause for their symptoms. Few data are available, however, to guide the timing of psychological therapies, although the temptation to withhold them for ''refractory'' patients should, perhaps, be tempered by the recognition that they may provide effective alternatives or adjuncts to existing drug treatments, although there are few comparative trials.

The choice of psychological treatment will depend on what type of therapy is available locally and on patient preference. Some patients are very reluctant to accept that psychological therapy is necessary, but may be prepared to take a small dose of an antidepressant to see if it helps the pain or other symptoms. Many more patients are prepared to accept that psychological factors could be important and would prefer a psychological, or ''talking'', therapy to drug treatment. As patients who do not wish to take antidepressants gain no benefit from them.[335 336] it is important to elicit and respect patients' preference for type of treatment.

7.3.6 Recommendations

All approaches to managing IBS should be informed by psychological understanding, recognising that the most important aspect of management is the relation between the patient and the physician. Empathic listening, respecting patients' views of symptom causation, and giving honest, clear explanations of the interplay between psychological and physical symptoms are essential. Conversely, collusion in seeking a physical cause and undertaking endless investigations must be resisted.

Referral for a psychological treatment in primary care should be considered if the patient wishes this or if there are marked anxiety or depressive symptoms. There has recently been a general increase in the availability of ''talking'' therapies in primary care. In secondary care, more specialised psychological treatment, focused on IBS, is preferable if it is available. Gastroenterologists are encouraged to develop close links with a particular psychotherapist or hypnotherapist as this facilitates referral of patients, who may express reservations about such treatments unless they are made to seem part of the entire process and not as a rejection by the gastroenterologist.

A summary of the recommendations for the psychological treatment of IBS is given in table 5.

7.4 Hypnotherapy

7.4.1 Evidence of benefit

The first controlled trial assessing the value of hypnotherapy in IBS patients refractory to other treatments was reported in 1984.[347] In that study hypnotherapy was shown to produce a significantly greater improvement over a three month period than supportive therapy combined with the administration of a placebo drug. Since that time continuing evidence for its value has accrued,[348 349] and there has recently been a systematic review of published reports assessing the efficacy of hypnotherapy in IBS.[350] In the 14 studies identified, of which only six included a control group, 599 patients were treated with hypnotherapy and 100 received some form of control treatment. It was concluded that, according to the clinical psychology division of the American Psychological Association guidelines, hypnotherapy qualified for the highest level of acceptance as being both effective and specific.[350] There is also some preliminary evidence that a home hypnosis programme might be useful, although the response rate is not so high as that in therapist led treatment,[351] and it is therefore probably not suitable for the more severe cases seen in referral centres. One particular advantage of hypnotherapy is that, rather than just relieving a single symptom, it has been shown that it improves many of the features of the condition, including quality of life and psychological status.[111] Furthermore, the beneficial effects appear to be sustained over time, with patients reporting continued relief from symptoms for at least five years.[352]

7.4.2 Mechanisms

There has been some research into establishing how hypnotherapy might mediate its beneficial effects. There is evidence to suggest that in patients with IBS, it normalises visceral sensation,[353] reduces colonic phasic contractions,[354] and reverses the patients' negative thoughts about their condition.[355] As has already been discussed above, the activation of the certain areas of the brain, especially the anterior cingulate cortex, in response to a painful rectal stimulus appears to be exaggerated in IBS compared with controls. It is therefore of interest that hypnotic reduction of somatic pain is associated with a reduction in activation of this particular region,[356] suggesting that hypnotherapy might enable IBS subjects to modify their central response to pain.

Table 5 Summary of recommendations for the psychological treatment of irritable bowel syndrome

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation
• Make a positive diagnosis and provide a clear explanation of the cause and nature of symptoms and an honest appraisal of prognosis and treatment options	Medium	Net benefit	Qualified
Psychological approaches to treatment			
• Relaxation therapy	Moderate	Trade-offs	Qualified
• Patients with moderate anxiety, not amounting to psychiatric disorder, who do not respond satisfactorily to standard treatment may benefit from relaxation therapy	Moderate	Trade-offs	Qualified
• Cognitive behavioural therapy	Moderate	Trade-offs	Qualified
• Psychodynamic interpersonal therapy	Moderate	Trade-offs	Qualified
• Specific psychological treatment for coexisting psychopathology	High	Net benefit	Definitive

7.4.3 Problems with application

Hypnotherapy, like all behavioural treatments, suffers from several disadvantages, especially in terms of its lack of availability and lack of therapists adequately qualified to provide it. It is labour intensive, requiring as many as 12 one-hour sessions of treatment, as well as being extremely operator dependent and therefore subject to variation in the quality of provision. Although most individuals can be hypnotised, for a successful therapeutic application there must be regular practice and commitment on the part of the patient, without which it is likely to fail. The best evidence for effectiveness is in patients refractory to standard treatments, so its efficacy as first line treatment is uncertain. Thus this form of treatment is probably best reserved for the more refractory patients, who could then be treated in a limited number of specialist centres where hypnotherapy can be integrated into an overall care package.[357]

A summary of the recommendations for hypnotherapy in the treatment of IBS is given in table 6.

7.5 Pharmacological treatments for IBS

7.5.1 Overview

Various pharmacological agents have been tried in the management of IBS, but these have proved of limited efficacy for the cardinal symptoms of abdominal pain and bloating. Therapeutic targets for these symptoms have changed over the years, initially focusing on relaxing the smooth muscle of the gut, latterly evolving into attempts to alter gut transit and to modulate the perception of visceral afferent information in the CNS. Treatment of bowel dysfunction is comparatively more straightforward, aimed at accelerating or slowing transit as required. The placebo response of up to 40–50% in IBS trials[358 359] confounds interpretation of many drug studies. Meta-analyses have shown that the placebo response is increased by more frequent dosing and by doctor/patient interactions. Several investigators have pointed out that rather than regarding this as a problem physicians should be harnessing the effect.[360 361]

Table 6 Summary of recommendations for hypnotherapy in the treatment of irritable bowel syndrome

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation
• Hypnotherapy for patients refractory to standard treatment	Moderate	Trade-offs	Qualified
• Hypnotherapy works best for Those without major psychiatric disease	Low	Trade-offs	Qualified

7.5.2 Antispasmodic agents

The rationale for using antispasmodic agents is to attenuate the heightened baseline and postprandial contractility seen in patients with IBS (particularly when diarrhoea predominant).[151] The efficacy of antispasmodic agents has been the subject of several meta-analyses.[362–366] Of the various agents shown to have some efficacy in these studies, only two are licensed in the United Kingdom—mebeverine (135–150 mg three times a day) and hyoscine (10–20 mg four times a day).

Comparisons between these and more recently developed drugs are difficult because at the time when the earlier drugs were developed the trials were much smaller than they are now, and by comparison underpowered. There may also have been a publication bias. A recent meta-analysis[364 366] give an odds ratio for benefit of 2.1 and global improvement of 56% for active drug *vs* 38% for placebo, and a number needed to treat (NNT) of 5.5. Relief of pain was seen in 53% and 41%, respectively, giving an NNT of 8.3. The odds ratio for benefit must be interpreted with caution as in a much larger modern trial of mebeverine *vs* alosetron (see below), alosetron was shown to be more effective than antispasmodic agents, with an odds ratio of benefit of only 1.7,[367] which is not much different from its benefit over placebo in other trials. Furthermore, these drugs do not seem to have any beneficial effect on the symptoms of diarrhoea or constipation.[365] Other antimuscarinic agents licensed in the United Kingdom lack RCT evidence of effectiveness (alverine citrate[368]) or are associated with significant side effects (dicycloverine).[364] Mebeverine is generally well tolerated and can be used on an as required basis (before meals) and hence is sometimes employed when simple reassurance fails to improve symptoms. Other classes of antispasmodic—for example calcium channel blockers[369] and opioid antagonists such as trimebutine[370]—have been shown to produce inconsistent benefit in IBS and have been made available in only a few countries worldwide.

7.5.3 Antidepressants

It is important that patients' preferences are taken into account when deciding whether to recommend antidepressants or psychological treatment, as both require good patient compliance to be effective.

7.5.3.1 Tricyclic antidepressants

The tricyclic antidepressants are drugs with anticholinergic and non-selective serotonin reuptake inhibitor effects. Tricyclic antidepressants are widely used in other specialties for their ability to potentiate analgesics, with NNT ranging from 2.3 to 3.6.[371] The drugs may alter pain perception,[372] especially during acute stress,[227] independent of their antidepressant or anti-anxiety effect (for a review, see Clouse and Lustman[373]). Approximately 10% of IBS patients, usually those with refractory symptoms, are tried on the tricyclic antidepressants.[105]

Several randomised placebo controlled studies have shown that low dose tricyclic agents effectively decrease symptoms. Although a meta-analysis has suggested a beneficial odds ratio of 4.0 compared with placebo, with an NNT of 3,[374] this meta-analysis was strongly influenced by a single trial that appeared to be a clear outlier.[362 375] If that study is excluded then no benefit remains, in keeping with the largest and most recent study in which no benefit was seen when analysed on an intention to treat basis (though benefit was seen in those able to tolerate the drug, with an NNT of 5.2).[335] Five tricyclic agents have been studied formally (amitriptyline, trimipramine, desipramine, clomipramine, and doxepin), in addition to the anti-serotonin agent mianserin. The effect of these agents primarily relates to pain, and it has been suggested that patients with diarrhoea predominant IBS obtain the greatest benefit.[335]

Even with low doses, side effects of constipation, dry mouth, drowsiness, and fatigue occur in over one third of patients treated with tricyclic agents. The number needed to harm with these drugs is 22.[371] These side effects often preclude good compliance, and so it is essential that the prescriber counsels the patient adequately about the potential for developing these problems, in addition to explaining the nature of the drug and the need to try it for at least four weeks (though effects may be seen as soon as one week[335 376]). The hypnotic side effect can be minimised or taken advantage of by night time dosing, and daily administration—starting at a dose of 10 mg for any of the tricyclic antidepressants, with a gradual increase to 25 to 100 mg—has been suggested.[377] The drug should be continued for 6 to 12 months, after which dose tapering may be attempted.[377] It should be noted that IBS patients, who show hypersensitivity to many stimuli, are often hypersensitive to drug side effects. Many practitioners therefore find the lower dose range (initially 10 mg increasing as tolerated up to 30 mg at night) is the most useful.

7.5.3.2 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed and well tolerated in the treatment of anxiety, depression, and somatisation disorders.[378] There have been four randomised controlled trials of SSRIs in IBS, but only one of reasonable size. This large cost-effectiveness trial showed that a standard dose of an SSRI antidepressant leads to a significant improvement in health related quality of life at no extra cost in patients with chronic or treatment resistant IBS.[309] All four studies showed global benefit without significant change in bowel symptoms or pain.[336 379–381] After the trial, patients on SSRIs were more likely to want to continue with the drug (84% *vs* 37% on placebo) so plainly they are providing benefit even if they do not change bowel symptoms. SSRIs have been shown to benefit patients with somatisation,[382] a common feature of more severe IBS. Treatment of this aspect may underlie the global improvement and why patients wish to continue with treatment.

7.5.4 Fibre and laxatives

Constipation is a common complaint in patients with IBS. Fibre supplementation with naturally derived concentrated non-starch polysaccharides such as bran, ispaghula husk, methylcellulose, and sterculia increases faecal mass and may accelerate transit. The odds ratio for benefit in global symptom relief with fibre is 1.33, but although constipation symptoms may improve there is no benefit for abdominal pain.[294] As already mentioned above, overall only 10% of patients are improved by such bulking agents, and insoluble fibre (such as bran) has been shown in randomised placebo controlled trials to have no effect on pain and to exacerbate flatulence and bloating.[383] This is recognised by IBS patients, of whom around half report that bran aggravates their symptoms.[292] Inorganic salts (for example, magnesium salts and polyethylene glycol based laxatives) act as an osmotic laxative and are effective and well tolerated in chronic constipation,[384] though data are lacking in IBS-C. These inorganic salts are preferred to organic alcohols and sugars, which are more expensive and may promote flatulence. One of the few randomised controlled trials in chronic constipation showed that polyethylene glycol was superior in efficacy and tolerability to lactulose, with less flatulence.[384] Stimulant laxatives act erratically and are associated with tachyphylaxis and dependency. Stimulants are therefore generally recommended only for occasional use.

7.5.5 Antidiarrhoeal agents

The opioid analogues loperamide and diphenoxylate stimulate inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and secretion. Loperamide reduces diarrhoea in patients with IBS[385] but has little effect on abdominal pain.[386] No such studies have been undertaken with cophenotrope (diphenoxylate–atropine) but loperamide is preferred as it causes neither confusion nor anticholinergic side effects. Codeine phosphate is also not favoured because of its potential for dependence and its tendency to induce nausea and dysphoria.[387] Loperamide and cophenotrope can be used both as regular medication and also on an as required basis. Tachyphylaxis does not develop with chronic dosing. Loperamide has particular potential value in that it is available in syrup formulation for fine tuning of dose to minimise the adverse effect of constipation.

Bile acid malabsorption has been variably reported in diarrhoea predominant IBS.[388] However, this has to be severe, with less than 5% of bile acid retained at seven days, before a reliable response to treatment can be expected.[281] Such patients made up approximately 10% of Williams' series of unexplained bile acid malabsorbers. Responders are often those with an acute, presumed infective onset[389] and nocturnal diarrhoea.[280 390]

7.5.6 Serotonin receptor agonists/antagonists

Serotonin (5-HT), acting particularly through the 5-HT_3 and 5-HT_4 receptors, plays a significant role in the control of gastrointestinal motility, sensation, and secretion.[391–393] Furthermore, recent observations that plasma 5-HT concentrations are reduced in IBS patients with constipation,[169 240] but raised in those with diarrhoea,[169 394] especially those showing postprandial symptoms,[394] provide further support for its involvement in the motor and sensory dysfunction associated with this condition. Thus there has been considerable interest in these receptors as possible therapeutic targets for IBS, with agonists at the 5-HT_4 receptor predicted to enhance gastrointestinal propulsion (that is, to be prokinetics)[379 395 396] and antagonists at the 5-HT_3 receptor to slow gastrointestinal transit and reduce visceral sensation.[379 397–399]

7.5.6.1 5-HT$_4$ receptor agonists

8Tegaserod is a selective partial agonist at the 5-HT$_4$ receptor, available in the USA since 2002 and in many other countries, though not in Europe, for the treatment of IBS with constipation. Tegaserod has been assessed in multiple, large, and well designed clinical trials[379 395 400 401] and has also been shown to have promotility effects in both the small and the large bowel.[396] A Cochrane review identified seven high quality placebo controlled trials of tegaserod in IBS-C, which included 4040 patients treated for up to a maximum of 20 weeks, and a small study in IBS-D.[401] Again, a small benefit was identified, with a relative risk (RR) of global relief of gut symptoms with tegaserod at 6 mg twice daily of 1.19 (95% confidence interval (CI), 1.09 to 1.29; NNT = 14) and at 2 mg twice daily of 1.15 (1.02 to 1.31; NNT = 20). The most improved symptoms were those related to defecatory frequency. A more recent randomised controlled trial conducted in 2660 female patients, with 1191 entering a repeat treatment phase, showed that global and individual symptoms were significantly improved by tegaserod in both phases (33.7 *vs* 24.2% and 44.9 *vs* 28.7%, respectively).[69] Extended use studies suggest that benefit continues to be experienced (*Am J Gastroenterol* 2006;**101**: 2558–69).

In addition, quality of life was also significantly improved.[69] Other recent studies have similarly shown a positive effect on quality of life,[402 403] and a decrease, although small, in absenteeism from work (2.6%) and activity impairment (5.8%).[404] It should be noted that, as there have been no direct comparisons, it is unknown whether this agent superior to older stimulant laxatives. The commonest side effect of tegaserod 6 mg twice daily is predictably diarrhoea (RR = 2.75 (95% CI, 1.90 to 3.97)), with the number needed to harm = 20.[401] Despite initial good experience concerning safety, the use of tegaserod has recently been restricted owing to concerns about an apparent small excess of cases of myocardial ischaemia and stroke (13 events per 11 614 patients treated) (see www.fda.gov/cder/drug/advisory/tegaserod.htm). Whether this will prove to be a problem with other 5-HT$_4$ agonists under development remains uncertain.

7.5.6.2 5-HT$_3$ receptor antagonists

Alosetron, a selective 5-HT$_3$ receptor antagonist used for the treatment of female IBS patients with diarrhoea, has recently been reapproved by the US Food and Drug Administration after being withdrawn in the USA in 2000 because of side effects of constipation and ischaemic colitis.[405] It is unavailable for use in any country other than the USA. Meta-analyses have shown it to be helpful in women with IBS-D (odds ratio = 2.2 (95% CI, 1.9 to 2.6)),[400 406] being more effective than placebo at inducing adequate relief of abdominal pain and discomfort, and improvement in bowel frequency, consistency, and urgency of bowel movement,[379 400] with NNT = 7.[406] Again extended use studies suggest that the benefit continues as long as the drug is taken.[407]

7.5.6.3 Developmental 5-HT drugs

Cilansetron, another 5-HT$_3$ receptor antagonist for the treatment of IBS-D, has been reported in two RCTs published in abstract form to relieve abdominal pain or discomfort and abnormal bowel habit in both male and female patients at three and six months.[408 409] Renzapride—a mixed 5-HT$_4$ receptor agonist/5-HT$_3$ receptor antagonist—has been shown to accelerate colonic transit in a small, randomised placebo controlled trial for two weeks in patients with IBS-C but to be without effect on symptoms.[410]

7.5.7 Alternative pharmacological strategies

7.5.7.1 Antibiotics and probiotics

Approximately three quarters of IBS patients have been found to have a positive lactulose hydrogen breath test, defined as a double peak in breath hydrogen, the first occurring less than 90 minutes after ingestion, with a rise of more than 20 parts per million.[411] The significance of this is disputed, as double peaks can be seen once lactulose reaches the colon and do not usually represent fermentation within the small bowel.[412] However, the investigators interpreted this finding as suggestive of the presence of small intestinal bacterial overgrowth,[411] providing the rationale for antibiotic treatment. When given a 10 day course of broad spectrum antibiotics (neomycin, ciprofloxacin, metronidazole, or doxycycline), one third of these patients became asymptomatic, at least in the short term.[413] A similar result has been seen in an RCT of rifamixin which showed benefit lasting up to 10 weeks after treatment.[414].

No other group has adopted this treatment, which cannot be recommended until replicated in well designed studies by others. An elemental diet has been shown to normalise the lactulose hydrogen breath test, possibly because of alteration in gut microflora.[415] Again, the durability of this response is unknown.

Probiotics are a more attractive though possibly less effective way of altering bowel flora, and five randomised placebo controlled trials of probiotics have shown benefit for some symptoms, notably bloating and flatulence, using a variety of probiotic agents including *Lactobacillus rhamnosus plantarum* and VSL#3, a mixture of lactobacilli, bifidobacteria, and a streptococcus.[416–420] A more recent study using *Bifidobacterium infantis* suggested benefit and linked this to a downregulation of immune response,[246] but this finding also needs to be replicated. A subsequent larger study[421] has confirmed the benefit of *B infantis*, though problems with formulation mean that further studies are needed before this can be firmly recommended.

7.5.7.2 Miscellaneous agents

An alternative approach to modifying neuroimmunology of the gut is to use an immunosuppressive agent. There has been only one small placebo controlled trial of prednisolone 30 mg which failed to show a beneficial effect after three weeks.[422] Similar disappointing results with leuprolide—a gonadotrophin releasing hormone antagonist that induces a medical menopause—mean that this approach cannot be recommended either.[423]

Three underpowered placebo controlled studies looked at the D2 antagonist domperidone: two found no effect[424 425] but the third reported significant improvement in flatulence, pain, and altered bowel habit compared with placebo.[426]

Herbal preparations have also been the subject of several trials. The plant preparations (STW-5 containing bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, celandine herbs, angelica root, and milk thistle fruit) have been shown to improve overall IBS scores and abdominal pain but it is unclear which is the active ingredient.[427] A longer study of 16 weeks with Chinese herbal preparations reported significant symptom alleviation.[428] Herbal mixtures individualised for each patient by Chinese medical practitioners were compared with a standardised mixture of 20 herbs and found to offer no advantage. As with probiotics, this area of treatment is attractive to patients and needs further studies with well characterised preparations to help elucidate which formulations will benefit which patient groups.

A summary giving details of all the studies cited here is provided in appendix 2, which is available online at the journal website (http://www.gutjnl.com/supplemental).

7.5.8 Sequence of treatments

Given that most treatments benefit only a minority, it will often be logical to try a sequence of treatments, starting with the safest and least expensive drugs. However, the reader should be aware that the sequences shown in table 7 are based on expert opinion only and the effectiveness of such strategies needs to be tested in controlled trials. The evidence for bloating is particularly weak; however, recent studies suggest that it is important to distinguish between the perception of bloating and visible distension. Both symptoms together are associated with constipation and may respond to laxatives.[251] Another approach in non-constipated subjects might be to try reducing dietary fibre, particularly excluding wheat bran. By contrast, bloating without distension may be caused by visceral hypersensitivity[429] for which tricyclic agents may be a more logical treatment. Some probiotics have been shown to benefit bloating, but more experience is needed before definitive recommendations can be made. A summary of the recommendations for the pharmacological treatment of IBS is provided in table 8.

8 TREATMENT IN PRIMARY AND SECONDARY CARE

8.1 Spectrum of severity in primary care

Patients with IBS managed in primary care comprise the entire spectrum, from those with mild or ill defined symptoms to those with severe or persistent problems. In contrast, those referred to a specialist are more likely to be at the more severe end of the spectrum—in terms of both physical symptoms and psychopathology—and primary care management has proved to be difficult or ineffective. In the United Kingdom up to 29% of patients with IBS are referred to a specialist[19] but the majority of these will return to their general practitioners for long term management.

Treatment approaches in primary care are influenced by the awareness that functional diseases present with a variable combination of undifferentiated symptoms, many of which—such as tiredness or backache—are non-gastrointestinal and non-specific. The specialist led diagnostic criteria for IBS, such as the Manning or Rome criteria, are not commonly known or applied in primary care, where the management approach is more likely to reflect the presenting problem. A formal diagnosis of IBS is not necessarily made, even though treatments which are recognised as being associated with IBS might be used.[430] For example, constipation is often diagnosed as a problem in its own right and managed as such rather than identified as a possible symptom of IBS. In contrast, patients with loose motions are more likely to be asked about other symptoms such as bloating and to receive a formal label of IBS. A rigid distinction between the different subtypes of IBS (constipation or diarrhoea predominant or alternating) is often difficult to achieve in practice, and in a large community survey there was a substantial mismatch between categorisation based on the Rome II criteria and the patients' own classification.[38]

Table 7 Suggested sequence of pharmacological treatment for irritable bowel syndrome

Predominant symptom	First line	Second line
Pain	Antispasmodic agents	Tricyclic antidepressives Hypnosis Psychological treatments
Diarrhoea	Loperamide	5-HT_3 antagonist*
Constipation	Ispaghula	5-HT_4 agonist*
Bloating with distension	Dietary manipulation Polyethylene glycols	Probiotics 5-HT_4 agonist*
Bloating without distension	Antispasmodic agents	Probiotics Tricyclics

*No representative of this class of drugs is currently licensed for IBS in Europe but there are other related drugs in development.

8.2 Nature of the relation between the patient and the primary care doctor

Various other factors are specific to primary care, influencing the management and distinguishing it from secondary care. First, patients tend to have a long term, longitudinal consultation pattern with their general practitioners, and time plays an important role in the understanding of the problem by the patient and the evolution of its management. This enables treatment to take place through a series of steps which may be characterised by the use of different treatments or types of management, including drugs and psychological interventions. Second, the recurrent, relapsing, and non-lethal nature of IBS—including a change in the pattern of symptoms to involve other systems[29]—enables both the patient and the clinician to come to terms with the problem using remedies that appear effective. Finally, it is known that only a minority of IBS sufferers consult a doctor. While those doing so probably have more severe symptoms and are seeking an explanation, they do not necessarily want a prescription medication.

8.3 Use of self management

Most patients will have tried various approaches to self management of their IBS. In two large community studies,[29 430] 37% of IBS sufferers had not consulted a health professional at all, 60% had tried an over-the-counter remedy, 47% had altered their diet, and a large number of complementary health carers had been consulted. Substances used included laxatives, supplements, and various ''natural remedies''. A range of self help organisations offers advice and information which may assist patients to manage and come to terms with their condition (for example, the IBS Network, available at www.ibsnetwork.org.uk).

8.4 Prescribed drugs in primary care

Prescribed drugs in primary care do not differ substantially from those in secondary care. Commonly used medicines, irrespective of their actual effectiveness, are the bulking agents (ispaghula), laxatives (osmotic or stimulant), antispasmodics, and antidepressants.[74] With regard to antidepressants, general practitioners have considerable experience in their use because psychological problems are commonly managed in primary care. As general practitioners tend to take a holistic approach they are comfortable with exploring psychological factors associated with IBS; indeed, a consideration of psychological factors is often prominent in making the diagnosis and in influencing treatment.

8.5 Psychological approaches in primary care

Recent research suggests that many IBS patients are not committed to seeking a somatic explanation for their symptoms and they readily accept the possibility of a psychological contribution to their gut problems.[431] Allied with the use of the drug treatment, GPs commonly use counselling and other psychological therapies. Many general practices have in-house counsellors; while these are not trained to deal specifically with IBS, most have strategies for the management of anxiety and somatisation. Research has supported the use of cognitive behaviour therapy.[112] Though this not routinely available in primary care, it can be accessed in some localities without referral to a gastroenterologist. Hypnotherapy for IBS has been shown to be effective in specialist centres (see 7.4) and new data from general practice suggests that this is effective during the first three months, although the effect is less marked after that.[432] A recent report has also highlighted the success of a

Table 8 Summary of recommendations for pharmacological treatment of irritable bowel syndrome

Intervention	Quality of evidence	Benefit/ harm	Strength of recommendation	Comments
Antispasmodics				
Mebeverine	Low	Net benefit	Qualified	
Alverine citrate	Very low	Uncertain trade-offs	Definitive	
Dicyclomine	Very low	Uncertain trade-offs	Definitive	
Fibre supplements				
Ispaghula	High	Net benefit	Definitive	
Bran	High	No net benefit	Definitive	Half are made worse
Opioids				
Loperamide	High	Net benefit	Definitive	Helps diarrhoea but less effect on pain/discomfort
Tricyclic antidepressants				
Desimipramine	Moderate	Trade-offs	Qualified	Ineffective on intention to treat analysis Poorly tolerated at full dose
Amitriptyline Nortriptyline	Low	Trade-offs	Qualified	Poorly tolerated at full dose
SSRIs				Better tolerated than TCAs
Paroxetine	High	Net benefit	Qualified	Global benefit without benefit to specific bowel symptoms
Fluoxetine	High	Net benefit	Qualified	Global benefit
5-HT$_4$ agonists				Prokinetic; benefit IBS-C
Tegaserod	High	Net benefit	Definitive	NNT = 14
5-HT$_3$ antagonists				Antidiarrhoeal; benefit IBS-D
Alosetron	High	Trade-offs	Definitive	NNT = 7 ''Ischaemic'' colitis, 1/700
Probiotics	Moderate	Trade-offs	Qualified	
Antibiotics	Low	Trade-offs	Qualified	Controversial; needs replicating

IBS-C, constipation predominant irritable bowel syndrome; IBS-D, diarrhoea predominant irritable bowel syndrome; NNT, number needed to treat; TCA, tricyclic antidepressant.

patient derived information and explanation booklet in primary care, although this has not been used widely.[433 434]

8.6 Patients' perspective

These guidelines were reviewed by some members of the IBS Network, who created 10 ''top requests'' in answer to the question ''When I visit my health professional about my IBS, I would like them to give me….?

- A clear knowledgeable explanation of what IBS is.
- A statement that there is no miracle cure.
- A clear indication that it is my body, my illness, and that it is up to me to take control.
- A clear explanation that there will be good days and bad days, but that there will be light at the end of the tunnel.
- An explanation of the different treatment options.
- Recognition that IBS is an illness.
- Consider and discuss complementary/alternative therapies.
- Offer at least one complementary/alternative therapy.
- Offer support and understanding.
- Be aware of conflicting emotions in someone who is newly diagnosed.

9 APPLICABILITY OF GUIDELINES

These guidelines are relevant to adult patients with IBS in both primary and secondary care.

9.1 Organisational barriers in implementing the recommendations

9.1.1 Consultation time

IBS is a complicated condition which requires identification of important psychosocial factors for optimal management. Such patients often need longer consultations than normal in order to determine the role of psychological and social factors in exacerbating the symptoms and to offer the full explanation and reassurance that may be required. This is likely to prove a problem within fixed timed appointments. Dedicated longer time slots may be an appropriate way to manage the disorder rather than repeated brief consultations—often with different doctors—which usually lead to numerous negative investigations, more frequent attendances, and a poorer long term outcome.

Educational booklets should be freely available, but patients may need the opportunity to discuss their concerns again once they have read such material. A suitably trained specialist nurse may be best suited to this task, but may not be available in many centres.

9.1.2 Provision of hypnotherapy, cognitive behavioural therapy, or other psychological treatments

This is limited by lack of trained practitioners and the reluctance of some providers to budget for it.

9.1.3 Availability of certain drugs

Some drugs which are of proven benefit have not been licensed in the United Kingdom and at present patients are left to try to obtain drugs themselves over the internet at their own expense.

9.1.4 Training in functional gastrointestinal diseases

Lack of adequate training leaves some gastroenterologists feeling uncomfortable managing such patients. Most primary care physicians are not aware of diagnostic criteria for IBS and about one third of secondary care doctors do not use them in practice.[261] Recent advances in knowledge and treatments mean that much needs to be done during training to ensure that best practice becomes the norm. Trainee or practising gastroenterologists and associated staff (for example, specialist nurses or other therapists) may require further training in the techniques of consultation suitable for IBS patients. The training of general practitioners usually includes generic consultation skills, but training in more specialised techniques of reassurance, explanation, and exploration of psychological factors in patients who prefer to speak of bodily symptoms may be helpful.

9.2 Costs of applying the recommendations

Costs of any condition and the cost–benefit ratio depend critically on whether indirect costs are included. Currently available drugs are cheap, though consultation time is not. Indirect costs can, however, be much greater.[435] These derive from time lost from work, which is increased by 21%,[3] and costs of investigations and procedures which were increased by 69% in one study.[3 436] These costs were based on the average IBS patient, but costs for the more severely affected cases can be much greater.[322] Annual total costs (health care and loss of productivity) are approximately £1000 in patients with severe IBS which has not responded to usual treatment, but this is nearly doubled in those patients who also have a depressive or panic disorder.[323] Both psychotherapy and an SSRI have been shown to improve health related quality of life in these patients at no extra cost.[336] Psychotherapy, but not antidepressant use, has been shown to reduce the direct health care costs significantly in patients with severe and persistent IBS, and psychotherapy appears also to reduce the chances of patients being on disability benefits.[336] However, local health authorities are unlikely to see the wider picture and will focus on costs generated within their own budget, namely the costs of investigations and prescribing. There is evidence that IBS patients undergo more unnecessary surgery[18 437] and consult more frequently than the normal population.[438] Whether optimum management will be able to show reduction in consultation rates and procedures is a question that requires urgent study.

Increased consultation time costs money but may be cost-effective if it saves further investigations and unnecessary operations. However, demonstrating that this is the case requires further cost-effectiveness studies. Better training in managing functional gastrointestinal diseases may involve some reorganisation of training programmes but should not be expected to incur much extra cost.

9.3 Criteria for audit

Suggested criteria for audit are as follows: improvement in patient satisfaction with management in primary care after initial diagnosis (demonstrating this would require systematic patient surveys using validated questionnaires); improvement in patient understanding of their disorder; increase in confidence of gastroenterologists in dealing with IBS; increase in the proportion of referrals to secondary care which meet these guidelines; reduction in the number of negative investigations initiated in primary care after initial diagnosis of IBS has been confirmed in secondary care; reduction in number of elective cholecystectomies in IBS patients in whom no gall stones are found; and reduction in number of acute appendectomies with normal appendices in patients subsequently diagnosed as IBS.

10 SUGGESTIONS FOR FURTHER RESEARCH

As brief perusal of our recommendations will show much of the available evidence is poor. Major limitations include small patient numbers and lack of adequate characterisation in terms of the variables known to affect outcomes, particularly psychological factors. There is therefore an urgent need for better research in many areas. The following list provides some examples:

- Large community based follow up studies to enable a better definition of the natural history, in particular its relation to life events.
- Improved ability to recognise food intolerances and response to food challenge using objective measures including genetic, blood, urine, and stool tests.
- Large high quality randomised controlled trials of dietary manipulation in hospital-naive patients.
- Studies of mechanisms underlying gut sensory, motor, and reflex changes in response to stress to identify potential novel pharmacological targets.
- Improvement in behavioural assessment of visceral sensation, to move from current subjective measures to a combination of behavioural assessments, with objective measures such as cortical evoked potentials and autonomic function tests.
- PET studies using ligands for various receptors known to be relevant in visceral pain may be helpful in understanding the neuropharmacology of visceral pain.
- Large high quality randomised, double blind, placebo controlled trials to evaluate psychological therapies.
- Large community based clinical trials comparing tricyclic antidepressants with SSRIs.
- Mechanistic studies to define putative mechanisms and hence possible targets for treatment.
- Community studies of behavioural interventions, including patient education and empowerment, should be further evaluated for cost-benefit.
- Long term intervention studies are needed to determine whether changes in management can reduce excess surgery rates associated with IBS.

A summary form of this document and appendixes 1 and 2 are available on the journal website (http//www.gutjnl.com/supplemental).

Authors' affiliations
R Spiller, Wolfson Digestive Diseases Centre, University of Nottingham, Nottingham, UK
Q Aziz, Department of Gastroenterology, St Barts and Royal London Hospital, London, UK
F Creed, University Department of Psychiatry, Manchester Royal Infirmary, Manchester, UK
A Emmanuel, Digestive Disorders Institute, University College Hospital, London, UK
L Houghton, Neurogastroenterology Unit, Wythenshawe Hospital, Manchester, UK
P Hungin, Centre for Integrated Research, University of Durham, Durham, UK
R Jones, Department of General Practice and Primary Care, Kings College London, London, UK
D Kumar, Department of Surgery, St George's Hospital, Tooting, London, UK
G Rubin, University of Sunderland, Sunderland, UK
N Trudgill, Sandwell General Hospital, West Bromwich, UK
P Whorwell, University Hospital of South Manchester, Manchester, UK

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