

# Irritable bowel syndrome

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Irritable bowel syndrome (IBS) is one of the most common 'functional' gastrointestinal disorders accounting for 3% of all primary care consultations, with a strong female predominance. Although most of the literature comes from Western industrialized societies, when it has been looked for, this disorder appears to be equally common in the Third World. It is characterized by chronic abdominal pain or discomfort associated with disordered bowel habit and visceral hypersensitivity. Anxiety and somatization are more common in IBS than in the general population and may encourage consultation; however, they correlate poorly with symptoms. Bacterial gastroenteritis may be followed by the development of IBS in 5–10% of patients, depending on the severity of initial illness and prior anxiety or depression. The Rome criteria allow reliable diagnosis provided that there are no 'alarm' features which mandate further investigation. Microscopic colitis and bile salt malabsorption can easily be mistaken for IBS, as can chronic infestations or infections which should be considered, while recognizing that these are extremely uncommon in westernized societies. Some patients respond to exclusion diets as lactose and wheat intolerance are common. Others with prominent anxiety and/or depression respond to psychotherapy or antidepressants. Diarrhoeal symptoms respond to loperamide and 5HT<sub>3</sub> receptor antagonists, while constipation responds to 5HT<sub>4</sub> agonists. Antispasmodics may have limited benefit in treating pain. Low-dose tricyclic antidepressants are also helpful in alleviating pain and anxiety, even in those without obvious psychiatric disorders. If diagnostic criteria are met, then once diagnosed, new diagnoses rarely appear.

## Definition

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As ideas about the cause of irritable bowel syndrome (IBS) have changed over the years, so its name has varied from 'nervous colitis' to 'mucous colitis' or 'spastic colon', to name but a few. IBS is the most common of the 'functional gastrointestinal disorders', so-called because it was believed that most of the symptoms originated in the central nervous system. A more sophisticated analysis shows that patients with IBS have disorders both peripherally in the gut and centrally in the brain, and symptoms arise because of an interaction between the two. At present,

**Table 1** Rome II Diagnostic Criteria for IBS<sup>1</sup>

At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

1. Relieved with defecation and/or
2. Onset associated with a change in frequency of stool and/or
3. Onset associated with a change in form/appearance of stool

in the absence of objective markers, the diagnosis is established by means of symptom-based criteria. Over the last 15 years these have been systematized by a number of working committees who have attempted to generate criteria with the aim of facilitating comparison between various treatments and investigations carried out throughout the world (see <http://www.romecriteria.org/rome12biblio.html>). The current Rome II criteria are shown in Table 1. These criteria are constantly evolving and a new set of definitions (the Rome III criteria) is due to be published in 2006.

## Clinical features

The main features are recurrent abdominal pain and/or discomfort, whose clear relationship to changes in stool frequency or consistency and its relief by defecation implies that they originate in the colon. This relationship distinguishes abdominal pain due to colonic dysfunction from that due to gynaecological, urinary or musculoskeletal disorders. However, relief by defecation is not always uniform. Although not in the criteria, the pain is frequently stimulated by eating,<sup>2</sup> probably because this induces colonic contractions (the gastrocolonic response to feeding). In addition to these gastrointestinal (GI) symptoms, patients commonly report non-GI symptoms of lassitude, headache, backache, dysmenorrhoea, and dyspareunia.<sup>3</sup> Symptoms characteristically wax and wane. Patients typically have pain a median of 3 days a week, usually in clusters.<sup>4</sup> Patient recall is notoriously unreliable and a patient diary is helpful in order to obtain a more objective measure of the severity of the symptoms. A simple and informative diary used by the author to document patient symptoms is shown in Figure 1

## Epidemiology

This condition is ubiquitous and has been found in every country in which it has been sought<sup>5,6</sup>. The balance of diarrhoea versus constipation as the main symptom varies in a somewhat unpredictable way, with constipation predominating in rural Bangladesh<sup>7</sup> and Singapore,<sup>8</sup> while

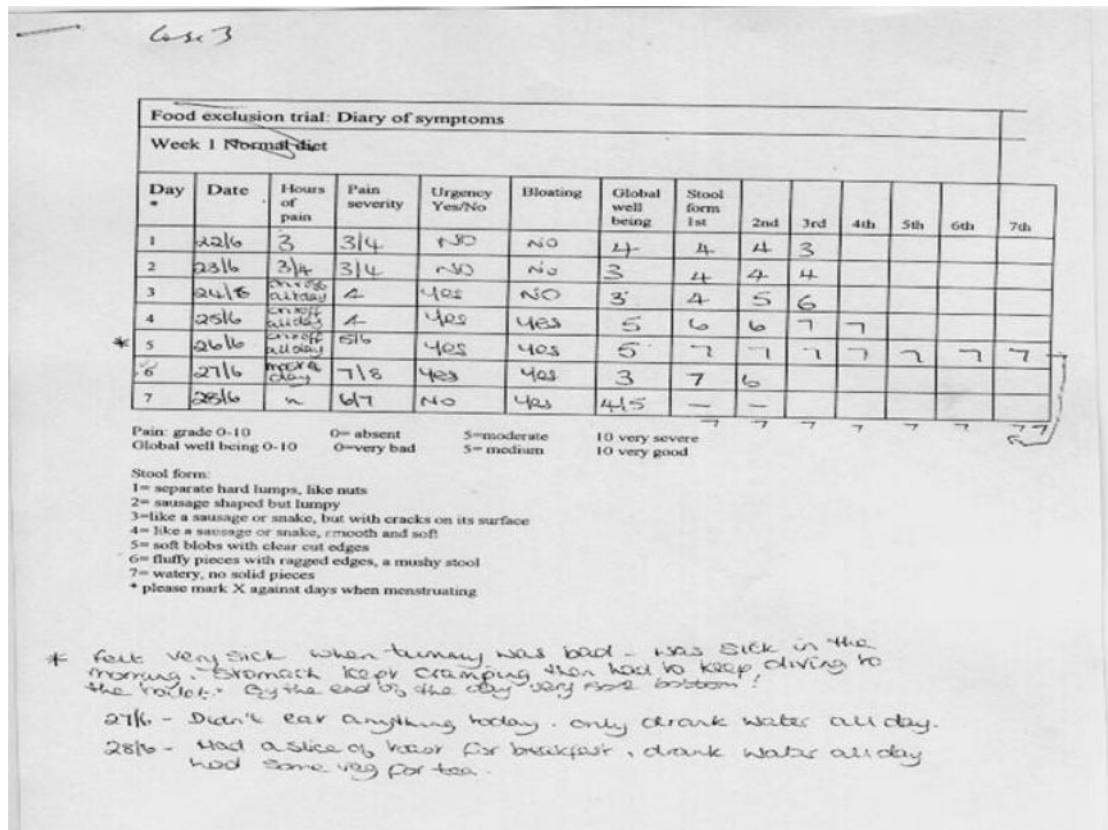
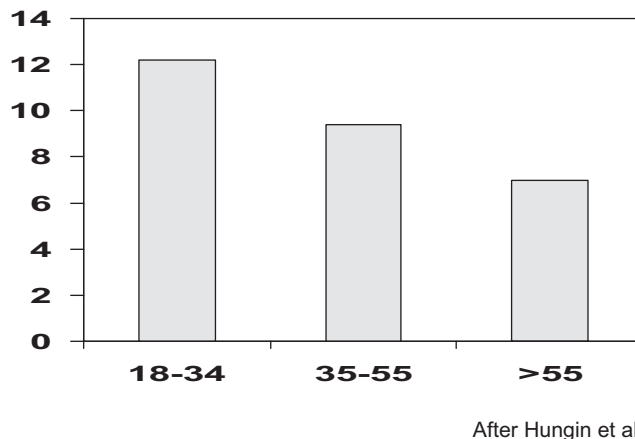


Fig. 1 Symptom diary of patient with D-IBS. Note the fluctuating and socially disabling symptoms. The handwriting says: 'felt very sick ... did not eat anything all day...'

diarrhoea predominates in Southern India<sup>9</sup> and Guangzhou City, China.<sup>10</sup> The precise incidence depends very considerably on the wording of the questionnaire used but averages around 5–10%. Abdominal pain itself is extremely common (approximately two-thirds of the population admit to some pain in any one year), although if one restricts it to pain occurring at least weekly the frequency drops considerably, and if one insists that it is associated with abnormal bowel habit, the frequency falls to 5–10%. Few studies have assessed the incidence of new diagnoses; one large UK survey of over 580 000 general practice records reported this to be around four cases per 1000 patients per year.<sup>11</sup> This study, which examined age, sex, socioeconomic status and the occurrence of bacterial infection, found that the only significant predictor was a bacterial infection in the previous year. The relative risk of developing IBS within the following year was approximately 11 times greater than for those with no infection. Once acquired, the illness appears to be long



**Fig. 2** Percentage of population reporting symptoms of IBS in a telephone survey of eight European countries. Reproduced from A. P. Hungin *et al. Aliment Pharmacol Ther* 2003; **17**: 643–50.

lasting, since the prevalence is around 20 times the incidence. The syndrome is most common in the age group 18–34 years (Fig. 2).<sup>4</sup>

## Genetic influences

Although IBS clusters in families, part of this may be due to learnt illness behaviour. Levy *et al.*<sup>12</sup> reported that rewarding childhood illness was associated with increased frequency of IBS in adulthood. However, twin studies suggest a concordance of functional bowel disease in 33% of monozygotic twins compared with just 13% of dizygotic twins, implying that genetic factors are important.<sup>13</sup> With such a poorly defined phenotype there are problems with bias in case ascertainment, which may exaggerate the apparent inheritability. One study suggests that a genetic tendency to underproduce the anti-inflammatory cytokine interleukin 10 may be more common in IBS,<sup>14</sup> and more recently the *ss* polymorphism in the serotonin transporter promoter region, which leads to reduced expression of the transporter, has been found to be more common in diarrhoea-predominant IBS.<sup>15</sup>

## Consulting behaviour

IBS accounts for 3% of all general practitioner consultations.<sup>16</sup> Reported severity of pain appears to be the main predictor of consultation. The role of anxiety is slightly controversial, with some, but not all, studies indicating that those that are more anxious are more likely to consult.<sup>17</sup>

Predictors of referral from primary to secondary care have been looked at in some detail. Again, severity of symptoms is important, as is failure of reassurance by the general practitioner and belief that the disease is something serious.<sup>16</sup> More recent work has emphasized that lack of a medical confidant with whom to discuss one's symptoms is a strong factor increasing consultation in functional GI disorders.<sup>18</sup>

## Association with psychiatric diseases

IBS patients, in common with other sufferers from functional GI disorders, are more anxious than healthy controls, showing greater anxiety and depression.<sup>19</sup> They also show a greater lifetime incidence of treatment for anxiety and depression.<sup>20</sup> This excess of psychiatric disease is more marked in those in tertiary care centres than in those in the community. However, increased levels of anxiety are features of all patients consulting, regardless of the nature of their disease, and are a general feature of patient behaviour. Anxiety should not influence one's work-up of a patient, since it does not help significantly in making the diagnosis;<sup>21</sup> however, it should and does influence management once the diagnosis has been established.

## Aetiology

### Stress

Many patients believe that stress induces symptoms. As already indicated, IBS is associated with an increased incidence of psychiatric disease. However, it has proved difficult to document a relationship between stress and abdominal symptoms on a daily basis. Only a small proportion of the variance in symptoms is accounted for by stress.<sup>22</sup> In animal studies stress readily induces diarrhoea and alterations in gastric emptying, but it is uncertain how well these animal models of extreme stress model the chronic 'daily hassles' of normal life. Certainly, chronic stressful disorders impair the resolution of symptoms, and in most patients recovery is delayed until chronic ongoing difficulties are resolved.<sup>23</sup>

### Infection

Bacterial infection has recently been recognized as an important cause of IBS. Infections such as *Campylobacter jejuni*, *Salmonella enteritidis* and *Shigella flexneri* produce diarrhoea and abdominal pain which usually

resolves rapidly. However, a small percentage of patients go on to develop chronic IBS symptoms, as documented in several studies. Patients with post-infectious IBS account for 6–17% of the IBS population,<sup>24</sup> and typically have the diarrhoea-predominant subtype (D-IBS). Compared with patients with other types of IBS, they are less likely to have a history of psychiatric disease requiring treatment<sup>25</sup> and have a better prognosis. Several studies have demonstrated evidence of ongoing low-grade inflammation, with increased numbers of T lymphocytes and serotonin-containing enterochromaffin cells and the production of interleukin-1 $\beta$ , a pro-inflammatory cytokine<sup>26,27</sup> (reviewed by Spiller<sup>28</sup>). Patients with IBS of both the diarrhoeal and constipated subtypes have been reported to have increased numbers of mast cells in the descending colon.<sup>29</sup> The origin of this increase in mast cells is uncertain, but the inflammatory mediators they release, including prostaglandins, substance P and serotonin, could contribute to both abdominal pain and abnormal bowel habit.

### *Visceral hypersensitivity*

Visceral hypersensitivity is a feature in the majority of IBS patients and has been extensively studied using rectal distension, a safe way of inducing abdominal discomfort in such patients. How closely it mimics IBS pain is unknown, since in many cases the pain may well arise because of strong contractions rather than excessive distension. This hypersensitivity is most clearly seen when the patient knows that the distensions will continue to increase until they say that they experience pain. However, when the stimuli are unpredictable, the ability of patients to detect distension does not appear to be better than that of normal subjects, suggesting that most hypersensitivity is due to a ‘response bias’, i.e. a tendency to use pain to describe a lesser sensation than that described by normal subjects.<sup>30</sup> This may reflect a conditioned fear of gut stimuli based on previous experience. Recent studies have used functional brain imaging to show increased response to both actual and sham rectal distension in the anterior cingulate cortex,<sup>31</sup> an area where the emotional response to afferent signals is registered. Afferent signalling of pain is modulated by descending antinociceptive pathways.<sup>32</sup> There is also preliminary evidence that activation of the periaqueductal grey area, where descending antinociceptive pathways may originate, is defective in IBS.<sup>31</sup>

### *Differential diagnosis*

Patients in North America meeting the Rome I criteria without alarm symptoms (Table 2) may confidently be diagnosed as having IBS without

**Table 2** Alarm symptoms requiring further investigations

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1. Relevant abnormalities on physical examination
  2. Documented weight loss
  3. Nocturnal symptoms
  4. Blood mixed in stools
  5. History of antibiotic use
  6. Family history of colon cancer
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further investigation.<sup>33</sup> However, whether such a confident diagnosis could be made in other parts of the world remains to be proved.

Obviously any of the alarm symptoms listed in Table 2 mandate further investigation. A further set of patients will require investigating because they have atypical symptoms and do not precisely satisfy the Rome criteria. When the predominant symptom is constipation and the patient is a young female, no further investigations are usually warranted. However, colonic imaging is usually indicated in those aged >50 years whose bowel habit has changed significantly because of the increased risk of colon cancer in this age group. However, when diarrhoea is the predominant symptom, the differential diagnosis is much wider (Table 3).

Lactose intolerance can cause abdominal pain, bloating and diarrhoea. The incidence of lactose intolerance varies widely by racial groupings and geographical area, being ~90% in Chinese, ~60% in Africans, ~40% in Asians and ~10% in Northwest Europeans. Response to 50 g of lactose is usually diagnostic when combined with breath hydrogen measurements to detect malabsorbed lactose entering the colon.<sup>34</sup>

Acute onset of such symptoms should suggest the possibility of infection such as giardiasis. This ubiquitous protozoan is found in groundwater throughout the world and infection is common in travellers or campers. Stool microscopy for ova is diagnostic in only 50% of patients, and duodenal biopsy or microscopy of duodenal mucus is required for the remainder<sup>35</sup>

Studies in both North and South America found relatively few positive stool cultures (2%) in patients being considered for entry into a clinical trial for IBS.<sup>36</sup> One would predict that stool cultures would have a

**Table 3** Differential diagnosis of diarrhoea-predominant IBS

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1. Lactose intolerance
  2. Giardiasis
  3. Tropical sprue
  4. Parasitic infections
  5. Crohn's ileocolitis
  6. Coeliac disease
  7. Microscopic colitis
  8. Bile salt malabsorption
  9. Food allergy
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higher yield in areas where worm infestations are common,<sup>37</sup> and most practitioners in such environments will have tried a course of anti-helminthics before considering a diagnosis of IBS, although regrettably there are few published papers addressing this issue. One report suggests that many patients treated with the presumptive diagnosis of chronic amoebiasis have IBS and the amoebae seen in their stools are coincidental to their symptoms.<sup>38</sup> The authors supported this contention by showing no difference in colonic histology or symptoms between those with or without cysts in their stool.

Tropical sprue,<sup>39</sup> a chronic diarrhoeal syndrome, is the most common cause of chronic malabsorption in many parts of the world.<sup>40</sup> It should be suspected if patients present with anaemia, but can only be diagnosed by means of a small bowel biopsy showing patchy partial villous atrophy with increase intra-epithelial lymphocytes.<sup>41</sup> Minor abnormalities with villous shortening can be seen in apparently healthy individuals with no evidence of malabsorption who have spent their childhood in tropical countries, and so exposure to recurrent GI infection in childhood plainly leaves its mark.<sup>42</sup>

Subtle forms of inflammatory bowel disease, including small bowel Crohn's disease, microscopic colitis and coeliac disease, all need serious consideration. Furthermore, bile acid malabsorption (BAM) should also be considered, especially if there is nocturnal diarrhoea which is typical of such cases. Diagnosing BAM is important, since the diarrhoea responds well to bile salt binding agents such as cholestyramine.

Food allergy sufferers who develop urticaria after ingesting certain foods such as strawberries or shellfish rarely see gastroenterologists and hence are not misdiagnosed. However, there may be some with a more muted form of allergy without skin manifestations who may be identified by exclusion diets (see below).

Screening investigations for those with diarrhoea will typically include a full blood count, erythrocyte sedimentation rate, serum ferritin and vitamin B<sub>12</sub>, together with calcium and albumin and endomysial antibodies to exclude coeliac disease. Stool microscopy may diagnose chronic infections such as giardiasis and worm infestations, although these are usually uncommon in the IBS population. In the elderly, colonoscopy is mandatory to exclude microscopic colitis, which is common and can account for up to 20% of unexplained diarrhoea in patients aged >70 years.<sup>43</sup>

## Treatments

Treatments can be divided into dietary and lifestyle modifications, psychological treatments and drug therapy.



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### *Dietary and lifestyle modifications*

A careful dietary history may reveal a diet inadequate in 'fibre', more accurately termed non-starch polysaccharide (NSP), which includes gels as well as fibrous material. Increasing dietary 'fibre' intake may cure constipation, but many patients will try this first and so doctors generally see those who have failed to respond to such treatment. Alternatively, and perhaps more commonly, there is an excessive intake of NSP or unabsorbable mono-, di- and tetrasaccharides, such as sorbitol, mannitol (found in fruits and chewing gum), lactose (found in milk, chocolate, cream, cheese and yoghurt) and scodarose (found in onions), which can all cause diarrhoea, abdominal pain and excessive flatulence. Excessive consumption of caffeine-containing drinks may also be responsible for diarrhoea through their direct stimulatory effect on the colon. Wheat fibre (bran) is one of the most effective dietary laxatives, and excessive amounts of wholemeal bread or wholemeal cereals may be responsible for diarrhoea. Other common offending items include citrus fruit, onions and nuts. Where a systematic approach has been tried, approximately half of all IBS patients can be shown to respond to a diet excluding certain foods, the benefits of which last for >1 year.<sup>44</sup> For those who fail diet therapy other treatments should be considered.

### *Psychological treatments*

Hypnotherapy and relaxation therapy have been shown to be effective in randomized control trials. Hypnotherapy in particular has been shown to produce a long-lasting benefit.<sup>45</sup> Psychotherapy may also benefit those with chronic disabling symptoms who are resistant to conventional treatment.<sup>46</sup>

### *Pharmacological treatments*

Although meta-analyses indicate that a range of treatments can be effective, none are highly so and the number needed to treat ranges from 4 to 14. Most agents are directed at altering bowel habit, while only a few are directed at the primary symptom of pain.

#### **Loperamide**

This  $\mu$ -opioid agonist, which does not cross the blood-brain barrier, is generally well tolerated without the sedative or nauseating effects of codeine. It is extremely effective in controlling excessive bowel frequency<sup>47</sup> but less so in reducing abdominal pain, and may aggravate bloating. Treatment should be started at 2 mg per day, increasing to a maximum of 16 mg daily. Care should be avoided to induce severe

constipation which may aggravate abdominal pain and, by causing ‘constipation with overflow’, may paradoxically aggravate some symptoms such as urgency and loose stools.

### **Antispasmodics**

These drugs, which inhibit smooth muscle contractions, were mostly developed in an era with much less rigorous regulatory requirements, and so the pivotal trials were small and of poor quality. However, two recent meta-analyses conclude that they do have a beneficial effect on abdominal pain.<sup>48,49</sup> The average difference from placebo was 18%, giving a number needed to treat (NNT) of 5.5 (3.5–14).<sup>49</sup>

### **Bulking agents**

Many patients with constipation will have been tried on fibre supplements or high-fibre diets. Although effective for painless constipation, high-fibre diets, especially those relying on bran, are rather poorly tolerated in IBS,<sup>50</sup> and in randomized controlled trials bran actually worsened symptoms of bloating and flatulence<sup>51</sup>. Ispaghula, derived from the husk of the cluster bean, is better tolerated and has shown benefit in randomized placebo controlled trials in patients with constipation-predominant IBS<sup>52</sup> with an NNT of 3.4. However, several other trials have shown no benefit on pain or bloating, the only consistent effect being to increase stool bulk. A recent meta-analysis concluded that the benefits of bulking agents were unproven.<sup>48</sup>

### **Tricyclic antidepressants**

Tricyclic antidepressants are widely used as an analgesic in a range of painful somatic disorders,<sup>53</sup> including chronic back pain and trigeminal and diabetic neuralgias, often in combination with other drugs. In low doses they are also successful in treating IBS although there are few controlled trials. Meta-analysis indicates an NNT of just 4.2.<sup>54</sup> The most recent trial,<sup>55</sup> which was performed to modern standards, showed no benefit on an intention to treat analysis (responder rate 60% with desimipramine 50–150 mg/day versus 47% on placebo), largely because so many participants dropped out because they were unable to tolerate the side effects. Those who could tolerate the treatment showed a benefit with a responder rate of 73% versus 49% for placebo, giving an NNT of 5.2. The analgesic properties may relate to enhancement of descending antinociceptive pathways. Selective serotonin-reuptake inhibitors (SSRIs) may also be effective in treating psychological symptoms associated with IBS,<sup>56</sup> although a substantial proportion of patients discontinued the drug owing to side effects including nausea and diarrhoea.

### **Bile salt binding agents**

Cholestyramine is a bile salt binding agent which reduces the diarrhoea experienced by patients who have had terminal ileal resections. Bile salt malabsorption may also occur after an acute infectious illness and these patients respond well to cholestyramine.<sup>57</sup>

### **Newer serotonergic agents**

#### *5HT<sub>3</sub> antagonists*

Serotonin stimulates intestinal secretion and propulsion acting through both 5HT<sub>3</sub> and 5HT<sub>4</sub> receptors. 5HT<sub>3</sub> antagonists slow colonic transit, inhibit GI secretions, improve stool consistency and reduce urgency in D-IBS. Alosetron was the first drug in this class to be widely used in IBS. Direct comparison with the most frequently used agent, mebeverine, showed it to be superior with a response rate of 58% versus 48% at 3 months (NNT = 10).<sup>58</sup> Although successful in alleviating symptoms in D-IBS patients, especially urgency and diarrhoea (NNT = 7) there were a number of adverse effects. Constipation occurred in about 25% of patients, and was severe enough to cause discontinuation of the drug in around 5%. More seriously, but much rarer, was the complication of ischaemic colitis. This is generally a short-lived but alarming condition characterized by exacerbation of abdominal pain and the development of superficial mucosal ulceration causing profuse rectal bleeding. There were no recorded fatalities and the incidence was around 1 in 700. However, because of this unexpected effect the drug was withdrawn from general use and is now marketed under a strictly limited licence. Other 5HT<sub>3</sub> antagonists (e.g. Cilansetron) are likely to be marketed in the near future and appear to have similar clinical profile to Alosetron.

#### *5HT<sub>4</sub> agonists*

So far there is only one agent marketed in this class, Tegaserod. This stimulates colonic transit in both healthy volunteers and patients with constipated IBS. It is successful in improving global symptoms, increasing the frequency of bowel movement, softening stool consistency and reducing the symptoms of bloating (NNT = 10–12). Prucalopride, another 5HT<sub>4</sub> agonist, was even more effective in treating constipation but had to be withdrawn after failing teratogenicity testing.

## **Prognosis**

Many studies have clearly documented the long-term prognosis to be good. The diagnosis needs revision in very few cases, although symptoms often persist. Prognosis is probably better in post-infective IBS, with ~40% recovering over a 5-year period.<sup>59,60</sup>

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## Health care utilization and effect on quality of life

Although benign, IBS is a condition which is far from trivial for the sufferers. Not only does it account for around 40% of all consultations in the UK in secondary care, but because it is so common it accounts for a substantial absence from work in the whole population.<sup>61,62</sup> Although direct medical costs are relatively inexpensive, overall costs are substantial. In American managed care populations, total costs incurred by patients with IBS are around 50% higher than individuals without it. Furthermore, IBS patients report 3-fold higher rates of cholecystectomy, 2-fold higher rates of appendectomy and hysterectomy and 1.5-fold increases in back surgery, implying that unnecessary surgery contributes considerably to the overall cost.<sup>61</sup> IBS patients consult more frequently than other patients for non-GI causes and successful treatment of IBS, for example by hypnotherapy, reduces both GI and non-GI consultations.<sup>56</sup>

## Summary

IBS is a benign condition but it is capable of causing considerable suffering and impairment of quality of life. Underlying causes include excessive responses to stress, visceral hypersensitivity and dietary intolerances. These patients are far from intractable, and a careful history and physical examination allows a confident diagnosis. Most patients will respond to appropriate therapies, and many new treatments are being developed which could improve the lives of patients with this ubiquitous syndrome.

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