2 Chambers J, Bass C. Chest pain with normal coronary anatomy: a review of natural history and possible etiologic factors. Review. *Prog Cardiovasc Dis* 1990; 33:161–84.
3 Liuzzo JP, Ambrose JA, Diggs P. Proton-pump inhibitor use by coronary artery disease patients is associated with fewer chest pain episodes, emergency department visits and hospitalizations. *Aliment Pharmacol Ther* 2005;22:95–100.
4 Drossman DA, Whitehead WE, Toner BB *et al.* What determines severity among patients with painful functional bowel disorders? *Am J Gastroenterol* 2000;95: 974–80.
5 National Institute of Clinical Excellence. *Dyspepsia: management of dyspepsia in adults in primary care.* Newcastle upon Tyne: NICE, 2004.
6 Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005;54:40–5.
7 Wang WH, Huang JQ, Zheng GF *et al.* Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain?: a meta-analysis. Review. *Arch Intern Med* 2005;165:1222–8.
8 Dickman R, Emmons S, Cui H *et al.* The effect of a therapeutic trial of high-dose rabeprazole on symptom response of patients with non-cardiac chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Aliment Pharmacol Ther* 2005;22:547–55.
9 Bredenoord AJ, Weusten BL, Curvers WL, Timmer R, Smout AJ. Determinants of perception of heartburn and regurgitation. Review. *Gut* 2006;55:313–8.
10 Tutuian R, Castell DO. Esophageal function testing: role of combined multichannel intraluminal impedance and manometry. *Gastrointest Endosc Clin N Am* 2005;15: 265–75.
11 Dekel R, Pearson T, Wendel C *et al.* Assessment of oesophageal motor function in patients with dysphagia or chest pain – the Clinical Outcomes Research Initiative experience. *Aliment Pharmacol Ther* 2003; 18:1083–9.
12 Hobson AR, Furlong PL, Sarkar S *et al.* Neurophysiologic assessment of esophageal sensory processing in noncardiac chest pain. *Gastroenterology* 2006;130:80–8.
13 Ofman JJ, Gralnek IM, Udani J, Fennerty MB, Fass R. The cost-effectiveness of the omeprazole test in patients with noncardiac chest pain. *Am J Med* 1999;107:219–27.
14 Cremonini F, Wise J, Moayyedi P, Talley NJ. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain: a metaanalysis. *Am J Gastroenterol* 2005; 100: 1226–32.
15 Cannon RO 3rd, Quyyumi AA, Mincemoyer R *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411–7.
16 Drossman DA, Toner BB, Whitehead WE *et al.* Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003;125:19–31.

Treating functional lower gastrointestinal symptoms

Nora Thoua BSc MBBS MRCP, Research Fellow

Anton Emmanuel MD FRCP, Consultant Gastroenterologist

Gastrointestinal Physiology Unit, University College Hospital, London

Clin Med 2006;6:449–52

The most frequently occurring lower gastrointestinal (GI) symptoms can be considered in three groups:

- abdominal pain and/or bloating
- altered bowel function symptoms: constipation, increased bowel frequency or looser consistency stools
- rectal symptoms: the sensation of incomplete evacuation and the increased passage of mucus.

Symptoms tend to occur in clusters: for example, the irritable bowel syndrome (IBS), loosely definable as abdominal pain associated with any of the above symptoms. The frequent occurrence of these symptoms can be gauged from population-based studies showing a UK prevalence of approximately 20%.

Aetiology

The aetiology of lower GI symptoms is the focus of much research and it is clear that there are multiple relevant factors at peripheral gut, spinal and central nervous system levels. Advances in the understanding of how stress and mood disorders may influence the autonomic nervous system, visceral sensitivity and motility have led to a combined hypothesis that psychological factors and gut physiological abnormality may combine to result in functional symptoms (Fig 1).[1] No single treatment is likely to help all symptoms in these syndrome clusters so treatment is generally directed at individual symptoms, primarily pain, constipation and diarrhoea.

General management

The key to successful management of functional bowel disorders is strong, empathic reassurance, individually directed according to the patient's particular symptoms, beliefs and anxieties. A central component is provision of a simple explanation of the benign nature and prognosis of the condition. Patients should be advised that fewer than 2% of patients need functional diagnosis revision at 30 years of follow-up. The less good news is that 88% of patients have recurring episodes of GI symptoms, so reassurance should be tempered by awareness of their chronic and recurrent nature.[2]

The presence of alarm features mandates serological and luminal investigation to exclude organic disease. It is important not to overinvestigate younger patients as this may both exacerbate anxieties and undermine confidence in the clinician. One important diagnosis to consider, especially in the presence of low-grade anaemia, is coeliac disease. Approximately

5% of patients fulfilling IBS diagnostic criteria will have histological evidence of coeliac disease compared with 0.5% of controls without IBS symptoms.[2]

Lifestyle interventions

Several lifestyle and dietary interventions have their proponents but these have not always proved reproducible.[3] Four placebo-controlled crossover studies of dietary fibre augmentation have shown some acceleration of transit but no significant effect on symptoms. Two of these studies suggested an increase in abdominal bloating, discomfort and flatulence during fibre supplementation.[4,5] It may be worth bearing in mind that patients with a tendency to frequent stool passage may be helped by reducing intake of caffeine and sorbitol (present in chewing gum and sweeteners). True food allergies are much rarer than lay perception would predict; food fads and avoidances should be discouraged.[5]

Psychological treatment

Cognitive behavioural therapy

A landmark study by Creed *et al*[6] showed that cognitive behavioural therapy (CBT) directed towards bowel symptoms is effective in treating women with IBS (number-needed-to-treat (NNT) 3). The essence of such treatment is that it should be gut focused because general CBT and relaxation therapies are no more effective than standard care. A frequent criticism of psychotherapeutic approaches towards functional GI symptoms is that they are neither cost-effective nor beneficial in the long term. However, a cost-effectiveness study of CBT in 2003 showed unequivocal benefit at follow-up one year after the cessation of therapy, with healthcare costs at that time of £610 compared with £1,040 with standard care.[6]

Hypnotherapy

Several studies now in the literature show the benefit of hypnotherapy in IBS at up to six years following the cessation of therapy. Three-quarters of patients report symptom alleviation after hypnotherapy, with over 80% of these responders remaining well at a median follow-up of five years.[7] Hypnotherapy has particular efficacy in treating pain and bloating, the latter being a complaint for which there is no other treatment.

Abdominal pain

The rationale for using antimuscarinics (eg dicycloverine, hyoscine) and antispasmodics (eg mebeverine, alverine) is to attenuate the heightened baseline and postprandial contractility that may underlie functional pain and diarrhoea.

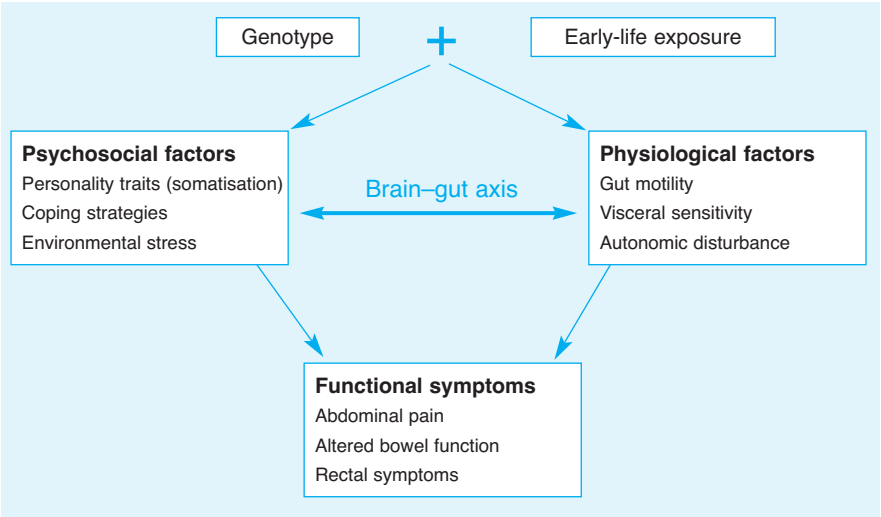

Fig 1. The aetiology of functional symptoms is multifactorial and is hypothesised to be a combination of psychological factors and gut physiological abnormality. Reproduced with kind permission from the American Gastroenterological Association.[1]

The conclusion from a number of meta-analyses on the efficacy of these agents is that there is slight evidence of a minor advantage over placebo.[8,9] Only two of the agents shown to have some efficacy are licensed in the UK: mebeverine (135–150 mg tds) and hyoscine (10–20 mg qds). The effects on pain however are modest and these drugs do not seem to have any beneficial effect on diarrhoea or constipation. Generally they are well tolerated and can be used on an as-required basis (before meals) – hence they are sometimes used when simple reassurance fails to improve symptoms.[5,9]

By contrast, several randomised placebo-controlled studies have shown that low-dose tricyclic antidepressants effectively decrease symptoms (NNT 3).[8] They have anticholinergic and non-selective serotonin re-uptake inhibitor (non-SSRI) effects, altering pain perception independent of mood or anxiety effects. The effects of the newer SSRIs are more modest, with an odds ratio for pain improvement of 1.5 (*v* 4.2 for tricyclics). It has been suggested that the SSRIs may have efficacy in treating constipation-predominant IBS, with tricyclics favoured for diarrhoea predominance.[5] Though logical, given their respective side effect profiles, this hypothesis remains unproven.

Even with low-dose use, side effects of constipation, dry mouth, drowsiness and fatigue occur in one-third of patients, often precluding good compliance. It is essential that the patient is adequately counselled about these potential side effects and given a clear explanation that an antidepressant is being used for its gut effect. The hypnotic side effect can be minimised by night-time dosing and daily administration, starting at a dose of 10–25 mg for amitriptyline, nortriptiline or prothiaden. The drug should be continued for 6–12 months and then dose tapering may be attempted.[5,8]

Diarrhoea

The opioid analogues loperamide and diphenoxylate inhibit peristalsis and gut secretion. Loperamide, in titrated doses up to 12 mg/day, effectively improves stool frequency and consistency in

patients with functional diarrhoea but has no effect on abdominal pain.[10] No such studies have been performed with Lomotil (diphenoxylate–atropine) but loperamide is preferred since it has neither mood related nor anticholinergic effects. Codeine phosphate is not favoured due to the potential for dependence and its tendency to induce dysphoria. Loperamide and Lomotil 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 utility in that it is available in syrup formulation for fine-tuning of dose to minimise the adverse effect of constipation. Bile acid-induced steatorrhoea is present in about one-third of diarrhoea-predominant IBS patients and may respond to a bile acid binder such as cholestyramine.

The recent focus of drug development has been towards single receptor targets, particularly on serotonin (5-HT) receptors in the gut, since these influence motor, sensory and secretory responses to food. Alosetron and cilansetron are 5-HT_3 receptor antagonists developed to reduce pain and retard transit in patients with diarrhoea. However, the efficacy of both drugs is slight (better-than-placebo response of just 12%)[11] and they are associated with potentially fatal ischaemic colitis. There has been no comparison of 5-HT receptor antagonists with loperamide or Lomotil and they remain unlicensed in the UK.

Constipation

Fibre supplementation

Fibre supplementation increases gut transit and stool bulk by only a fraction of the starting value and is effective only in patients with mild constipation. Few patients seen in hospital will not have tried fibre supplementation but can be advised about a gradual stepwise increase in fibre intake. Patients need to be counselled that the effect is not apparent for several weeks and that the diet needs to be continued in the long term, which can be difficult for most patients.[4,5] Increasing liquid intake and maintaining regular meal times may improve constipation, particularly in the elderly.

Laxatives

There are widely held misconceptions of the danger of 'self poisoning' without a daily bowel action and the first step in the management of constipation is to discourage laxative abuse. Laxatives have only a modest effect; meta-analyses have shown increased stool frequency with bulking agents and other laxative classes of 1.4 and 1.5 bowel movements per week, respectively. Detailed discussion of rational laxative usage is beyond the scope of this article but a few brief principles are given below:

- *Bulking agents* have limited utility in patients with severe constipation, their place being primarily in patients who cannot consume adequate dietary fibre.
- *Colonic stimulants* (senna, bisacodyl) are best used on an as-required basis, generally having an effect within 12 hours of ingestion.
- *Osmotic agents* are useful in patients with slow transit; they are dose titratable with generally good efficacy.
- *Lactulose* often results in flatulence and bloating; the inorganic salts are usually more effective.
- *Stool softeners* are best used as adjunctive agents in combination with one of the above.
- *Suppositories* and *enemas* are best used in patients with a frequent frustrated urge to open their bowels where rectal evacuation is the problem.

Biofeedback

Gut-directed behavioural therapy (biofeedback) is now an established therapy for functional constipation. Biofeedback is a learning strategy based on operant conditioning and is effective for patients with both slow transit and evacuation dysfunction. Short- and long-term benefit is evident in over 60% of unselected patients, although the efficacy with pain is poor.[12] There is evidence that successful outcome with biofeedback is associated with specifically improved autonomic innervation to the colon and improved transit time for patients with slow and normal transit. Of importance is that biofeedback is successful not just in patients with mild symptoms but also in those with intractable symptoms.

5-HT_4 receptor agonist

Tegaserod, a 5-HT_4 receptor agonist, accelerates transit and modifies sensation, representing a potential treatment for constipation and bloating. Efficacy studies again show modest advantages over placebo and no effect on pain. The NNT is 14–20, with some efficacy for constipation and possibly bloating. No comparative study with a laxative has

Key Points

Tricyclic antidepressants, hypnotherapy and psychotherapy should be considered for patients with functional pain or who have more severe symptoms

Loperamide is optimal initial therapy for patients with diarrhoea-predominant irritable bowel syndrome (IBS)

Fibre supplementation and adequate fluid intake are recommended as initial therapy for patients with constipation-predominant IBS

Use of newer agents such as alosetron and tegaserod should be limited to selected patients with more severe disease because of adverse effects, high cost and limited efficacy

Probiotics offer a novel, low side-effect potential therapy for a variety of functional symptoms

KEY WORDS: abdominal pain, biofeedback, constipation, diarrhoea, hypnotherapy

been performed and the drug remains unlicensed in the UK.

Emerging therapeutic approaches

The limited efficacy of existing drugs and the almost uniformly dismal experience of surgery in patients with functional disorders mean that, despite the disappointing experience of 5-HT agents to date, there remains an interest in developing new pharmaceuticals. This need is heightened by the prevalence of symptoms in the community.

Broad-spectrum antibiotics

There has been interest in the use of broad-spectrum antibiotics (neomycin, ciprofloxacin, metronidazole or doxycycline) following the controversial report that three-quarters of IBS patients have a positive lactulose hydrogen breath test, suggestive of the presence of small intestinal bacterial overgrowth.[13] Open-label use is reported as improving overall symptoms in the short term. However, neither the prevalence of bacterial overgrowth nor the response to antibiotics has been corroborated by all researchers. Overall, these observations need to be tempered by the clinical experience that antibiotics exacerbate symptoms in as many patients as they anecdotally improve.

Probiotics

Probiotics have been used in a number of studies which have been the subject of a meta-analysis. Most studies have shown improvements in normalising bowel frequency and bloating using a variety of probiotic agents.[14] Some may even alter mucosal cytokines, suggesting a possible mechanism of action. Overall, this is an area of ongoing research interest and no specific recommendation can be made for one agent as superior to another.

Immunosuppression

An alternative approach to altering neuro-immunology of the gut is to use an immunosuppressive agent. A placebo-controlled trial failed to show a beneficial effect after a three-week trial of prednisolone 30 mg.

Chinese medicine

Chinese herbal and plant preparations improve overall IBS scores and abdominal pain. No advantage has been found from Chinese medical practitioners individualising herbal mixtures for each patient, suggesting that this approach is general rather than targeting specific symptoms.[15] As with probiotics, this area of treatment is attractive to patients and needs further study.

Conclusions

The first-line management of functional lower gut symptoms is focused on empathic discussion of the nature and cause of symptoms. This should lead to a focused consultation with two aims: to help the patient understand the rationale for the chosen treatments and to seek symptom palliation rather than necessarily cure. Patients are often interested in the role of alternative therapies for this chronic functional problem and there is a proven place for hypnotherapy, psychological therapy and emerging herbal therapies.

Most patients will not need pharmacological treatments, but for those with refractory symptoms there are a number of existing and emerging agents of proven efficacy both in terms of symptom relief and quality of life improvement.

References

1 Murray CD, Flynn J, Ratcliffe L *et al.* Effect of acute physical and psychological stress on gut autonomic innervation in irritable bowel syndrome. *Gastroenterology* 2004; 127:1695–703.

2 Locke GR 3rd. Natural history of irritable bowel syndrome and durability of the diagnosis. Review. *Rev Gastroenterol Disord* 2003;3(Suppl 3):S12–7.

3 King TS, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. *Lancet* 1998;352:1187–9.

4 Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. *Lancet* 1994;344:39–40.

5 Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2005;No.2:CD003460.

6 Creed F, Fernandes L, Guthrie E *et al.* The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology* 2003;124:303–17.

7 Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. *Gut* 2003;52:1623–9.

8 Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med* 2000;133:136–47.

9 Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355–61.

10 Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984;29:239–47.

11 Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003; 15:79–86.

12 Roy AJ, Emmanuel AV, Storrie JB, Bowers J, Kamm MA. Behavioural treatment (biofeedback) for constipation following hysterectomy. *Br J Surg* 2000;87:100–5.

13 Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003;98:412–9.

14 Hamilton-Miller JM. Probiotics in the management of irritable bowel syndrome: a review of clinical trials. *Microbial Ecol Health Dis* 2001;13:212–6.

15 Madisch A, Holtmann G, Plein K, Hotz J. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled multi-centre trial. *Aliment Pharmacol Ther* 2004;19:271–9.