Drug therapy of irritable bowel syndrome

R. Fraser, Gwendolyn Michell Senior Lecturer, University Department of Medicine, Royal Adelaide Hospital, Adelaide

SYNOPSIS

Irritable bowel syndrome is a common disabling condition in the community. It is characterised by abdominal pain and disordered bowel habit, but the pathophysiology of the condition is unclear. Multiple factors including diet, gastrointestinal infection, disordered gut motility and emotional stress have all been implicated as potential triggers. Recent advances in our understanding of gastrointestinal physiology suggest that visceral hypersensitivity may underlie at least some of the clinical features. The key role of serotonin in gastrointestinal neural function has led to the development of new drugs that show therapeutic promise in management of irritable bowel syndrome. Treatment currently remains symptomatic with disorders of defaecation responding more readily than abdominal pain.

Index words: diarrhoea, hypersensitivity, spasmolytics, serotonin.

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Introduction

Irritable bowel syndrome is a group of chronic or recurrent gastrointestinal symptoms attributed to the small intestine and colon for which there is no underlying structural or biochemical explanation. The symptom complex is defined by abdominal pain and disordered defaecation. It may also be associated with features such as bloating and distension.[1] The diagnosis is based on identification of positive symptoms (Table 1) and the cost-effective exclusion of other clinical diagnoses with a similar presentation. In practice the diagnosis is often attached to any patient with an abdominal complaint where no other underlying pathology can be found.

Irritable bowel syndrome is common. It affects up to 15–20% of the population at any one time and is responsible for 30–40% of gastroenterology consultations. Many patients can be managed with advice on diet and lifestyle changes and do not require drug therapy. During the past 10 years better understanding of the pathways of gastrointestinal sensation have changed the strategy of drug development away from medications for abnormal gastrointestinal motility to drugs designed to modify visceral sensation.[2]

Aetiology

For many years irritable bowel syndrome was considered a psychosomatic condition with a heterogeneous presentation. Patient subgroups have been classified according to their dominant symptom combination, for example constipation- or diarrhoea-predominant. Although there has been a lot of research into the underlying causes there is no current unifying theory as to specific aetiology.

In an attempt to unify the various aetiological factors, a multifactorial model has been proposed in which inflammatory, allergic, dietary, genetic and psychological factors affect enteric visceral sensory neural pathways. These changes result in a hypersensitive system that overreacts to a wide array of emotional and peripheral stimuli.

Abnormal motility

Gastrointestinal smooth muscle has intrinsic patterns of motor activity which are under the control of the enteric nervous system. This is a complex network of nerves and ganglia located in the wall of the intestine. The motor activity is modulated by inputs from many areas via the autonomic nervous system and circulating humoral substances.

For many years gastrointestinal dysmotility was considered the main contributor to the symptoms of irritable bowel syndrome. Abdominal discomfort and pain were assumed to be caused by contractions that were too strong or prolonged, and disorders of transit were considered to result from altered patterns of gastrointestinal smooth muscle contraction. This approach provided a strategy for treatment. However, although there are a number of changes in gastrointestinal motor function,

Table 1

Rome II diagnostic criteria for irritable bowel syndrome*[1]

In the preceding 12 months, the patient has had at least 12 weeks (not necessarily consecutively) of abdominal discomfort or pain with two of the following three features:

- relieved by defaecation and/or
- onset associated with a change in stool frequency and/or
- onset associated with a change in form (appearance) of stool

Symptoms that cumulatively support the diagnosis of irritable bowel syndrome

- abnormal stool frequency (for research purposes may be defined as more than three bowel movements per day and less than three bowel movements per week)
- abnormal stool form (lumpy/hard or watery/mushy)
- abnormal stool passage (straining, urgency or feeling of incomplete evacuation)
- passage of mucus
- bloating or feeling of abdominal distension

* in absence of structural or metabolic abnormalities to explain symptoms

a clear relationship between symptoms and abnormal motility, in either the small intestine or colon, has never been shown. Irritable bowel syndrome is therefore probably not a primary motor disorder of the gut.

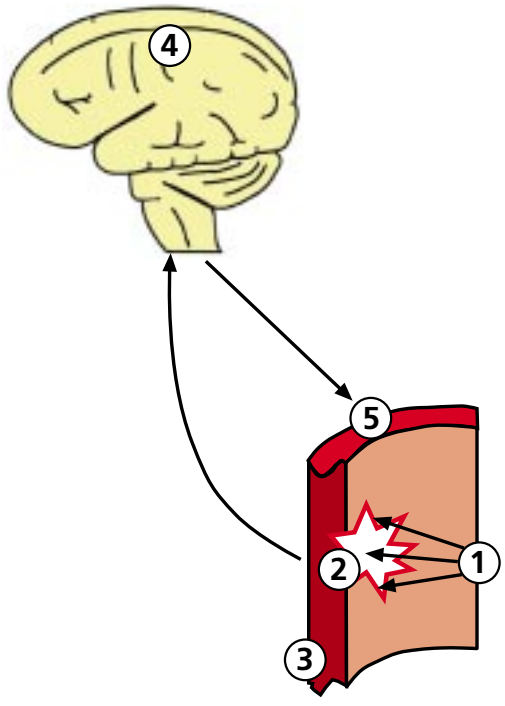
Abnormal sensation

Recent attention has focused on gastrointestinal sensation in patients with irritable bowel syndrome.[2] Stimuli within the gut (especially food) are continually sensed and sensory neural transmission integrated and processed by both the enteric nervous system and the central nervous system. Most of the sensory stimuli do not reach perception, but they can alter motor activity.

The key role of abdominal pain in irritable bowel syndrome led to the theory that abnormal gut sensation could underlie the condition with visceral hypersensitivity suggested as a possible aetiology. Irritable bowel syndrome patients are abnormally sensitive to distension throughout the entire length of the gut although their somatic sensitivity to painful stimuli is normal. Possible mechanisms that could result in abnormal visceral sensation are receptor hypersensitivity, abnormal integration or transmission of dorsal horn changes or changes in central processing perception (Fig. 1).

Fig. 1

Possible mechanisms for symptom production in irritable bowel syndrome



1. Abnormal stimulation of normal gastrointestinal receptors
2. Abnormal response of gastrointestinal receptors to normal stimuli
3. Abnormal gastrointestinal motility
4. Abnormal central perception of normal gastrointestinal afferent signals
5. Abnormal central stimulation of gastrointestinal tract via efferent pathways

(Courtesy Dr D. Armstrong, McMaster University, Canada)

Infection and inflammation

Many patients have a well-defined gastrointestinal infection preceding the development of irritable bowel syndrome. A number of investigators have described an increase in the mucosal mast cell population in post-infective irritable bowel syndrome. It is possible that these cells release inflammatory mediators which then affect enteric neurotransmitters and perpetuate symptoms associated with acute infection.

Role of stress

Acutely stressful situations are often associated with transient changes in bowel function. Their importance in irritable bowel syndrome is less clear, although they may function as triggers in some patients. Chronically stressful situations, particularly abuse in early life, have been associated with an increased incidence of irritable bowel syndrome.[3]

Non-drug treatment

Lack of exercise and insufficient time at stool are common problems which are relatively simple to remedy. Many patients also understand that anxiety can alter bowel function acutely and a positive diagnosis and explanation together with a supportive therapeutic relationship may be all that is required. In patients without major psychiatric disease, biofeedback and hypnotherapy have also been reported to be effective.

Specific dietary advice

Lactase deficiency is common, but its role in irritable bowel syndrome is uncertain and restriction of calcium intake especially in women needs monitoring because of the risks of osteoporosis. Many patients identify a dietary trigger for their symptoms and a sensible reduction in specific foods can be beneficial particularly for symptoms such as bloating and diarrhoea. Other patients eat large amounts of indigestible carbohydrate or artificial sweeteners and improve with appropriate restriction of these. In contrast, patients with constipation may require an increase in dietary fibre. Formal exclusion diets are time-consuming and require referral to a dietitian.

Drug treatment

In the absence of a well-defined aetiology, drug treatments for irritable bowel syndrome aim at the predominant symptoms.[4] As there is considerable inter- and intra-patient variability in the symptom pattern, it is perhaps not surprising that the response to many drugs is unclear. In addition, there is a 30–40% placebo effect which confounds drug efficacy studies.

Specific drug treatments for disturbed transit are the most successful treatments currently available for irritable bowel syndrome.[5] However, as patients' symptoms switch from constipation to diarrhoea, treatment strategies may also require modification.

Antidiarrhoeal drugs

Opiates have been used for centuries to reduce diarrhoea. These drugs slow gut transit largely by acting on specific sub-types (μ) of the opioid receptors of enteric nerves. The newer opioid drugs diphenoxylate and loperamide are preferred

to drugs such as codeine as they are relatively safe, effective and, as they do not cross the blood-brain barrier, they have minimal central effects. Loperamide may also increase anal sphincter tone. Patients can use these drugs as required and titrate the dose according to their needs, remembering that they may be quite sensitive to opiates and easily become constipated. Taking antidiarrhoeal drugs before travelling to work, social activities or stressful situations may enhance the patient's quality of life.

Drugs used to treat nausea, such as the 5-HT_3 antagonists granisetron and ondansetron, are well recognised causes of constipation. More recently alosetron, another 5-HT_3 antagonist, was shown to markedly slow left sided colonic transit, suggesting a possible future role for this class of drugs in diarrhoea-predominant irritable bowel syndrome. These 5-HT_3 antagonists may also affect gut sensation. However, alosetron has been withdrawn due to serious adverse effects.

Laxatives (Table 2)

The simplest means of tackling constipation is the addition of fibre (such as bran) to the diet. If bran is not tolerated other bulking agents such as psyllium can be substituted although these are more expensive. The goals of therapy need to be realistic and patients need to be warned of the potential adverse effects of bloating, abdominal distension and flatulence.

The addition of laxatives needs to be incremental and graded as it takes a few days to achieve a new 'steady state'. In addition to an increase in flatus production, they may exacerbate symptoms such as bloating and abdominal distension if the dose is increased too rapidly. Patients should be instructed to look for a bulkier, more easily passed stool as a sign that they are taking an effective dose of fibre. Bulking agents should be taken on both good days and bad days. If the predominant symptom switches from constipation to diarrhoea a reduction in bulking agents is indicated.

Drugs to reduce spasm

No drug has been convincingly shown to have benefits beyond placebo. Abdominal pain in irritable bowel syndrome has been treated with antispasmodic and anticholinergic drugs for more than half a century without them clearly being shown to be of benefit. Meta-analyses show some benefit over placebo for abdominal pain, but not for constipation.[6] Painful muscle cramps may be treated with drugs such as mebeverine, dicyclomine and cimetropium.

Muscarinic antagonists such as atropine or hyoscine that block cholinergic stimulation are non-specific smooth muscle relaxants. They may be helpful in reducing severe episodes of pain arising from gut spasm. These non-specific drugs may have adverse effects on the bladder, eyes and salivary glands. They are best used on demand rather than routinely.

Drugs to modulate sensory feedback

Tricyclic antidepressants

Up to half of the patients with irritable bowel syndrome show some clinical features of depression and these patients require appropriate treatment. There are however many observations which show that patients who are not depressed may benefit from taking tricyclic antidepressants in doses which are smaller than those used to treat depression (e.g. amitriptyline 10–50 mg). Although central modification of pain pathways may occur, the exact mechanisms of action are unclear as the tricyclic antidepressants also have anticholinergic effects.

Table 2
Drug therapy for constipation

Drug	*Dose*
Psyllium	1 tablespoon twice daily with meals
Methylcellulose	1 tablespoon twice daily with meals
Lactulose*	15–30 mL twice daily
Sorbitol*	20 mL 2–3 times per day

Suggested starting doses for bulking agents in treatment of constipation. Subsequent doses should be titrated against clinical effects.
* may cause bloating

5-hydroxytryptamine (5-HT) antagonists

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has a key role in gastrointestinal motor function through its actions on nerve receptors within the enteric nervous system.[7] A number of receptor sub-types may be involved in gastrointestinal sensation. Most recently it has been suggested that 5-HT_3 receptors may have a key role in visceral hyperalgesia. Studies are ongoing with a number of 5-HT_3 antagonists to determine their effects on visceral hypersensitivity. Preliminary studies indicate that these drugs may improve symptoms such as urgency and abdominal pain in diarrhoea-predominant irritable bowel syndrome. It is unclear whether this effect is mainly due to the drug's action on gastrointestinal transit. A number of other drugs that modulate sensory transmission and perception are also under investigation.

Conclusion

There is at present no 'magic bullet' for the treatment of irritable bowel syndrome. This is not surprising in view of the variability of symptoms and the probability that multiple aetiologies contribute to symptoms. Many patients cope well with reassurance alone after exclusion of serious pathology. Drug treatment aims at symptom relief and is directed at maintaining normal work and recreational activities. Therapy needs to be individually tailored to the patient's current symptoms with a preparedness to switch strategies if the predominant symptoms alter.

E-mail: robert.fraser@adelaide.edu.au

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Dr Fraser is currently involved in a multicentre trial of irritable bowel syndrome treatment (tegaserod).

Self-test questions

The following statements are either true or false (answers on page 75)

9. Some patients with irritable bowel syndrome do not experience abdominal pain.
10. Up to half the patients with irritable bowel syndrome have clinical features of depression.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Buprenorphine

Subutex (Reckitt Benckiser)

2 mg, 4 mg and 8 mg sublingual tablets

Approved indication: opiate dependence

Australian Medicines Handbook Section 18.6.3

Buprenorphine is a partial agonist of opioid receptors. The drug has been used, at low doses (0.2 mg), as a sublingual analgesic. Higher doses have now been approved for the treatment of opiate dependence. Buprenorphine can be used in detoxification or as a maintenance treatment. Its action on the receptors reduces the cravings for opioid drugs.

The drug is taken sublingually because of the first-pass metabolism which follows an oral dose. Even when given sublingually, the tablets only have a bioavailability of 30–35%. Buprenorphine is metabolised by the cytochrome P450 system. As CYP3A4 is involved, inhibitors of this enzyme, such as macrolide antibiotics, have the potential to increase concentrations of buprenorphine. Most of the metabolites are excreted in the bile. As buprenorphine has a mean half-life of 35 hours it is feasible to give some patients less than daily dosing.

A randomised trial has compared the efficacy of buprenorphine with that of clonidine and naltrexone in 162 patients undergoing detoxification. The detoxification was successfully completed by 65% of the patients given clonidine, 81% of those given clonidine and naltrexone, and 81% of those given buprenorphine.[1] The Cochrane Collaboration has reviewed the evidence supporting buprenorphine in the management of opioid withdrawal, but has not reached a firm conclusion.[2]

For maintenance treatment, buprenorphine should be taken at least six hours after the last dose of heroin. This is to reduce the risk of triggering withdrawal symptoms. For patients transferring from methadone there should be a delay of at least 24 hours before starting buprenorphine. Treatment begins with a 4 mg dose which is increased according to the patient's response. The maximum dose is 32 mg a day. Once the patient is stable the dose frequency can be reduced. Some patients will manage with three doses a week.

Buprenorphine has been compared with methadone. One trial studied 72 patients for six months. While more patients taking methadone were retained in treatment, both treatments worked well. Urine tests showed reduced opioid use; 60% of the tests were negative for patients taking buprenorphine compared to 66% of the tests from patients taking methadone.[3]

A major problem with buprenorphine is the risk of abuse. As patients given buprenorphine for pain can become addicted it is clear that it can cause dependence. Some patients grind up the tablets so that they can inject the drug. This is dangerous, particularly if the patient is also using benzodiazepines. Deaths have occurred from cardiorespiratory depression when buprenorphine and benzodiazepines have been injected.

Other adverse effects are difficult to identify as the adverse reactions reported in clinical trials may be due to withdrawal or opioid toxicity. Symptoms reported include headache, abdominal pain, chills, insomnia, nausea, vomiting and diarrhoea. Liver function may be altered and some patients will develop hepatitis.

If a decision is made to cease treatment, buprenorphine should not be stopped suddenly. A gradual reduction of the dose over three weeks is recommended.

Buprenorphine has been used to treat drug addiction in France since 1996. *Australian Prescriber's* sister journal *La Revue Prescrire* has reviewed its use and found it to be an effective treatment. The French experience confirms that the main risks of buprenorphine are linked to misuse. They recommend that there should be good communication between the prescribing doctor and the pharmacist, particularly about how many tablets to dispense at a time. Using buprenorphine as one part of a co-ordinated medical and psychosocial treatment program is also important.[4]