

Treatment and Retreatment of Irritable Bowel Syndrome with Constipation

a report by

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Irritable bowel syndrome (IBS) is a condition characterised by episodes of symptoms referring to the large bowel in the absence of organic disease that readily explains them. IBS symptoms include abdominal pain or discomfort, bloating and disordered bowel habits. Relief of symptoms by defecation is a key characteristic feature of IBS. In a subset of patients, aggravation of abdominal symptoms occurs after a meal. In addition, a number of non-colonic features, including upper gastrointestinal (GI) symptoms, urinary symptoms, lower back pain and chronic fatigue, are also highly prevalent in IBS patients.

Definition and Sub-divisions According to Stool Pattern

No diagnostic markers for IBS exist, so the diagnosis rests on the recognition of characteristic symptom patterns and the exclusion of organic disease. To help clinicians recognise and manage IBS, and to allow a more uniform selection of patients entering clinical trials, diagnostic criteria have been proposed. The first symptom criteria were proposed by Manning et al. and these were adapted in the Rome I diagnostic criteria. The currently accepted symptom criteria were proposed by the Rome II working team.

IBS is usually classified according to the predominant bowel habit:

- IBS with constipation (IBS-C);
- IBS with diarrhoea (IBS-D); or
- IBS with alternating symptoms of both constipation and diarrhoea (IBS-A).

Epidemiology and Economic Impact

Studies have shown that the Rome criteria also have some diagnostic usefulness. This observation allows the use of the Rome criteria to study the prevalence and impact of IBS in the general population.

Hungin et al. applied random-digit dialling technology to conduct telephone interviews in more than 40,000 subjects 18 years and older in Europe. Using a structured questionnaire to obtain information on IBS, they demonstrated that the overall prevalence of this

disorder varied from 7% in The Netherlands to 17% in Italy, and approximately two-thirds of the subjects with IBS were females. When standardised criteria were applied to sub-divide individuals according to the stool pattern, 16% were assigned to the constipation-predominant category, 21% to the diarrhoea-predominant category and 63% to the alternating type.

The morbidity and life expectancy in patients with IBS does not differ from that in the general population, but a considerable impact on daily life is present and quality of life is impaired in IBS patients. Patients with IBS experience symptoms that interfere with normal daily activities for which they repeatedly see physicians, and they have a higher number of days absent from work or school. Direct medical costs in patients with IBS are significantly higher than those in a control population.

Pathophysiology of IBS

The pathophysiology of IBS is incompletely understood, but several mechanisms may contribute to IBS symptoms. Historically, several hypotheses have been suggested to underlie symptoms in IBS. Until the 1990s, symptoms in functional bowel disorders have mainly been viewed as expressions of altered motor function of the gut. More recently, alterations in visceral sensitivity, infection and inflammation and abnormalities of the central nervous system have been implicated. However, considerable pathophysiological heterogeneity seems to exist and IBS symptom pattern and severity are likely to be determined in a multifactorial way. Alterations in bowel function observed in IBS seem to be related to intestinal and colonic transit times, with slower transit in C-IBS and more rapid transit in D-IBS. More recently, impaired colonic transit of gas was demonstrated in IBS patients and this was mainly associated with symptoms of bloating.

Over 20 years ago, Ritchie showed that in patients with IBS, the distention volume required to induce pain from the pelvic colon was, on average, lower than in controls. In the last 15 years, the visceral hypersensitivity hypothesis has been a major area of research with several well-controlled studies showing



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a reduction in the threshold pressure or volume of colorectal distention required to induce perception or a sensation of discomfort or pain in patients with IBS. Somatic sensitivity is not enhanced in patients with IBS. Additional studies confirmed that rectal hypersensitivity is a feature of IBS and not of other colonic disorders, and that the presence of hypersensitivity has good sensitivity and specificity for the diagnosis of IBS. Hence, in addition to motility abnormalities, visceral hypersensitivity is considered a major mechanism in IBS.

Patients with IBS have more psychological and psychiatric disturbances than the general population, but less than psychiatric out-patients. However, the psychological disorders in patients with IBS are non-specific and there is no single psychological or psychiatric trait that equates with IBS. The observation that only a minority of persons with symptoms suggestive of IBS is seeing a physician led to the hypothesis that psychopathology might not determine the symptoms. Patients with IBS experience more stress than asymptomatic controls and patients often report a temporal relationship between stress and symptoms. Well-controlled studies are unfortunately lacking and in a prospective study, a correlation with stress could only be found in 25% of the exacerbations of irritable bowel symptoms.

Several recent studies have focused on the potential role of infection and inflammation in IBS. Both in retrospective and in prospective studies, it has now been well established that IBS may follow an acute intestinal infection. Several studies have reported signs of on-going low-grade inflammation on rectal, colonic or ileal biopsies of IBS patients that, in turn, associated with increased counts of serotonin-containing enterochromaffin cells. Studies investigating post-prandial release of 5-hydroxytryptamine (5-HT) in IBS were only able to demonstrate an increase in a small subset of patients.

Traditional Treatment Options for IBS

Once the diagnosis of IBS has been made (after the initial examinations and exclusion of organic pathology), patients should be reassured and extensively informed about the nature of their complaints. A retrospective analysis from the Mayo Clinic suggests that reassurance and explanation do have a significant clinical impact. Although many physicians will prescribe dietary measures (such as a diet rich in fibre in constipated patients and reduced intake of carbohydrates in patients with diarrhoea or bloating), the value of dietary interventions has never been proven.

Fibre supplements are traditionally prescribed to patients with IBS-C and they may improve

constipation. However, for alleviating abdominal pain, fibre is not superior to placebo and there is often an adverse influence on symptoms of abdominal pain, bloating or diarrhoea. Alternatively, bulking agents such as psyllium or isphagula can be prescribed, but their efficacy has not been proven. In systematic reviews from the American College of Gastroenterology (ACG) and from Switzerland, it was concluded that fibre is appropriate for the treatment of painless constipation, but it is not recommended for the treatment of IBS. There is a surprising lack of evidence-based data on the efficacy of other laxatives in the treatment of IBS and no randomised controlled trials (RCTs) have been conducted.

Anti-spasmodics cause relaxation of the intestinal smooth muscle cells, mostly by inhibiting the influx of calcium. Anti-cholinergics inhibit GI motility by blocking muscarinic receptors on the intestinal smooth muscle. The ACG review concluded that there were insufficient data to make a recommendation about the effectiveness of the anti-cholinergic or anti-spasmodic agents available in the US. Anti-spasmodics are more widely available and used more extensively in Europe than in the US. Placebo-controlled studies show an inconsistent effect, but meta-analyses of smooth muscle relaxant studies suggest a benefit of these drugs on abdominal pain. However, many of the controlled studies with anti-spasmodics were of short duration, included small numbers of patients and did not use the Rome diagnostic criteria. A recent Swiss meta-analysis concluded that there was insufficient evidence for the efficacy of specific anti-spasmodic drugs in IBS when only high-quality studies were taken into account, with the exception of otilonium bromide. Anti-spasmodics are generally well tolerated, but constipation has been cited as a complication in clinical trials so these drugs should be used with caution in patients with IBS-C or IBS-A. Anti-cholinergic drugs often cause systemic anti-cholinergic side effects; effects in the long term have not been proven.

Loperamide, a synthetic opiate derivative widely used in Europe and available over the counter, is the only anti-diarrhoeal agent that has been investigated in IBS. Although widely used in clinical practice, only few placebo-controlled trials of inadequate quality are available. These confirmed the effect of loperamide on stool frequency and improved stool consistency, but no significant improvement in global IBS symptoms or abdominal pain or bloating was seen. Reviews concluded that loperamide may be effective for the treatment of diarrhoea, but there is no evidence for effectiveness in global IBS symptoms or pain. ■

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