

# Investigation of the patient with bloating

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Dr Pokorny is a member of the Board of Continuing Education, Royal Australasian College of Physicians, and a Gastroenterologist in private practice, Sydney, NSW. Abdominal bloating, often in combination with altered bowel habit or abdominal discomfort, is a common reason for presentation to GPs and gastroenterologists. Patients may complain of visible abdominal distension, belching and increased flatulence. It is usually associated with a functional gastrointestinal disorder, irritable bowel syndrome (IBS) and non-ulcer dyspepsia. The sensation of bloating has a number of causes (Table 1).

Gastrointestinal hyperaesthesia is the most common pathology behind bloating. With functional disorders, gas production is essentially normal, but the patient has heightened visceral sensitivity and exaggerated gastrointestinal motor responses. Some studies have shown impaired intestinal transit associated with abdominal pain and distension in patients who have IBS.<sup>1,2</sup>

However, bloating can be a feature of many diseases affecting the gastrointestinal system,

including gastroparesis from any cause, partial or complete bowel obstruction, coeliac disease, lactose intolerance, bacterial overgrowth, exocrine pancreatic insufficiency, gastrointestinal parasitic or bacterial infection, inflammatory bowel disease or acute hepatitis. Constipation and ascites often present as 'bloating', as can intra-abdominal malignancy, particularly ovarian malignancy.

Gas production is a significant cause of bloating where there is impaired gut motility or reduced bile acid that encourages bacterial overgrowth. The hallmark bacterial gas production disease used to be pneumatosis cystoides intestinalis. The withdrawal of chloral hydrate from the pharmaceutical formulary has led to this being an excessively rare disease nowadays. Chloral hydrate and other alkyl halide compounds inhibit colonic bacterial consumption of hydrogen,<sup>3</sup> which can cause bubbles of gas to be trapped in the intestinal mucosa, giving the

- Gastrointestinal hyperaesthesia is the most common cause of abdominal bloating.
  - Detailed history taking and physical examination of a patient with bloating will direct further investigations.
  - Irritable bowel syndrome is likely to underlie bloating if a functional psychosocial context is present and symptoms have been present over a long period of time.
- A diagnosis other than irritable bowel syndrome or hyperaesthesia is suggested by particular symptoms, abnormal physical findings, the presence of medical conditions predisposing to gastroparesis or bacterial overgrowth, and family history of colon cancer, coeliac disease or inflammatory bowel disease. The symptoms include bloating onset after the age of 50 years, bloating that wakes the patient from sleep, weight loss, gastrointestinal bleeding, increasing pain and gut obstruction.

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IN SUMMARY

### Table 1. Causes of the sensation of bloating

- Excessive swallowing and trapping of nitrogen (air)
- Gastrointestinal hyperaesthesia
- Hydrogen or methane gas production by bacteria
- Impaired absorption of gas or fluid due to obstruction
- Overindulgence
- Spastic gut motility

## Table 2. Bloating: 'alarm' features suggesting a diagnosis other than IBS

- Abnormal physical findings
- Bloating that wakes the patient from sleep
- Family history of colon cancer, coeliac disease or inflammatory bowel disease
- Gastrointestinal bleeding
- Medical conditions predisposing to gastroparesis or bacterial overgrowth
- Onset of bloating after 50 years of age
- Progressive or unrelenting pain
- Symptoms of gut obstruction
- Unintentional weight loss

disease its name. It is analogous to the 'bends', in which nitrogen becomes trapped in the tissues of deep sea divers who do not undergo proper decompression.<sup>4</sup> The condition was always rare but was more common in patients with vascular and solidus or pulmonary disease that resulted in impaired diffusion of gases and their clearance via the lungs.

#### **Clinical assessment**

Patients with bloating should be assessed for the positive features of IBS and for symptoms that suggest an organic cause of the bloating. IBS is more likely to underlie bloating if a functional psychosocial context is present and where symptoms

#### Table 3. Symptom-based criteria for the diagnosis of IBS<sup>5-7</sup>

#### Manning criteria

- Abdominal pain relieved by defaecation
- Looser stools with onset of pain
- More frequent stools with the onset of pain
- Abdominal distension
- · Passage of mucus in stools
- Sensation of incomplete evacuation

(The more of these present, the greater the likelihood of IBS)

#### Rome I criteria

At least 12 weeks of continuous or recurrent symptoms of abdominal pain or discomfort that has:

- one or more of the following features:
  - relieved with defaecation
  - associated with a change in frequency of stool
  - associated with a change in consistency of stool
- plus two or more of the following present at least 25% of the time:
  - altered stool frequency
  - altered stool form
  - altered stool passage
  - passage of mucus
  - bloating or feeling of abdominal distension

#### Rome II criteria

At least 12 weeks (which need not be consecutive) in the past 12 months of abdominal discomfort or pain that has two or more of the following features:

- relieved with defaecation
- onset associated with a change in frequency of stool
- onset associated with a change in form of stool

have been present over a long period of time without 'alarm' features (Table 2).

IBS has been considered a diagnosis of exclusion. Symptom-based criteria, the most recognised being the Manning criteria and the Rome I and Rome II criteria, are validated clinical tools for diagnosing IBS (Table 3).<sup>5-9</sup> Bloating or distension is included in the Manning and Rome I criteria. In patients with a history that meets the diagnostic criteria for IBS and there are no 'alarm' features and a normal physical examination, there is no indication for routine investigation of other gastrointestinal disorders, with the possible exceptions of lactose intolerance and coeliac disease screening.<sup>10</sup>

#### continued

### Table 4. Some investigations used in abdominal bloating

#### **Directed investigations**

- For suspected IBS: trial of treatment with the aim of reducing the frequency and severity of symptoms
- If symptom onset at age above 50 years, family history of organic disease or no psychosocial difficulty: full blood count, faecal occult blood testing, colonoscopy (colorectal cancer screening)
- For suspected infection or inflammatory bowel disease: inflammatory markers, haematology, biochemistry, stool microscopy
- For suspected microscopic colitis: colonic biopsies
- For suspected lactose malabsorption: hydrogen breath testing, small intestinal lactase measurement

#### Other relevant investigations

- Serum endomysial IgA and antitissue transglutaminase IgA – for coeliac disease screening
- Barium meals and small bowel series

   for gastric motility
- Colonoscopy for visualisation of changes and biopsy taking
- Hydrogen breath testing for intestinal bacterial overgrowth and lactose malabsorption
- Small bowel series for mucosal architecture
- Small intestinal biopsy for coeliac disease and small intestine infections
- Thyroid function testing for thyroid dysfunction
- Ultrasound and CT scan for portal hypertension, ascites, intra-abdominal malignancy
- Upper endoscopy for gastroparesis
- X-ray for gastroparesis, intestinal pseudo-obstruction, infection, inflammatory bowel disease, constipation, faecal loading

The positive predictive value of the Manning criteria for the diagnosis of IBS ranges from 65 to 75%, depending on the number of symptoms present and the number of symptoms used for the analysis.<sup>5</sup>

The Rome I criteria have a reported 65% sensitivity, 100% specificity and 98% positive predictive value in distinguishing between IBS and organic



#### **Clinical investigation**

Directed investigation to confirm or exclude gastrointestinal pathology is warranted when symptoms consistent with organic disease are present or there is persistent nonresponse to symptom directed therapy (Table 4; see box on pages 54 and 55).<sup>11</sup>

Full blood count, faecal occult blood testing or a colorectal cancer screening colonoscopy may be independently indicated when onset of symptoms occurs at an older age, there is a family history of organic disease or a lack of psychosocial difficulty.<sup>11</sup> Inflammatory markers, biochemistry and stool microscopy should be performed if infection or inflammatory bowel disease is suspected. Where the colon appears macroscopically normal but there is diarrhoea, colonic biopsies are indicated to look for microscopic colitis.

Routine hydrogen breath testing or measurement of small intestinal lactase levels from biopsy specimens to investigate lactose malabsorption may be useful, as may routine thyroid function testing, although both lactose malabsorption and thyroid dysfunction can be assessed clinically.<sup>10,12</sup> These tests find a proportion of patients with abnormal results, with a prevalence similar to that of the general population. The relationship between thyroid dysfunction and gastrointestinal symptoms is unclear as trials have not evaluated symptom response following correction of thyroid abnormalities.

There is limited evidence supporting serological screening for coeliac disease in IBS patients, although bloating is a common symptom in patients with both these diseases. A trial of 600 patients compared the prevalence of positive coeliac disease serology (antigliadin IgA and IgG and endomysial IgA; coeliac disease confirmed on small bowel biopsy) in patients with and without symptoms consistent with IBS (on Rome II criteria).<sup>13</sup> Of those with suspected IBS, 22% had positive antibody results and some 5% had histological evidence of coeliac disease, compared with 0.67% of controls. It should be noted that serum endomysial IgA (sensitivity, 85 to 98%; specificity, 97 to 100%) and antitissue transglutaminase IgA (sensitivity, 90 to 98%; specificity, 95 to 97%) have now replaced antigliadin IgA (sensitivity, 80 to 90%; specificity, 85 to 95%) and IgG (sensitivity, 75 to 85%; specificity, 75 to 90%) as screening tests for coeliac disease, due to the much greater sensitivity and specificity of the newer tests.14,15

Other investigations that may be appropriate in bloating include various

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#### continued



Figure. Ascites and fluid-filled dilated loops of intestine in a patient with advanced chronic intestinal pseudo-obstruction complicated by protein-losing enteropathy and small bowel bacterial overgrowth.

imaging studies, upper endoscopy, small intestinal biopsy, colonoscopy and breath hydrogen testing (see Table 4). A simple abdominal x-ray series may show a distended stomach consistent with gastroparesis, bowel loops with fluid levels

The management of bloating

#### **IBS-related bloating**

For bloating associated with IBS, management involves making a firm diagnosis of IBS and educating the patient regarding its aetiology and benign nature. The therapeutic goal is a reduction in the severity and frequency of symptoms and an overall improvement in the patient's quality of life. Identification of psychosocial stressors that trigger or maintain symptoms and strategies to reduce stress will help reduce patients' symptoms.<sup>16</sup> Usually a sympathetic discussion is all that is required; however, additional input from social workers, psychologists or psychiatrists may be required for some patients.

#### **Reducing gastrointestinal gas**

Swallowed air is the major source of stomach gas and may be increased by eating rapidly, gulping liquids, nervousness, carbonated beverages, smoking or chewing gum. Colonic gas production is increased with 'colonic' foods (foods that are incompletely digested in the small intestine but are used by the resident bacteria in the colon in a beneficial way). These are the residue (or fibre-containing) foods, such as legumes, beans, onions, celery, cabbage, brussel sprouts, broccoli, cauliflower and whole grains.<sup>17</sup> Reducing the intake of these foods may help some patients (a low residue/low fibre diet). A trial of restricted lactose intake may improve bloating caused by lactase deficiency.

It is, however, important to maintain a regular bowel habit by a regular and appropriate intake of fluid and fibre. Fibre supplementation is effective for constipation-predominant IBS, but in trials does not improve symptoms of diarrhoea or abdominal pain, and importantly can make bloating worse if there is too much or it is taken sporadically.<sup>18,19</sup> Some noncoeliac patients with bloating will respond to a gluten-free diet, probably because of the reduced fibre intake when wheat is cut out of the diet.<sup>20</sup>

laxative therapy.

consistent with intestinal pseudo-

obstruction, or an oedematous, thick-

ened bowel wall consistent with infection

or inflammatory bowel disease. Abdomi-

nal x-ray may also confirm constipation and faecal loading as a cause of bloating; however, awareness of the possibility of over-reporting of faecal loading (where,

in fact, a physiological distribution of

faeces is present) will avoid unnecessary

diagnosis of gastroparesis, in which the

usual findings are a food and/or fluid

Upper endoscopy is useful in the

#### Pharmacological agents

#### **Prokinetic agents**

Prokinetic agents such as metoclopramide (Maxolon) and cisapride (Prepulsid) have been shown to be helpful for improving abdominal discomfort and bloating in a small number of clinical trials, but are 'in the small print' compared to a sympathetic ear and explanation.<sup>21,22</sup> Cisapride now has restricted availability.

#### Antispasmodics

Chronic use of antispasmodic agents is unhelpful in the experience of the authors, although occasional use provides acute relief of abdominal discomfort. Analgesics and narcotics exacerbate the situation. Peppermint oil (Mintec) has been trialled for the management of abdominal discomfort associated with IBS, with conflicting results.<sup>23</sup> Peppermint oil has a relaxant effect on gastrointestinal smooth muscle, demonstrated by its worsening of gastro-oesophageal reflux symptoms. It may have an intestinal antispasmodic action.

#### Simethicone and charcoal

Other pharmacological agents used for treating gaseous complaints include simethicone and activated charcoal. These are available in single-agent formulations (simethicone: DeGas Capsules, Gasbusters, Medefoam-2; activated charcoal: Ad-sorb Charcotabs, Charcocaps, Nature's Own Charcoal 200 mg) and also in formulations containing other active ingredients.

#### Probiotics

A preliminary trial with VSL-3 suggests that probiotics may be

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residue in the stomach after a six-hour fast. Small intestinal biopsy is the gold standard test for coeliac disease and small intestinal infections. Barium meals and small bowel series give information about gastric motility, and in the case of the latter, show gross abnormality of small intestinal mucosal architecture. Colonoscopy permits visualisation of any changes and the taking of biopsy specimens for histopathology. Abdominal ultrasound scan or CT scan can be useful in the diagnosis of portal hypertension, ascites and intra-abdominal malignancy (see Figure).

Breath hydrogen testing for bacterial overgrowth (and lactose malabsorption) in the small intestine relies on fermentation of substrate by bacteria and the subsequent release of excess hydrogen, which is detected in the exhaled breath. Small bowel bacterial overgrowth causing malabsorption and bloating from excessive bacterial gas production occurs in patients with conditions associated with intestinal stasis, such as previous gastric surgery with the creation of blind loops (Bilroth II procedure), strictures,

beneficial in diarrhoea-predominant IBS, and may even decrease bloating.24

The current data for clinical usefulness of probiotics, simethicone and activated charcoal are limited.<sup>25,26</sup>

#### Antidepressant agents

Pain perception modulation with low dose tricyclic antidepressants has been shown to be effective in IBS in a number of randomised controlled trials.<sup>27</sup> Some studies indicate greater benefit in patients with diarrhoea-predominant IBS.<sup>28,29</sup> The beneficial effect of these drugs on IBS symptoms, and bloating in particular, is not explained by their antidepressant action because much higher doses are required to treat depression. Anticholinergic side effects of these drugs are uncommon at low doses. SSRIs do not improve IBS symptoms, but do improve the reporting by patients of overall wellbeing.<sup>30</sup>

#### Serotonin receptor agonists

Drugs targeting specific serotonin receptors on enteric sensory neurons have an emerging role in the management of IBS.<sup>31</sup> Alosetron, a serotonin-3 receptor antagonist, reduces diarrhoea and urgency.<sup>32</sup> Randomised, double-blind, placebo-controlled trials of alosetron 1 mg twice daily showed absolute responses of 12% (p<0.05) and 17% (p<0.001) in women with IBS without constipation compared with the placebo group.<sup>33,34</sup> Side effects of alosetron included constipation in 25 to 30% of patients and ischaemic colitis in about one in 700 patients.<sup>35</sup> This drug, and a similar compound, cilansetron, are not currently available in Australia.

Tegaserod (Zelmac), a serotonin-4 receptor partial agonist, accelerates small bowel transit and caecal filling at a dose of 2 mg twice daily in patients with IBS.<sup>36</sup> In constipation-predominant IBS, tegaserod 6 mg twice daily reduced pain and constipation at one and three months, as compared with placebo.<sup>37,39</sup> There was an absolute improvement at three months in global symptoms of IBS of 9.3% compared with the placebo group, but the effect on bloating was not consistent across the studies.<sup>40</sup> Tegaserod should be reserved mainly for women with constipation-predominant IBS refractory to fibre supplementation and laxatives.

adhesions and chronic intestinal pseudoobstruction. The breath hydrogen level rises quickly following ingestion of a normally well absorbed substrate such as glucose when bacterial overgrowth is present. A raised fasting breath hydrogen level (above 10 ppm) occurs typically with pneumatosis cystoides intestinalis, where it may be in the 1000 ppm range even with fasting.

#### Conclusion

Bloating is a common complaint that is due in most cases to functional gastrointestinal disorders. Few investigations are required in these cases. However, a small number of patients will have alternative diagnoses suggested by careful history taking and examination. Where 'alarm' symptoms and signs are present, directed investigations are suggested. MI

A list of references is available on request to the editorial office.

#### **Further reading**

 Rogers J, Henry MM, Misiewicz JJ. Increased segmental activity and intraluminal pressures in the sigmoid colon of patients with the irritable bowel syndrome. Gut 1989; 30: 634-641.
 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 1987; 92: 1885-1893.

3. Florin TH. Alkyl halides, super hydrogen production and the pathogenesis of pneumatosis cytoides coli. Gut 1997; 41: 778-784.

4. Florin TH, Hills BA. Does counterperfusion supersaturation cause gas cysts in pneumatosis cystoides coli, and can breathing heliox reduce them? Lancet 1995; 345: 1220-1222.

 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel syndrome. BMJ 1978; 2: 653-654.
 Thompson WG, Dotevall G, Drossman DA, et al. Irritable bowel syndrome: guidelines for the diagnosis. Gastroenterol Int 1989; 2: 92-95.

#### **DECLARATION OF INTEREST: None**

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#### References

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 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 1987; 92: 1885-1893.

 Florin TH. Alkyl halides, super hydrogen production and the pathogenesis of pneumatosis cytoides coli. Gut 1997; 41: 778-784.

 Florin TH, Hills BA. Does counterperfusion supersaturation cause gas cysts in pneumatosis cystoides coli, and can breathing heliox reduce them? Lancet 1995; 345: 1220-1222.

 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel syndrome. BMJ 1978; 2: 653-654.

 Thompson WG, Dotevall G, Drossman DA, et al. Irritable bowel syndrome: guidelines for the diagnosis. Gastroenterol Int 1989; 2: 92-95.

 Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lisner SA. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(Suppl 2): II43-II47.

 Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol 1999; 94: 2912-2917.
 Saito YA, Locke GR, Talley NJ, Zinsmeister AR, Fett SL, Melton LJ 3rd. A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome. Am J Gastroenterol 2000; 95: 2816-2824.

10. Hamm LR, Sorrells SC, Harding J,P et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria. Am J Gastroenterol 1999; 94: 1279-1282.

 Cash BD, Chey WD. Irritable bowel syndrome – an evidence-based approach to diagnosis. Aliment Pharmacol Ther 2004; 19: 1235-1245.

 Schmulson MW, Chang L. Diagnostic approach to the patient with irritable bowel syndrome. Am J Med 1999; 107(5A): 20S-26S.

 Sanders DS, Carter MJ, Hurlstone DP, et al.
 Association of adult coeliac disease with irritable bowel syndrome: a case control study in patients fulfilling the Rome II criteria referred to secondary care. Lancet 2001; 358: 1504-1508.  Maki M. The humoral immune system in coeliac disease. Baillieres Clin Gastroenterol 1995; 9: 231-249.
 Kelly CP. Coeliac disease: non-invasive tests to screen for gluten sensitive enteropathy and to monitor response to dietary therapy. Dublin University, Trinity College, Dublin 1995.

 Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long term prognosis and the physician–patient interaction. Ann Intern Med 1995; 122: 107-112.
 James SL, Muir JG, Curtis SL, Gibson PR. Dietary fibre: a roughage guide. Intern Med J 2003; 33: 291-296.
 Lucey MR, Clark ML, Lowndes JO, Dawson AM. Is

bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study. Gut 1987; 28: 221-225.

 Cann PA, Read NW, Holdsworth CD. What is the benefit of coarse wheat bran in patients with irritable bowel syndrome? Gut 1984; 25: 168-173.

20. Jones VA, McLaughlan P, Shorthouse M, Workman E, Hunter JO. Food intolerance: a major factor in the pathogenesis of irritable bowel syndrome. Lancet 1982;
2: 1115-1117.

 Johnson AG. Controlled trial of metoclopramide in the treatment of flatulent dyspepsia. BMJ 1971; 2: 25-26.
 Van Outryve M, Milo R, Toussaint J, Van Eeghem P. 'Prokinetic' treatment of constipation-predominant irritable bowel syndrome: a placebo-controlled study of cisapride. J Clin Gastroenterol 1991; 13: 49-57.
 Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. Am J Gastroenterol 1998; 93: 1131-1135.

 Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2003; 17: 895-904.
 Friis H, Bode S, Rumessen JJ, Gudmand-Hoyer E. Effect of simethicone on lactulose-induced H2 production and gastrointestinal symptoms. Digestion 1991; 49: 227-230.
 Hall RG Jr, Thompson H, Strother A. Effects of orally administered activated charcoal on intestinal gas. Am J Gastroenterol 1981; 75: 192-196.

27. Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. Am J Med 2000; 108: 65-72.

28. Greengaum DS, Mayle JE, Vanegeren LE, et al. Effects of desipramine on irritable bowel syndrome compared

with atropine and placebo. Dig Dis Sci 1987; 32: 257-266.
29. Lancaster-Smith MJ, Prout BJ, Pinto T, Anderson JA, Schiff AA. Influence of drug treatment on the irritable bowel syndrome and its interaction with psychoneurotic morbidity. Acta Psychiatr Scand 1982; 66: 33-41.
30. Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. Am J Gastroenterol 2004; 99: 914-920.
31. Mertz HR. Irritable bowel syndrome. N Engl J Med 2003; 349: 2136-2146.

Gunput MD. Clinical pharmacology of alosetron.
 Aliment Pharmacol Ther 1999; 13(Suppl 2): 70-76.
 Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med 2001; 16: 1733-1740.

 Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000; 355: 1035-1040.
 Friedel D, Thomas R, Fisher RS. Ischemic colitis during treatment with alosetron. Gastroenterology 2001; 120: 557-560.

 Prather CM, Camilleri M, Zinsmeister AR, McKinzie
 Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000; 118: 463-468.
 Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003; 52: 671-676.
 Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002; 16: 1877-1888.

 Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001; 15: 1655-1666.
 Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. Chichester: John Wiley.