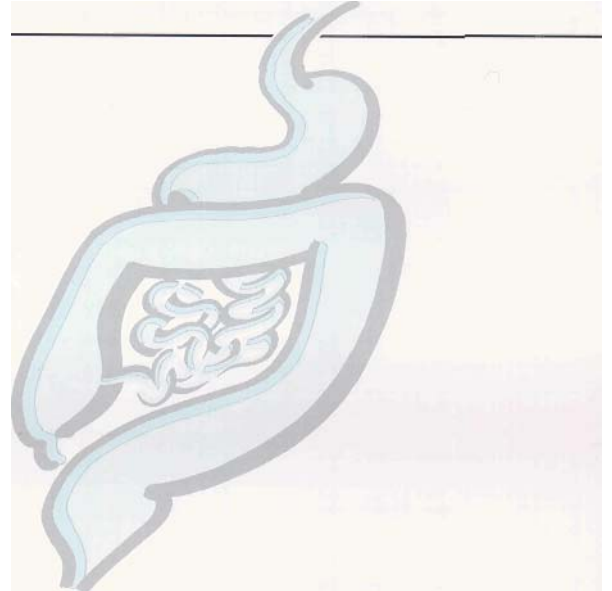


## Functional Bowel Disorders



Recent Advances 12

A review of current literature by  
L A. Houghton and P. J. Whorwell



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## **Editorial Policy**

Despite accounting for a major portion of the gastroenterologist's workload, functional bowel disorders still receive relatively little attention from a research point of view - although there are signs that this situation may be slowly changing. The major journals are not overburdened with papers on the subject and consequently definitive publications tend to be scattered throughout the literature and hard to track down. Furthermore, for those of us undertaking research in this area, presenting work at major meetings can pose difficulties as many learned societies do not even have a functional bowel category. Authors are then left with the problem of having to decide, to which of a series of sections, such as "stomach", "colon", "colorectal" or "motility", their work is most suited. Fortunately, the American Gastroenterological Association has had the foresight to introduce a functional bowel disorder category and it is to be hoped that others will follow this lead.

The purpose of this booklet is to try and bring together under one cover as many publications as possible on the subject of functional bowel disorders relevant to clinical practice. The references are listed under five main headings: "irritable bowel syndrome", "functional dyspepsia", "functional oesophageal disorders", "pharmacology" and "miscellaneous" - inevitably, this latter heading contains an assortment of conditions that some

people might classify differently. However, these categories are only intended as a general guide and when a paper covers several topics, it may be listed in more than one place. In some cases it can be difficult to decide whether a topic should be classified under functional bowel disorders at all and some arbitrary decisions had to be made. For instance, we decided to exclude the majority of oesophageal disorders because they are covered adequately elsewhere. Thus, we have only listed references on oesophageal problems where a strong functional element is currently suggested - eg. angiogram negative chest pain. In order to facilitate more selective scanning of titles, each heading is further sub-divided into clinical and non-clinical with the latter covering items of a more mechanistic nature. Animal work has been excluded all together.

Each issue is accompanied by a brief editorial written around a collection of publications which either illustrate a particular theme or are especially topical. The abstracts of papers chosen for editorial comment are published in full but in no way does this imply that these are necessarily judged to be the best pieces of research for the period covered by that issue of booklet.

We hope this booklet will help to keep busy clinicians abreast of developments in the world of functional bowel disorders and possibly stimulate further research in this difficult area.

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## Review of abstracts

Following on from our review of the literature in booklet 11, interest in the role of infection in the pathogenesis of irritable bowel syndrome (IBS) continues<sup>1</sup>, with further evidence supporting an inflammatory process involved in post-infectious IBS<sup>2</sup>. This study demonstrates that patients who develop IBS after gastroenteritis exhibit greater IL-1beta mRNA expression, both during and after the infection, compared with individuals who do not develop post infectious IBS<sup>2</sup>, whilst another study suggests that the mucosal inflammation associated with coeliac disease may have a sensitizing effect or predispose a patient to IBS type symptoms<sup>3</sup>. However in contrast to current dogma, it has been suggested that IBS may be in fact more frequent "before" diagnosis in individuals with bacterial gastroenteritis who present to their primary care physician than those who do not<sup>4</sup>, and that the incidence of IBS is no different between those travellers who do and do not develop gastroenteritis<sup>5</sup>. Furthermore, it appears unlikely that acquired lactose intolerance has a role to play in the symptomatology of post infectious IBS<sup>6</sup>.

Irritable bowel syndrome is significantly more common in women than men raising the possibility of a role for sex hormones in its pathogenesis. Thus it is of interest to read that hormone replacement therapy might be associated with an increased risk of IBS similar to that observed among pre-menopausal women<sup>7</sup>. In addition, male and female patients with non-constipation predominant IBS appear to differ in activation of their brain networks concerned with cognitive, autonomic, and antinociceptive responses to delivered and anticipated aversive visceral stimuli<sup>8</sup> as well as in synthesis of brain serotonin (5-HT)<sup>9</sup>. A role for 5-HT in the post-prandial exacerbation of symptoms in female patients with diarrhoea predominant IBS is also supported by the observation that symptoms following meal ingestion is associated with elevated levels of plasma 5-HT compared to when no symptoms are generated in either patients or

healthy controls<sup>10</sup>. Whether meal ingestion in these female patients increased visceral sensitivity, as has been suggested by previous studies (Gut 2001; 48: 20) is unknown but it is noteworthy that the 5-HT<sub>3</sub> receptor antagonist alosetron, tends to reduce colonic sensitivity to duodenally infused lipid in patients with diarrhoea predominant IBS<sup>11</sup>.

Increased visceral sensitivity of the gastrointestinal tract to mechanical and chemical stimulants is now generally believed to be an important factor in the pathogenesis of IBS. It has been suggested that rectal hypersensitivity is a biological marker for IBS (Gastroenterology 1995; 109: 40) and in an evaluation of the diagnostic potential of this phenomenon a Canadian group have claimed that it might have considerable utility in separating IBS from other causes of abdominal pain<sup>12</sup>. However, it should be remembered that a proportion of constipation predominant IBS patients have reduced sensitivity (Gut 1990; 31: 458, Gastroenterology 2000; 118 (Suppl 2): 830, Gut 1998; 43: 388), and recognising this alteration in rectal sensation may help the management of this and other hindgut disorders<sup>13</sup>.

The prevalence, symptom pattern and impact of IBS between countries was assessed in a recent collaborative study across eight European nations in which over forty thousand community individuals were approached. The overall prevalence was 11.5% but varied considerably between countries with the majority of cases being undiagnosed<sup>14</sup>. The prevalence and bowel habit sub-types also depended on the diagnostic criteria used (Mannings, Rome I and Rome II) indicating a limited utility of such criteria in the clinical setting and for the transferability of research findings<sup>14</sup>. Indeed most general practitioners in the UK have not even heard of these various criteria, never mind used them<sup>15</sup>. In addition, more general practitioners than hospital consultants believed functional GI disorders to have a largely psychological basis<sup>15</sup>. Psychopathology may not explain symptom change over time, but appears to be linked to the persistence of symptoms and increased health care seeking behaviour<sup>16</sup>. Anxiety<sup>17</sup>,



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somatic attributional style<sup>18</sup> and severe pain<sup>19</sup> all lead to increased health care use and cost, although psychological morbidity does not appear to predict whether a patient will decide to use either conventional or alternative health care<sup>20</sup>. Interestingly IBS patients with an alternating bowel habit appear to make greater demands on health care than other sub-types<sup>21</sup>. The economic burden of IBS on health care systems is now fairly well documented but now a recent study from the USA has attempted to quantitate the substantial costs of this disorder to the employer<sup>22</sup>.

Successful treatment for functional gastrointestinal disorders remains elusive. With further evidence for efficacy of tegaserod for IBS in the clinical trial setting<sup>23,24</sup> it will be of interest to see how this drug performs now it has reached the "market place" in

so many countries. Psychotherapy and paroxetine seem to have superiority to the routine medical treatment of IBS in improving health related quality of life with some suggestion that the effects of psychotherapy may persist longer<sup>25</sup>. Another subject of great interest in several areas of gastroenterology is the possible beneficial effect of probiotics. These agents are also being assessed in functional bowel disorders and a recent trial of VSL#3<sup>26</sup> was somewhat disappointing. However these agents vary in efficacy according to bacterial content so it is possible more promising formulations may be forthcoming. Whether the finding of altered opioidergic activity<sup>27</sup> or the elegant demonstration of antro-fundic dysfunction in patients with functional dyspepsia<sup>28</sup>, will lead to better therapeutic approaches remains to be determined.



## 1. Postinfectious irritable bowel syndrome.

Spiller RC

Gastroenterology, 2003, 124 (6), 1662-71.

A small but significant subgroup of patients with irritable bowel syndrome (IBS) report a sudden onset of their IBS symptoms after a bout of gastroenteritis. Population-based surveys show that although a history of neurotic and psychologic disorders, pain-related diseases, and gastroenteritis are all risk factors for developing IBS, gastroenteritis is the most potent. More toxigenic organisms increase the risk 11-fold, as does an initial illness lasting more than 3 weeks. Hypochondriasis and adverse life events double the risk for postinfective (PI)-IBS and may account for the increased proportion of women who develop this syndrome. PI-IBS is associated with modest increases in mucosal T lymphocytes and serotonin-containing enteroendocrine cells. Animal models and some preliminary human data suggest this leads to excessive serotonin release from the mucosa. Both the histologic changes and symptoms in humans may last for many years with only 40% recovering over a 6-year follow-up. Celiac disease, microscopic colitis, lactose intolerance, early stage Crohn's disease, and bile salt malabsorption should be excluded, as should colon cancer in those over the age of 45 years or in those with a positive family history. Treatment with Loperamide, low-fiber diets, and bile salt-binding therapy may help some patients. Serotonin antagonists are logical treatments but have yet to be evaluated.

## 2. Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome.

Gwee KA; Collins SM; Read NW; Rajnakova A; Deng Y; Graham JC; McKendrick MW; Moochhala SM Gut, 2003, 52 (4), 523-6.

Background and aims: Chronic bowel disturbances resembling irritable bowel syndrome (IBS) develop in approximately 25% of patients after an episode of infectious diarrhoea. Although we have previously shown that psychosocial factors operating at the time of, or prior to, the acute illness appear to predict the development of post-infectious IBS (PI-IBS), our finding of an increased inflammatory cell number in the rectum persisting for at least three months after the acute infection suggested that there is also an organic component involved in the development of PI-IBS. To evaluate this further, we measured expressions of interleukin 1beta (IL-1beta) and its receptor antagonist (IL-1ra) in these patients to provide additional evidence that the pathogenesis of PI-IBS is underpinned by an inflammatory process. METHODS: Sequential rectal biopsy samples were prospectively

obtained during and three months after acute gastroenteritis, from eight patients who developed post-infectious IBS (INF-IBS) and seven patients who returned to normal bowel habits after acute gastroenteritis (infection controls, INF-CON). Eighteen healthy volunteers who had not suffered from gastroenteritis in the preceding two years served as normal controls (NOR-CON). IL-1beta and IL-1ra gene expressions were assayed by reverse transcriptase-polymerase chain reaction, and their levels of expression were quantitated by optical densitometry after electrophoresis on agarose gel. RESULTS: INF-IBS patients exhibited significantly greater expression of IL-1beta mRNA in rectal biopsies than INF-CON patients both during and three months after acute gastroenteritis. Moreover, IL-1beta mRNA expression had increased in biopsies taken from INF-IBS patients at three months after the acute infection but no consistent change was observed in INF-CON patients. IL-1beta mRNA expression of INF-IBS patients at three months post gastroenteritis was significantly greater than NOR-CON whereas that of INF-CON patients was not significantly different from NOR-CON. Despite these differential changes in IL-1beta mRNA expression, no significant changes were observed in IL-1ra mRNA expression among the three groups. CONCLUSIONS: These findings indicate that those patients who develop IBS post infection exhibit greater IL-1beta mRNA expression, both during and after the infection, compared with individuals who do not develop PI-IBS. We conclude that such patients may be susceptible to inflammatory stimuli, and that inflammation may play a role in the pathogenesis of PI-IBS.

## 3. Celiac disease and irritable bowel-type symptoms.

O'Leary C; Wieneke P; Buckley S; O'Regan P; Cronin CC; Quigley EM; Shanahan F  
The American journal of gastroenterology, 2002, 97 (6), 1463-7.

OBJECTIVES: Previous reports have linked irritable bowel syndrome (IBS) etiologically with various forms of mucosal inflammation, including infectious enterocolitides and inflammatory bowel disease. The mechanism is uncertain but may involve sensitization by inflammatory mediators. The enteropathy of celiac disease has theoretical advantages as a study model because it can be controlled with dietary gluten exclusion; however, whether it also predisposes to functional bowel disorders is unclear. Therefore, we assessed the prevalence of IBS-type symptoms in adult celiac patients and correlated this with dietary compliance with gluten exclusion. METHODS: Adult patients (n = 150; 106 women and 44 men) with confirmed celiac disease were randomly selected from a computerized database of >350 patients, and were asked to complete a bowel questionnaire and the Short Form 36 Health Survey (SF-36). The control



group (n = 162; 133 women and 29 men) had no history of celiac disease and had similar mean age and sex profile. RESULTS: Of 150 celiac patients reviewed, 30 of 150 (20%) fulfilled the Rome criteria compared with eight of 162 (5%) controls. Of the celiac patients 10 of 46 (22%) had partial or no compliance with a gluten-free diet, whereas 20 of 104 patients (19%) adhered to the diet; this difference did not achieve statistical significance. Celiac patients with IBS-type symptoms had a markedly lower quality of life than those without, all eight domains being impaired to a clinically significant extent. Dietary gluten exclusion improved QOL in four of eight scales measured. CONCLUSIONS: The hypothesis that mucosal inflammation in celiac disease may have a sensitizing effect or may predispose to IBS-type symptoms is supported by these results. Failure to attain optimal subjective well-being is common in celiac patients, particularly in those with coexisting IBS. Compliance with a gluten-free diet confers some benefit.

**4. Is irritable bowel syndrome more common in patients presenting with bacterial gastroenteritis? A community-based, case-control study.**

Parry SD; Stansfield R; Jelley D; Gregory W; Phillips E; Barton JR; Welfare MR  
The American journal of gastroenterology, 2003, 98 (2), 327-31.

OBJECTIVE: Irritable bowel syndrome (IBS) has been reported to follow infectious diarrhea. Food-borne infections affect 76 million people in the United States and 9.4 million in England per year; of these, only a small percentage of patients see their doctor, and even fewer will have stool culture confirmation. We hypothesized that patients who present to their doctor with gastroenteritis and have positive stool samples may be different from the normal population with regard to their pre-existing bowel symptoms. Our aim was to determine if patients with bacterial gastroenteritis were more likely to have prior IBS, functional dyspepsia, or functional diarrhea, compared with a control population. METHODS: Between January, 2000 and January, 2001, subjects with stool positive bacterial gastroenteritis and control subjects from the same primary care practice were invited to participate. The main outcome measure was the presence of IBS, functional dyspepsia, or functional diarrhea diagnosed using self-report Rome II modular questionnaires. RESULTS: A total of 217 people with recent bacterial gastroenteritis and 265 community controls consented to participate in the study. Of these, 89/217 cases and 46/265 controls had one of the functional GI disorders (OR = 3.3; 95% CI = 2.17-5.00). IBS was present in 67 cases (31%) and 26 controls (10%) (OR = 4.1; 95% CI = 2.49-6.72). There was no statistically significant difference in the presence of prior functional dyspepsia or

functional diarrhea. CONCLUSIONS: IBS is more frequent before diagnosis in people with bacterial gastroenteritis presenting to their primary care physician than in community controls. Studies that examine the rate of IBS after bacterial gastroenteritis need to carefully exclude people with prior IBS in a systematic way.

**5. Post-traveler's diarrhea irritable bowel syndrome: a prospective study.**

Ilnyckyj A; Balachandra B; Elliott L; Choudhri S; Duerksen DR  
The American journal of gastroenterology, 2003, 98 (3), 596-9.

OBJECTIVE: Anecdotal evidence suggests that irritable bowel syndrome (IBS) can develop after an episode of traveler's diarrhea (TD). This observation supports a contemporary paradigm proposed for the etiology of IBS and may have important implications for public health strategies aimed at preventing TD. This study aimed to determine the incidence of IBS in people experiencing TD. METHODS: A total of 109 healthy adults traveling outside of Canada or the United States were identified and enrolled in a prospective, cohort field study. GI symptoms before and after travel were assessed using the Rome I criteria. Travel diaries and questionnaires were used to assess for TD. RESULTS: The incidence of TD in the study cohort was 44%. Among those experiencing TD, the incidence of IBS was 4.2%. In those not experiencing TD, the incidence of IBS post-travel was 1.6% (relative risk = 2.5, 95% CI = 0.2-27.2, p = 0.41, ns). There was no significant difference in the incidence of IBS between the exposed and nonexposed groups. CONCLUSIONS: This study does not support a large association between TD and an increased risk of developing IBS. A small increase in relative risk may have been undetected because of the size of the study.

**6. Is lactose intolerance implicated in the development of post-infectious irritable bowel syndrome or functional diarrhoea in previously asymptomatic people?**

Parry SD; Barton JR; Welfare MR  
European journal of gastroenterology & hepatology, 2002, 14(11), 1225-30.

OBJECTIVE: The relationship between lactose intolerance and post-infectious irritable bowel syndrome (IBS) in adults is uncertain. Bowel symptoms may persist after bacterial gastroenteritis and as post-infectious IBS. Acquired lactose intolerance may follow viral enteric infections in children. We compared the frequency of lactose intolerance after bacterial gastroenteritis in adults with and without symptoms of IBS or functional diarrhoea at 3-6-months' follow-up. DESIGN: A prospective cohort study was



conducted. **METHODS:** All subjects with bacterial gastroenteritis confirmed by stool culture from the microbiology laboratory and without prior IBS or functional diarrhoea were eligible to participate. IBS and functional diarrhoea were diagnosed via self-completed Rome II modular questionnaires. Lactose intolerance was determined from a rise in breath hydrogen and plasma glucose and symptoms. **RESULTS:** One hundred and twenty-eight subjects with bacterial gastroenteritis were followed prospectively, from which a smaller cohort of 42 subjects took part in this study. The cohort was comprised of 24/25 subjects who developed post-infectious IBS (n = 16) or functional diarrhoea (n = 8) (9 male, 15 female) and 18 random controls (8 male, 10 female) chosen from the group without IBS or functional diarrhoea. The mean age of the subjects was 44.4 years (range 25-76 years). In the group with functional diarrhoea or IBS, four subjects had failure of the plasma glucose to rise but none had abnormal glucose hydrogen breath tests. In the control subjects, one had a positive combined test and six had failure of plasma glucose to rise alone. No subject developed symptoms during the test. **CONCLUSIONS:** Bacterial gastroenteritis did not cause persistent lactose intolerance in our study population. Lactose intolerance does not appear to be implicated in the aetiology of post-infectious bowel symptoms, including IBS. Advice to avoid dairy products in patients presenting with post-infectious IBS on the basis that they may have lactose intolerance appears unnecessary in patients from northern England.

#### **7. Is hormone replacement therapy associated with an increased risk of irritable bowel syndrome?**

Ruigomez A; Garcia Rodriguez LA; Johansson S; Wallander MA  
Maturitas, 2003, 44 (2), 133-40.

**OBJECTIVE:** Hormonal status could be involved in the occurrence of irritable bowel syndrome (IBS). The authors examined the risk of developing IBS in women using hormone replacement therapy (HRT). **METHODS:** Women 50-69 years old with at least one prescription for HRT during 1994-1999 were identified from the General Practice Research Database in the UK (n=40, 119). An aged-matched cohort of 50000 women who never used HRT was sampled from the source population where the HRT cohort was ascertained. Women in the two cohorts were followed to assess the risk of development of IBS. Authors performed a nested case-control analysis to assess the role of duration, route and regimen of HRT use and other risk factors for IBS. The IBS diagnosis was validated by means of a questionnaire sent to the general practitioners (n=660). **RESULTS:** The incidence rate of IBS per 1000 person-years was 1.7 in the cohort of never HRT users and 3.8 among HRT users,

respectively. Both current and past users of HRT presented an increased risk of IBS compared to non-users, after adjusting for co-morbidity and consultation patterns. This increased risk was observed irrespective of treatment duration, regimen or route of administration of HRT. **CONCLUSION:** The result suggests that HRT use is associated with an increased risk of IBS similar to the one observed among younger premenopausal women with endogenous oestrogenic activity.

#### **8. Sex-related differences in IBS patients: central processing of visceral stimuli.**

Naliboff BD; Berman S; Chang L; Derbyshire SW; Suyenobu B; Vogt BA; Mandelkern M; Mayer EA  
Gastroenterology, 2003, 124 (7), 1738-47.

**BACKGROUND:** Women have a higher prevalence of irritable bowel syndrome (IBS) and possible differences in response to treatment, suggesting sex-related differences in underlying pathophysiology. The aim of this study was to determine possible sex-related differences in brain responses to a visceral and a psychological stressor in IBS. **METHODS:** Regional cerebral blood flow measurements using H(2)(15)O positron emission tomography were compared across 23 female and 19 male nonconstipated patients with IBS during a visceral stimulus (moderate rectal inflation) and a psychological stimulus (anticipation of a visceral stimulus). **RESULTS:** In response to the visceral stimulus, women showed greater activation in the ventromedial prefrontal cortex, right anterior cingulate cortex, and left amygdala, whereas men showed greater activation of the right dorsolateral prefrontal cortex, insula, and dorsal pons/periaqueductal gray. Similar differences were observed during the anticipation condition. Men also reported higher arousal and lower fatigue. **CONCLUSIONS:** Male and female patients with IBS differ in activation of brain networks concerned with cognitive, autonomic, and antinociceptive responses to delivered and anticipated aversive visceral stimuli.

#### **9. Sex differences of brain serotonin synthesis in patients with irritable bowel syndrome using alpha-[11 C] methyl-L-tryptophan, positron emission tomography and statistical parametric mapping.**

Nakai A; Kumakura Y; Boivin M; Rosa P; Diksic M; D'Souza D; Kersey K  
Canadian journal of gastroenterology = Journal canadien de gastroenterologie, 2003, 17 (3), 191-6.

**BACKGROUND:** Irritable bowel syndrome (IBS) is the most common functional bowel disorder and has a strong predominance in women. Recent data suggest that the brain may play an important role in the pathophysiology of



IBS in the brain-gut axis. It is strongly suspected that serotonin (5-HT), a neurotransmitter found in the brain and gut, may be related to the pathophysiology of IBS. It is reported that a 5-HT<sub>3</sub> antagonist is effective only in female patients with diarrhea-predominant IBS. **OBJECTIVE:** In the present study, 5-HT synthesis was measured using positron emission tomography, with alpha-[<sup>11</sup>C] methyl-L-tryptophan as the tracer, in patients with IBS. The aim of the present study was to compare 5-HT synthesis in the IBS patients with that in the controls, and to compare 5-HT synthesis between male and female IBS patients. **METHODS:** Six male and six female nonconstipated IBS patients were scanned. Age-matched healthy volunteers were scanned as controls. Eighty minute dynamic scans were performed. Functional 5-HT synthesis images were analyzed using statistical parametric mapping. **RESULTS:** 5-HT synthesis was greater only in the female IBS patients in the right medial temporal gyrus (multimodal sensory association cortex) compared with the female controls ( $P < 0.001$ ). **CONCLUSIONS:** The greater brain 5-HT synthesis in the female IBS patients than in the controls may be related to the pathological visceral pain processing of the IBS patients, a larger female predominance of the disorder, and the sex difference of the efficacy of the 5-HT<sub>3</sub> antagonist in treatment.

**10. Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome.**

Houghton LA; Atkinson W; Whitaker RP; Whorwell PJ; Rimmer MJ  
Gut, 2003, 52 (5), 663-70.

**BACKGROUND:** Meal ingestion is often associated with exacerbation of gastrointestinal symptoms in subjects with irritable bowel syndrome (IBS). Furthermore, recent preliminary data suggest that 5-hydroxytryptamine (5-HT) concentration in platelet poor plasma is elevated following meal ingestion in some subjects with diarrhoea predominant IBS (d-IBS) compared with healthy subjects, although it is not known whether this is related to postprandial symptomatology. **Aim:** To expand on previous data by evaluating a larger number of subjects but also to assess plasma 5-hydroxyindole acetic acid (5-HIAA) concentrations, 5-HT turnover, platelet 5-HT stores, and any relationship to symptomatology. **Methods:** We assessed platelet depleted plasma 5-HT and 5-HIAA concentrations for two hours (60 minute intervals) under fasting conditions, and then for a further four hours (30 minute intervals) after a standard carbohydrate meal (457 kcal), together with fasting platelet 5-HT concentrations in 39 female subjects with d-IBS (aged 19-52 years; mean age 33) and 20 healthy female volunteers (aged 20-46 years, mean

age 28). IBS symptomatology, in particular abdominal pain and bloating, and urgency to defecate were assessed throughout the study **RESULTS:** When related to fasting levels, there was no statistically significant difference in postprandial plasma 5-HT concentrations between d-IBS and healthy subjects. However, when fasting levels were not taken into consideration, d-IBS subjects exhibited higher postprandial plasma 5-HT concentrations compared with healthy subjects ( $p = 0.040$ ). Furthermore, d-IBS subjects who exhibited postprandial symptomatology had higher levels of postprandial plasma 5-HT, whether assessed with respect to fasting baseline levels ( $p = 0.069$ ) or not ( $p = 0.047$ ), compared with d-IBS subjects who did not report postprandial symptomatology. This appeared to be associated with a concomitant increase in plasma 5-HIAA ( $p = 0.16!$ ) but reduction in turnover ( $p = 0.058$ ). Lastly, d-IBS subjects had higher platelet concentrations of 5-HT than healthy subjects ( $p = 0.009$ ). **CONCLUSIONS:** These data suggest that postprandial symptomatology may be associated with increased platelet depleted plasma 5-HT concentrations in female subjects with d-IBS. In addition, the presence of increased platelet stores of 5-HT may act as a useful marker for the diagnosis and management of d-IBS.

**11. Lipid-induced colonic hypersensitivity in irritable bowel syndrome: the role of 5-HT<sub>3</sub> receptors.**

Simren M; Simms L; D'Souza D; Abrahamsson H; Bjoernsson ES  
Alimentary pharmacology ft therapeutics, 2003, 17 (2), 279-87.

**BACKGROUND:** Irritable bowel syndrome patients demonstrate colonic hypersensitivity after duodenal lipid infusion. **AIM:** To investigate the role of 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptors in this sensory component of the gastrocolonic response in irritable bowel syndrome. **METHODS:** Fifteen female patients with diarrhoea-predominant irritable bowel syndrome completed a trial with the 5-HT<sub>3</sub> receptor antagonist alosetron (1 mg b.d.) or placebo (b.d.) over 15 days, followed by the alternative treatment. Each treatment period was followed by a colonic distension trial before and after duodenal lipids. Changes in colonic thresholds, tone and compliance and viscerosomatic referral pattern after lipids were compared between treatments. **RESULTS:** With placebo, the colonic thresholds after lipids were significantly reduced for all studied sensations, whereas, with alosetron, the thresholds were significantly reduced only for first sensation and discomfort, but not for gas and pain. The reductions in thresholds did not differ significantly between treatments, but the pain threshold after alosetron tended to be less reduced compared with placebo ( $P = 0.10$ ). The effects of lipids on tone, compliance and viscerosomatic referral pattern were



unaffected by alosetron relative to placebo. **CONCLUSIONS:** 5-HT<sub>3</sub> receptor antagonism reduces the lipid-induced colonic hypersensitivity in irritable bowel syndrome. However, 5-HT<sub>3</sub> receptors do not seem to be the principal mediator, but may be a cofactor for the exaggerated sensory component of the gastrocolonic response in irritable bowel syndrome.

**12. Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds.**

Bouin M; Plourde V; Boivin M; Riberdy M; Lupien F; Laganier M; Verrier P; Poitras P *Gastroenterology*, 2002, 122 (7), 1771-7.

**BACKGROUND & AIMS:** Visceral hypersensitivity was detected in patients with functional gastrointestinal disorders and has been proposed as a biological marker of irritable bowel syndrome (IBS). The purpose of this study was to assess the sensitivity, specificity, and the predictive values of pain thresholds evaluated by rectal distention using an electronic barostat in patients with or without IBS and in control subjects. **METHODS:** Patients were diagnosed according to Rome II criteria. Rectal sensory thresholds were determined in 164 patients (86 IBS patients, 26 painless constipation, 21 functional dyspepsia, and 31 miscellaneous conditions) and in 25 normal controls. All subjects underwent a series of rectal isobaric distentions using an electronic barostat. The bag was progressively distended from 0 to 48 mm Hg and, in response to distention, subjects reported on discomfort or pain. **RESULTS:** Pain thresholds were lower in IBS patients (30.4 ± 6.7 mm Hg) compared with controls (44.5 ± 5), painless constipated (45.4 ± 5.3), functional dyspepsia (39.4 ± 7.8), and miscellaneous patients (43.2 ± 5.5). At the level of 40 mm Hg, the sensitivity of the rectal barostat to identify IBS patients from normal subjects and non-IBS patients was 95.5% and its specificity was 71.8%. The positive predictive value was 85.4%. The negative predictive value was 90.2%. **CONCLUSIONS:** Lowered rectal pain threshold is a hallmark of IBS patients. Rectal barostat testing is useful to confirm the diagnosis of IBS and to discriminate IBS from other causes of abdominal pain.

**13. Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and fecal incontinence.**

Gladman MA; Scott SM; Chan CL; Williams NS; Lunniss PJ *Diseases of the colon and rectum*, 2003, 46 (2), 238-46.

**PURPOSE:** Blunted rectal sensation, or rectal hyposensitivity, has been reported anecdotally in patients with functional disorders of evacuation and continence. The purpose of this

study was to determine the prevalence of rectal hyposensitivity and whether the finding of such an abnormality was associated with any clinical impact. **METHODS:** One thousand three hundred fifty-one patients, referred for anorectal physiologic investigation, were divided according to presenting symptoms into the following categories: constipation (subdivided into infrequency of and/or obstructed defecation), fecal incontinence (subdivided into passive, postdefecation, and urge incontinence), fecal incontinence and constipation, or "other." Rectal hyposensitivity was judged to be present when at least one of the sensory threshold volumes was elevated beyond the normal range (mean plus 2 standard deviations). The prevalence of rectal hyposensitivity was then calculated in each group and in relation to other investigations. **RESULTS:** Rectal hyposensitivity was present in 16 percent of patients, with males and females equally affected. Twenty-three percent of patients with constipation, 10 percent of patients with fecal incontinence, 27 percent of patients with incontinence associated with constipation, and only 5 percent of patients with other symptoms were found to have rectal hyposensitivity. In patients with obstructed defecation, rectal hyposensitivity was present in 33 percent with rectocele, 40 percent with intussusception, and 53 percent with no mechanical obstruction evident on evacuation proctography. **CONCLUSION:** Rectal hyposensitivity is common in patients with constipation and/or fecal incontinence and may thus be important in the etiology of such conditions. Although the clinical relevance of this physiologic abnormality is unknown, its presence may have implications regarding the management of hindgut dysfunction and particularly the selection of patients for surgery.

**14. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects.**

Hungin AP; Whorwell PJ; Tack J; Mearin F *Alimentary pharmacology & therapeutics*, 2003, 17 (5), 643-50.

**AIM:** To determine the prevalence, symptom pattern and impact of the irritable bowel syndrome, across eight European countries, using a standardized methodology. **METHODS:** A community survey of 41 984 individuals was performed using quota sampling and random digit telephone dialing to identify those with diagnosed irritable bowel syndrome or those meeting diagnostic criteria, followed by in-depth interviews. **RESULTS:** The overall prevalence was 11.5% (6.2-12%); 9.6% had current symptoms, 4.8% had been formally diagnosed and a further 2.9%, 4.2% and 6.5% met the Rome II, Rome I or Manning criteria, respectively. Bowel habit classification varied by



criteria: 63% had an 'alternating' bowel habit by Rome II vs. 21% by self-report. On average, 69% reported symptoms lasting for 1 h, twice daily, for 7 days a month. Irritable bowel syndrome sufferers reported more peptic ulcer (13% vs. 6%), reflux (21% vs. 7%) and appendectomy (17% vs. 11%), but not hysterectomy, cholecystectomy or bladder procedures. Ninety per cent had consulted in primary care and 17% in hospital; 69% had used medication. Irritable bowel syndrome substantially interfered with lifestyle and caused absenteeism. **CONCLUSIONS:** Irritable bowel syndrome is common with major effects on lifestyle and health care. The majority of cases are undiagnosed and the prevalence varies strikingly between countries. Diagnostic criteria are associated with varying prevalences and bowel habit sub-types. This limits their utility in clinical practice and the transferability of research findings using them.

### 15. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders.

Gladman LM; Gorard DA  
Alimentary pharmacology 8t therapeutics, 2003, 17 (5), 651-4.

**BACKGROUND:** Functional gastrointestinal symptoms generate a large workload in primary care. Research on functional gastrointestinal disorders is focused on hospital patients, but these patients may differ from those managed in primary care. **AIM:** To investigate any differences in attitudes of general practitioners and hospital specialists towards functional gastrointestinal illnesses. **METHODS:** A questionnaire was sent to 200 general practitioners and 200 British Society of Gastroenterology members. **RESULTS:** The response rate was 76%. Sixty-two general practitioners believed that functional gastrointestinal symptoms represented a 'real' currently unexplained gastrointestinal disorder, and 67 believed such symptoms probably represented somatization of a psychological illness. In contrast, most consultants (120) believed that functional gastrointestinal symptoms represented a 'real' gastrointestinal disorder, with only 36 perceiving them to have a psychological basis ( $\chi^2 = 26.7, P < 0.001$ ). More consultants than general practitioners believed that the understanding of functional gastrointestinal disorders had improved in the last 20 years ( $\chi^2 = 4.31, P < 0.05$ ). Most consultants and most general practitioners thought that treatment for these disorders had not improved over this period. Only 21% of general practitioners had heard of the Manning criteria for the diagnosis of irritable bowel syndrome, compared to 81% of consultants ( $\chi^2 = 107, P < 0.0001$ ); 12% of general practitioners and 83% of consultants had heard of the Rome criteria for the diagnosis of functional gastrointestinal disorders ( $\chi^2 = 154, P < 0.0001$ ); 37% of consultants used the Manning

criteria and 40% used the Rome criteria; 11% of general practitioners used the Manning criteria and 3% used the Rome criteria. **CONCLUSIONS:** General practitioners and consultants have differing views on functional gastrointestinal disorders. In both primary and secondary care, most doctors do not use diagnostic criteria. Further research on the factors used to diagnose functional gastrointestinal disorders in primary care is warranted.

### 16. Does psychological distress modulate functional gastrointestinal symptoms and health care seeking? A prospective, community cohort study.

Koloski NA; Talley NJ; Boyce PM  
American Journal of Gastroenterology, 2003, 98/4 (789-797).

**OBJECTIVE:** Little is known about the natural history of functional GI symptoms, including what factors influence GI symptom patterns and health care seeking for them over the long term. We aimed to determine whether psychological factors play a role in the development and long-term course of these symptoms. **METHODS:** A random sample of community subjects ( $n = 361$ ) who reported having unexplained abdominal pain for (greater-than or equal to) 1 month in a previous population survey were included in the study. Controls ( $n = 120$ ) were defined as not having abdominal pain for (greater-than or equal to) 1 month from this initial survey. Subjects were prospectively followed up via a questionnaire every 4 months over a 12-month period. The questionnaire asked about the presence of GI symptoms over the past week and psychological distress over the past 3 wk (psychological caseness being defined as a score of (greater-than or equal to) 2 of 12 on the General Health Questionnaire). The number of visits made to a physician or medical specialist over the past 4 months was evaluated. **RESULTS:** GI symptoms were common among community controls and subjects with abdominal pain. Similar onset and disappearance rates were observed for the majority of GI symptom categories, accounting for the stability of the prevalence rates over a 1-yr period. Changes in a state measure of psychological distress were not significantly associated with changes in GI symptom status between the 4- and 8-month ( $r = 0.14, p = 0.08$ ) and 8- and 12-month ( $r = 0.02, p = 0.77$ ) follow-ups. Baseline psychological distress, however, was an independent predictor of having persistent GI symptoms, including abdominal pain, bloating, and constipation, and frequently seeking health care for GI symptoms over 1 yr. **CONCLUSIONS:** Psychological distress levels do not seem to be important in explaining GI symptom change over a 1-yr period. Psychological distress, however, is linked to having persistent GI symptoms and frequently seeking health care for them over time. Clinicians should consider psychological



factors in the treatment of this subset of irritable bowel syndrome patients.

**17. Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study.**

Hu WH; Wong WM; Lam CL; Lam KF; Hui WM; Lai KC; Xia HX; Lam SK; Wong BC *Alimentary pharmacology & therapeutics*, 2002, 16 (12), 2081-8.

**AIMS:** To study the prevalence of dyspepsia and irritable bowel syndrome and the effects of co-existing anxiety and depression on health care utilization by a population survey in Chinese. **METHODS:** Ethnic Chinese households were invited to participate in a telephone survey using a validated bowel symptom questionnaire and the hospital anxiety and depression scale. Gastrointestinal symptoms were classified as dyspepsia and irritable bowel syndrome according to the Rome I criteria and gastro-oesophageal reflux disease by the presence of weekly heartburn or acid regurgitation. The anxiety and depression scores were compared between patients who sought medical attention and those who did not, using multiple logistic regression analysis. **RESULTS:** One thousand, six hundred and forty-nine subjects completed the interview (response rate, 62%). The population prevalences of dyspepsia, irritable bowel syndrome and gastro-oesophageal reflux disease were 18.4%, 4.1% and 4.8%, respectively. Dyspepsia and irritable bowel syndrome were associated with anxiety, depression, medical consultation, sick leave and adverse effects on social life. The degree of anxiety was an independent factor associated with health care-seeking behaviour in both dyspeptics ( $P = 0.003$ ) and irritable bowel syndrome patients ( $P = 0.036$ ). **CONCLUSIONS:** Irritable bowel syndrome and dyspepsia are associated with anxiety, depression, significant social morbidity, health care utilization and days off work. Anxiety is an independent factor in determining health care utilization in patients with dyspepsia and irritable bowel syndrome.

**18. Cognition and the body: Somatic attributions in Irritable Bowel Syndrome.**

Martin M; Crane C  
*Behavioural and Cognitive Psychotherapy*, 2003, 31/1 (13-31).

How do somatic causal attributions for symptoms relate to treatment seeking behaviour in Irritable Bowel Syndrome (IBS)? How might a tendency to make somatic attributions influence an individual's cognitive representation of their illness once a diagnosis of IBS is established? In Study 1 attributions about symptoms were investigated in

treatment-seekers and non treatment-seekers with IBS. Treatment-seekers had an increased tendency to make somatic attributions for both gastrointestinal symptoms and physiological symptoms characteristic of anxiety and depression, although they did not differ from non treatment-seekers in the severity of these symptoms or in their reports of psychological distress. Treatment-seekers also perceived themselves to be significantly less resistant to illness and to be significantly more likely to have poor health in the future than non treatment-seekers. In Study 2, 20 treatment seekers with chronic symptoms of IBS completed measures of mood and of the degree to which they viewed a range of symptoms as a part of their IBS. Physiological symptoms of anxiety and depression were seen as a part of IBS by a considerable proportion of the sample. Higher levels of depression were associated with an increased tendency to see physiological symptoms of anxiety and depression and even symptoms of colds as "a part of" IBS. It is concluded that a somatic attributional style may contribute both to initial treatment seeking for symptoms of IBS and the subsequent maintenance and exacerbation of the disorder once a diagnosis is established.

**19. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective.**

Longstreth GF; Wilson A; Knight K; Wong J; Chiou CF; Barghout V; Freeh F; Ofman JJ *The American journal of gastroenterology*, 2003, 98 (3), 600-7.

**OBJECTIVE:** We performed an evaluation of patient symptoms, health care use, and costs to define the burden of illness of irritable bowel syndrome (IBS) and the relation to the severity of abdominal pain/discomfort in a large health maintenance organization. **METHODS:** All 6500 adult health maintenance organization members who had undergone flexible sigmoidoscopy in the year 2000 were mailed a questionnaire that elicited Rome I symptom criteria and severity ratings for abdominal pain/discomfort. Multiple health care use measures were obtained from various administrative databases. IBS patients were compared with a control group of non-IBS subjects, and analyses were adjusted for age and sex. **RESULTS:** We received 2613 (40.2%) responses. Compared with non-IBS subjects over 2 yr, IBS patients had more outpatient visits (medical, surgery, and emergency,  $p < 0.05$ ), were hospitalized more often ( $p < 0.05$ ), and had more total outpatient prescriptions ( $p < 0.05$ ) and IBS-related prescriptions ( $p < 0.05$ ). Over 1 yr, total costs were 51% higher in IBS patients, who also had higher costs for outpatient visits, drugs, and radiology and laboratory tests ( $p < 0.05$ ). Total costs were increased by 35%, 52%, and 59% in IBS patients with mild, moderate, and severe



symptoms of abdominal pain/discomfort compared with non-IBS subjects ( $p < 0.05$ ). CONCLUSIONS: Using Rome I symptom criteria, we found that IBS is associated with a broad pattern of increased health care use and costs. The severity of abdominal pain/discomfort is a significant predictor of health care use and costs for patients with IBS compared with non-IBS subjects.

**20. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia.**

Koloski NA; Talley NJ; Huskic SS; Boyce PM  
Alimentary pharmacology & therapeutics, 2003, 17(6), 841-51.

BACKGROUND: The drivers of conventional and, especially, alternative health care use for irritable bowel syndrome and functional dyspepsia are not clear. AIM: To determine the predictors of conventional and alternative health care use for irritable bowel syndrome and functional dyspepsia. METHODS: Two hundred and seven subjects with irritable bowel syndrome or functional dyspepsia, identified from a previous population survey, were included in the study. Individuals with irritable bowel syndrome/functional dyspepsia were defined as consulters ( $n = 103$ ) if they had visited their doctor for gastrointestinal symptoms more than once in the past year. Controls ( $n = 100$ ) did not report having any abdominal pain. Subjects were given structured interviews to assess the Diagnostic and Statistical Manual - version IV (DSM-IV) and International Classification of Disorders - version 10 (ICD-10) psychiatric diagnosis for anxiety, depression, somatization or any psychiatric diagnosis, aspects of health care use and symptom factors. RESULTS: About one-half ( $n = 103$ , 49.8%) of community subjects with irritable bowel syndrome/functional dyspepsia had sought conventional care for gastrointestinal symptoms in the past 12 months. Lifetime rates for alternative health care use for gastrointestinal symptoms were 20.8% ( $n = 43$ ). Independent predictors of conventional health care use were more frequent abdominal pain, greater interference of gastrointestinal symptoms with work and activities and a greater satisfaction with the physician-patient relationship. Being female independently predicted alternative health care use. CONCLUSIONS: Psychological morbidity did not predict conventional or alternative health care use for gastrointestinal symptoms. Other factors were more important.

**21. Irritable bowel syndrome subtypes according to bowel habit: revisiting the alternating subtype.**

Mearin F; Balboa A; Badia X; Baro E; Caldwell E; Cucala M; Diaz-Rubio M; Fueyo A; Ponce J; Roset M; Talley NJ  
European journal of gastroenterology et hepatology, 2003, 15(2), 165-72.

BACKGROUND: Disturbed bowel habit, diarrhoea or constipation is a key manifestation of irritable bowel syndrome (IBS). In some patients, diarrhoea and constipation alternate, giving rise to the so-called alternating subtype. AIMS: To assess IBS subtype breakdown (constipation (C-IBS), diarrhoea (D-IBS) or alternating (A-IBS)) according to the Rome II criteria and patients' self-assessment, the predominance in the alternating subtype (i.e. constipation, diarrhoea or neither), and the medical and personal impact, including health-related quality of life (HRQoL), of the different IBS subtypes. SUBJECTS AND METHODS: Two thousand individuals selected randomly to represent the general population were classified as potential IBS subjects ( $n = 281$ ) or as non-potential IBS subjects ( $n = 1719$ ) according to a validated questionnaire. Bowel habit classification was determined using the Rome II IBS supportive symptoms. RESULTS: Among 201 subjects meeting the Rome I criteria, 15% presented with D-IBS, 44% presented with C-IBS, 19% presented with A-IBS, and 22% presented with normal bowel habit. Among the 63 subjects meeting the Rome II criteria, 23% presented with A-IBS. According to the subjects' self-assessment, of those meeting the Rome I criteria, 16% considered themselves to have D-IBS, 66% to have C-IBS and 18% to have A-IBS. In subjects meeting the Rome II criteria, 24% considered themselves to have A-IBS. Among those classified with A-IBS by the Rome II criteria, most considered themselves to be constipated. Regardless of the subtype self-classification, most subjects reported a normal frequency of bowel movements. Clinical manifestations in A-IBS were very similar to those of C-IBS but with the added presence of defecatory urgency. Abdominal discomfort/pain and frequency of visits to physicians were greater in the A-IBS subtype than in the other two IBS subtypes. HRQoL was affected similarly in all IBS subtypes. CONCLUSIONS: Approximately one-quarter of subjects with IBS belong to the A-IBS subtype by the Rome II criteria, although the majority consider themselves to be constipated; indeed, clinical manifestations are more akin to the C-IBS subtype than to the D-IBS subtype. Abdominal discomfort/pain and frequency of visits to physicians are greater in the A-IBS subtype than in the other two IBS subtypes, while HRQoL is impaired similarly.



**22. The economic consequences of irritable bowel syndrome: a US employer perspective.**

Leong SA; Barghout V; Birnbaum HG; Thibeault CE; Ben-Hamadi R; Freeh F; Ofman JJ  
Archives of internal medicine, 2003, 163 (8), 929-35.

**BACKGROUND:** The objective of this study was to measure the direct costs of treating irritable bowel syndrome (IBS) and the indirect costs in the workplace. This was accomplished through retrospective analysis of administrative claims data from a national Fortune 100 manufacturer, which includes all medical, pharmaceutical, and disability claims for the company's employees, spouses/dependents, and retirees. **METHODS:** Patients with IBS were identified as individuals, aged 18 to 64 years, who received a primary code for IBS or a secondary code for IBS and a primary code for constipation or abdominal pain between January 1, 1996, and December 31, 1998. Of these patients with IBS, 93.7% were matched based on age, sex, employment status, and ZIP code to a control population of beneficiaries. Direct and indirect costs for patients with IBS were compared with those of matched controls. **RESULTS:** The average total cost (direct plus indirect) per patient with IBS was 4527 dollars in 1998 compared with 3276 dollars for a control beneficiary ( $P < .001$ ). The average physician visit costs were 524 dollars and 345 dollars for patients with IBS and controls, respectively ( $P < .001$ ). The average outpatient care costs to the employer were 1258 dollars and 742 dollars for patients with IBS and controls, respectively ( $P < .001$ ). Medically related work absenteeism cost the employer 901 dollars on average per employee treated for IBS compared with 528 dollars on average per employee without IBS ( $P < .001$ ). **CONCLUSION:** Irritable bowel syndrome is a significant financial burden on the employer that arises from an increase in direct and indirect costs compared with the control group.

**23. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome.**

Kellow J; Lee OY; Chang FY; Thongsawat S; Mazlam MZ; Yuen H; Gwee KA; Bak YT; Jones J; Wagner A Gut, 2003, 52 (5), 671-6.

**BACKGROUND:** Tegaserod has been shown to be an effective therapy for the multiple symptoms of irritable bowel syndrome (IBS) in Western populations. However, little information is available regarding the use of tegaserod

in the Asia-Pacific population. **AIMS:** To evaluate the efficacy, safety, and tolerability of tegaserod versus placebo in patients with IBS from the Asia-Pacific region. **PATIENTS:** A total of 520 patients from the Asia-Pacific region with IBS, excluding those with diarrhoea predominant IBS. **METHODS:** Patients were randomised to receive either tegaserod 6 mg twice daily ( $n=259$ ) or placebo ( $n=261$ ) for a 12 week treatment period. The primary efficacy variable (over weeks 1-4) was the response to the question: "Over the past week do you consider that you have had satisfactory relief from your IBS symptoms?" Secondary efficacy variables assessed overall satisfactory relief over 12 weeks and individual symptoms of IBS. **RESULTS:** The mean proportion of patients with overall satisfactory relief was greater in the tegaserod group than in the placebo group over weeks 1-4 (56% v 35%, respectively;  $p < 0.0001$ ) and weeks 1-12 (62% v 44%, respectively;  $p < 0.0001$ ). A clinically relevant effect was observed as early as week 1 and was maintained throughout the treatment period. Reductions in the number of days with at least moderate abdominal pain/discomfort, bloating, no bowel movements, and hard/lumpy stools were greater in the tegaserod group compared with the placebo group. Headache was the most commonly reported adverse event (12.0% tegaserod v 11.1% placebo). Diarrhoea led to discontinuation in 2.3% of tegaserod patients. Serious adverse events were infrequent (1.5% tegaserod v 3.4% placebo). **CONCLUSIONS:** Tegaserod 6 mg twice daily is an effective, safe, and well tolerated treatment for patients in the Asia-Pacific region suffering from IBS and whose main bowel symptom is not diarrhoea.

**24. Tegaserod, a 5-HT<sub>4</sub> receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects.**

Coffin B; Farmachidi JP; Rueegg P; Bastie A; Bouhassira D Alimentary pharmacology & therapeutics, 2003, 17 (4), 577-85.

**BACKGROUND:** Tegaserod reduces the symptoms associated with irritable bowel syndrome, and anti-nociceptive effects have been demonstrated in animals. Its effect on the rectal sensitivity in humans has not been delineated clearly. **AIM:** To evaluate the action of tegaserod on rectal sensitivity in response to distension by means of a reflexological technique based on electrophysiological recordings of the Rill nociceptive reflex. **METHODS:** A randomized, double-blind, placebo-controlled study, performed in 20 healthy women, quantified the effects of slow or rapid rectal



distensions on the Rill reflex at baseline and on day 8 following treatment with either placebo or tegaserod (6 mg b.d.). RESULTS: At baseline, slow distensions performed up to the pain threshold induced gradual inhibitions of the Rill reflex. On day 8, these inhibitory effects were significantly reduced in the tegaserod group, but not in the placebo group ( $P = 0.0001$ ). The effects of rapid distensions were not significantly modified by tegaserod or placebo. The intensity of subjective pain perception and rectal compliance were not altered by either treatment. CONCLUSION: These results suggest that tegaserod reduces the sensitivity to rectal distension in healthy subjects and interacts with the processing of sensory visceral information.

**25. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome.**

Creed F; Fernandes L; Guthrie E; Palmer S; Ratcliffe J; Read N; Rigby C; Thompson D; Tomenson B  
Gastroenterology, 2003, 124 (2), 303-17.

BACKGROUND et AIMS: Psychotherapy and antidepressants are effective in patients with severe irritable bowel syndrome (IBS), but the cost-effectiveness of either treatment in routine practice has not been established. METHODS: Patients with severe IBS were randomly allocated to receive 8 sessions of individual psychotherapy, 20 mg daily of the specific serotonin reuptake inhibitor (SSRI) antidepressant, paroxetine, or routine care by a gastroenterologist and general practitioner. Primary outcome measures of abdominal pain, health-related quality of life, and health care costs were determined after 3 months of treatment and 1 year later. RESULTS: A total of 257 subjects (81% response rate) from 7 hospitals were recruited; 59 of 85 patients (69%) randomized to psychotherapy and 43 of 86 (50%) of the paroxetine group completed the full course of treatment. Both psychotherapy and paroxetine were superior to treatment as usual in improving the physical aspects of health-related quality of life (SF-36 physical component score improvement, 5.2 [SEM, 1.26], 5.8 [SEM, 1.0], and -0.3 [SEM, 1.17];  $P < 0.001$ ), but there was no difference in the psychological component. During the follow-up year, psychotherapy but not paroxetine was associated with a significant reduction in health care costs compared with treatment as usual (psychotherapy, \$976 [SD, \$984]; paroxetine, \$1252 [SD, \$1616]; and treatment as usual, \$1663 [SD, \$3177]). CONCLUSIONS: For patients with severe IBS, both psychotherapy and paroxetine improve health-related quality of life at no additional cost.

**26. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome.**

Kim HJ; Camilleri M; McKinzie S; Lempke MB; Burton DD; Thomforde GM; Zinsmeister AR  
Alimentary pharmacology 8t therapeutics, 2003, 17 (7), 895-904.

AIM: To investigate the effects of a probiotic formulation, VSL#3, on gastrointestinal transit and symptoms of patients with Rome II irritable bowel syndrome with predominant diarrhoea. METHODS: Twenty-five patients with diarrhoea-predominant irritable bowel syndrome were randomly assigned to receive VSL#3 powder (450 billion lyophilized bacteria/day) or matching placebo twice daily for 8 weeks after a 2-week run-in period. Pre- and post-treatment gastrointestinal transit measurements were performed in all patients. Patients recorded their bowel function and symptoms daily in a diary during the 10-week study, which was powered to detect a 50% change in the primary colonic transit end-point. RESULTS: There were no significant differences in mean gastrointestinal transit measurements, bowel function scores or satisfactory global symptom relief between the two treatment groups, pre- or post-therapy. Differences in abdominal bloating scores between treatments were borderline significant ( $P = 0.09$ , analysis of covariance). Further analysis revealed that abdominal bloating was reduced ( $P = 0.046$ ) with VSL#3 [mean post- minus pre-treatment score, - 13.7; 95% confidence interval (CI), - 2.5 to - 24.9], but not with placebo ( $P = 0.54$ ) (mean post- minus pre-treatment score, - 1.7; 95% CI, 7.1 to - 10.4). With the exception of changes in abdominal bloating, VSL#3 had no effect on other individual symptoms: abdominal pain, gas and urgency. All patients tolerated VSL#3 well. CONCLUSION: VSL#3 appears to be promising in the relief of abdominal bloating in patients with diarrhoea-predominant irritable bowel syndrome. This is unrelated to an alteration in gastrointestinal or colonic transit.

**27. Pituitary-adrenal response to naloxone in non-ulcer dyspepsia: preliminary evidence for a reduction in central opioid tone.**

Scott LV; Rathore O; Dinan TG; Keeling PW  
Digestion, 2002, 65 (2), 67-72.

BACKGROUND: Non-ulcer dyspepsia (NUD) is one of the core functional bowel disorders. There has been recent emphasis on possible abnormal brain-gut interactions as being central to its pathophysiology. In this preliminary



study, we examined central opioid tone in *Helicobacter pylori*-negative NUD patients using naloxone, an opioid antagonist, which stimulates pituitary-adrenal activity. The opioid system is known to govern nociceptive processing and to play a role in gut motor activity. **SUBJECTS:** Eight subjects with NUD and 8 age- and sex-matched healthy subjects were examined. **METHODS:** Naloxone, 0.125 mg/kg, was administered at time 0. Adrenocorticotropin (ACTH) and cortisol responses were measured over a 120-min period. Maximum pituitary-adrenal responses in the 2 groups were compared. **RESULTS:** The ACTH response was significantly attenuated in the NUD group ( $p < 0.05$ ). The cortisol response did not differ between the 2 groups ( $p = 0.7$ ). **CONCLUSIONS:** Central opioid tone may be reduced in subjects with NUD. Our preliminary findings suggest that altered opioidergic activity may contribute to NUD pathophysiology, influencing the symptom profile through altered gut motor activity or possibly by influencing visceral sensitivity.

markedly impaired. **CONCLUSIONS:** Antral and fundic dysfunctions interact to produce the symptoms of functional dyspepsia, and impaired control of fundic accommodation may lead to overload of a hypersensitive antrum.

#### **28. Antro-fundic dysfunctions in functional dyspepsia.**

Caldarella MP; Azpiroz F; Malagelada JR  
Gastroenterology, 2003, 124 (5), 1220-9.

**BACKGROUND et AIMS:** Symptoms in functional dyspepsia have been related to impaired accommodation and hypersensitivity of the proximal stomach. We hypothesized that identification of putative antral dysfunctions provides a more comprehensive pathophysiological interpretation. **METHODS:** In 30 patients with functional dyspepsia and 22 healthy subjects, 2 consecutive studies were performed. In study I, with the subjects in the upright position, the proximal and distal stomach were selectively distended by bags containing air and water, respectively, while perception and fundic relaxation in response to antral distention were measured. In study II, by using air-filled bags connected to a tensostat, the proximal and the distal stomach were selectively distended by positioning the subjects on the right and left lateral decubitus, respectively, while perception, compliance, and the responses to intestinal nutrient infusion were measured. **RESULTS:** Patients with dyspepsia showed hypersensitivity of both the proximal stomach (discomfort at  $30 \pm 3$  g vs.  $62 \pm 2$  g in controls;  $P < 0.05$ ) and the antrum (discomfort at  $31 \pm 2$  g vs.  $53 \pm 4$  g in controls;  $P < 0.05$ ). Fundic and antral fasting tone was normal, but reflex fundic relaxation induced either by antral distention ( $3 \pm 16$  mL at 80 mL of distention vs.  $38 \pm 10$  mL in controls;  $P < 0.05$ ) or by intestinal nutrients ( $35 \pm 7$  mL vs.  $107 \pm 8$  mL in controls;  $P < 0.05$ ) was