

Functional Bowel Disorders



Recent Advances 14

A review of current literature by
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REVIEW

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As the pathophysiology of functional gastrointestinal disorders continues to be explored identification of new pieces of the jigsaw puzzle begin to emerge creating a complex picture of a heterogeneous condition influenced by genetic, psychological and social factors. One interesting study has shown that female patients with irritable bowel syndrome (IBS) have an altered neuroendocrine and cellular immune response to a nutrient load compared with healthy women². Others have confirmed the presence of mast cell infiltration and increased mediator release in these patients; with mast cell activation in close proximity to enteric nerves being suggested as a possible mechanism of increased sensory perception^{12,14}. Activation of mast cells along with peripheral corticotrophin releasing-factor (CRF) receptors has also been implicated in stress related changes in gut physiology⁷, and increased exposure of the duodenum to acid may be one mechanism by which sensory thresholds and gastric accommodation are reduced in some patients with functional dyspepsia¹⁶.

IBS patients with a history of abuse tend to exhibit greater pain reporting coupled with poorer health status and outcome than patients without such a history. It is therefore interesting to note that these patients actually have less sensitive rectums to distension than non abused IBS subjects suggesting that psychological factors may not always account for rectal sensitisation²³.

With the concept that low grade inflammation may be important in some cases of IBS comes the possibility of an anti-inflammatory approach to treatment. IBS has previously been noted to be less common in steroid users and another study has now confirmed this observation with a modest reduction in IBS prevalence in steroid users¹¹. So far, there has

been only one trial of steroids in IBS which was negative. Faecal calprotectin has been suggested as a non invasive marker of inflammation which may be used to monitor the activity of inflammatory bowel disease. However it is probably only going to be measurable in the presence of reasonably active disease and therefore it is probably not surprising that it is not detectable in IBS²¹ where inflammation, even when it is present, is going to be quite subtle.

It seems that an increased number of enterochromaffin cells and depression both appear to be important independent predictors of developing postinfectious IBS²², whilst reduced expression of the serotonin transporter protein (SERT) in patients with diarrhoea predominant IBS¹⁸ might explain the finding of increased post-prandial plasma serotonin concentration in these patients. Conversely, it has been suggested that some IBS patients who produce methane rather than hydrogen on lactulose breath testing appear to have lower concentrations of post-prandial plasma serotonin concentration which may be linked to constipation¹⁵.

Despite the complex nature of the pathophysiology of functional gastrointestinal disorders, new potential therapies continue to be explored including the use of electrical stimulation. This approach appears to improve rectal sensitivity and symptoms in patients with constipation and rectal hyposensitivity¹³. On the other hand acupoint transcutaneous electric nerve stimulation (TENS) seems to have the opposite effect on rectal sensory thresholds in patients with diarrhoea predominant IBS which is also accompanied by an improvement in symptoms⁹. It is becoming increasingly difficult to ignore the possible beneficial effects of herbal preparations in functional gastrointestinal disorders although the most recent promising reports all come from the same group^{3, 20, 27} and therefore need confirming by others. Most herbal remedies have multiple ingredients so it will be important to identify which components are active as well as ensuring that these moieties are safe. Although the tricyclic antidepressants seem to have unequivocal



utility in IBS there is less certainty concerning the selective serotonin re-uptake inhibitors. A recent trial of paroxetine in IBS showed improvement in quality of life but not abdominal symptomatology⁵ and the issue of the use of antidepressants in IBS still requires further clarification⁴. With more 5-HT₃ receptor antagonists in the pipeline, the exact relationship between this group of drugs and colonic ischemia needs to be unravelled. This is particularly important as it is now being recognised that IBS, on its own, is associated with colonic ischemia⁹ suggesting that its relationship to medication may have been somewhat over estimated.

Lastly, our miscellany includes studies on genetics, familial aggregation and childhood adversity in relation to functional gastrointestinal disorders^{10, 24, 17}; the apparent high prevalence of *Blastocystis hominis* in IBS⁶; the observation that fibromyalgia in IBS appears to be confined to females²⁶; observations on the pattern of symptomatology in IBS over time¹⁹ and a cautionary note about the differences in the way general practitioners may diagnose IBS²⁵.



1. Are there alterations of neuroendocrine and cellular immune responses to nutrients in women with irritable bowel syndrome?

Elsenbruch S, Holtmann G, Oezcan D, Lysson A, Janssen O, Goebel MU, Schedlowski M

The American journal of gastroenterology, 2004, 99 (4), 703-10.

OBJECTIVES: The goal was to investigate the neuroimmune axis in irritable bowel syndrome (IBS) by analyzing the neuroendocrine and cellular immune responses to nutrient load. **METHODS:** In the fasting state and 20, 40, 70, and 100 min following nutrient load, blood samples were collected and cardiovascular recordings were accomplished in 15 female IBS patients and 15 healthy women. Plasma norepinephrine, prolactin, cortisol, and growth hormone were analyzed, and blood pressure and heart rate responses were measured. The distribution of peripheral leukocytes and lymphocyte subpopulations and the in vitro production of tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) after whole blood stimulation with in lipopolysaccharide (LPS) were analyzed. **RESULTS:** IBS patients demonstrated significantly greater postprandial increases in plasma norepinephrine and systolic blood pressure ($p < 0.05$), but no cortisol response. A postprandial redistribution of circulating leukocytes and lymphocyte subpopulations was observed in both groups, including significant increases in the numbers of leukocytes and granulocytes and significant decreases in the numbers of monocytes, T-cells, and natural killer (NK) cells (all $p < 0.05$). However, IBS patients demonstrated significantly greater postprandial increases in leukocytes and granulocytes, while changes in the numbers of monocytes and NK cells were significantly diminished (all $p < 0.05$). Patients also failed to show the postprandial decrease in the in vitro TNF-alpha production observed in controls. Postprandial norepinephrine concentrations were negatively correlated with NK cell numbers in IBS patients ($r = 0.58$, $p < 0.05$) but not controls. **CONCLUSIONS:** IBS may involve an autonomic hyper-responsiveness to visceral stimuli, which occurs throughout the entire gut, is independent of acutely perceived GI symptoms, and does not necessarily involve HPA axis activation. Women with IBS show altered cellular immune responses to food intake, which may at least in part be mediated by adrenergic mechanisms. Thus, autonomic disturbances may have implications for cellular immune function along the neuroendocrine-immune axis in patients with IBS.

2. Treatment of functional dyspepsia with a herbal preparation. A double-blind, randomized, placebo-controlled, multicenter trial.

Madisch A, Holtmann G, Mayr G, Vinson B, Hotz J
Digestion, 2004, 69 (1), 45-52.

BACKGROUND: We aimed to assess the efficacy and safety of a herbal preparation STW 5-II containing extracts from bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm for the treatment of patients with functional dyspepsia. **METHODS:** 120 patients with functional dyspepsia were randomly assigned to 1 of 4 treatment groups. Each patient received the treatment for three consecutive 4-week treatment blocks. The first two treatment blocks were fixed. For the third treatment period, medication was based upon the investigator's judgement of symptom improvement during the preceding treatment period. In patients without adequate control of symptoms, the treatment was switched, or if symptoms were controlled, the treatment was continued. The primary outcome measure was the improvement of a standardized gastrointestinal symptom score (GIS). **FINDINGS:** During the first 4 weeks, the GIS significantly decreased in subjects on active treatment compared to the placebo ($p < 0.001$). During the second 4-week period, symptoms further improved in subjects who continued on active treatment or who switched to the active treatment ($p < 0.001$), while symptoms deteriorated in subjects who switched to placebo. After 8 weeks 43.3% on active treatment and 3.3% on placebo reported complete relief of symptoms. ($p < 0.001$ vs. placebo). **CONCLUSION:** In patients with functional dyspepsia, the herbal preparation tested improved dyspeptic symptoms significantly better than placebo.

3. Antidepressants in IBS: are we deluding ourselves?

Talley NJ

The American journal of gastroenterology, 2004, 99 (5), 921-3.

The benefit of selective serotonin reuptake inhibitors (SSRIs) in the irritable bowel syndrome (IBS) has not been clear. In the latest randomized trial published this month in the Journal, paroxetine was superior to placebo in terms of improving well-being, but not abdominal pain or bloating. Based on the results of the most recent studies, both tricyclic antidepressants and SSRIs may improve patient satisfaction or quality-of-life without relieving most of the primary gastrointestinal symptoms. This suggests that antidepressant therapy represents at best only a "band-aid" approach to management. Optimizing the use of antidepressants in IBS is a challenge, and these issues are explored in this Editorial.



4. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial.

Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G
The American journal of gastroenterology, 2004, 99 (5), 914-20.

OBJECTIVES: The purpose of the trial was to determine whether a high-fiber diet (HFD) alone or in combination with paroxetine or placebo was effective treatment for patients with irritable bowel syndrome (IBS). **METHODS:** Design: Trial of HFD alone (Group 1) followed by a randomized, double-blind trial of HFD with paroxetine or placebo (Group 2). Setting: Gastroenterology office in a 524-bed university-affiliated community hospital in Pittsburgh. Patients: Men and women, aged 18-65 yr, previously diagnosed with IBS but otherwise healthy. Intervention: Institution of HFD in 98 participants consuming low- or average-fiber diets. Allocation of paroxetine to 38 and placebo to 43 symptomatic participants consuming HFDs. Measurements: Overall well-being, abdominal pain, and abdominal bloating (Groups 1 and 2); food avoidance, work functioning, and social functioning (Group 2). **RESULTS:** In Group 1, overall well-being improved in 26% patients, and abdominal pain and bloating decreased in 22% and 26% patients, respectively, with an HFD. In Group 2, overall well-being improved more with paroxetine than with placebo (63.3%vs 26.3%; $p=0.01$), but abdominal pain, bloating, and social functioning did not. With paroxetine, food avoidance decreased ($p=0.03$) and work functioning was marginally better ($p=0.08$). Before unblinding, more paroxetine recipients than placebo recipients wanted to continue their study medication (84%vs 37%; $p < 0.001$). **CONCLUSIONS:** The difference in overall well-being found in our paroxetine/placebo trial is greater than that found in previously published drug/placebo trials for IBS. Moreover, the difference in well-being applied to nondepressed recipients of paroxetine.

5. Irritable bowel syndrome: in search of an etiology: role of Blastocystis hominis.

Yakoob J, Jafri W, Jafri N, Khan R, Islam M, Beg MA, Zaman V
The American journal of tropical medicine and hygiene, 2004, 70 (4), 383-5.

This study was designed to examine stool specimens of irritable bowel syndrome (IBS) patients for Blastocystis hominis, a common intestinal parasite. One hundred fifty patients were enrolled, 95 IBS cases and 55 controls. These

patients provided a medical history, and underwent physical and laboratory evaluations that included stool microscopy and culture for B. hominis and colonoscopy. The 95 cases (51 males and 44 females) had a mean +/- SD age of 37.8 +/- 13.2 years. Stool microscopy was positive for B. hominis in 32% (30 of 95) of the cases and 7% (4 of 55) of the controls ($P = 0.001$). Stool culture was positive in 46% (44 of 95) of the cases and 7% (4 of 55) of the controls ($P < 0.001$). Stool culture for B. hominis in IBS was more sensitive than microscopy ($P < 0.001$). Blastocystis hominis was frequently demonstrated in the stool samples of IBS patients; however, its significance in IBS still needs to be investigated. Stool culture has a higher positive yield for B. hominis than stool microscopy.

6. Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function.

Tache Y, Perdue MH
Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society, 2004, 16 Suppl 1, 137-42.

Central corticotrophin releasing-factor (CRF) signalling pathways are involved in the endocrine, behavioural and visceral responses to stress. Recent studies indicate that peripheral CRF-related mechanisms also contribute to stress-induced changes in gut motility and intestinal mucosal function. Peripheral injection of CRF or urocortin inhibits gastric emptying and motility through interaction with CRF2 receptors and stimulates colonic transit, motility, Fos expression in myenteric neurones and defecation through activation of CRF1 receptors. With regard to intestinal epithelial cell function, intraperitoneal CRF increases ion secretion and mucosal permeability to macromolecules. The motility and mucosal changes induced by peripheral CRF mimic those induced by acute stress. In addition, CRF receptor antagonists given peripherally prevent acute restraint and water avoidance stress-induced delayed gastric emptying, stimulation of colonic motor function and mucosal permeability. Similarly, early trauma enhanced intestinal mucosal dysfunction to an acute stressor in adult rats and the response is prevented by peripheral injection of CRF antagonist. Chronic psychological stress results in reduced host defence and initiates intestinal inflammation through mast cell-dependent mechanisms. These findings provide convergent evidence that activation of peripheral CRF receptors and mast cells are important mechanisms involved in stress-related alterations of gut physiology.



7. Rectal hypersensitivity reduced by acupoint TENS in patients with diarrhea-predominant irritable bowel syndrome: a pilot study.

Xiao WB, Liu YL

Digestive diseases and sciences, 2004, 49 (2), 312-9.

Our aim was to compare rectal perception of patients with diarrhea-predominant irritable bowel syndrome (IBS-D), constipation-predominant irritable bowel syndrome (IBS-C), functional constipation (FC), and healthy controls and to evaluate the therapeutic effect of acupoint transcutaneous electric nerve stimulation (TENS). Age- and sex-matched patients (24 IBS-D, 20 IBS-C, and 30 FC) were selected, and 30 volunteers served as healthy controls. Rectal sensory thresholds were evaluated by rectal balloon distension. Short- and long-term acupoint TENS was given respectively. IBS-D patients had significantly lower rectal sensory thresholds of the first sensation of stool, urgency of defecation, and pain than IBS-C or FC patients or healthy controls ($P < 0.05$), but there were no differences in rectal sensory thresholds among IBS-C and FC patients and healthy controls. In each group, females had significantly lower rectal sensory thresholds than males ($P < 0.05$), but there was no difference between younger ($< \text{or} = 50$ years old) and older (> 50 years old) patients. Short-term acupoint TENS increased rectal sensory thresholds of IBS-D patients. After 2-month acupoint TENS treatment in IBS-D patients, rectal sensory thresholds were significantly increased, stool times and the intensity of abdominal pain were decreased, and psychological scores were relieved to normal. Lowered rectal perception threshold is a hallmark of IBS-D patients. Females have significantly lower rectal sensory thresholds than males. Acupoint TENS is effective to treat IBS-D.

8. Occurrence of colon ischemia in relation to irritable bowel syndrome.

Cole JA, Cook SF, Sands BE, Ajene AN, Miller DP, Walker AM
The American journal of gastroenterology, 2004, 99 (3), 486-91.

OBJECTIVE: In November 2000, alosetron HCl (Lotronex), a treatment for irritable bowel syndrome (IBS), was removed from the U.S. market in part because of the occurrence of colon ischemia in treated patients. Since the relation between colon ischemia and IBS is poorly understood, we evaluated the incidence of colon ischemia among people with and without IBS. METHODS: Using medical claims data from a large health care organization in the United States, we identified 87,449 people with an IBS diagnosis between

January 1995 and December 1999. We calculated age- and sex-specific incidence rates in the general population and in IBS patients. RESULTS: There were 740 cases of colon ischemia during 8.5 million person-years of observation in 5.4 million persons. The crude incidence rate was 42.8 cases per 100,000 person-years for IBS patients. By comparison, the incidence rate was 7.2 per 100,000 person-years in the general population. After adjustment for age, sex, and calendar year, the incidence of colon ischemia in people with IBS was 3.4 times higher than in persons without (95% CI 2.6-4.5). CONCLUSIONS: Rates of colon ischemia among patients carrying a diagnosis of IBS are substantially higher than in the general population. Colon ischemia, though unusual in IBS patients, may nonetheless constitute a distinct part of the IBS natural history. Alternatively, it may be a consequence of therapy, or a manifestation of other bowel pathology that is sometimes confused with IBS.

9. Familial aggregation of irritable bowel syndrome: a prospective study.

Kalantar JS, Locke GR 3rd, Zinsmeister AR, Beighley CM, Talley NJ
Gut, 2003, 52 (12), 1703-7.

BACKGROUND: Patients with irritable bowel syndrome (IBS) often report family members with similar symptoms, but family studies are lacking. We hypothesised that if there is familial aggregation, there would be an increased frequency of IBS in first degree relatives of IBS patients compared with relatives of controls (the patient's spouse). METHODS: A valid self report bowel disease questionnaire (BDQ) that recorded symptoms, the somatic symptom checklist (a measure of somatisation), and a family information form (FIF) to collect the names and addresses of all first degree relatives were mailed to two groups of patients and their spouses (patients attending an IBS educational programme and residents of Olmsted County, Minnesota, who had been coded as IBS on a database). A BDQ was then mailed to all first degree relatives of subjects identified from the FIF. IBS diagnosis in the relatives was based on the Manning criteria. RESULTS: The BDQ was sent to a total of 355 eligible relatives; 71% responded (73% relatives of patients, 67% relatives of spouses). Relatives were comparable in mean age, sex distribution, and somatisation score. IBS prevalence was 17% in patients' relatives versus 7% in spouses' relatives (odds ratio adjusted for age and sex 2.7 (95% confidence interval (CI) 1.2, 6.3)). When also adjusted for somatisation score, the odds ratio was reduced to 2.5 (95% CI 0.9, 6.7). CONCLUSIONS: Familial aggregation of IBS occurs, supporting a genetic or intrafamilial environment component, but this may be explained in part by familial aggregation of somatisation.



10. Users of oral steroids are at a reduced risk of developing irritable bowel syndrome.

Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S
Pharmacoepidemiology and drug safety, 2003, 12 (7), 583-8.

PURPOSE: To study whether irritable bowel syndrome (IBS) is associated with the use of oral steroids and whether there is a dose- or duration-response. **METHODS:** We followed up a cohort of 65,270 patients aged 20-74 years old enrolled in the General Practice Research Database in the UK with at least one prescription for steroids between 1994 and 1999. We performed a nested case-control analysis to estimate the adjusted relative risk (RR) associated with the use of steroids using unconditional logistic regression. Cases were 466 patients with a first episode of IBS during follow-up and controls were 5000 individuals randomly selected from the study cohort. **RESULTS:** Current users of oral steroids presented an RR of 0.6 (95% CI: 0.4-0.9) compared to non-users. Doses greater than 10 mg of prednisolone daily were associated with an RR of 0.4 (95% CI: 0.2-0.9). When we stratified by age, no reduced risk of IBS was apparent under the age of 40 years. The reduced risk of IBS was greater among females than males. **CONCLUSIONS:** Our results suggest that oral steroids can reduce the risk of a diagnosis of IBS. The apparent effect modification of age and sex deserves further research.

11. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome.

Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R
Gastroenterology, 2004, 126 (3), 693-702.

BACKGROUND & AIMS: The mechanisms underlying abdominal pain perception in irritable bowel syndrome (IBS) are poorly understood. Intestinal mast cell infiltration may perturb nerve function leading to symptom perception. We assessed colonic mast cell infiltration, mediator release, and spatial interactions with mucosal innervation and their correlation with abdominal pain in IBS patients. **METHODS:** IBS patients were diagnosed according to Rome II criteria and abdominal pain quantified according to a validated questionnaire. Colonic mucosal mast cells were identified immunohistochemically and quantified with a computer-assisted counting method. Mast cell tryptase and histamine release were analyzed immunoenzymatically. Intestinal nerve to mast cell distance was assessed with electron microscopy. **RESULTS:** Thirty-four out of 44 IBS patients (77%) showed an increased area of mucosa occupied by mast cells as compared with controls (9.2% +/- 2.5% vs. 3.3 +/- 0.8%, respectively; $P < 0.001$). There was a 150%

increase in the number of degranulating mast cells (4.76 +/- 3.18/field vs. 2.42 +/- 2.26/field, respectively; $P = 0.026$). Mucosal content of tryptase was increased in IBS and mast cells spontaneously released more tryptase (3.22 +/- 3.48 pmol/min/mg vs. 0.87 +/- 0.65 pmol/min/mg, respectively; $P = 0.015$) and histamine (339.7 +/- 59.0 ng/g vs. 169.3 +/- 130.6 ng/g, respectively; $P = 0.015$). Mast cells located within 5 microm of nerve fibers were 7.14 +/- 3.87/field vs. 2.27 +/- 1.63/field in IBS vs. controls ($P < 0.001$). Only mast cells in close proximity to nerves were significantly correlated with severity and frequency of abdominal pain/discomfort ($P < 0.001$ and $P = 0.003$, respectively). **CONCLUSIONS:** Colonic mast cell infiltration and mediator release in proximity to mucosal innervation may contribute to abdominal pain perception in IBS patients.

12. Effect of electrical stimulation in constipated patients with impaired rectal sensation.

Chang HS, Myung SJ, Yang SK, Jung HY, Kim TH, Yoon IJ, Kwon OR, Hong WS, Kim JH, Min YI
International journal of colorectal disease, 2003, 18 (5), 433-8.

BACKGROUND AND AIMS: A subgroup of constipated patients complain of absent or diminished sense of wanting to defecate, suggesting that one of the causes of constipation is impaired rectal sensation. Electrical stimulation therapy (EST) has recently been used to treat patients with urinary and/or fecal incontinence. This study evaluated the efficacy of EST in constipated patients, especially those with impaired rectal sensation. **PATIENTS AND METHODS:** Of the 130 patients with functional constipation as defined by Rome II criteria, 22 patients who had impaired rectal sensation (rectal desire threshold volume $>$ or $=90$ ml) on an anorectal manometry were selected. We treated 12 with EST and 10 with biofeedback therapy (BFT) according to a randomized order. **RESULTS:** Overall symptoms of patients significantly improved after each therapy in both groups. Interestingly, frequency of sense of wanting to defecate improved only after EST. On objective findings there was significant improvement in anal residual pressures on attempted defecation only after BFT solely. On the other hand, rectal sensory threshold volumes for desire and urge to defecate and maximal tolerated volume improved significantly only in the EST group. **CONCLUSION:** Our findings show that the efficacy of EST can be comparable to BFT in a subgroup of constipated patients, especially those with impaired rectal sensation. EST might be considered as an adjunctive therapeutic modality for the management of functional constipation with impaired rectal sensation.



13. Activated mast cells infiltrate in close proximity to enteric nerves in diarrhea-predominant irritable bowel syndrome.

Park CH, Joo YE, Choi SK, Rew JS, Kim SJ, Lee MC
Journal of Korean medical science, 2003, 18 (2), 204-10.

Mast cells (MC) may be one factor influencing the response of visceral afferent nerves to mechanical and chemical stimuli. The aim of this study was to evaluate the degree of infiltration and activity of colonic MC in irritable bowel syndrome (IBS). Biopsy specimens were obtained from the cecum and rectum of 14 diarrhea predominant IBS and 14 normal controls. Electron microscopy was used to determine the number of intact and degranulated colonic MC and to quantify these separately according to the distance between MC and enteric nerves. An increased number of MC in both cecum and rectum in the IBS group in comparison with the control group was demonstrated ($p < 0.05$). Activated MC in close proximity to enteric nerves were significantly increased in both cecum and rectum of the IBS group compared to control group ($p < 0.005$). In addition, activated MC were significantly increased in close proximity to the nerves compared to those in the remote area in both cecum and rectum of the IBS group ($p < 0.0001$). MC were significantly increased and activated in both cecum and rectum of the IBS group compared to controls. MC may play a role in the gut sensory hypersensitivity of IBS.

14. IBS subjects with methane on lactulose breath test have lower postprandial serotonin levels than subjects with hydrogen.

Pimentel M, Kong Y, Park S
Digestive diseases and sciences, 2004, 49 (1), 84-7.

We have previously shown that methane on lactulose breath test (LBT) is highly associated with constipation in IBS and that methane gas itself slows small bowel transit in dogs. Previous studies suggest that serotonin may have a role in the control of transit in IBS. In this study, we aim to evaluate the role of serotonin in methane producing IBS subjects. Rome I-positive IBS subjects were recruited into the study after exclusion criteria were met. A fasting LBT was performed after subjects filled out a questionnaire rating the degree of constipation and diarrhea. Within 7 days of this test, subjects returned fasting for determination of serotonin before and after a 75-g oral glucose meal. The serotonin response was compared between hydrogen and methane producing IBS subjects. After 2 subjects were excluded for inadequate blood samples, 18 subjects completed the study. Four of 18 subjects produced methane. The postprandial serotonin level in methane producing IBS subjects was lower than in hydrogen producers ($P < 0.05$). Methane producers had a reduction in

serotonin after glucose. Methane producing IBS subjects have reduced postprandial serotonin. Whether methane is a surrogate marker of constipation or contributing to the reduced serotonin remains to be determined.

15. Influence of duodenal acidification on the sensorimotor function of the proximal stomach in humans.

Lee KJ, Vos R, Janssens J, Tack J
American journal of physiology. Gastrointestinal and liver physiology, 2004, 286 (2), G278-84.

Decreased acid clearance and increased exposure to acid of the duodenum have been reported in a subset of functional dyspepsia patients. However, the mechanism by which increased duodenal acid exposure may affect symptoms is unclear. The aim of the present study was to investigate the effects of duodenal acidification on proximal gastric tone and mechanosensitivity in humans. An infusion tube with a pH electrode attached was positioned in the second part of the duodenum, and a barostat bag was located in the gastric fundus. In 12 healthy subjects, fundic tone and sensitivity to distensions were assessed before and during duodenal infusion of 0.1 N hydrochloric acid or saline in a randomized, double-blind design. In 10 healthy subjects, meal-induced accommodation was measured during duodenal infusion of acid or saline. Acid infusion in the duodenum significantly increased fundic compliance and decreased fasting fundic tone. This was accompanied by a significant decrease in the pressures and the corresponding wall tensions at the thresholds for discomfort. During infusion of acid, significantly higher perception and symptom scores were obtained for the same distending pressures. The meal-induced fundic relaxation was significantly smaller during acid infusion compared with saline infusion. In conclusion, duodenal acidification induces proximal gastric relaxation, increases sensitivity to gastric distension, and inhibits gastric accommodation to a meal. Through these mechanisms, increased duodenal acid exposure may be involved in the pathogenesis of dyspeptic symptoms.

16. Effect of childhood adversity on health related quality of life in patients with upper abdominal or chest pain.

Biggs AM, Aziz Q, Tomenson B, Creed F
Gut, 53 (2), 2004, 180-6.

BACKGROUND AND AIMS: This study assessed whether childhood and current adversities: (a) were more prevalent in patients with functional dyspepsia (FD) or non-cardiac chest pain (NCCP) than in patients with gastro-oesophageal reflux disease (GORD) or ischaemic heart disease (IHD); and



(b) predicted health related quality of life in these disorders. PATIENTS: Cohort study of consecutive attenders to gastroenterology and cardiology clinics in a secondary/tertiary referral centre. METHODS: Patients were interviewed using the childhood experience of care and abuse and life events and difficulties schedules. Distress was assessed by questionnaire. Outcome was assessed using SF36 at the index clinic visit and six months later. RESULTS: A total of 133 patients were included (40 NCCP, 43 FD, 29 GORD, and 21 IHD) (67% response rate). The diagnostic groups did not differ significantly in the proportion reporting childhood adversity (30%), ongoing social stress (40%), lack of a close confidant (14%), or level of psychological distress. Reported childhood adversity was associated with poor outcome at the index visit (SF36 physical component score: 36.6 (SEM 1.8) v 42.3 (SEM 1.2) for the remainder; $p = 0.014$). In multiple regression analysis, childhood adversity was a significant independent predictor for patients with functional disorders (NCCP and FD) but not organic disorders (GORD or IHD). Change in SF36 score at six months was determined by age and distress score at the index visit in both groups. CONCLUSION: Childhood adversity was common among this consecutive sample but was associated directly with poor outcome only in patients with functional gastrointestinal syndromes. Distress is an important predictor of outcome in all patients. Greatest impairment occurs when lack of social support accompanies reported childhood adversity.

17. Platelet serotonin transporter in patients with diarrhea-predominant irritable bowel syndrome both before and after treatment with alosetron.

Bellini M, Rappelli L, Blandizzi C, Costa F, Stasi C, Colucci R, Giannaccini G, Marazziti D, Betti L, Baroni S, Mumolo MG, Marchi S, Del Tacca M
The American journal of gastroenterology, 2003, 98 (12), 2705-11.

OBJECTIVES: Serotonin reuptake is mediated by a transporter protein (SERT), and its dysfunctions can alter serotonergic transmission. The present study examines the binding profile of platelet SERT in healthy volunteers as well as in patients with diarrhea-predominant irritable bowel syndrome (D-IBS), both before and after treatment with the 5-HT(3) receptor antagonist alosetron. METHODS: Binding of [(3)H]paroxetine to SERT was assayed in platelet membranes collected from D-IBS patients (12 women, age 21-73 yr) and healthy volunteers (12 women, age 24-68 yr). Both maximal binding capacity (B(max)) and dissociation constant (K(d)) were estimated. In D-IBS patients, binding parameters and symptom severity score were evaluated at

baseline and after treatment with alosetron (1 mg b.i.d. for 8 wk). RESULTS: At baseline, B(max) and K(d) values of [(3)H]paroxetine binding were respectively lower and higher in D-IBS patients than in healthy volunteers (B(max): 518.7 +/- 155.9 vs 1151.9 +/- 187.4 fmol/mg, $p < 0.001$; K(d): 0.19 +/- 0.05 vs 0.06 +/- 0.02 nmol/L, $p < 0.001$). Symptom severity score in D-IBS patients (50.9 +/- 18.8) was negatively correlated with B(max) ($r = -0.964$; $p < 0.001$) but not K(d) values ($r = -0.164$; $p = 0.609$). After treatment with alosetron, symptom severity score decreased significantly (14.4 +/- 3.7; $p < 0.001$), whereas B(max) (522.7 +/- 39.7 fmol/mg) and K(d) values (0.17 +/- 0.07 nmol/L) did not change. CONCLUSIONS: The present results indicate that SERT expressed on platelet membranes of D-IBS patients is characterized by low density and binding affinity and suggest a possible correlation between the reduced capacity of serotonin reuptake and the severity of D-IBS symptoms.

18. Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability.

Mearin F, Baro E, Roset M, Badia X, Zarate N, Perez I
The American journal of gastroenterology, 2004, 99 (1), 113-21.

OBJECTIVES: The clinical course of irritable bowel syndrome (IBS) remains poorly known. In 209 IBS patients meeting Rome II criteria (137 females and 72 males) we evaluated: (1). changes in frequency and intensity of abdominal pain/discomfort, abnormal number of bowel movements, loose or watery stools, defecatory urgency, hard or lumpy stools, straining during bowel movements, and feeling of incomplete evacuation); (2). use of resources, HRQoL, and psychological well being. METHODS: Observational, prospective, multicenter study. Symptoms were registered in a diary over two 28-day periods with an interval of 4 wk; direct resource use and indirect costs were noted weekly. Three HRQoL questionnaires were administered. RESULTS: High-intensity symptoms were present on more than 50% of the days. Sixty-one percent were classified in the same IBS subtype on both occasions ($kappa = 0.48$), while 49% had the same symptom predominance and intensity ($kappa = 0.40$). The greatest instability was observed among diarrhea (D-IBS) and constipation (C-IBS) subtypes: only 46% and 51% remained in the same pattern with a tendency to shift to alternating diarrhea/constipation subtype (A-IBS); however, practically no patient changed from D-IBS to C-IBS, or vice versa. The most reliable symptom characteristic was frequency, followed by intensity and number of episodes. Symptom frequency and intensity were directly related to resource use and HRQoL



impairment. CONCLUSIONS: IBS symptoms are instable over time and variables in intensity. Many patients with D-IBS or C-IBS move to A-IBS; however, shift from D-IBS to C-IBS, or vice versa, is very infrequent.

19. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial.

Holtmann G, Adam B, Haag S, Collet W, Gruenewald E, Windeck T

Alimentary pharmacology & therapeutics, 2003, 18 (11-12), 1099-105.

BACKGROUND: This study aimed to assess the efficacy of artichoke leaf extract (ALE) in the treatment of patients with functional dyspepsia (FD). METHODS: In a double-blind, randomized controlled trial (RCT), 247 patients with functional dyspepsia were recruited and treated with either a commercial ALE preparation (2 x 320 mg plant extract t.d.s.) or a placebo. The primary efficacy variable was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms (four-point scale). Secondary variables were the scores of each dyspeptic symptom and the quality of life (QOL) as assessed by the Nepean Dyspepsia Index (NDI). RESULTS: Two hundred and forty-seven patients were enrolled, and data from 244 patients (129 active treatment, 115 placebo) were suitable for inclusion in the statistical analysis (intention-to-treat). The overall symptom improvement over the 6 weeks of treatment was significantly greater with ALE than with the placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, P < 0.01). Similarly, patients treated with ALE showed significantly greater improvement in the global quality-of-life scores (NDI) compared with the placebo-treated patients (- 41.1 +/- 47.6 vs. - 24.8 +/- 35.6, P < 0.01). CONCLUSION: The ALE preparation tested was significantly better than the placebo in alleviating symptoms and improving the disease-specific quality of life in patients with functional dyspepsia.

20. Role of faecal calprotectin as non-invasive marker of intestinal inflammation.

Costa F, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, Sterpi C, Marchi S, Maltinti G

Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 2003, 35 (9), 642-7.

BACKGROUND/AIM: Faecal calprotectin, a neutrophil granulocyte cytosol protein, is considered a promising marker of intestinal inflammation. We assessed and compared the faecal calprotectin concentration in patients

with organic and functional chronic intestinal disorders. PATIENTS AND METHODS: The study was carried out, using a commercially available ELISA test, measuring calprotectin in stool samples collected from 131 patients with inflammatory bowel diseases, 26 with intestinal neoplasms, 48 with irritable bowel syndrome and 34 healthy subjects. RESULTS: Median faecal calprotectin was significantly increased in Crohn's disease (231 microg/g, 95% confidence interval (CI) 110-353 microg/g), ulcerative colitis (167 microg/g, 95% CI 59-276 microg/g), and neoplasms (105 microg/g, 95% CI 0-272 microg/g), whereas normal values were found in patients with irritable bowel syndrome (22 microg/g, 95% CI 9-35 microg/g) and in healthy subjects (11 microg/g, 95% CI 3-18 microg/g). A positive correlation was observed with clinical activity scores in Crohn's disease and ulcerative colitis. In both groups, patients with clinically active disease showed higher calprotectin levels than those observed in patients with quiescent disease (405 microg/g, 95% CI 200-610 microg/g vs. 213 microg/g, 95% CI 85-341 microg/g in CD patients, p<0.05, and 327 microg/g, 95% CI 104-550 microg/g vs. 123 microg/g, 95% CI 40-206 microg/g in UC patients, p<0.001). CONCLUSIONS: Faecal calprotectin appears to be a promising and non-invasive biomarker of intestinal inflammation. If these findings are confirmed, it may provide a useful test for the diagnosis and follow up of inflammatory bowel diseases.

21. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS.

Dunlop SP, Jenkins D, Neal KR, Spiller RC
Gastroenterology, 2003, 125 (6), 1651-9.

BACKGROUND & AIMS: Both psychological and mucosal changes (increased enterochromaffin [EC] cells and T lymphocytes) have been associated with postinfectious irritable bowel syndrome (PI-IBS). However, previous studies have been underpowered to determine the relative importance of these changes in predicting the development of PI-IBS. Our aim was to prospectively determine the relative importance of both psychological and histologic factors in the development of PI-IBS after Campylobacter infection. METHODS: Questionnaires detailing psychological and bowel symptoms were sent to 1977 patients 3 months after infection. Twenty-eight patients with new-onset PI-IBS, 28 age- and sex-matched patient controls who were asymptomatic after infection, and 34 healthy volunteers underwent rectal biopsy, which was assessed for serotonin-containing EC cells, mast cells, and lamina propria T lymphocytes. RESULTS: PI-IBS, predominantly of the diarrhea-predominant subtype, occurred in 103 of 747



(13.8%) of those infected. EC cell counts per high-power field (hpf) were higher in patients with PI-IBS (35.8 +/- 1.2) compared with patient controls (30.6 +/- 1.9; $P = 0.022$) and volunteers (29.1 +/- 1.8; $P = 0.006$). Lamina propria T lymphocytes per hpf were higher in patients with PI-IBS (127.1 +/- 8.7) and patient controls (113.4 +/- 6.2) in contrast to healthy volunteers (97.1 +/- 5.7) ($P = 0.006$ and $P = 0.058$, respectively). Anxiety, depression, and fatigue were significantly increased in patients with PI-IBS compared with patient controls. Multivariate analysis indicated that increased EC cell counts and depression were equally important predictors of developing PI-IBS (relative risk, 3.8 and 3.2 for each standard deviation increase in respective values). **CONCLUSIONS:** Both increased EC cells and depression are important independent predictors of developing PI-IBS.

22. Sexual and physical abuse are not associated with rectal hypersensitivity in patients with irritable bowel syndrome.

Ringel Y, Whitehead WE, Toner BB, Diamant NE, Hu Y, Jia H, Bangdiwala SI, Drossman DA
Gut, 2004, 53 (6), 838-842.

BACKGROUND: Patients with irritable bowel syndrome (IBS) have reduced pain thresholds for rectal distension. In addition, the prevalence of sexual/physical abuse in referred IBS patients is high and is associated with greater pain reporting, poorer health status, and poorer outcome. This lead to a hypothesis that abuse history may sensitise patients to report pain at a lower threshold. **Aim:** To compare rectal pain thresholds in women with IBS who had a history of severe abuse to IBS women with no history of abuse. **Methods:** We studied 74 IBS patients with a history of severe physical and/or sexual abuse and 85 patients with no history of abuse. Abuse history was assessed by a previously validated self-report abuse screening questionnaire. Rectal sensory thresholds were assessed using an electronic barostat and determined by the ascending method of limit (AML) and by the tracking technique. **Results:** IBS patients with a history of severe abuse had significantly higher rectal pain thresholds, as measured by AML ($F(1, 111) = 6.06$; $p = 0.015$) and the tracking technique ($F(1, 109) = 5.21$; $p = 0.024$). Patients with a history of severe abuse also reported a significantly higher threshold for urgency to defecate ($F(1, 113) = 11.23$; $p = .001$). **Conclusion:** Severe sexual/physical abuse is associated with higher urge and pain thresholds for rectal distension in IBS patients. This suggests that the greater pain reporting and poorer health status in IBS patients with abuse history are not related to increased rectal pain sensitivity. Further studies are needed to determine the causes of these findings.

23. Association of distinct alpha(sub(2)) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders.

Kim HJ, Camilleri M, Carlson PJ, Cremonini F, Ferber I, Stephens D, McKinzie S, Zinsmeister AR, Urrutia R
Gut, 2004, 53 (6), 829-837.

BACKGROUND: The role of genetics in the phenotypic manifestations of irritable bowel syndrome (IBS) is unclear. Our aims were: (1) to compare the prevalence of polymorphisms of alpha 2 (alpha2) adrenoceptors, norepinephrine transporter, and serotonin transporter protein (soluble carrier protein member 4 (SLC6A4)) promoter in patients with lower functional gastrointestinal disorders (FGID) and in healthy controls; and (2) to test associations of these genetic variations with symptoms of IBS and high somatic symptom scores. **Methods:** Validated bowel and somatic symptom questionnaires characterised the phenotype: 90 with IBS constipation (IBS-C), 128 IBS diarrhoea, 38 IBS alternating bowel function, and 20 chronic abdominal pain. Logistic regression analyses assessed associations of different polymorphisms for alpha(sub(2)) adrenoceptor and SLC6A4 with IBS or chronic abdominal pain phenotypes and high somatic score. **Results:** Two distinct polymorphisms independently appeared to be associated with the phenotype IBS-C: alpha(sub(2))C Del 322-325 (odds ratio (OR) 2.48 (95% confidence interval (CI) 0.98, 6.28); $p = 0.05$) and alpha(sub(2))A -1291 (C(rightwards arrow)G) (OR 1.66 (95% CI 0.94, 2.92); $p = 0.08$) relative to wild-type. Overall, the alpha(sub(2C)) Del 322-325 polymorphism (alone or combined with other polymorphisms) was also significantly associated with a high somatic symptom score (OR 2.2 (95% CI 1.06, 4.64); $p = 0.03$). Combinations of polymorphisms were also associated with high somatic scores. **Conclusion:** Functionally distinct alpha(sub(2))A and alpha(sub(2C)) adrenoceptor and serotonin transporter polymorphisms are associated with constipation and high somatic symptoms in patients with lower functional gastrointestinal disorders, although the strength of the genetic contribution to the phenotype is unclear.

24. Diagnosing irritable bowel syndrome: Poor agreement between general practitioners and the Rome II criteria.

Vandvik PO, Aabakken L, Farup PG
Scandinavian Journal of Gastroenterology, 2004, 39 (5), 448-453.

BACKGROUND: The new guidelines for diagnosing irritable bowel syndrome (IBS) in clinical practice recommend the use of the Rome II criteria. In this study the agreement



between general practitioners (GPs) and the Rome II criteria for diagnosing of IBS and functional bowel disorders (FBD) is examined. Methods: Consecutive patients in general practice were asked to report on abdominal complaints, for which they had consulted or wanted to consult a GP. Patients with such complaints completed a questionnaire based on the Rome II criteria for FBD. After consultations, the GPs reported their diagnoses on the abdominal complaints. Results: Of 3097 screened patients, 553 patients were diagnosed by their GP and had complete data in the questionnaire. Of these patients, 107 had IBS according to the GPs and 209 had IBS according to the Rome II criteria (agreement 58%, kappa 0.01 (CI: -0.06; 0.09)). Agreement on IBS and FBD in patients without organic disease, without reflux or dyspepsia and in patients with a verified diagnosis was 45%-58%, with kappa values from -0.02 to 0.13. IBS and FBD cases were diagnosed by the Rome II criteria more often than by the GPs in all these groups of patients ($P < 0.001$). In patients with diagnostic discrepancies concerning IBS, 'stress-related symptoms' was predictive of a diagnosis of IBS made by the GPs only (OR 2.17 (CI: 1.1; 4.2)). Conclusions: This study shows poor agreement in the diagnosis of IBS between GPs and the Rome II criteria. Therefore, current knowledge about IBS based on strict criteria is not necessarily transferable to patients with IBS in general practice.

25. Is female predominance in irritable bowel syndrome related to fibromyalgia?

Akkus S, Senol A, Ayvacioglu NB, Tunc E, Eren I, Isler M
Rheumatology International, 2004, 24 (2), 106-109.

Irritable bowel syndrome (IBS) and fibromyalgia (FM) are common functional diseases in adult women. The aim of this study was to investigate whether female predominance in IBS is related to FM. Fifty patients with IBS and 50 healthy controls were enrolled. All participants answered questionnaires including personal and medical history. In addition, psychiatric interviews were conducted. Patients were divided into two groups according to the coexistence of FM (IBS + FM or IBS only). The data obtained from patients with or without FM and the control group were compared. There was a significant female predominance in patients with IBS + FM (83.4%, F:M = 5:1), but IBS-only patients consisted mainly of males (59.4%, F:M = 2:3) ($P < 0.01$). Comparison of IBS + FM and IBS-only patients showed no significant difference in depression and anxiety status. However, both anxiety and depression scores were found to be higher in female IBS patients than their male counterparts ($P < 0.01$ and $P < 0.05$, respectively). Our findings suggest that the female predominance in IBS patients may result from coexisting FM.

26. Treatment of irritable bowel syndrome with herbal preparations: Results of a double-blind, randomized, placebo-controlled, multi-centre trial.

Madisch A, Holtmann G, Plein K, Hotz J
Alimentary Pharmacology and Therapeutics, 2004, 19 (3), 271-279.

BACKGROUND: Herbal medications have been used in many countries for the treatment of patients with irritable bowel syndrome. Controlled data supporting the efficacy of these treatments in patients with irritable bowel syndrome are lacking. Aim: To assess the efficacy and safety of a commercially available herbal preparation (STW 5) (nine plant extracts), the research herbal preparation STW 5-II (six plant extracts) and the bitter candytuft mono-extract in patients with irritable bowel syndrome. Methods: Two hundred and eight patients with irritable bowel syndrome were recruited after standardized diagnostic work-up into a double-blind, placebo-controlled, multi-centre trial and were randomly assigned to receive one of four treatments: commercially available herbal preparation STW 5 ($n = 51$), research herbal preparation STW 5-II ($n = 52$), bitter candytuft mono-extract ($n = 53$) or placebo ($n = 52$). The main outcome variables were the changes in total abdominal pain and irritable bowel syndrome symptom scores. Results: Two hundred and three patients completed the trial. STW 5 and STW 5-II were significantly better than placebo in reducing the total abdominal pain score (intention-to-treat: STW 5, $P = 0.0009$; STW 5-II, $P = 0.0005$) and the irritable bowel syndrome symptom score (intention-to-treat: STW 5, $P = 0.001$; STW 5-II, $P = 0.0003$) at 4 weeks. There were no statistically significant differences between the bitter candytuft mono-extract group and the placebo group ($P = 0.1473$, $P = 0.1207$). Conclusions: The commercially available herbal preparation STW 5 and its research preparation STW 5-II are both effective in alleviating irritable bowel syndrome symptoms.