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VISION

The International Pelvic Pain Society

Professionals engaged in pain management for men and women.

IRRITABLE BOWEL SYNDROME

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For healthcare providers managing patients with chronic pelvic pain, Irritable Bowel Syndrome (IBS) is a clinical challenge. IBS accounts for 12% of all primary care visits, and annual costs in the US are estimated to be over one billion dollars.[1] Despite many scientific advances, the cause and optimal treatment of IBS remains elusive. This review will address etiology, diagnosis of and treatment options for IBS, as well as new directions in research.

ETIOLOGY OF IBS

The etiology of IBS is unknown; however, many factors may play a role in symptoms. Visceral hypersensitivity is widely thought to play a major role in IBS symptoms. Patients with IBS will have more discomfort with rectal distension than normal controls. The hypersensitivity occurs at the level of the central nervous system, as the output of peripheral nerves is the same in IBS and controls using an established rat model.

Emotional trauma, particularly childhood traumatic events, also plays a role in the development of IBS. This can be demonstrated with the use of a rat model. Rat pups separated from their mothers for 3 hours each day develop symptoms of IBS. Further, IBS symptoms worsen in patients during times of stress.[2] Another contributing factor is enteric nervous system dysfunction. Serotonin, acetylcholine, and tachykinins play a role in GI motility and nociception. These substances are being studied as promising sources of new treatments. Cellular immune dysfunction can be demonstrated in IBS patients, with biopsies of bowel mucosa showing increased numbers of mast cells, as well as increased degranulation of mast cells.[3] The significance of the mast cells is unknown.

Colonic propagation has also been studied in patients with IBS. Anal manometry in patients with constipation predominant IBS show fewer high-amplitude contractions over a 24-hour period.[4] EMG studies of patients with all types of IBS show irregular action potentials. A post-infectious IBS has been described, and research continues as to whether there is an infectious component to IBS, although to date there has been no definitive evidence. Finally, a patient's dietary choices may impact their bowel function. Studies on humans and rats have shown that the infusion of lipids into the colon increases bowel sensitivity and increases pain with bowel distension.[5] These etiologic components increase understanding of IBS and direct future research.

Diagnosis of IBS

Patients with IBS display altered bowel habits (diarrhea, constipation, or alternating), pain, and abdominal bloating. They may also exhibit extra intestinal symptoms such as sleep disturbances, sexual dysfunction, and urinary frequency. IBS is not a diagnosis of exclusion. The diagnosis of IBS is made based on a positive constellation of symptoms as described by the Rome II Criteria (Table 1). Further diagnostic workup is only necessary if there is concern for infectious etiology, cancer, or inflammatory bowel disease. Patients with history of exotic travel, fevers, blood in the stool, significant weight loss, family history of colon cancer, or onset after menopause should have further evaluation.

Table 1: ROME II CRITERIA[6]

In the past year, at least 12 weeks of abdominal discomfort/pain with 2 of 3 features:

1) pain relieved following defecation

2) onset of pain associated with change in stool frequency
3) onset of pain associated with change in stool appearance

Supported by abnormal stool form, abnormal stool passage, passage of mucus, bloating.

Patients with IBS may also have co-existing pain processes such as interstitial cystitis, endometriosis, musculoskeletal pains, or fibromyalgia. These should be aggressively sought out and addressed.

TREATMENT OPTIONS

Due to the great variety in symptoms expressed by IBS patients, there is no single treatment regimen that is effective for all patients. It is preferable to examine each patient's symptoms and formulate an individual treatment plan. This may require a trial of multiple medications, as well as titration of doses used. Basic management should include lifestyle changes, such as stress reduction techniques, daily exercise, and psychiatric services for patients with concurrent depression or anxiety disorders. A multidisciplinary approach to patients with IBS is helpful.

COMMON TREATMENT OPTIONS

These treatments are the most common medications used for IBS, and include bulking agents, osmotic laxatives, anti-spasmodics, anti-diarrheal agents, and tricyclic antidepressants. The literature regarding these medications is limited by sample size or study design. Due to side effects, not all patients will respond well to these groups of medications.

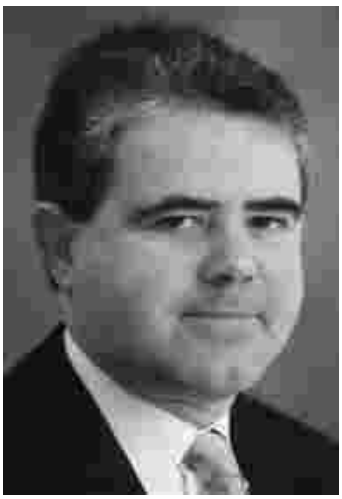
Bulking agents (Psyllium): Limited studies show an improvement in bowel function but no change in pain scores or global scores. Some patients will have worsening symptoms of bloating and gas formation.

Osmotic laxatives (Polyethylene glycol): There are no studies in patients with IBS, but may be helpful on a daily or as needed basis for patients with constipation who are unable to tolerate bulking agents. Polyethylene glycol may be used at high doses with few side effects.

Antispasmodics (Dicyclomine, hycosamine, and propantheline): Antispasmodics inhibit bowel motility and alleviate bowel "spasms". Multiple trials show mixed results. Although some patients may note an improvement in cramping, others may have more trouble with constipation.

Anti-diarrheal agents (Loperamide, atropine/diphenoxylate): Three randomized controlled trials (RCT's) show improvement in stool frequency, but no change in global functioning or pain scores.

The President's Perspective



R. W. Stones, M.D. • President

1 September 2004

As always the Annual Scientific Meeting was an opportunity to catch up with long standing friends, but on this occasion, demand for registrations exceeded supply, and some who could have become new friends were unable to join us. Participation by physical therapists was extremely strong in both the postgraduate course and main meeting agenda. The opportunity to undertake cadaver lab work was particularly appreciated by many. Some noteworthy main agenda presentations were given including contributions from local faculty. I was particularly pleased to welcome the president of AAGL, Andrew Brill, who showed his approach to laparoscopic treatment for pelvic pain. Another fascinating surgical presentation was on the topic of pudendal nerve entrapment, where the concept and neurosurgical technique have made the transatlantic journey from Nantes, France, and the group of Professor Robert and the late Dr Bensignor to Houston, Texas, in the hands of Dr Lee Ansell. I was most interested to hear of the substantial but often rather delayed improvement experienced by many patients after surgery, and the uncertain significance of pudendal nerve motor latency studies in the preoperative evaluation.

Has pelvic congestion become a radiologically diagnosed and treated condition? Skeptics might suggest that ovarian vein embolization is a procedure looking for a disease, but there is no doubt that interest in this condition, its diagnosis and management is increasing. A workshop held in association with the Annual Scientific Meeting considered the current status of knowledge in the field, and colleagues were interested to learn of the forthcoming availability of a disposable needle for diagnostic transuterine venography. Particular advantages of the transuterine approach are its technical simplicity and the ability to fully image dilated uterine veins that are not shown via selective catheterization of the ovarian veins.

The Board's thoughts have been of Australia: specifically Sydney, the venue for next year's Scientific Meeting, arranged so as to coincide with the World Congress of Pain. This will be a wonderful opportunity to share experience with colleagues from Australia and New Zealand, as well as to enrich our own very clinical perspective with the world class neuroscience and psychology be available at the World Congress. Start planning your itinerary now!

Sincerely,

R. W. Stones, M.D.
President, International Pelvic Pain Society

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Tricyclic antidepressants (Amitriptyline, nortriptyline, and desipramine): Three of six RCT's show improvement in abdominal pain, and two showed improvement in global scores. TCA's may be useful for patients with diarrhea-predominant IBS, those with some depressive symptoms, or with trouble sleeping.

Complementary and Alternative Treatment Options (Hypnosis, Psychiatric Counseling, Chinese Herbal remedies, Peppermint Oil): Multiple trials of complementary treatments have been done, but have been limited by small numbers or lack of randomization or appropriate controls. Two RCT's looking at hypnosis had small sample sizes and design limitations, but positive results. One RCT using Chinese herbal remedies seems promising, but further studies would confirm reproducibility. Psychiatric counseling combined with medication appears to be superior to medication alone, as shown in one study. Other studies of behavioral therapies had mixed results. Six RCT's showed no improvement with the use of peppermint oil. Standardization, larger sample sizes, and blinding should be used in future trials of complementary treatments.

NEWER TREATMENT OPTIONS

This group of medications has had stronger literature supporting its

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use in IBS. The studies use an IBS specific quality of life survey to follow global scores, as well as using pain scores. The GnRH Analog, leuprolide, Selective Serotonin Reuptake Inhibitors (SSRI's), and tegaserod have all been shown to be superior to placebo in treating IBS. Alosetron is also superior to placebo, but has had significant side effects and requires special training to prescribe.

GnRH Analog (Leuprolide): It has been documented that the hormonal changes in the menstrual cycle lead to worsening of symptoms in IBS with the onset of menses.[7] Two RCT's showed leuprolide to be superior to placebo in improvement of global and specific symptom scores. Duration of treatment was 3-4 months, and neither study used estrogen add-back therapy. Neither study reported on results after cessation of the medication.

SSRI's (Paroxetine): Two RCT's with paroxetine showed improved global scores and quality of life, though no change was noted in pain scores. This is a good choice for patients with constipation, as it increases bowel motility. It is also useful in patients with IBS and either depression or anxiety.

Tegaserod: Tegaserod is a serotonin 5-HT$_4$ agonist which increases bowel motility and fluid secretion. It has been approved by the FDA for treatment in women with constipation-predominant IBS. Four trials show improvement in both global scores and pain scores.

Alosetron: Alosetron is a serotonin 5-HT3 antagonist which decreases bowel motility and fluid secretion. It was approved by the FDA for the treatment in women with diarrhea predominant IBS. Months later, it was voluntarily withdrawn from the market due to 7 deaths from constipation and ischemic bowel. Due to protests from patients and advocacy groups, the medication was re-approved by the FDA, but requires a special license from the manufacturer to prescribe. A 2002 decision analytic model found that the benefits of use outweigh the risks in patients with moderate to severe symptoms; however, the cost of a modest benefit is substantial.[8] For a prescribing application, physicians should contact the pharmaceutical company, GlaxoSmithKline.

NEW DIRECTIONS IN RESEARCH

There are a number of new directions in IBS that appear to be promising, including prokinetics, tachykinins, sacral neuromodulation, and colonic pacing.

Prokinetics: Prokinetic medications include serotonin agonists, such as the serotonin 5-HT$_4$ agonist, tegasarod, and partial agonist/antagonists that may have fewer side effects and less resultant diarrhea. Renazapride is a combination agonist/antagonist undergoing clinical trials in Europe.[9] Neurotrophin-3 is an injectable prokinetic, which is found to accelerate colonic transit in normal and constipated patients. It is in the early stages of trials.

Tachykinins: Tachykinins are biologically active peptides involved in bowel function. Research has focused on two tachykinins, substance P and neurokinin A, which are most active in small and large gut function, with minimal action on the esophagus and stomach. Substance P binds the neurokinin receptor NK1 which is involved with bowel nocioception. The NK1 receptor antagonist, ezlopitant (CJ-11974), was tested in a small trial, and showed improvement in pain with rectal distension compared to placebo.[10] Neurokinin A binds the neurokinin receptor NK2, involved in bowel motility and smooth muscle contractility. Nepadutant, the most widely-tested NK2 antagonist, has been shown to reduce bowel motility in healthy volunteers.[11] Current studies of nepadutant are focusing on patients with IBS.

Sacral Neuromodulation: Sacral nerve stimulation, using Interstim® (Medtronic Inc, Minneapolis, MN) has been used for patients with urinary frequency, urinary urge incontinence, and interstitial cystitis with good results. Sacral nerve stimulation has also been used in patients with chronic, severe constipation.[12] Although the numbers of patients are small, preliminary work seems promising. No studies of IBS patients have been published, but the use of sacral neuromodulation in IBS seems like a natural progression.

Colonic Pacing: Colonic pacing is an experimental procedure which has been performed in a small series of patients with severe IBS, who have not responded to medical management.[13] Nine patients had a cardiac pacemaker inserted into a subcutaneous pouch and the leads placed at the colosigmoid junction. Pacing was performed after each meal. Patients had normalization of their EMG activity, and improvement in bowel function and pain. Pacing was discontinued after 6 months in 7 patients, and all 9 had continued improvement at 13 month follow up. Further studies with larger numbers are needed.

CONCLUSION

IBS is a difficult entity to manage, as patients may have a variety of symptoms and aggravating factors such as stress and history of abuse. A treatment plan needs to be individualized for each patient. Basic health measures such as daily exercise and a healthy diet are crucial. Behavioral therapy, especially addressing stress reduction, complements medical treatments. Initial pharmacologic treatment should address predominant bowel symptoms, as well as extra-intestinal symptoms. Side effects of medications can help in choosing a medication. For example, a patient with constipation predominant IBS and depression symptoms may do well with an SSRI, while one with diarrhea predominant symptoms may do better with a tricyclic antidepressant. Although IBS is a clinical challenge, with patience and a trial and error approach, most patients will be able to achieve an improved quality of life.

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