Evidence of Efficacy for Treatment of Irritable Bowel Syndrome - The Bottom Line

Irritable bowel syndrome (IBS) is a chronic and usually intermittent disorder, characterised by episodes of pain associated with bloating and altered bowel habits, in the absence of any structural abnormality or organic lesion. In the developed world, IBS is the most commonly diagnosed gastrointestinal disorder, with prevalence in the general population estimated between 5% and 25%, with two-thirds of patients being female. IBS accounts for 12% of visits to GPs and 28-36% of visits to gastroenterologists. Proposed pathologic mechanisms include post-infectious development, mucosal inflammation, visceral hypersensitivity of muscles and nerves, altered motility, altered central nervous system modulation of the gut, and imbalance of serotonin.

Management of IBS presents challenges. Patients become frustrated with coping with persistent symptoms and clinicians disappointed with limitations of therapeutic options.

No therapy has been shown to alter the long-term natural course of the condition and no gold-standard for treatment exists. As symptoms fluctuate over time, treatment is often directed at managing predominant symptoms when they occur. What's the evidence of efficacy for available therapeutic options?

**Fiber and bulking agents** - are often recommended. A review of 17 RCTs (n=1363), revealed that soluble fiber (psyllium, ispaghula, calcium polycarbophil) was more effective than placebo for reduction of global symptoms and constipation, whereas, insoluble fiber (corn or wheat bran) showed no significant difference compared with placebo, and in some cases worsened clinical outcome; no evidence was found suggesting either type of fiber resulted in relief of pain. Another review of 12 RCTs (n=591) evaluating therapy with psyllium, ispaghula, bran, or unspecified fiber showed no significant effect, when only high-quality studies were included (7 of 12 RCTs). A Cochrane review of 11 studies using fiber...
showed a lack of benefit for pain, global assessment or symptom score.\textsuperscript{14}

**Antispasmodics** - may be tried empirically and are usually scheduled before meals for patients with postprandial pain or "as needed" for acute attacks.\textsuperscript{15,16} Reduced colonic diameter and increased small bowel transit time have been documented in IBS.\textsuperscript{13} Antispasmodics may decrease pain and stool frequency by reducing contraction of the colon and transit time\textsuperscript{13,15} and are considered first line therapy.\textsuperscript{17} A review of 22 RCTs (n=1778) comparing 12 different antispasmodics (including pinaverium, trimebutine and dicyclomine) showed a statistically significant effect of therapy; persistent symptoms occurred in 39\% and 56\% of patients receiving treatment and placebo, respectively (NNT=5).\textsuperscript{13} When specific agents were assessed, pinaverium (3RCTs, n=188) showed a statistically significant effect of therapy; persistent symptoms occurred in 28\% and 61\% of patients receiving treatment and placebo, respectively (NNT=3).\textsuperscript{13,14} Trimebutine (3RCTS, n=140) did not show significant benefit.\textsuperscript{13,14}

**Loperamide** - is considered the antimotility agent of choice for diarrhea. Most clinicians suggest use of this agent "as needed", however for severe diarrhea, scheduled dosing for a short time may be required.\textsuperscript{15} It may prevent diarrhea when taken prior to a meal or an activity, which often leads to this symptom.\textsuperscript{10,15,17} Two RCTs (n=42) evaluating loperamide in IBS with diarrhea showed that 100\% of loperamide-treated patients had improved stool consistency, but there was no greater effect compared to placebo for relief of pain, global symptoms or bloating.\textsuperscript{11,15}

**Laxatives** - No RCTs have been conducted, comparing laxatives to placebo.\textsuperscript{7,11} These agents may be considered for use in IBS with constipation.\textsuperscript{17} Fiber supplementation is 1.5 times more likely to relieve patients of constipation compared to use of placebo and should be tried before other laxatives.\textsuperscript{15}

**Antidepressants** - As in treatment of neuropathic pain, increased pain threshold may be the mechanism of action of these agents; present data does not support improvement in co-existing depression as the cause for improvement of symptoms.\textsuperscript{18} TCAs are considered second line therapy in the U.K., if antispasmodics, laxatives or loperamide have not provided sufficient relief; SSRIs may be considered if TCAs are ineffective.\textsuperscript{17} A meta-analysis of 13 RCTS (n=789) assessing desipramine, trimipramine, amitriptyline, imipramine, doxepin, fluoxetine, paroxetine, and citalopram concluded that in the short-term, treatment is effective, with NNT=4 to prevent persistence of symptoms. TCAs and SSRIs were found equally effective.\textsuperscript{18} Another meta-analysis of 5 RCTs (n=>220) assessing SSRIs, including fluoxetine, paroxetine and citalopram, showed a trend for improvement of pain, however, there was no statistically significant evidence for improvement of pain, bloating or other symptoms.\textsuperscript{19} A Cochrane review of 6 studies using antidepressants showed a lack of benefit for pain and global assessment.\textsuperscript{14}
**Herbal Medicines** - A Cochrane review of 75 RCTs (n=7957; range 45-453) evaluated effects of 71 different herbal preparations (single herbs or mixtures of 2-20 different herbs); some herbal medicines improved symptoms such as pain, diarrhea and/or constipation. The methodological quality of the majority of the trials was generally poor; small, poor quality trials with positive findings are more likely to demonstrate exaggerated effects. The review concluded herbal medicines may be promising, however, it is premature to recommend their routine use.

**Peppermint Oil** - Menthol, in peppermint oil, may relax smooth muscle in the gut by a calcium channel blocking effect, and may also cause relaxation of the gastroesophageal sphincter, which may cause gastroesophageal reflux; therefore, enteric-coated (EC) products are often used to bypass the upper GI tract, and limit effects to the lower GI tract. Some evidence exists to suggest that EC peppermint oil capsules may be modestly effective in reducing pain, bloating and gas associated with IBS. A meta-analysis of 4 RCTs (n=392), with 1 study using EC capsules, revealed a statistically significant effect of treatment compared to placebo, with persistent symptoms in 26% and 65% of patients receiving treatment and placebo, respectively (NNT=2.5).

**Probiotics** - are live microbial food supplements containing lactobacillus and bifidobacteria, which retain viability during storage and transit through the stomach and small intestine. These bacteria multiply and live on the surface of epithelial cells in the small intestine, and act as a barrier to harmful microorganisms by producing substances with an antibiotic effect, as well as stimulating immune processes. Compared to controls, patients with IBS have been shown to have significantly lower concentrations of lactobacilli and bifidobacteria, and higher concentrations of Streptococcus, E. coli and Clostridia. Bacterial overgrowth of the small intestine occurs in up to 78% of patients with IBS and may be directly responsible for development of symptoms. It is thought that fermentation, with formation of hydrogen, methane and carbon dioxide, results in distention of the small intestine, and production of the sensation of bloating, discomfort, and disruption of motility. By increasing the concentration of probiotic-type bacteria and decreasing the concentration of Streptococcus, probiotic therapy has been documented to modify fermentation in the large intestine.

Two meta-analyses of probiotic therapy of 16 RCTs have been conducted. Combined data suggest a modest improvement in overall symptoms. A great number of limitations of the studies were identified including variations in measured outcomes, length of therapy, and number, type, dosage and strengths of probiotics, and lack of standardized diagnostic criteria and quality-of-life assessments.

**Summary:** Evidence of efficacy for most treatments of irritable bowel syndrome is weak. As
most treatments are directed at the predominant symptoms and restricted to the time symptoms are occurring, agents providing effective short-term relief are desired. Fiber, antispasmodic agents and peppermint oil may be effective to produce short-term relief in some individuals. With the limited therapeutic options currently available, decreasing and accepting, rather than eliminating symptoms, appears to be a reasonable goal for patients with IBS.\(^{10}\)

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References:

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