

DRUG TREATMENT FOR IBS (IRRITABLE BOWEL SYNDROME)

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Highlights

- IBS is a functional, NOT structural bowel disorder.
- All patients should receive **reassurance** that their symptoms are not part of a life threatening illness.
- **Lifestyle modifications can provide more relief than medications!** Avoid food triggers; increase dietary fibre, fluid intake, exercise; reduce stress.
- **Addressing underlying psychosocial issues** will help improve the patient's IBS symptoms.
- **No single drug** targets all IBS symptoms.
- Evidence supporting the use of drugs to treat IBS is limited – and sometimes conflicting. However, an empiric trial of a medication targeting the patient's **most troublesome symptom** may be beneficial.
 - ♦Fiber supplement (e.g. Psyllium) for constipation
 - ♦Loperamide for diarrhea
 - ♦TCA antidepressant for pain +/- diarrhea;
 - ♦SSRI if pain accompanied by anxiety or depression

Irritable Bowel Syndrome (IBS) is a functional bowel disorder without structural or biochemical abnormalities. Chronic abdominal pain altered bowel habits (constipation, diarrhea) and bloating are the classic symptoms.¹⁻⁴ (see Table 1: Rome III & Manning criteria) Symptoms of this benign disorder cycle through phases of exacerbations and remissions.⁵⁻⁷ The one-year prevalence rate in Canadian adults is around 12%⁶. Most cases are diagnosed before age 45. Females are twice as likely as men to suffer from IBS.^{2,8} Patients often experience significant emotional distress and ~50-90% suffer from co-morbid mental health disorders, such as anxiety or depression. Surgical procedures (e.g. hysterectomy, appendectomy) are more common in this population impacting quality of life.⁹ The exact cause of IBS is unknown.^{1,3} There are three interrelated factors thought to affect symptoms to varying degrees: altered gut motility, increased gut sensitivity and dysregulation of the brain-gut axis.^{1,8}

Table 1: Criteria for IBS Diagnosis & Alarm features

<p>Rome III <small>Drossman 27:</small> IBS if at ≥ 3 months, with onset ≥ 6 months previously of recurrent abdominal pain or discomfort <small>not described as pain</small> assoc. with ≥ 2 of:</p> <ul style="list-style-type: none"> • Improve with defecation; &/or onset assoc. with a change in frequency of stool; &/or change in form <small>appearance</small> of stool (present ≥ 3 days/month) <p>Manning <small>Cayley, BMJ 2005</small> Diagnose IBS if ≥ 3 are present*:</p> <ul style="list-style-type: none"> • Abdominal pain, relief of pain on defecation, increased stool frequency with pain, looser stools with pain, mucus in stools, feeling of incomplete evacuation <p>“Red Flag” / ALARM signs for further evaluation:</p> <ul style="list-style-type: none"> • weight loss, blood in stools, anaemia, fever; onset after age 50; recent antibiotic use; family history of colon cancer or inflammatory bowel disease; physical findings (abdominal mass, stool +ve for occult blood, enlarged lymph nodes), extra-GI symptoms (arthritis, skin abnormalities, lymphadenopathy)

* average sensitivity 60% & specificity 80%; diagnostic accuracy ↑ if younger & female

IBS Subtypes/Findings

IBS can be broken down into three main subtypes: **IBS-C** with constipation, **IBS-D** with diarrhea, or **IBS-M** mixed constipation & diarrhea changes over hours or days, plus IBS-U unsubtyped.

Subtypes are based on the single classification of stool consistency from the Bristol Stool Scale.²⁸ (Type 1-7)

However, it is recommended that **treatment is sought for symptoms, not subtypes** – which can change over time.^{3, 6, 8} The goal of therapy is to improve abdominal pain, bloating and altered bowel habits.⁸ Unfortunately, there is no single drug that targets all of the IBS symptoms.^{6, 10}

IBS General Management Considerations

Provide Patient Education

Often patients who seek medical care are concerned that their symptoms may represent life-threatening disorders. Despite having an impact on quality of life, IBS does not have an effect upon life expectancy, nor has it been linked to structural diseases such as diverticular disease, cancer or inflammatory bowel disease.^{4,6,7,12} The importance of providing education and reassurance to all IBS patients should not be overlooked.

Encourage Lifestyle Modification

Lifestyle changes (e.g. identifying food triggers, diet modification, stress management) typically offer more benefit than medications do.⁶ Encourage patients to keep a diary record of their symptoms for at least a two week period to help identify possible triggers (e.g. fat, alcohol, caffeine, sorbitol, meal size).^{1,5} When possible, refer patients to a dietitian to assist with dietary recommendations.

Treat Co-morbid Psychiatric Disorders

For patients with underlying mental health issues (e.g. depression, anxiety and stress), addressing the psychosocial issues may provide IBS symptom relief.

Investigate Possible Drug-Induced Causes

Check for medications that may cause or contribute to the primary IBS symptom complaint.

Table 2: Drugs that can cause IBS symptoms

Constipation	anticholinergics (especially tricyclic antidepressants: amitriptyline > imipramine > nortriptyline, desipramine), opioids, anticonvulsants, iron and calcium supplements, calcium channel blockers (esp. verapamil), Al ⁺⁺⁺ containing antacids, high dose diuretics, loperamide
Diarrhea	Mg ⁺⁺ containing antacids/supplements, NSAIDs, antibiotics, chemotherapy, antiarrhythmics, laxatives, herbal medications and teas that contain senna
Abdom. pain	NSAIDs, corticosteroids, antibiotics, iron

Drug Treatment

Drug therapy may be initiated when IBS symptoms start to diminish the patient's quality of life.^{5,8} Evidence to support chronic drug therapy is lacking, however trials of medications targeting the predominant symptoms may be used empirically during exacerbations.¹⁰

Limitations with the Evidence^{8, 10-14}

There are several limitations with the available literature. These lead to conflicting results between trials, meta-analysis and systematic reviews.

Table 3: IBS Study design limitations

- small sample size; lack of sample size calculations
- short durations
- inconsistently reported IBS subtype classification
- criteria to identify IBS patients not always used (e.g. Manning, ROME, ROME II, ROME III criteria)
- some endpoints inadequately designed, outcomes varied
- compliance seldom measured
- placebo response rate high (40-70%)
- often in gastroenterology and not primary care setting

Diarrhea

Loperamide **IMODIUM** is the antidiarrheal of choice for treating IBS related diarrhea and is the only drug in this class to be evaluated for this indication. It has a better safety profile, since it does not cross the blood brain barrier like other opiates.^{5, 10, 12}

Loperamide, when scheduled for short periods of time (i.e. <5 weeks), has been shown to decrease stool frequency from 1.9/day to 1.3/day, and decrease the incidence of urgency from 2.4 days/week to 1.1 days/week when compared to placebo (p<0.05 for both).¹⁵ When studied in patients suffering from painless diarrhea, all patients (100%) noted an improvement in stool frequency and stool consistency (versus 40% and 50%, respectively, in the placebo group, p<0.001).¹⁶ The doses used in these trials ranged from 2-12mg daily in divided doses.¹⁵⁻¹⁷ Patients were allowed to titrate the dose up or down to balance relief of symptoms with adverse events.

Loperamide has not been shown to relieve global IBS symptoms, abdominal pain or bloating.^{8, 10, 18} In fact, loperamide may increase nighttime abdominal pain.¹⁰ Therefore, loperamide is recommended in patients with painless diarrhea.¹⁰

Despite being used in trials, most recommendations suggest that loperamide should be limited to PRN use.^{2,5} It can be used intermittently to reduce postprandial urgency or to help prevent predictable episodes of diarrhea, especially for important events.^{2,3,5,10} However, if the diarrhea is severe, a short-term course of scheduled dosing may be needed.² Avoid in patients with constipation, and use with caution in patients suffering from IBS alternating between diarrhea and constipation.^{2,5,12}

Cholestyramine (**QUESTRAN**) may be useful when there is a component of bile-salt diarrhea, especially pertinent in post-cholecystectomy IBS.

Constipation

Non-pharmacological measures, like increasing dietary fruits and vegetables, exercise and fluid intake should be recommended in all patients suffering from constipation.³ If constipation continues despite these lifestyle modifications, fibre supplementation can be tried. There are two types of fibre – soluble (e.g. bulking agents – psyllium, calcium polycarbophil, oats) and insoluble (e.g. wheat bran).² Patients who are on fibre supplementation are 1.5 times more likely to experience relief from their constipation compared to those who are not (RR 1.56, 95% CI 1.21-2.02).¹⁹ Fibre will not improve abdominal pain or bloating, and **insoluble fibre may actually worsen these symptoms** - especially if introduced too quickly.^{19,20} {Fibre supplementation has also been evaluated in diarrhea-predominant IBS patients as well. However, due to previously listed literature limitations, current evidence only supports the use of fibre supplementation for treating constipation.^{11, 19, 20}}

There is little randomized controlled trial evidence for laxative use in this population.⁸ If fibre supplementation fails, other laxatives are sometimes necessary.^{2,3,5} Osmotic laxatives (such as Mg++ Citrate, PEG solution, sorbitol) are somewhat safer in the long term. Occasionally a stimulant is necessary and in such cases an agent such as bisacodyl may be used.

Abdominal Pain

Both antispasmodics and antidepressants have been investigated for relieving abdominal pain associated with IBS. Most recommendations suggest avoiding opioid analgesics, due to concerns involving adverse events, the abuse potential, and the lack of evidence in this population.⁵

Antispasmodics

Antispasmodics are thought to relieve abdominal pain by reducing intestinal smooth muscle contractions.^{1,2,10,12} The published reviews assessing the efficacy of antispasmodics in IBS patients have yielded conflicting summaries.^{8,10-14} Some of the reviews included up to eleven different antispasmodic agents – however, only three of these are available in Canada with an official indication for irritable bowel syndrome: dicyclomine **BENTYLOL**, pinaverium **DICETEL** and trimebutine **MODULON**.^{6,21} Therefore, these medications may be trialed empirically in patients suffering from abdominal pain. They can be used as-needed for acute attacks of abdominal pain or scheduled before meals in patients with postprandial symptoms.² Use with caution in patients with constipation, as antispasmodics may worsen this symptom.

Antidepressants

Antidepressants are used for their analgesic properties, as well as their ability to alter gastrointestinal transit and treat psychiatric co-morbidity.^{1,2} Only tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been investigated for IBS, with the bulk of the studies involving TCAs. There is only one trial comparing a TCA (imipramine) to a SSRI (citalopram). **Unfortunately, neither agent was superior to placebo for improving global IBS symptoms or abdominal pain.**²²

Tricyclic Antidepressants (TCA)

As with the antispasmodics, the reviews assessing the efficacy of TCA use for relieving IBS-related abdominal pain have lead to inconsistent conclusions.^{8, 11, 12, 14} A physiological study showed that a TCA (imipramine) prolonged intestinal transit time.²³ The anticholinergic properties of TCAs, along with this finding, support the use of these agents for treating diarrhea. Therefore, patients suffering from IBS-related abdominal pain may benefit from a TCA when a diarrhea component is also present, or when indicated for a co-morbid mental health disorder. Avoid using in patients with constipation, as TCAs may provoke or aggravate constipation.^{2, 10, 12}

Selective Serotonin Reuptake Inhibitor (SSRI)

No systematic reviews or meta-analysis, for this indication, have been conducted with the SSRIs, largely due to the small number of trials involving these agents. Although the clinical significance has yet to be determined, the above mentioned physiological study also showed that a SSRI (paroxetine) accelerated intestinal transit time - thus suggesting that SSRIs would be more suited for treating constipation.²³ A study involving fluoxetine in IBS patients suffering from pain and constipation (ROME II criteria) strengthened this notion. In this trial, 44 patients (61% ♀, mean age 34.9 [±10 years]) were randomized to fluoxetine 20mg po OD x 12 weeks or placebo, in a tertiary setting. By week 4, abdominal discomfort, bloating, hard stool consistency, frequency of bowel movements <3 times a week and change in bowel habit were all significantly improved in the fluoxetine group (p<0.05 for each). This effect continued to week 12. Four weeks after the study medications were discontinued, all of the above endpoints – except change in bowel habit, were still significantly less in the fluoxetine group.²⁴

In other words, in patients suffering from IBS-related abdominal pain and constipation may benefit from a SSRI. The SSRIs have also been investigated in patients suffering from diarrhea-predominate IBS. However, until additional evidence is available, reserve this class of

antidepressants for co-morbid mental health disorders in these patients.

Only three SSRI antidepressants have been studied in IBS patients to date – fluoxetine **PROZAC**, paroxetine **PAXIL** and citalopram **CELEXA**.^{22, 24, 25} {For studied doses in IBS, see Comparison Chart.}

Abdominal Bloating

Alleviating constipation, if present, may help reduce bloating. If using fiber supplementation to treat constipation, use cautiously as fibre may worsen bloating.⁵ Fluoxetine has been shown to relieve constipation, abdominal pain and bloating in patients suffering from constipation-predominant IBS and associated pain.²⁴ Otherwise, medications are not useful for bloating.

Herbal Medications, Probiotics & Alternatives

A Cochrane review assessed the effectiveness and safety of Chinese herbal medicines in IBS patients, but concluded that there is limited evidence to suggest using herbal agents at this time.²⁶ Currently, there is insufficient data to recommend any probiotics for IBS. Hypnosis, yoga, meditation, tai chi & acupuncture has no or limited evidence, but anecdotal cases of success. Cognitive behavioral therapy, standard psychotherapy and hypnotherapy³² may help selected IBS patients.

Agents on the Horizon

Asimadoline (a peripheral kappa-opioid agonist), cilansetron (competitive type 3 serotonin 5-HT₃ receptor antagonist), renzapride (a novel benzamide related to cisapride) & talnetant (a neurokinin-3 receptor-specific antagonists) are four examples of potentially promising agents for IBS.

Table 4: A note on Tegaserod (ZELNORM)

- A retrospective analysis reported that 13 patients (0.1%) on ZELNORM experience a cardiovascular ischemic event compared to 1 patient (0.01) in the placebo group (p=0.024), resulting in the removal of ZELNORM from the market.
- The FDA is now allowing the use of ZELNORM in female constipation-predominant IBS patients who are <55 years old with no history of heart problems.^{August 2007; Treatment IND program}
- Patients taking ZELNORM 12mg/day are 1.2 times more likely to experience relief from global IBS symptoms compared to those who are not (NNT=14).
- Diarrhea is the most common side effect and is 3 times more likely to occur in patients on ZELNORM, versus those on placebo (NNH=20).
- **Health Canada has suspended the approval of tegaserod.**

References available at www.RxFiles.ca

Links to:

IBS Drugs for Symptom Management – Chart:

<http://www.rxfiles.ca/acrobat/CHT-GI-IBS.pdf>

RxFiles Drug Comparison Charts book: www.RxFiles.ca

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(Type 1: separate hard lumps, like nuts, Type 2: sausage shaped but lumpy, Type 3: Like sausage or snake but with cracks on its surface, Type 4: Like sausage or snake, smooth and soft, Type 5: Soft blobs with clear cut edges, Type 6: Fluffy pieces with ragged edges, a mushy stool, Type 7: Watery, no solid pieces, entirely liquid)



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2. Canada N. Health Canada Endorsed Important Safety Information on Zelnorm: Health Canada; 2007.
3. See also RxFiles Q&A Summary