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Key Inforbits

- Irritable Bowel Syndrome
- Signs and Symptoms
- Risk Factors, Causes and Triggers
- Diagnosis and Tests
- Treatment Options
- Lotronex ® and Amitiza®
- IBS diet
- Safety and Efficacy of Amitiza®



April is Irritable Bowel Syndrome Awareness Month!

Irritable Bowel Syndrome (IBS)

IBS is a common condition in the United States. It is more of a functional disorder than a disease, due to that fact the bowel is not properly working.¹ In addition, no structural gastrointestinal (GI) impairments are typically present in IBS patients. It commonly presents in the form of lower abdominal pain, cramps, diarrhea or constipation. About 25 to 45 million individuals are estimated to have IBS in the United States.² Females are two times more likely to have IBS compared to male patients. About \$21 billion per year is estimated to be related to direct and indirect effects due to this disorder.³ IBS does not have an inflammatory component like other diseases such as ulcerative colitis and Crohn's disease, therefore it is not a risk factor for developing colorectal cancer.⁴ Other medical conditions commonly present in patients with IBS includes anxiety, chronic pelvic pain and fibromyalgia.⁵

1. Irritable Bowel Syndrome [Home page on the Internet]. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases; [updated May 2007, cited 2009 March 16]. Available from: http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/
2. Facts about IBS. [Home page on the internet]. Milwaukee: International Foundation for Functional Gastrointestinal Disorders; [updated February 2008, cited 2009 March 13]. Available from: <http://www.aboutibs.org/site/about-ibs/facts-about-ibs>
3. Talley NJ. Irritable Bowel Syndrome. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger & Fortran's Gastrointestinal and Liver Disease: Pathophysiology, diagnosis, management. 8th ed. Philadelphia: Saunders Elsevier, 2006, p. 2633-2652.
4. Mayo Clinic.com [Homepage on the internet]. Mayo Foundation for Medical Education and Research. [Updated August 6, 2008, cited on March 14, 2008]. Available from: <http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106>
5. Mayer E. Irritable Bowel Syndrome. N Engl J Med. 2008 Apr 17;358: 1692-99.

Signs and Symptoms

The signs and symptoms of IBS vary with each individual. Symptoms could be mild or severe and adversely affect the daily activities of the patient. There are periods of remission when the patient is free of IBS symptoms.^{1,2} IBS symptoms are not specific for only IBS because it can occur in other types of intestinal diseases.^{1,2} The symptoms associated with IBS include:

- Diarrhea or constipation (they can occur together, individually or alternating)
- Mucus material in the feces
- Abdominal pain or discomfort
- Bloating sensation or swollen abdominal region
- Gas
- Feeling of having an incomplete bowel movement.

Other symptoms associated with IBS includes heartburn, nausea and abdominal fullness.²

Stress can affect the displayed symptoms with IBS by increasing the sensitivity of the bowel. Stress stimuli can occur in different forms such as physical, environmental, dietary or psychological. Females with IBS typically have a flare up of symptoms during their menstrual cycle due to hormonal fluctuations.^{1, 2, 3}

1. Mayo Clinic.com [Homepage on the internet]. Mayo Foundation for Medical Education and Research. [Updated August 6, 2008, cited on March 14, 2008]. Available from: <http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106>
2. IBS. [Home page on the internet]. Milwaukee: International Foundation for Functional Gastrointestinal Disorders; [update February 2008, cited 2009 March 13]. Available from: <http://www.aboutibs.org/site/about-ibs>
3. Talley NJ. Irritable Bowel Syndrome. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger & Fortran's Gastrointestinal and Liver Disease: Pathophysiology, diagnosis, management. 8th ed. Philadelphia: Saunders Elsevier, 2006, p. 2633-2652.

Risk Factors

- Gender: Females
- Age: Typically occurs in patients < 35 years old
- Family history of IBS



1. Mayo Clinic.com [Homepage on the internet]. Mayo Foundation for Medical Education and Research. [Updated August 6, 2008, cited on March 14, 2008]. Available from: <http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106>

Causes/Triggers of IBS

The underlying reason for the occurrence of IBS is not fully understood. It seems to be related to the poor communication between the brain, nervous system and GI tract.¹ Under normal physiological processes, the intestinal muscles contract and relax in a regular manner. In the IBS patient, there is an abnormal muscle contraction of the intestine which ultimately affects the passage of food through the GI tract. When the food passes too quickly, the symptoms manifest in the form of diarrhea and bloating while they manifest as constipation when the intestinal contraction is slow.² Patients should avoid known triggers of their IBS symptoms such as food and stress. Patients should limit the amount of physical and mental stress on their body.² Some patients experience exacerbation of IBS symptoms when they consume certain foods such as wheat, dairy foods, onions and potatoes. These foods are patient-specific, however, and cannot be generalized for all patients.^{2,3}

1. IBS. [Home page on the internet]. Milwaukee: International Foundation for Functional Gastrointestinal Disorders; [updated February 2008, cited 2009 March 13]. Available from: <http://www.aboutibs.org/site/about-ibs/>
2. Mayo Clinic.com [Homepage on the internet]. Mayo Foundation for Medical Education and Research. [Updated August 6, 2008, cited on March 14, 2008]. Available from: <http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106>
3. Talley NJ. Irritable Bowel Syndrome. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger & Fortran's Gastrointestinal and Liver Disease: Pathophysiology, diagnosis, management. 8th ed. Philadelphia: Saunders Elsevier, 2006, p. 2633-2652.

Diagnosis

The proper diagnosis of IBS is important because it has symptoms similar to other intestinal diseases. A diagnosis can be made based on physical examination, medical history and basic laboratory tests. Additional tests such as blood studies, complete cell count and stool studies might be required in patients reporting warning signs such as rectal bleeding, anemia, family history of colon cancer, loss of weight, fever, symptoms starting after age 50, or major alteration in symptoms. The Rome III criteria is the gold standard diagnostic tool that aids in the proper diagnosis of GI conditions using the symptoms displayed by the patient and is utilized in the diagnosis of IBS. According to the criteria, abdominal discomfort or pain should be exhibited for at least 3 days in a month within a period of 3 months. In addition, two or more other symptoms should accompany the abdominal pain.

These symptoms include:

- Pain relieved with defecation; and/or
- Abdominal pain typically occurring with an alteration of stool frequency and/or
- Abdominal pain or discomfort related to a change in form or appearance of stool



Other common signs and symptoms including the presence of mucus in stool, change in stool frequency, form or passage, and abnormal bloating.^{1,2,3}

1. IBS. [Home page on the internet]. Milwaukee: International Foundation for Functional Gastrointestinal Disorders; [updated February 2008, cited 2009 March 13]. Available from: <http://www.aboutibs.org/site/about-ibs/>
2. Mayo Clinic.com [Homepage on the internet]. Mayo Foundation for Medical Education and Research. [Updated August 6, 2008, cited on March 14, 2008]. Available from: <http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106>
3. Mayer E. Irritable Bowel Syndrome. N Engl J Med. 2008 April 17;358: 1692-99
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. In: Drossman DA, Corazziari E, Delvaux M, et al., eds. Rome III: the functional gastrointestinal disorders. 3rd ed. McLean, VA: Degnon, 2006:487-555.

Treatment Options

Unfortunately, the causes of IBS are unclear, but the symptoms can be treated so that the patient can live a relatively normal life.¹ In many patients who have mild IBS, treatment may consist of a few lifestyle modifications such as diet, exercise and managing stress.¹ In those who have more moderate to severe IBS, other therapies are available such as fiber supplements, anti-diarrheal medications, anticholinergic medications, antidepressants, eliminating high-gas-producing foods, and counseling.¹ There are currently two medications used specifically approved by the FDA for the treatment of severe IBS in women: Lotronex® (alosetron) and Amitiza® (lubiprostone).¹ Zelnorm® (tegaserod), a partial 5-HT₄ receptor agonist, was used for the treatment of constipation-predominant IBS in women until it was suspended in March 2007 due to analyzed data from clinical trials suggesting a significant increase in cerebrovascular ischemic events in patients taking the drug versus placebo.² Zelnorm® was subsequently approved by the FDA to be available via a restricted access program that has since been discontinued by Novartis as of April 2008.^{2,3}

1. Mayo Clinic.com [Home Page]. Mayo Foundation for Medical Education and Research. Updated 9 May 2009. <http://mayoclinic.com/health/irritable-bowel-syndrome/DS00106/DSECTION=lifestyle-and-home-remedies> "Irritable Bowel Syndrome" Accessed 15 March 2009.
2. Mayer, EA. Irritable Bowel Syndrome. N Engl J Med 2008; 358:1692-9.
3. Zelnorm. [Homepage on the Internet]. East Hanover NJ: Novartis; 2008 [Cited 2009 Mar 19]. Available from: <http://www.zelnorm.com/index.jsp>

Lotronex® (alosetron)

Lotronex® (alosetron) is a 5-HT₃ antagonist FDA indicated for treatment of severe diarrhea-predominant IBS in women.¹ Alosetron works by decreasing intestinal motility and pain signals.² The medication is limited to women with severe, chronic diarrhea that have not responded well to conventional treatments.^{1,2} Physicians must enroll in the "Prescribing Program for Lotronex® (PPL)" that mandates patient education and an initial dose of 0.5mg twice daily.^{1,2} Serious gastrointestinal adverse effects have been associated with alosetron including severe constipation and ischemic colitis; however, these occurred rarely during clinical trials before it was approved.²

Alosetron was pulled from the market in February 2000 over concerns of serious GI side effects.² Eventually, the FDA allowed it to be reintroduced with a 50% lower starting dose and a narrower indication with marketing restrictions.²

1. Lotronex [package insert]. San Diego, CA: Prometheus Laboratories Inc. http://www.lotronex.com/PDF/us_lotronex.pdf. Accessed 19 March 2009.
2. Alosetron (Lotronex) Revisited. Medical Letter on Drugs and Therapeutics. (Vol.44, Issue W1136A). Aug 2002

Amitiza®(lubiprostone)

Amitiza® (lubiprostone) is a chloride channel activator that was approved by the FDA in April 2008 for the treatment of chronic idiopathic constipation in adults, and constipation-predominant IBS in women ≥18 years of age.¹ "Chronic constipation" is defined as having difficulties passing stool or infrequent bowel movements for at least three months.² "Idiopathic" refers to the unknown cause of the constipation.² Who should not take Amitiza?¹



- Pregnant patients
- Known or suspected bowel blockage
- Severe diarrhea

What are some common side effects? ¹

- Nausea
- Diarrhea
- Headache

1. Amitiza [package insert]. Bethesda, MD: Sucampo Pharmaceuticals. 2008. <http://www.amitiza.com/index.aspx>. Accessed 15 March 2009.
2. Mayo Clinic.com [Home Page]. Mayo Foundation for Medical Education and Research. Updated 9 May 2009. <http://mayoclinic.com/health/irritable-bowel-syndrome/DS00106/DSECTION=lifestyle-and-home-remedies> "Irritable Bowel Syndrome" Accessed 15 March 2009.

From the Medical Literature

A study published in the *American Journal of Gastroenterology* in 2008 looked at the safety and efficacy of lubiprostone in adults with IBS with chronic constipation. In this double blinded, parallel-group study, located at 20 centers across the United States, investigators enrolled 242 patients with constipation, and randomized them to receive either lubiprostone 24 mcg or placebo twice a day for four weeks. The primary outcome of this study was the number of spontaneous bowel movements (SMBs) after 1 week of treatment with lubiprostone vs. placebo. Secondary outcomes included SMBs at weeks 2, 3 and 4, along with other bowel movement characteristics.

The results at week 1 showed those patients receiving lubiprostone reported significantly more SMBs than the placebo group (5.69 vs. 3.46, $P=0.0001$). The secondary outcomes also showed greater frequency of SBMs with lubiprostone at weeks 2, 3, and 4 ($P\leq 0.002$). The two most common side effects reported were nausea (31.7%) and headache (11.7%). The investigators concluded that most patients will experience bowel movements with lubiprostone within 24-48 hours of the first dose and it improves frequency over a 4 week treatment period.

1. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol.* 2008; 103(1):170-7.

More Info on IBS

- aboutIBS.org: <http://www.aboutibs.org/>
- Mayo Clinic: <http://mayoclinic.com/health/irritable-bowel-syndrome/DS00106>
- Medline Plus: <http://www.nlm.nih.gov/medlineplus/irritablebowelsyndrome.html>
- JAMA patient page: Irritable Bowel Syndrome: <http://jama.ama-assn.org/cgi/reprint/295/8/960.pdf>



The last "dose" ...

"A successful individual typically sets his next goal somewhat but not too much above his last achievement. In this way he steadily raises his level of aspiration."

Kurt Lewin, US (German-born) psychologist (1890 - 1947)

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