Understanding and Managing Pain in Irritable Bowel Syndrome

Reviewed by:

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Irritable bowel syndrome: A functional GI disorder

- The term 'functional gastrointestinal disorder (FGID)' is an umbrella term that describes variable combinations of chronic or recurrent gastrointestinal (GI) symptoms that lack an identified underlying pathophysiology[1]
- Irritable bowel syndrome (IBS) is one of the most prevalent FGIDs; that displays the symptoms of gastrointestinal dysmotility and visceral hypersensitivity and always in the focus of gastroenterologists, because of their polymorphic symptomatology and insufficiently defined causes and habits that influence the appearance of FGD[2,3]
- IBS is the most common gastrointestinal disorder and the prevalence varies from 4-22% in the population based studies[3]
- IBS has significant impact on patients' everyday activities and quality of life, inducing emotional distress because of their chronic symptoms. It also results in heavy economic burdens through direct medical expenses and loss of productivity.[4]

Pathophysiology of IBS: Novel mechanisms

- Multiple factors are thought to contribute to the symptom complex experienced by IBS patients
- Classical pathogenetic mechanisms include: (i) changes in gastrointestinal motility that are, however, poorly related to the patient's symptoms; (ii) increased visceral perception, seen only in a sub-group of patients; and (iii) psychosocial factors[5]
- For long, the underlying disease mechanism of FGID such as IBS was centred on alterations of GI motility, visceral sensory function and psychological factors. Though, alterations in these factors were likely to be relevant for the manifestation of symptoms; for some it simply represent markers for underlying disturbances seen in IBD[6,7]
- New areas of research in the field of IBS pathophysiology have been continuously explored highlighting the number of novel mechanisms involved in IBS pathophysiology
- The role of several mechanisms has been explored in IBS, including disorders of the gut–brain axis; diet; genetic factors; infections and disturbances in the intestinal microbiota; low-grade mucosal inflammation, immune activation, and altered intestinal permeability; disordered bile salt metabolism; abnormalities in serotonin metabolism; and alterations in brain function (Table 1).[8]

Table 1: Factors and underlying mechanisms for the manifestation of IBS symptoms

Factors	Mechanism	Causes
Central processing of afferent stimuli	Alteration of the central processing of afferent stimuli (including visceral afferents)	Minimal systemic inflammation Effects of early childhood trauma
Psychological factors: Anxiety and depression	Alter the central processing of afferents (including visceral)	Multifactorial Activation of immune systems
Post-infectious IBS	Post-inflammatory neuroplastic changes, visceral hyperalgesia	Exposure to pathogens causing alterations of gut permeability Inflammation
Post-inflammatory IBS	As for post-infectious	A chronic or transient immune process (ie, controlled by appropriate immune modulation)
Bile acid malabsorption	Genetically determined alteration of the function of the apical ileal bile acid transporter	Type 2, or idiopathic, likely due to a genetic defect in the apical ileal bile acid transporter
Visceral hyperalgesia	Central and peripheral mechanisms	Infections or inflammation (post-inflammatory visceral hyperalgesia), or CNS-mediated visceral hyperalgesia after psychological trauma can occur
Mutations in SCN5A	SCN5A encodes the α-subunit of the voltage-gated sodium channel NaV1.5	Genetically determined

Sources : Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016 Oct;1(2):133-146.

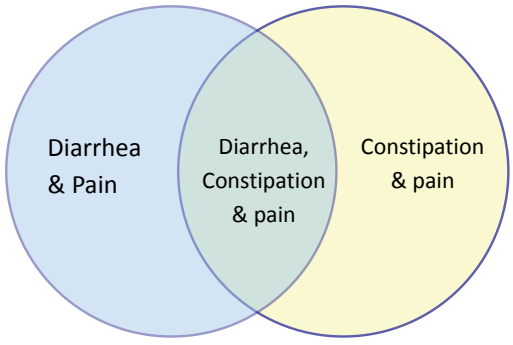
Clinical manifestations of IBS

- The hallmark of IBS is abdominal pain or discomfort associated with either a change in bowel habits or disordered defecation
- The pain or discomfort associated with IBS is often poorly localized and may be migratory and variable. It may occur after a meal, during stress or at the time of menses
- The three subcategories of pain in IBS along with altered bowel habits involve pain associated with diarrhea; pain associated with constipation; and pain and diarrhea alternating with constipation (Figure 1)
- While pain in IBS may occur as an occasional nuisance for some patients, others may experience pain that can range from inconvenient to incapacitating, and can prevent individuals from participating in everyday activities and compromise their quality of life
- Patients also complain of bloating or abdominal distension, mucous in the stool, urgency, and a feeling of incomplete evacuation
- Other functional gastrointestinal disorders including chest pain, heartburn, nausea or dyspepsia, difficulty swallowing, or a sensation of a lump in the throat or closing of the throat
- Extraintestinal symptoms include dysmenorrhea, dyspareunia, urinary urgency or frequency, and fibromyalgia[9,10]

Reaching a positive diagnosis of IBS: Rome IV criteria to rescue

- Patients with suspected IBS consult a physician when their symptoms are bothersome enough to affect their daily life and warrant them seeking medical attention
- The recently updated Rome IV criteria were designed to facilitate making a positive diagnosis of IBS, based on the presence of characteristic symptoms and the absence of objective findings owing to limited number of standard diagnostic tests and investigations (Table 2).[11,12]

Figure 1: The subcategories of pain in irritable bowel syndrome



Source: Irritable Bowel Syndrome (IBS): Introduction. Available at: https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/small_large_intestine/irritable_bowel_byndrome_ibs.pdf. Accessed on: 05/03/2020.

Pain in IBS and deteriorating QoL: The most disruptive and challenging symptom

- Pain is the most dominant and distressing symptom of IBS, regardless of the IBS subtype with adverse impact on quality of life. Three out of 4 patients with IBS report continuous or frequent abdominal pain that makes IBS challenging both for patients and healthcare providers[13,14]
- Patients with IBS report lower health-related quality of life (QoL) as compared to healthy controls. 15 Symptom severity, especially in relation to bowel function or abdominal pain, has been shown to have detrimental effect on QoL in IBS[16]
- As a global impact of IBS, patientsoften report uncertainty and unpredictability, with loss of freedom, spontaneity, social contacts, and feelings of fearfulness, shame and embarrassment. Psychological symptoms have an additive effect on reducing QoL.[16]

Table 2: Reaching a positive diagnosis of IBS and Rome IV diagnostic criteria for IBS

Patient presentation • Recurrent bothersome symptoms of abdominal pain • Altered bowel habits (constipation, diarrhea or both for at least 3 months	**Rome IV diagnostic criteria[a] for irritable bowel syndrome** Recurrent abdominal pain, on average, at least one day per week in the last three months, associated with ≥ 2 of the following criteria: 1. Related to defecation. 2. Associated with a change in frequency of stool. 3. Associated with a change in form (appearance) of stool. *Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.
Assess • Take a history and conduct physical examination • Minimal investigations • Concern for organic pathology, further investigation required	
Diagnosis • No concern for organic pathology • Rome IV diagnostic criteria for irritable bowel syndrome	

Source: Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. United European Gastroenterol J. 2017;5(6):773–788.

Major goals for treating IBS patients

1. Improve the individual symptoms of IBS (i.e. abdominal pain and discomfort, bloating, constipation, and diarrhea)
2. Ameliorate the global symptoms of IBS
3. Prevent complications of IBS (unnecessary surgery, risky diagnostic procedures, and adverse medication side effects from polypharmacy)
4. Reduce the impact of IBS by improving quality of life, and its impact on society

Source: Lacy BE, Weiser K, De Lee R. The treatment of irritable bowel syndrome. *Therap Adv Gastroenterol.* 2009;2(4):221–238.

An interdisciplinary approach in IBS pain management: Focusing on the use of smooth muscle relaxants

- Pharmacological therapy for abdominal pain over the past two decades has focused on the use of smooth muscle relaxants (commonly called antispasmodics)[17]
- Jailwala and colleagues published a systematic review of randomized controlled trials (RCTs) of pharmacotherapy for IBS, in which it was concluded that smooth-muscle relaxants are beneficial for the abdominal pain of IBS[18]
- Jailwala and colleagues recently published a systematic review of randomized controlled trials (RCTs) of pharmacotherapy for IBS, in which 28 high-quality trials reporting outcomes of global improvement or IBS-specific symptom improvement were identified. The trial involved use of bulking agents (various fiber products), smooth-muscle relaxants (e.g., cimetropium [not marketing a brand name yet]), pro-kinetic agents (e.g., cisapride), loperamide, and psychotropic agents (e.g., amitriptyline). The authors concluded that smooth-muscle relaxants were beneficial for the abdominal pain of IBS and thereby, reinstated the effective use of smooth muscle relaxant in management of IBS.[19]

Drotaverine: An effective antispasmodic for pain management in IBS

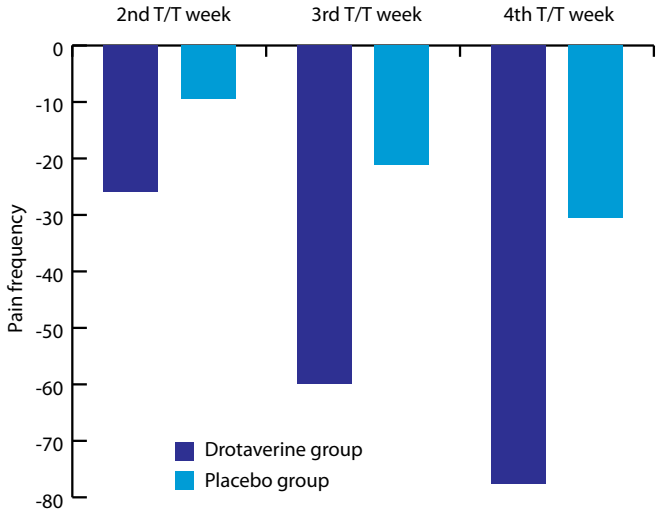
» Antispasmodics that are commonly used comprise hyoscyamine, dicyclomine, propantheline, and mebeverine, but they are associated with lot of anticholenergic side effects, which restricts their use[20]

» Drotaverine, a selective inhibitor of phosphodiesterase isoenzyme IV, is considered an effective antispasmodic, intestinal smooth muscle relaxant that helps in alleviating pain without anticholinergic side effects and found to be effective in improving abdominal symptoms in patients with IBS.[20, 21]

Clinical rationale for the use of drotaverine in IBS pain management

- Rai et al conducted a randomized double-blind placebo-controlled parallel group study[20] in a total of 180 patients with IBS were randomized to drotaverine and placebo treatment groups. Pain frequency decreased significantly ($P < 0.01$) in 22 (25.9%), 51 (60%), and 66 (77.7%) patients in the drotaverine group, at the end of 2nd, 3rd, and 4th weeks, respectively, as compared with 8 (9.4%), 18 (21.2%), and 26 (30.6%) in the placebo group (Figure 2). Pain severity scores also decreased significantly in the drotaverine group 66 (77.7%) as compared with placebo 26 (30.6%) after 4 weeks. Drotaverine HCl was shown to provide significant improvement ($P < 0.01$) in global relief in abdominal pain as perceived by the patient (85.9% vs 39.5%) and the clinician (82.4% vs 36.5%) in the drotaverine group as compared with placebo. There is significant ($P < 0.01$) improvement in stool frequency in drotaverine HCl treatment group as compared with placebo. Thus, a 4-week treatment with drotaverine significantly improves abdominal symptoms in patients with IBS.
- Another study by Xue et al[22] in 144 patients with IBS who were randomly divided into treatment group and placebo group in a 1:1 ratio and received either DHC or placebo 80-mg tablet, 3 times daily for a total of 4 weeks.The total and different types of IBS in VAS, stool frequency, and Bristol score were significantly better in the treatment group than those in the placebo group at the end of 4-week treatment. It was again confirmed that drotaverine was effective in alleviating symptoms of IBS.

Figure 2: Pain frequency in IBS among drotaverine and placebo group



Source: Rai RR, Dwivedi M, Kumar N. Efficacy and safety of drotaverine hydrochloride in irritable bowel syndrome: a randomized double-blind placebo-controlled study. Saudi J Gastroenterol. 2014;20(6):378–382.

- A prospective, self-control, multicentre clinical trial was performed in 217 IBS patients treated with oral drotaverine hydrochloride tablets 80 mg three times a day for 2 weeks. Compared with those before treatment, the average weekly score for abdominal pain in IBS patients was significantly decreased (0.66± 0.59 vs. 1.42±0.42, P=0.0000), and the overall efficacy rate was 77.9%; the average daily stool frequency was significantly increased in IBS with constipation (IBS-C) group (0.8±0.3 vs. 0.6±0.4, P=0.0004), while significantly decreased in IBS with diarrhea (IBS-D) group (1.6±0.8 vs. 2.8±1.2, P=0.0000). Stool form and feeling of incomplete defecation, straining and urgency in both groups were improved in different extents. Drotaverine hydrochloride efficacy was confirmed in all subtypes of IBS.[23]

Psychological approach in pain management in IBS

- Psychological approaches use the mind's own ability to alter pain sensations by sending signals, thoughts or nerve impulses, which close the pain gate. These techniques have found to be of great clinical utility in managing pain in IBS patients apart from pharmacological therapies
- There are an array of psychological pain management techniques, ranging from hypnosis to relaxation therapies to meditation along with cognitive behavioral therapy that can help ease symptoms and restore a sense of control over the pain in IBS patients.[14]

Conclusion

Irritable bowel syndrome IBS is one of the most prevalent FGIDs. A number of novel mechanisms involved in IBS pathophysiology have been explored that has given a novel insight towards a better understanding of the disease complex. The hallmark of IBS is abdominal pain or discomfort associated with either a change in bowel habits or disordered defecation. Pain is the most dominant and distressing symptom of IBS, regardless of the IBS subtype with adverse impact on quality of life.Pharmacological therapy for abdominal pain over the past two decades has focused on the use of smooth muscle relaxants (commonly called antispasmodics). Antispasmodics that are commonly used comprise hyoscyamine, dicyclomine, propantheline, and mebeverine, but they are associated with lot of anticholenergic side effects, which restricts their use. Drotaverine, a selective inhibitor of phosphodiesteraseisoenzyme IV, is considered an effective antispasmodic, intestinal smooth muscle relaxant that helps in alleviating pain without anticholinergic side effects and found to be effective in improving abdominal symptoms in patients with IBS.

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